Author’s response to reviews

Title: Longitudinal shortening remains the principal component of left ventricular pumping in patients with chronic myocardial infarction even when the absolute atrioventricular plane displacement is decreased

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Version: 1 Date: 05 Jul 2017

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To the Editor of BMC Cardiovascular Disorders

Please consider our revised manuscript “Longitudinal shortening remains the principal component of left ventricular pumping in patients with chronic myocardial infarction even when the absolute atrioventricular plane displacement is decreased” for publication in the journal. We have responded to all the comments of the editor and reviewers and included a new age-matched control material per reviewers’ suggestion. We have added a new author who analyzed the new control material (Ulrika Pahlm) and have filled out and attached the signed forms for changing authors. We believe that the manuscript has improved significantly and hope that it is now acceptable for publication.
The manuscript is not under consideration for publication elsewhere, and the data has not been published previously. All authors have read and approved the manuscript. All authors met the full criteria and requirements for authorship. Ethical approval has been obtained and is stated in the manuscript.

Sincerely
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Response to Reviewers´ comments

Editor Comments:
The paper is interesting
Some issues

1) more data about time of ischemia (potential impact of remote ischemic preconditioning should be added)

Editor comments. Response 1. This data is unfortunately not available due to the retrospective nature of the study. We have added the time from the infarct to the CMR and patients´ medications to the new Table 1 and the text below in Response 2 to the Limitations.

2) more data about procedural features (kind of vessel) should be added
Editor comments. Response 2. We have divided the patient data according to vessel territory. We have gone through all patient charts and more detailed data is unfortunately not available. We have added the following sentences to the Limitations (Page 13):

“Detailed coronary angiography data was not available in all patients due to the retrospective nature of the study. Thus, we could not assess the procedural features in cases of percutaneous coronary interventions and the potential impact of the amount of vessel disease. Neither was time from pain onset to reperfusion during the STEMI available in this study and potential impact of remote ischemic preconditioning cannot be assessed.”

3) potential impact of different vessels' disease should be commented on (quote on PMID: 28131320)


This paper describes the “Incidence, predictors, and impact on prognosis of target lesion revascularization (TLR) for patients treated with second-generation drug-eluting stents (DESs) on unprotected left main (ULM)” . Our study is focused on a different patient population, namely chronic infarcts and we have therefore not been able to see how the results of this reference apply to the submitted paper. The proposed PMID may be a mistake and another publication intended.
Reviewer reports:

Zhong Liang (Reviewer 1): The authors quantified the atrioventricular plane displacement (AVPD) and investigated the longitudinal, septal and lateral contributions to LV pumping in a group of MI patients. It was concluded that the contribution percentage from AVPD remains the same in MI patients compared to normal controls.

1. This was a retrospective study with small number of patients. The results demonstrated limited clinical value. It would be more clinically impactful if a study is designed to investigate the diagnostic and predictive performance of the method and parameters described in this manuscript.

Reviewer 1 comments. Response 1. We agree that a study showing the predictive performance is of interest. Longitudinal function is increasingly being used clinically, e.g. global longitudinal strain. Longitudinal motion of the mitral plane (AVPD) from CMR has also shown to have strong and independent prognostic value. The purpose of our study was however to increase the fundamental understanding from a physiological point of view. When we use the clinical tools of global longitudinal strain and MAPSE it is important to describe how the pumping mechanics of the left ventricle are affected by a chronic MI. Extracting diagnostic and predictive information from these findings is very interesting and will possibly be addressed in future studies. The rationale for the study have been clarified in the Introduction and the need of further studies highlighted in the Discussion as follows:

Introduction Page 4

“The rationale of this study was to increase the fundamental physiological understanding of longitudinal left ventricular function in chronic MI patients so that the clinical tools of longitudinal function, e.g. global longitudinal strain and MAPSE can be better understood.”
“Studies including larger patient numbers and prognostic information on e.g. exercise capacity, morbidity and mortality as well as potential additional diagnostic value from the AVPD, septal and lateral contributions to LVSV, would be of interest.”

2. The contribution to LVSV from longitudinal, septal and lateral movement was quantified in this study. However, LVEF would be a more important and clinically relevant parameter that worth investigation. Are there any differences in the contribution to LVEF from each component in the patient group in comparison to controls?

Reviewer 1 comments. Response 2. We are not sure how it would be possible to examine the longitudinal/septal/lateral contributions to LVEF but have included the relationship between infarct size and LV volumes and LVEF to the Results page 7.

“Left ventricular volumes showed a positive correlation with infarct size, EDV=7.3xIS-15.9, r=0.75, p<0.001 and ESV=7.78xIS-1.6, r=0.82, p<0.001. Ejection fraction had a negative correlation with IS, EF=-1.18xIS-0.8, r=0.79, p<0.001.”

3. The control subjects in this study were much younger than MI patients (31 yrs vs. 59 yrs). The authors should only include age- and gender-matched control group, since some cardiovascular structure and function are related to chronological age including LV volume, wall stiffness as well as AVPD.

Reviewer 1 comments. Response 3. We agree and have changed the control population to be more similar to the infarct patients (age 59±3 years in patients and 62±2 years in controls. The Results have been updated accordingly and the Limitation of different age groups have been deleted.
4. For the AVPD calculation, AVPD was measured as the difference from ED to ES in the basal part of the LV in two points in each long-axis views using manual method. How to select these two points? Different location along the line connecting the septal and lateral atrioventricular points will give different AVPD results. Some automated method based on CMR feature tracking shall improve the process (Leng et al. AJP 2015; 309:H1923-35; Leng et al. Annals of Biomedical Engineering; 2016;44(12):3522-3538.)

Reviewer 1 comments. Response 4. We agree that the methodology on how to choose the basal insertion points is important to get accurate AVPD results and we recently published an automated algorithm for AVPD. We have included the suggested references by Leng et al. along with our own work on this area (Seemann F et al. BMC Medical Imaging 2016) with the following text in the Discussion Page 12:

“Automatic software for AVPD tracking exists and can be used to minimize user dependency of the AVPD measurements (REFS Leng et al, Seemann F et al). In addition, this provides additional information of the AVPD over the entire cardiac cycle.”

5. Page 7 line 43, the patient with a MI in the RCA territory has normal AVPD? Is this a typical example? Since significantly reduced AVPD in RCA MI patients was reported in Table 1.

Reviewer 1 comments. Response 5. The reviewer is correct to point this out and this was not a typical example. Rather, the point is to show the difference between patients. This patient had a near-normal AVPD and is an example of how a decreased lateral contribution may be compensated in some patients by an increased longitudinal contribution. We have re-written this part, moved it to the Discussion (Page 11-12):

“Figure 6 illustrates how the regional contributions to LV pumping differ between patients. ….In contrast, the patient with an MI in the RCA territory has almost zero movement of the lateral epicardial contour, compared to the LAD-MI patient, i.e. decreased lateral contribution to SV due to the infarct in the lateral and inferior wall. This is compensated by a normal AVPD resulting in an increased longitudinal contribution to SV as the epicardial area in this patient is
increased. These cases can be contrasted with a patient shown in Figure 7… Thus, patients with LAD-infarctions and apical aneurysms can have both decreased and increased longitudinal function and the prognostic and functional importance of this finding remain to be elucidated.”

The Figure legend (now Figure 6) has been clarified as follows

“As a contrast, the RCA-MI patient shown in the lower panels has a normal AVPD despite the MI. This may be compensatory to the decreased lateral contribution to LVSV in this patient due to the MI.”

6. A detailed intra- and inter-observer reproducibility results should be given (in a table or figure) using correlation, Bland-Altman, intra-class correlation coefficient for all measurements, including absolute AVPD, short-axis area, contribution percentage from AVPD, septal and lateral movement.

Reviewer 1 comments. Response 6. We have added the intra-observer reproducibility of AVPD to the results. However, we have not performed Bland-Altman, correlation, intra-class correlation (ICC) for all values. The reason is that the input variables for these calculations are the AVPD measurements and short-axis area measurements which are not independent. From these, longitudinal contribution and septal/lateral contribution are calculated as a volume. Thus, it is more correct to perform bias according to Bland-Altman analysis only on the original measurements. We do not perform Bland-Altman analysis of the stroke volumes as we provide the internal validation when adding the longitudinal, septal and lateral contribution in percent. They should be 100% in an ideal situation. To add other measures of additional parameters would thus be to over-analyze the data. Also, we do believe that a bias according to Bland-Altman provide the information needed to assess reproducibility and to our understanding correlation analysis do not add additional information in this regard (Bland and Altman, Lancet 1986). We have added the following to the Results (Page 9):

“Intraobserver variability of AVPD in 20 patients analyzed >3 months apart, was 0.3 mm±0.7 mm.”
Dirk Lobnitzer (Reviewer 2): The authors present a paper aiming to determine the amount of longitudinal, septal and lateral contribution to LV-function after myocardial infarction. The study group includes one group of patients with LV, one group with RV infarct and a control group. Although AVPD (atrioventricular plane displacement was reduced in patients after MI, the longitudinal contribution to LV stroke volume was unchanged in MI and controls.

Major comments:

- the control group was much younger than the infarct group which can affect volumes and function significantly (see age group in normal MRI values by the ESC)

Reviewer 2 comments. Response 1. We agree and have changed the control population to be more similar to the infarct patients (age 59±3 years in patients and 62±2 years in controls). The results have been updated accordingly and the Limitations of different ages between group has been deleted.

- no Information is provided on the time delay between the MI and the MRI, remodeling can take longer than 3 months

Reviewer 2 comments. Response 2. We agree and have added this information to Table 1.

- there is no information on the revascularisation, medical therapy, the extend of coronary disease as well as the clinical status of the included subjects

Reviewer 2 comments. Response 3. We agree and have added the medical therapy Table 1. We have reviewed all patient charts and unfortunately the data on the extent of coronary disease and revascularization is not fully available due to the retrospective nature of the study. This has been clarified in the Limitations page 13:
“Detailed coronary angiography data was not available in all patients due to the retrospective nature of the study. Thus, we could not assess the procedural features in cases of percutaneous coronary interventions and the potential impact of the amount of vessel disease. Neither was time from pain onset to reperfusion during the STEMI available in this study and potential impact of remote ischemic preconditioning cannot be assessed.”

- data on transmurality of the myocardial scar would be helpful to understand and describe the extend of the infarct

Reviewer 2 comments. Response 4. The mean transmurality has been added to Table 2.

- you suggest a near normal systolic function under stress in the individual case in figure 6 with a large apex aneurysm which I can't believe based on the the amount of dilatation, the reduced LVEF, reduced ASPD and especially on the background of your explanations on reduced MAPSE and their correlation to worse outcome data

Reviewer 2 comments. Response 5. The reviewer is correct that this patient does not have normal systolic function under stress and we did not intend to make this claim. However, based on the fact that the patient has a normal exercise capacity the left ventricle must deliver a cardiac output during stress that is sufficient for the demand of the body. We have clarified this as follows at page 12:

“Thus, the increased piston-pumping of the AV-plane in this patient can produce a near normal aerobic capacity during stress.”

- there is no information on RV function after RV infarct

- RV infarction which affects the posterior LV wall usually also affect the inferior part of the interventricular septum as shown in figure 2. This part of the septum might be included in a standard 4 chamber orientated MRI image and have some impact on your measurements.
Reviewer 2 comments. Response 6. We agree that RV function also may be affected, especially in RCA infarctions and we did not include analysis of RV function in this study as the aim was to assess LV function. There were no isolated RV infarctions in the study but in some patients with infarct in the RCA-territory, the infarct in the inferoseptal part also extended to the diaphragmal RV wall. The part of the septum involved was included in the analysis and thus we do not believe this will cause any bias. We have clarified the role of RV infarction in the Limitations page 13 as follows:

“We did not include the effect of MI on RV function that may be seen in RCA-MI when part of the RV diaphragm wall sometimes is infarcted. Furthermore, in cases where the septum bulges to the RV during systole due to LV infarction, this movement will contribute to RV pumping. The effects of MI on the longitudinal, septal and lateral RV function may therefore be of interest for further studies.”

- illustration of the short axis measurements are missing

Reviewer 2 comments. Response 7. We have added an illustration of the short axis measurements as a new Figure 1.

- there is no discrimination of the contribution of the anterior, lateral and posterior free wall of the LV

Reviewer 2 comments. Response 8. The reviewer is correct that we did not discriminate between the anterior, lateral and inferior wall of the LV in this study and the reason is to avoid too many comparisons of the datasets as this could lead to type I errors. We have clarified this in the Limitations page 13-14.

“Finally, we did not discriminate the contribution of the anterior, lateral and inferior wall of the LV in this study but combined them to one parameter called lateral contribution. This was done to decrease the risk of type I errors due to a high number of comparisons in each subject.”
- The discussion suggest that there is always a dilation of the LV after MI. This depends on the infarct size and location.

Reviewer 2 comments. Response 9. We agree and have included the correlation analysis of LV dilatation (EDV, ESV) and infarct size to the Results page 7 and commented this in the Discussion page 9.

“Left ventricular volumes showed a positive correlation with infarct size, EDV=7.3xIS-15.9, r=0.75, p<0.001 and ESV=7.78xIS-1.6, r=0.82, p<0.001. Ejection fraction had a negative correlation with IS, EF=-1.18xIS-0.8, r=0.79, p<0.001.”

“…and the presence and degree of LV dilatation showed a correlation with infarction size.”

- comparison of the complex 3-dimensonal movement of the LV is not at all comparable with a simple piston pump movement (the LV is not a cylinder)

Reviewer 2 comments. Response 10. We agree that the intrinsic movement of the myocardium is complex. However, when viewing the LV from the epicardial border, the movement is simpler, comprising of a longitudinal shortening and a radial inward motion (Carlsson, et al. American Journal of Physiology 2007 and Ugander et al American Journal of Physiology 2009). Therefore, the LV motion using the described technique simplifies the LV to the combination of a piston motion seen as longitudinal shortening and an inward radial shortening (subdivided to the septal and lateral contribution Stephensen et al. American Journal of Physiology 2014). This has been clarified in the Discussion page 9:

Minor comments:

- page 7 line 47 increased systolic movement of the LV after RV infarction is not demonstrated in the figures

Reviewer 2 comments. Response 11. We are not entirely sure what the reviewer is referring to in this case but Figure 7 shows a patient with RCA-infarction and normal systolic AVPD in the LV and due to a larger epicardial area this results in an increased longitudinal contribution to stroke volume due to a decreased lateral contribution. We have clarified the Figure legend and moved the section from the Results to the Discussion as described above in “Reviewer 1 comments. Response 5”.

We have added the following to the legend of Figure 6:

“As a contrast, the RCA-MI patient shown in the lower panels has a normal AVPD despite the MI. This may be compensatory to the decreased lateral contribution to LVSV in this patient due to the MI.”