Author’s response to reviews

Title: Reduced flow in the left ventricle after anterior acute myocardial infarction: a case control study using 4D flow MRI

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We would like to thank the reviewers and BMC Medical Imaging for inviting us to submit a revised manuscript. We have revised the manuscript to address the concerns of the reviewers and submit a point-by-point response to each of those concerns below.

Reviewer #1:

Comment #1: Is KEi_SV a good measure to investigate altered hemodynamics in patients with AMI compared to healthy controls? If the SV is decreased in patients, it follows almost automatically that KEi_SV is increased, possibly even when the total LV KE is decreased in patients compared to controls, as is to be expected from the lower velocities. In my opinion in reference 10 it is not clearly described why normalization to SV is needed ("In sub-analysis, we also normalized the KE parameters to the stroke volume to develop insight into KE spent per unit of stroke volume."). Could the authors describe more explicitly why they chose to normalize KE to SV? Is it true that KE without normalization was decreased in patients with AMI as one would expect based on the flow results? Or are the results hampered by the effect of noise blow-up when reporting KE (as it is derived from velocity squared) in the patient data as the authors mention in the Discussion?
Kinetic energy is often normalized to account for differences in ventricle size because KE is positively correlated with EDV, ESV, and SV (see Carlsson M, et al. AJP Hear Circ Physiol 2012;302:H893–H900). KEiSV gives a surrogate measure of energy efficiency, whereby a high KEiSV is indicative of an inefficient ventricle which imparts high kinetic energy to the blood but in a way that does not generate a large stroke volume.

With than being said, the author’s point is well-taken that in this study the fact that KEiSV was increased in AMI patients relative to controls is not informative given the large decrease in SV in AMI patients. We have decided to remove the KEiSV measure and instead report only KEiEDV. We found that KEiEDV was increased, but not significantly, in AMI patients relative to controls. The difference was larger in unnormalized raw KE since KE is positively correlated with ventricle size and the AMI group had larger ventricles. The counterintuitive result of non-significantly increased KE despite decreased flow in patients may result from the increased noise in patient data from the 1.5T scans as you mentioned. This is now elaborated on in the discussion:

“This study did not find the reduction in KEiEDV that Garg et al. found in a cohort of 48 MI subjects [10]. This is likely caused by the smaller sample size of this study and the use of different scanners for different subjects, which we elaborate on in the limitations paragraph below. …

…The use of different scanners and contrast agents may have affected our KE measurements, however, as erroneously measured high-velocity voxels can dominate the KE sum since it is derived from velocity squared.”

Comment #2: In table 4 the flow parameters in the basal region predominantly correlate with functional parameters and circumferential strain. Considering that the average peak systolic flow is about two times lower in patients compared to controls (although not statistically significant), it is interesting to note that basal peak systolic flow in patients related to lower heart rate and circumferential strain. The title focusing on the apex alone neglects the interesting findings in the LV base.
While the flow in the basal region was lower in AMI patients than in controls, the difference was not significant in the multivariate regression model correcting for age, sex, and heart rate as covariates. In addition to sample size limitations, this lack of significance results from the negative correlation between peak systolic flow in the base and heart rate (Spearman’s correlation coefficient = -0.64). As the AMI group had higher heart rates than the controls, the peak systolic flow was lower, but the difference due to MI status was not significant in a model using heart rate as a covariate. Peak systolic flow in the apex was not correlated with heart rate (P=0.28), so it was significantly different between groups using the model.

However, you are right that the findings in the base are interesting, especially given the correlation with other clinical variables, so we have revised the title and tweaked some of the conclusions to not specifically focus on the apex. The new title is: “Reduced regional flow in the left ventricle after anterior acute myocardial infarction: a case control study using 4D flow MRI”

Reviewer 2:

Comment #1: 4D flow data provide much more information than solely the averaged through-plane velocity component in three intra-ventricular regions and averaged KE values as presented by the authors. What I am somehow missing is at least a discussion about the use of the other spatial flow components and further parameters that have been assessed by other researchers, for instance analysis of flow efficiency / different flow regimes (e.g. as proposed by Ebbers et al.), vortex flow analysis etc. in relation to your study (see also van der Geest and Garg. Advanced Analysis Techniques for Intra-cardiac Flow Evaluation from 4D Flow MRI).

This is fair criticism. These advanced analysis techniques yield valuable insight into ventricular function that 4D flow MRI is uniquely capable of measuring. Both methods (flow component separation and vortex analysis), however, integrate the velocity field over time and therefore compound velocity errors and are highly sensitive to noise. We originally declined to pursue these methods after initial attempts showed that our high-resolution (and therefore higher noise) data had limited compatibility with integrative analysis. Flow compartment analysis showed a relatively high percentage of pathlines (median of 31%) leaving or entering the LV through the ventricular wall and therefore representing non-physiological flow. Vortex analysis using the Lagrangian Coherent Structures method (Töger J, et al. Ann Biomed Eng 2012;40:2652–2662) showed a poorly defined vortex boundary requiring human subjectivity in segmenting the vortex to compute vortex volume.
Given your comment, we have chosen to revisit integrative analysis and include it in the resubmission. Specifically, we chose to include analysis of the different flow components (Eriksson J, et al. J Cardiovasc Magn Reson 2010;12:9) due to its automated nature and objectivity. We have lessened the noise-induced error by reconstructing a 2nd set of 4D flow images with lower resolution (by a factor of 2 in each spatial dimension) using a compressed sensing reconstruction technique with a spatial wavelet transform L1 norm penalty. The ability to retrospectively reconstruct a lower-resolution (and less undersampled) dataset after acquiring high-resolution data without a dramatically longer acquisition than would have been required to acquire only the low-resolution data prospectively is a feature of our radial acquisition technique that would not be possible with a cartesian acquisition. The low-resolution images performed better in the pathline analysis: a median of 24% of pathlines either left or entered the LV through the ventricular wall.

The results show stark differences between AMI patients and controls: AMI patients had markedly reduced direct flow fraction and increased residual volume fraction relative to controls. We have added to the Methods, Results, and Discussion sections in order to explain the flow compartment analysis method and our results. The following excerpts show our additions:

In Methods:

“Each set of 4D flow data was reconstructed in two ways: a high-resolution image set was reconstructed using a gridding technique and used to measure through-plane flow and intraventricular KE, and a low-resolution, low-noise image set was reconstructed using compressed sensing with a spatial-wavelet-transform L1-norm penalty (λ=0.01) in order to separate LV flow into different compartments by tracking flow pathlines. This separate reconstruction was used for pathline tracking because this method is sensitive to noise due to compounding errors in pathline integration. …

…The distribution of different LV flow components was determined in all subjects using the method of Eriksson et al [19]. Blood pathlines were emitted from the LV blood volume and traced forwards and backwards in time from end diastole until end systole, thus including the entire cardiac cycle. Pathlines were computed by integrating the velocity field using a 4th order Range-Kutta numerical integration through time. Pathline location was used to separate the pathlines into four different components of flow: Direct Flow (blood that enters the LV during diastole and leaves the LV during systole in the analyzed heartbeat), Retained Inflow (blood that enters the LV during diastole but does not leave during systole in the analyzed heartbeat), Delayed Ejection Flow (blood that starts and resides inside the LV during diastole and leaves during systole), and Residual Volume (blood that resides within the LV for at least two cardiac cycles). The fraction of EDV containing pathlines from each compartment was computed for all subjects.”
In Results:

“Figure 4 shows representative visualizations of flow compartment analysis in a control (a, b) and AMI subject (d, e). The AMI subject had a lower fraction of pathlines in the direct flow compartment and a higher fraction of pathlines in the residual volume compartment. Subpanels c) and f) show group-average pie charts of the distribution of flow among compartments. Among all subjects, the median number of pathlines passing through the ventricular wall (and therefore discarded) was 24%. ...

…Compared to controls, anterior AMI subjects had significantly less direct flow and significantly more retained inflow, delayed ejection flow, and residual volume.”

In Discussion: “Flow compartment analysis revealed a marked shift away from blood entering and leaving the LV in one heartbeat (direct flow) towards blood starting and residing in the LV for &gt;=2 heart beats (residual volume) in anterior AMI patients. This increase in residual volume is consistent with the decreased through-plane flow in the apex (since residual flow pathlines are typically located in or near the apex) and with the notion of increased stasis post MI. …

… Our control data however displays a greater fraction of flow in the direct flow compartment and less in the residual volume compartment than Eriksson et al found in 2010 [19] and 2013 [24]. We attribute this to differences in acquisition such k-space trajectory (radial vs. cartesian), spatial resolution (2.5x2.5x2.5mm3 vs. 3x3x3mm3), number of cardiac frames (20 vs. 40), and scan duration (9-14 min. vs. 16-57 min.), although it is unclear how this difference led to the observed differences in flow compartment distribution. Despite the fact that our baseline LV flow compartment distribution in controls differs from that in the literature, our finding of flow compartment shifts in AMI patients relative to controls is valid since all of the 4D flow data presented herein was acquired with the same sequence.”

Comment #2: Specific comments Methods: remove the X in "…were analysed by XXX".

The authors initially overlooked the fact that BMC Medical Imaging uses an open review process. We have removed the anonymized reference to mention the author’s initials.