Author's response to reviews

Title: Cardiac magnetic resonance imaging parameters as surrogate endpoints in clinical trials of acute myocardial infarction

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Author's response to reviews: see over
Editors-in-Chief  
TRIALS

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Dear Editors-in-Chief,

we wish to submit our revised manuscript entitled

“Cardiac magnetic resonance imaging parameters as surrogate endpoints in clinical trials of acute myocardial infarction”

for consideration of publication in TRIALS.

We cordially thank you and the reviewers for taking the time and effort to comment on our work which was very helpful for further improving the quality of the paper. We changed the manuscript according to the suggestions (see below).

We are looking forward to your answer. Please do not hesitate to contact us in case further details are required.

Yours sincerely,

Steffen Desch, MD on behalf of all co-authors

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**Reviewer #1**

**Major compulsory reviews:**

The authors state that reliability of infarct size is very high and thus, it could be used as an endpoint of clinical trials. However, since different sequences are used and different contrast- and signal-to-noise ratios as well as image qualities between different vendors exist, it is doubtful to what extend late gadolinium enhancement is reproducible between different scanners. Up to now, no prospective multi-center trial is available to clarify this point. Hence, it is a long way for late gadolinium enhancement to be used as a stand-alone endpoint in large multi-center trial, since previous work-up has to be done and validated. The authors should include this possible limitation in their manuscript. We agree with the reviewer and added the following sentence to the manuscript:

*It should be noted that there are yet no data on the reliability of infarct size measurements between scanners from different vendors. This, however, would be a prerequisite for infarct size to qualify as a reliable endpoint in multicenter trials with a variety of scanners.*

The manuscript fails to suggest a standardized analysis method, however above point needs to be taken into account. Although the manuscript contains an ample discussion on the pros and cons of different analyses methods, we hesitate to give a final recommendation due to the paucity of data comparing these methods (please see also answer to the second comment of reviewer #2). As stated above, we included a sentence on the potential variability of infarct size measurements between scanners from different vendors.

Presented myocardial salvage analysis approach is promising. However, since the contours are all drawn manually, a more quantitative approach is needed. Again, there is no validation in a multi-center trial available, not to speak of different imaging techniques and sequences. We agree with the reviewer and added the following sentence to the manuscript:

*As for infarct size, there is a lack of standardization with regard to image acquisition and analysis. Also, in the setting of multicenter trials, the potential variability of infarct size measurements between scanners from different vendors should be taken into account.*

Microvascular obstruction could be measured at different time-points using different imaging techniques and resulting in different extend of microvascular obstruction. A standard has to be found and validated before any statement of possible surrogate marker could be made. We address the methodological aspects of assessing microvascular obstruction by CMR with the following paragraph:

*Several methods for the assessment of microvascular obstruction by CMR have been proposed [1]. Image acquisition during first myocardial pass of gadolinium, early imaging in the first minutes after contrast administration and late imaging approximately 15 minutes after contrast injection. The extent of microvascular obstruction gradually declines between first-pass and late imaging. The observed differences over time reflect the persistent slow diffusion of contrast or collateral filling into areas with a less compromised microcirculation. These regions subsequently display smaller or completely absent zones of hypoenhancement on late imaging. Microvascular obstruction on late imaging therefore likely reflects areas of a more severely disturbed microcirculation whereas microvascular obstruction on early imaging is more sensitive for the detection of only small or less impaired areas of microvascular injury. At present, there is no consensus which of these slightly differing techniques to apply. However, in the largest patient series to date late image acquisition (approximately 15 minutes after contrast administration) was superior to early image acquisition (approximately 1 minute post contrast administration) in predicting clinical outcome [2]. Myocardial regions displaying delayed, yet not fully absent perfusion might therefore be of only minor importance for clinical prognosis. Given the time dependency of presence and extent of microvascular obstruction on the time between contrast administration and image acquisition, it is important to adhere to strict methodology within the clinical trial setting.*

As outlined, there is currently no consensus which method to apply. We agree with the reviewer that there is a need for further research and standardization.
We believe microvascular obstruction is already suited as a surrogate endpoint if a particular trial adheres to predefined strict and consistent methodology including reporting of the limitations of the imaging approach used.

It is well known that area of late gadolinium enhancement, area of T2 hyperintensity, and microvascular obstruction change during the first week on a daily basis. Hence, a standard has to be found when to perform the scan. Moreover, time since occurrence of first chest pain, revascularization time has to be taken into account to find a common basis.

We agree that timing of image acquisition is critical in the first days following myocardial infarction and close attention should be payed to adhere to a narrow and consistent time window. As highlighted by the reviewer, recent studies have demonstrated that infarct characteristics (infarct size, myocardial edema and microvascular obstruction) evolve over the first week after reperfusion [3-7]. It is therefore important to be aware of these changes when comparing data acquired at different time points, particularly in the context of clinical studies in which CMR surrogate end points are used. From the currently available data, we would advise that studies using CMR as end point should be performed within a narrow window during the first week after infarction, as otherwise the data will not be necessarily comparable. This important issue is already highlighted in our manuscript (Section Infarct size: Basic description).

We also added the following paragraph to the manuscript:

Although the time from symptom onset to image acquisition could be used to define the interval, time from revascularization to image acquisition might be more appropriate since reperfusion injury can exert a major influence on infarct size (and subsequent myocardial salvage) and microvascular obstruction. With the latter approach, it stands to reason that the variability in the time from symptom onset to reperfusion is a potential confounder and study sample size must be adapted accordingly.

Minor revisions:

The authors should comment on newer late gadolinium enhancement techniques, such as phase-sensitive IR sequences and their possible advantages to act as a surrogate end-point in clinical trials.

We added the following sentence:

Newer phase-sensitive inversion recovery sequences are able to achieve a more consistent contrast between infarcted and normal myocardium which in turn might influence measurement variability in image analysis [8].

Quantitative analysis of late gadolinium enhancement is an important tool to allow for serving as a surrogate end-point in infarction studies. However, transmurality of infarction is also important, since rest of myocardial viability is important for possible functional improvement. The authors should comment on that.

We thank the reviewer for this comment and added the following sentence:

Apart from quantitative analysis of infarct volume as described above, late enhancement imaging can also be used to measure the extent of infarct transmurality which provides additional information in predicting improvement in contractile function after myocardial infarction [9].

The authors should be more humble in their conclusions, since a lot of work has to be done before any statement of surrogate end-points could be made so far.

We agree with the reviewer that there are several unresolved issues with the CMR parameters mentioned. We tried to illuminate these shortcomings in the respective paragraphs and added the following sentence at the end of the manuscript:

Further studies should focus to address some of the limitations of CMR endpoints in myocardial infarction.
**Major Compulsory Revisions**

Page 4 Surrogate endpoints- reliability. The authors comment on intraobserver and interobserver repeatability as markers of reliability, but what about interstudy reproducibility (degree of variability when the study is repeated in the same individual)? This is particularly relevant when measurements are repeated over time, as some of the difference seen in the surrogate endpoint may be explained by interstudy variability. Are there any data on this for any of the surrogate endpoints described?

We have published data on interstudy reproducibility of infarct size and myocardial salvage measurements [10, 11].

In 21 patients (10 acute myocardial infarction and 11 chronic myocardial infarction), infarct size was assessed repeatedly on consecutive days [11]. Reproducibility was assessed by Bland-Altman analyses. Infarct size difference (bias) between scans 1 and 2 was -0.5 %LV, and limits of agreement were ±2.4 %LV.

In 20 patients who underwent CMR imaging on 2 consecutive days early after reperfused ST-elevation myocardial infarction, the average difference between scans 1 and 2 for myocardial salvage and myocardial salvage index was -0.6 %LV (upper limit of agreement 4.1 %LV; lower limit of agreement –5.3 %LV) and -1.7 (upper limit of agreement 5.5; lower limit of agreement –8.9) [10].

Both publications mentioned above are already cited in the manuscript.

To the best of our knowledge, there are yet no published data on interstudy reproducibility for microvascular obstruction in humans. However, in the canine model it has been shown that the extent of microvascular obstruction increases over the first 48 hour after infarction [6], but that the extent of MO is unchanged between 2 and 9 days after reperfusion [7].

Page 7 Infarct size- validity and reliability. It is stated that manual tracing of infarct size shows excellent interobserver variability. Are the authors aware of the availability of any reliability data for the semiautomated methods they describe?

We added the following sentence to the manuscript:

_Flett et al. compared the reproducibility of 7 late enhancement quantification techniques in 20 patients with acute myocardial infarction: Manual quantification, thresholding by 2, 3, 4, 5, or 6 standard deviations above remote myocardium, and the full-width at half-maximum technique [12]. The full-width at half-maximum technique was the most reproducible compared with any other method._

Page 13 Microvascular obstruction- comparison to alternative methods. The authors mention myocardial contrast echocardiography but do not make any comparison between this technique and CMR. Are the authors able to make a brief comparison?

To the best of our knowledge, there is only on animal study which directly compared both imaging modalities against the histopathologic standards of of radioactive microspheres and thioflavin-S staining [7]. Overall, both noninvasive techniques correlated well with microspheres. Myocardial contrast echocardiography was found to overestimate and CMR was found to unterestimate the extent of microvascular obstruction. Possible explanations as outlined by the authors include:

_“Gadolinium rapidly extravasates from the blood pool into the interstitium and hence, is an interstitial agent. Microbubbles, however, are purely intravascular. Because gadolinium can penetrate into extravascular spaces and travel where bubbles cannot, one may thus expect MRI hypoenhancement to be smaller than the CE defect. Different physical properties of the agents may also contribute. Albumin microbubbles are, on average, larger than gadolinium molecules. As such, microbubbles larger than gadolinium molecules could become temporarily lodged in microvessels that would allow passage of gadolinium.”_

Page 14 Left ventricular ejection fraction and volumes- comparison to alternative methods. The alternative techniques of echocardiography and SPECT are discussed, but how does CMR compare to multigated acquistion scanning (MUGA), which, although involves the use of ionising radiation, is also able to provide accurate information regarding EF and volumes?

We thank the reviewer for this comment.
In a heart phantom model, the accuracy and reproducibility of cardiac EF measurements between CMR imaging and MUGA were evaluated by comparing them with a volumetrically determined standard [13]. Cine MR was most accurate, with average relative errors ranging from 4.4% to 8.5%. MUGA EF measurements showed good correlation, with average relative errors ranging from 7.1% to 22.4%.

Another study compared right and left ventricular volumes and EF measurements between MUGA and CMR in 18 patients [14]. MUGA showed excellent correlation with CMR for both right and left ventricular volumes as well as left ventricular EF.

**Minor Essential Revisions**

Page 6 line 3- is there a reference for the equation given for calculating infarct size as a percentage of left ventricular mass?
The mass density or density of a material is defined as its mass per unit volume. Geiser and Bove reported a density value of 1.05 g/mL for the human heart [15]. We cite their work in the revised manuscript.

Page 7 line 5- typing error “und” should read “and”
The sentence was erased with regard to contents since in the meantime a study was published comparing the reproducibility of different late enhancement quantification techniques [12].

Page 10 line 6- AAR acronym needs changing to its unabbreviated form (presumably area at risk)
We changed the manuscript accordingly.

Page 14 line 7- change “ECG” to “electrocardiographic”
We changed the manuscript accordingly.

Page 15 line 1- change “LV” to “left ventricular”
We changed the manuscript accordingly.

References


