Author’s response to reviews

Title: Cardiovascular magnetic resonance 4D flow analysis has a higher diagnostic yield than Doppler echocardiography for detecting increased pulmonary artery pressure

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R1 GENERAL COMMENT: Michael Chuang (Reviewer 1 [R1]): As the authors note, the primary limitation of this study is the lack of gold standard (RHC) PAP. However, the paper is well written and clearly presented; methods appear appropriate. No significant concerns, but a few questions and suggestions.

R1 COMMENT 1: Please clarify what you mean by "All [echo] results were the mean of 3 measurements." Do you mean that TR velocities were measured from three heartbeats? If so, make this unambiguous, because it is possible to (mis?)interpret this statement as TR velocities were averaged across the 3 views (PLAX, PSAX, A4C). I am assuming you used the view from which TR jet was maximal/best aligned with Doppler, but make it clear.
RESPONSE: This has now been clarified in the manuscript, page 7, line 16, as follows:

“All results were calculated as mean of three consecutive TR velocities, as measured from the view from where the Doppler TR jet was maximal and best defined.”

R1 COMMENT 2: When were clinical characteristics in Table 1 acquired? At time of CMR, echo, both, or a separate time point?

RESPONSE: This has now been clarified in the manuscript, page 8, line 21, as follows:

“Data on clinical characteristics were acquired at the time of CMR.”

R1 COMMENT 3: Was any effort made to compare, e.g. BP and HR at echo vs at CMR?

RESPONSE: This has now been clarified in the manuscript, page 8, line 22, as follows:

“When comparing the time points of CMR and echocardiography, there were no significant differences in HR (p=0.07), systolic pressure (p=0.91) or diastolic pressure (p=0.06).”

R1 COMMENT 4: Eleven patients (18%) were apparently referred with indication of "acute MI". Of the diagnoses listed in Table 1, this category seems the most likely to change clinically between CMR and echo. Any idea how stable these patients were, hemodynamically (or otherwise) speaking? See also, next point (did the AMI patients tend to be in the E-C+ category?)

RESPONSE: This has now been clarified in the manuscript, page 11, line 16, as follows:

“This group of patients did not have any identifiable characteristics that differed from the remaining patient cohort. Indeed, patients in this group were hemodynamically stable and diverse in terms of underlying diagnosis, none of them being disproportionately represented.”

R1 COMMENT 5: Table 3 can be thought of as a 2x2 (with E-C- in the upper left 4 squares, E+C- in the upper right, E-C+ lower left, and E+C+ in the single bottom right square). The patients of most interest are the "off diagonals" where echo and CMR are not concordant. There are zero E+C-, and 12 E-C+ patients. Do the E-C+ patients differ from the concordant patients? If so, how?

RESPONSE: Please see the response above to R1 COMMENT 4.
R2 GENERAL COMMENT: Francisco Contijoch (Reviewer 2 [R2]): In the article, the authors compare CMR and echo-based estimates of increase PA pressure both quantitatively and categorically.

60 consecutive patients underwent both studies. MRI-based estimates of PA pressure were based on the presence of PA vortex duration while Doppler echo was used to measure TR and derive TRPG.

The authors quantify their findings with diagnostic yield (the fraction of identified cases).

While the comparison of these two approaches is interesting and has considerable clinical impact, several features of the approach limit interpretability of the findings.

R2 COMMENT 1: The study does not include gold-standard assessment of PH via RHC. The authors appear to suggest (in the discussion) that the CMR findings closely approximate the RHC values (based on prior papers). However, throughout the manuscript it is unclear whether the higher yield identified via CMR is correct. Specifically, while the comparison of CMR and echocardiography in Table 3 is useful/important, the notion that the diagnostic yield is higher remains unproven. It remains a possibility that some, all, or a significant portion of the patients identified via CMR are incorrectly being referred for further evaluation.

RESPONSE: We agree and this has now been clarified in the manuscript, page 13, line 1, as follows:

“Lastly, data from RHC would be necessary to definitively establish a potential superiority of this CMR method compared with echocardiography. While diagnostic yield is higher in CMR, it is not possible to claim that the diagnosis of elevated PA pressure was correct in all CMR cases without invasive measurements. Despite this, our results show that there is a notable discrepancy between CMR and echocardiography with regards to detection of increased PA pressure at the existing clinical thresholds.”

R2 COMMENT 2: Furthermore, as part of their comparison, two previously identified equations are used to derived mPAP from CMR and echo data, respectively. However, there is no analysis of whether the "higher yield" determined by CMR can be explained by a change in the fit or cutoff values. One significant contribution of this work could be that a "revised" cutoff of TR jet velocity is identified for more optimal identification of patients with elevated PA pressure.

RESPONSE: Firstly, the two previously published equations to derive mPAP from echocardiographic TRPG were contrasted to mPAP from CMR for purposes of methodological comparison. However, the cut-off for determining the presence of increased PA pressure was based only on TR (≥2.8 m/s).
With regards to establishing a revised TR cutoff for the presence of increased PA pressure based on CMR results as the reference standard has now been clarified in the Discussion of the manuscript, p. 11, line 20, as follows:

“Other reasons for the discrepancy between CMR and echocardiography could be a need for different thresholds for either CMR mPAP or echocardiographic TR velocity, or methodological limitations inherent to CMR or echocardiography with regards to the ability to either detect vortex presence, or accurately measure the peak TR velocity due to the angle of the main direction of Doppler flow. Using the current dataset, it is not possible to discern which of these is the main source of the discrepancy between CMR and echocardiography, and future studies are justified to address this question.”

R2 COMMENT 3: Technically, the percentage of cardiac cycle that has vorticity is discretized based on the number of reconstructed phases in the CMR cine (35 phases) and to some extent, the acquired temporal resolution of the acquisition (36 ms). However, values derived from these discrete sampling points appear to be treated as continuous variables. For example, mean values of vortex duration were 9.5 ± 9.7%. To improve clarity, the authors may consider describing both the number of frames labeled as well as the corresponding cardiac phase amount.

RESPONSE: All CMR vortex analyses were performed using, as stated in the Methods, 20 timeframes per cardiac cycle. The number of timeframes identified as having a vortex has now been clarified in the manuscript, page 9, line 6, as follows:

“Mean values of vortex duration in the pulmonary artery were 9.5±9.7% (1.9±1.9 timeframes with vortex) corresponding to an mPAP of 22.0±6.1 mmHg for reader 1 and 10.8±9.8% (2.2±1.9 timeframes with vortex) corresponding to an mPAP of 22.8±6.2 mmHg for reader 2, with an average measurement between both readers of 10.1±9.4% (2.0±1.9 timeframes with vortex) corresponding to an mPAP of 22.4±5.9 mmHg.”

R2 COMMENT 4: Along the same vein, when quantifying interobserver variability, each frame can be agreed or disagreed upon in terms of vorticity by the two observers. However, it does not appear that this was using to calculate the agreement.

RESPONSE: Please see the response above to R2 COMMENT 3, and this has also been further clarified in the manuscript, page 9, line 5, as follows:

“We quantified interobserver variability using the absolute values of vortex duration as a percentage of the cardiac cycle.”