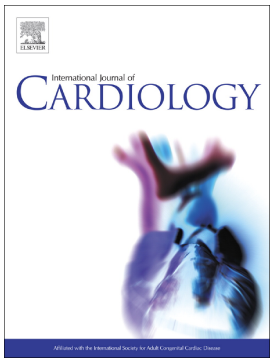

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Association of left ventricular flow energetics with remodeling after myocardial infarction: new hemodynamic insights for left ventricular remodeling

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Abstract

Background: Myocardial infarction leads to complex changes in left ventricular (LV) hemodynamics. It remains unknown how four-dimensional acute changes in LV-cavity blood flow kinetic energy affects LV-remodeling.

Methods and results: In total, 69 revascularised ST-segment elevation myocardial infarction (STEMI) patients were enrolled. All patients underwent cardiovascular magnetic resonance (CMR) examination within 2 days of the index event and at 3-month. CMR examination included cine, late gadolinium enhancement, and whole-heart four-dimensional flow acquisitions. LV volume-function, infarct size (indexed to body surface area), microvascular obstruction, mitral inflow, and blood flow KEi (kinetic energy indexed to end-diastolic volume) characteristics were obtained. Adverse LV-remodeling was defined and categorized according to increase in LV end-diastolic volume of at least 10%, 15%, and 20%. Twenty-four patients (35%) developed at least 10%, 17 patients (25%) at least 15%, 11 patients (16%) at least 20% LV-remodeling. Demographics and clinical history were comparable between patients with/without LV-remodeling. In univariable regression-analysis, A-wave KEi was associated with at least 10%, 15%, and 20% LV-remodeling (p=0.03, p=0.02, p=0.02, respectively), whereas infarct size only with at least 10% LV-remodeling (p=0.02). In multivariable regression-analysis, A-wave KEi was identified as an independent marker for at least 10%, 15%, and 20% LV-remodeling (p=0.09, p<0.01, p<0.01, respectively), yet infarct size only for at least 10% LV-remodeling (p=0.03).

Conclusion: In patients with STEMI, LV hemodynamic assessment by LV blood flow kinetic energetics demonstrates a significant inverse association with adverse LV-remodeling. Late-diastolic LV blood flow kinetic energetics early after acute MI was independently associated with adverse LV-remodeling.

Keywords: kinetic energy; left ventricular remodeling; ST-segment elevation myocardial infarction.

1. Introduction

Acute myocardial infarction (MI), a leading cause of morbidity and mortality worldwide, often leads to left ventricular (LV) systolic and diastolic dysfunction with a subsequent risk of adverse LV-remodeling (1). Although adverse LV-remodeling initially emerges as a compensatory mechanism to a reduced stroke volume, it adds to the workload of the damaged heart and its association with poor clinical outcome has been demonstrated in several studies (2, 3). Accurate identification of predictors of adverse LV-remodeling could enhance post-MI patient risk stratification and monitoring, and thus clinical outcome.

Previous studies documented a linear association between adverse LV-remodeling and cardiovascular magnetic resonance (CMR)-derived infarct size (4, 5). Furthermore, microvascular obstruction (MVO), an important indicator of no-reflow at the myocardial level (6), is related to adverse LV-remodeling (7, 8). However, recent studies reported that the relationship between infarct size and adverse LV-remodeling is not always coherent, and neither is the relationship between MVO presence/absence and adverse LV-remodeling (9, 10). For instance, it is not uncommon that patients with a small infarct size and without MVO experience adverse LV-remodeling. Adverse LV-remodeling is a complex process that is influenced by many factors (11, 12) in addition to infarct size and MVO.

The distortions in LV myocardial contraction and relaxation patterns following myocardial infarction lead to complex pathophysiological changes in LV blood flow hemodynamics (13). LV blood flow energetics, an essential factor in the hemodynamics (14), are likely to be altered after MI. Recent developments allow for a robust, non-invasive quantification of blood flow kinetic energy (KE) within all heart chambers using 4-dimensional (4D) flow CMR (15). Using this technique, our research group has previously demonstrated that MI leads to a decrease in the average LV blood flow KE (16).

As the LV blood flow energetics are directly related to the efficiency of filling and ejection function, it is plausible to assume an interplay between LV blood flow energetics and remodeling. In line with this postulation, a previous study observed a relationship between the KE of the LV flow components and the indexed end-diastolic LV volume in chronic ischemic heart disease patients, measured at a single time-point (17). Quantification of KE in the LV directly after MI may also provide novel insights

regarding how intra-cardiac hemodynamics could affect the temporal changes in end-diastolic volume. To the best of our knowledge, this question has not yet been studied and may enhance our understanding of the pathophysiology of adverse LV-remodeling after MI.

Moreover, LV blood flow hemodynamics evolve naturally throughout the cardiac cycle; for instance, the diastolic KE of LV blood generated as a result of active relaxation of the ventricle is higher than the KE of blood in systole (15, 18); thus different components of flow dynamics (e.g., systolic) may have particular links with cardiac function and LV-remodeling. Accordingly, a recent study reported that the distribution of LV hemodynamic forces during diastole may be an independent predictor of LV-remodeling after MI (19). Specific components of LV blood flow energetics are also likely to have critical pathophysiological roles regarding LV-remodeling that research to date has not yet determined.

We hypothesize that post-MI LV blood flow energetics are related to adverse LV-remodeling after 3-month of follow-up, and hence our objectives were: 1) to assess whether LV blood flow energetics early after MI and adverse LV-remodeling are associated, 2) to explore whether LV blood flow energetics are independently associated with adverse LV-remodeling, and 3) to investigate whether these potential associations differ depending on the severity of LV-remodeling.

2. Methods

This study was conducted according to the principles outlined in the 1964 Declaration of Helsinki and its later amendments. The collection and management of data were approved by the National Research Ethics Service in the United Kingdom (12/YH/0169). Written informed consent was obtained from all participants included in the study.

2.1 Study population

In this prospective cohort study, 69 patients with acute re-perfused ST-segment elevation MI (STEMI) were included. The patients were enrolled at Leeds Teaching Hospitals (Leeds, United Kingdom). All patients had a routine pre-treatment of acetylsalicylic acid, a P2Y12 inhibitor, and heparin as part of their clinical care at first medical contact and were treated in accordance with current STEMI guidelines (20). All included subjects were in sinus rhythm and underwent CMR examination within 2 days of the index event and at 3-month. Exclusion criteria were prior history of MI or any coronary

revascularization procedure, non-ischemic cardiomyopathy, significant renal impairment (defined as eGFR<30 ml/min/kg), haemodynamic instability, and any contraindication to CMR imaging. Patients with valvular diseases (mild to severe) were also excluded to avoid potential intra-cardiac flow interference.

2.2 CMR protocol and analysis

All CMR examinations were performed on a 1.5T system (Ingenia, Philips, Best, The Netherlands) with a phased-array 28-channel cardiac receiver coil. The CMR protocol included cine imaging, LGE imaging, and a 4D flow acquisition. Cine imaging uses an ECG-gated, balanced steady-state free precession sequence acquired in 4-chamber, 3-chamber, and 2-chamber views and contiguous short-axis cine stack covering the complete LV. Each cine image series was acquired during 1 breath-hold at mild expiration. LV volumes, mass, and ejection fraction were measured on the stack of short-axis cines. Late gadolinium enhancement (LGE) images were acquired 10-15 minutes after administration of a gadolinium-based contrast agent (Dotarem, Guerbet; 0.2mmol/kg), using a T1-weighed segmented inversion-recovery gradient-echo pulse sequence in a similar short-axis orientation as the cine images. Infarct size was calculated on the short-axis LGE images using the full-width-at-half-maximum method (21) and indexed to body surface area. For the assessment of mitral inflow and LV blood flow energy characteristics, 3D phase-contrast imaging with 3-directional velocity encoding (4D flow CMR) was used (16). The flow data were acquired using an Echo-Planar Imaging accelerated, a free-breathing sequence with retrospective ECG-triggering. Gradient non-linearity correction and Maxwell correction were automatically performed on the CMR scanner. Typical acquisition parameters were: TE/TR 3.7ms/11 ms, flip angle 10º, VENC 150 cm/s and voxel size 3.0x3.0x3.0mm (30 phases per cardiac cycle).

2.3 LV-remodeling

LV-remodeling over a 3-month follow-up was calculated by measuring the increase in LV end-diastolic volume (LVEDV) between baseline and follow-up. There is a lack of established definition for LV-remodeling. To avoid the potential bias of a single arbitrary definition and to investigate whether the potential relationships with LV-remodeling differ depending on the magnitude of the LV-remodeling, LV-remodeling was defined comprehensively in 3 categories: an absolute increase in LVEDV of at least 10%, 15%, and 20%.

2.4 Mitral inflow analysis

Mitral inflow analysis was performed on the 4D flow CMR images. The mitral valve position was determined on the LV two- and four-chamber cine acquisitions. Manual retrospective valve tracking over the mitral valve was performed. The planes of flow quantification followed the valve plane over the cardiac cycle and were adjusted according to the blood flow direction. On the reformatted valve plane phase-contrast images, the mitral inflow was identified as higher signal intensity during LV diastole and segmented appropriately throughout the complete cardiac cycle to obtain the trans-mitral flow curve. The following mitral inflow parameters were derived: E-wave flow (ml/s), A-wave flow (ml/s), E/A (ratio), and deceleration time (msec).

2.5 LV blood flow kinetic energy analysis

The blood flow KE within the LV was quantified for the region defined by the endocardial contours in the registered short-axis stack. For each voxel within the LV, KE was derived using the formula, $KE = \frac{1}{2}\rho.V.v^2$, assuming a blood density of 1.06 g/mL (ρ), the volume of a voxel (*V)*, and the velocity magnitude (*v)*. The global KE in the LV was computed by summation of KE over all voxels. LV mean and peak KE were quantified for all time parameters (entire cardiac cycle, during systole, during diastole, at E-wave, and at A-wave). KE parameters were normalized to the LVEDV and indicated as KEi. In addition, in-plane KE was calculated as the sum of all KE in the x-y direction and represented as a percentage of the total LV KE. Our research group previously demonstrated that infarct size is independently associated with the proportion of in-plane LV KE (16). In the present study, in-plane KE proportion was quantified to advance the knowledge regarding the post-MI in-plane flow dynamics.

All CMR examination analysis was performed using dedicated research software (MASS version 2021-Exp, Leiden University Medical Center, Leiden, the Netherlands). All CMR contour tracings, including volume/function, LGE, and the 4D flow CMR were performed by R.J.G. and confirmed by EACVI level-III certified CMR experts (P.G. and R.N.), all with over 10 years of CMR experience.

2.6 Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range, as appropriate. Comparisons between two groups were made with the independent-samples T-test for normally distributed data or Mann-Whitney U test for non-parametric data. Categorical variables are summarized by frequency (percentage), and relationships between categorical variables were tested with the $\chi 2$ test or Fisher-exact, if expected cell counts were low (<5). Association between continuous variables was quantified by Pearson's or Spearman's correlation, where appropriate. Linear regression models were used to assess associations with the absolute change of LV end-diastolic volume; and logistic regression models were used to assess associations with at least 10%, 15%, and 20% adverse LV-remodeling. Univariable regression analyses were first performed and followed by multivariable regression analyses using backward elimination. Only candidate predictors with $p<0.1$ were considered in the multivariable analysis. Receiver-operating characteristics (ROC) analysis was performed to assess the performance of A-wave KEi and infarct size to predict adverse LV-remodeling. Areas under the ROC curve were calculated and Youden's index was used to determine optimal cut-off values. The two-sided significance level was set at 5%. Statistical analysis was performed using the Statistical Package for Social Sciences software (IBM SPSS statistics 26).

3. Results

Patient population

Baseline characteristics of the study population are summarized in table 1. Twenty-four patients (35%) developed adverse LV-remodeling after MI (≥ 10% LVEDV increase over 3-month). The mean age and male/female proportion were comparable between MI patients with and without LV-remodeling. With respect to medical history and smoking, no statistical difference was observed between the MI patients with and without LV-remodeling.

3.1 LV volume, infarct, and blood flow characteristics

Table 2 provides a detailed assessment of the baseline LV volume, infarct, and flow characteristic differences between the main groups. MI patients with LV-remodeling had lower ejection fraction, larger infarct size, and more frequent anterior infarct at baseline than MI patients without LV-remodeling (Fig. 1). MVO presence was comparable between the groups. MI patients with adverse LV-remodeling showed a trend towards reduced A-wave mitral inflow compared to patients without remodeling ($p=0.06$). Figure 2 displays baseline LV blood flow KEi characteristics for MI patients with

and without adverse LV-remodeling. Overall, KEi values over the entire cardiac cycle were numerically lower in MI patients with adverse LV-remodeling than in MI patients without adverse LV-remodeling, but only the in-plane KE proportion and A-wave KEi showed a statistically significant difference in MI patients with remodeling compared to MI patients without remodeling (p=0.04, p=0.02, respectively).

3.2 Association with the change of LVEDV over time

LV mean systolic KEi, peak systolic KEi, in-plane KE proportion, and A-wave KEi demonstrated an inverse correlation with the absolute change of LVEDV over 3-month (r=-0.24, p=0.049; r=-0.24, p=0.04; r=0.28, p=0.03, r=-0.26, p=0.03, respectively) (Fig. 3). Infarct size also showed a correlation with the absolute change of LVEDV (r=0.25, p=0.04). No significant correlation was observed between mitral inflow characteristics and the absolute change of LVEDV.

In-plane KE proportion and A-wave KEi were the only energetic parameters that demonstrated an inverse correlation with the relative change (%) of LVEDV over 3-month (r=0.28, p=0.04; r=-0.27, p=0.03). No significant correlation was observed between infarct size, mitral inflow characteristics, and the relative change of LVEDV.

In univariable linear regression analysis, in-plane KE proportion, A-wave KEi, infarct size, and MVO presence were all associated with the absolute change of LVEDV (p=0.03, p=0.03, p=0.04, p=0.04, respectively; all relevant univariable analysis results are provided in the supplemental file). In multivariable linear regression analysis, A-wave KEi was identified as the only independent marker for association with the absolute change of LVEDV (Table 3).

3.3 Association with the adverse LV-remodeling

In order to obtain insights regarding whether associations with adverse LV-remodeling differ according to the definition and severity of LV-remodeling, 3 different definitions were used (at least 10%, 15% and 20%). Twenty-four patients (35%) developed at least 10%, 17 patients (25%) at least 15%, 11 patients (16%) at least 20% LV-remodeling. In univariable logistic regression analysis, higher A-wave KEi was associated with a lower likelihood of at least 10%, 15%, and 20% adverse LV-remodeling (p=0.03, p=0.02, p=0.02, respectively; all relevant univariable analysis results are provided in the supplemental file). Infarct size was only associated with a higher likelihood of at least 10% adverse LV-remodeling (p=0.02). MVO presence and mitral inflow parameters were not associated with any level of adverse LV-remodeling.

In order to identify independent associations with adverse LV-remodeling levels, a multivariable logistic regression analysis was performed (Table 4). Infarct size and A-wave KEi were identified as independent markers related to at least 10% adverse LV-remodeling (p=0.03, p=0.09, respectively). A-wave KEi was the only independent marker associated with at least 15% and 20% adverse LV-remodeling (both, p<0.01).

3.4 The ability of A-wave KE and infarct size to predict adverse LV-remodeling

Figure 4 depicts ROC curves of A-wave KEi and infarct size to predict adverse LV-remodeling. The ROC curve of A-wave KEi showed an area under the curve of 0.67, 0.70, and 0.71 for at least 10%, 15%, and 20% LV-remodeling, respectively (p=0.02, p=0.01, p=0.02, respectively). The ROC curve of infarct size revealed an area under the curve of 0.65, 0.62, and 0.58 for at least 10%, 15%, and 20% LV-remodeling, respectively (p=0.04, p=0.15, p=0.41, respectively). The ROC curve of A-wave KEi had noticeably a larger area under the curve than infarct size for at least 15% and 20% adverse LV-remodeling. The optimal cut-off level for A-wave KEi to predict at least 10% LV-remodeling was 11.75 uJ/ml (sensitivity and specificity, both 67%); to predict at least 15% LV-remodeling was 11.35 uJ/ml (sensitivity, 71%; specificity, 67%); and to predict at least 20% LV-remodeling was 12.35 uJ/ml (sensitivity, 82%; specificity 57%).

4. Discussion

The findings of our study support the hypothesis that adverse LV-remodeling is not only influenced by the severity and characteristics of myocardial damage, but that flow hemodynamics may also play an important role. In the present study, we investigated and revealed the association between LV blood flow energetics and adverse LV-remodeling after MI for the first time. This relationship was most prominent with late-diastolic (A-wave) energetics. Notably, A-wave LV blood flow KEi may provide incremental value over CMR-derived infarct size as an indicator of advanced levels of adverse LV-remodeling. The graphical abstract provides a summary of the main findings in a visual and conceptual manner.

Adverse LV-remodeling is progressive and linked to unfavorable clinical outcomes (2, 3). Therefore, characterizing the relevant determinants of LV-remodeling is of high clinical importance. Previous studies reported an association between altered LV blood flow components KE and indexed LV end-diastolic volume and impaired preservation of late-diastolic energetics in patients even with no to mild

LV-remodeling (17, 22). The results of these studies suggested that LV blood flow hemodynamics/energetics may be used to detect subtle changes in LV dysfunction and remodeling. Another study reported reduced indexed LV blood flow energetics in patients with moderate-to-severe heart failure versus controls (23). More recently, our research group examined LV blood flow energetics specifically in MI patients, in a relatively large study cohort (16), and found that the majority of LV blood flow KEi parameters are reduced in patients with MI. Whilst these studies provide valuable insights, our present study sheds new light on the potential prognostic associations between LV blood flow energetics and LV-remodeling.

4.1 LV blood flow late-diastolic energetics and LV-remodeling

The present study shows that LV blood flow KEi during the A-wave shows the most significant association with adverse LV-remodeling. Additionally, A-wave LV blood flow KEi shows a significant association with all levels of adverse LV-remodeling. These findings support our hypothesis that the altered LV hemodynamics due to the MI may precipitate changes in pressure gradients, leading to adverse remodeling over time (24). The intra-ventricular pressure gradients facilitate the suction force for active relaxation and are attributed to energy expenditure (25, 26). It is known that MI leads to an overall increase in LV diastolic pressures and that severe elevations in diastolic pressure are associated with the development of heart failure (27, 28). Normally, diastolic pressure levels are highest at the end of the diastole due to the left atrial contraction, or atrial kick (29). Therefore, this diastolic pressure increase has most likely the largest effect and the most importance at the end of the diastole. This phenomenon yields a narrower pressure difference between the left atrial and LV pressure levels, and accordingly, the atrial contraction cannot exert sufficient mechanical force to generate a wide pressure gradient to direct the flow to mid/apical LV levels. As a result, late-diastolic LV flow volume transition and flow velocities decrease, and since KE is a parameter quadratically related to velocity, KE reduction is more pronounced during late-diastole (A-wave).

4.2 LV blood flow energetics, mitral inflow, and LV-remodeling

The graphical abstract of our study demonstrates LV filling dynamics reflected in 4D-flow derived volumetric LV blood flow energetics and corresponding mitral inflow curves in keeping with the different levels of adverse LV-remodeling, for the first time. Normally, most LV filling occurs in early-diastole with the peak filling rate during early-diastole (E-wave) is being larger than during atrial-

contraction (A-wave), and with diastolic dysfunction, the LV filling patterns change (30, 31). When mild diastolic dysfunction emerges, the E-wave is reduced and becomes smaller than the A-wave: A-wave sharply increases as a compensatory mechanism to maintain diastolic adequate filling. As diastolic dysfunction progresses, the mitral E-wave increases, resulting in a pseudonormal and eventually a restrictive pattern (E-wave > 2 x A-wave). In the graphical abstract, it could be seen that a mild LV diastolic dysfunction pattern (mitral inflow E-wave<A-wave) is present with mild adverse LV-remodeling, and as LV-remodeling advances, LV diastolic dysfunction pattern evolves into a restrictive pattern (mitral inflow E-wave > 2 x A-wave). It should be noted that LV blood flow kinetic energy curves demonstrate a coherent pattern with mitral inflow curves against different grades of LV-remodeling. Early-diastolic KE levels are lower than late-diastolic KE levels with mild adverse LV-remodeling; however, as LV-remodeling advances, this pattern switches: early-diastolic KE levels become larger than late-diastolic KE levels. Therefore, the pronounced KE reduction during late-diastole, which may partly explain the significant association with advanced LV-remodeling, can be remarkably appreciated in the graphical abstract of the present study.

Moreover, Crandon S et al. demonstrated that specific diastolic (E-wave and A-wave) LV blood flow KE parameters show correlations with 2D mitral inflow velocity assessments (32). In a sub-analysis, we also found that E-wave and A-wave LV blood flow KE values and mitral inflow characteristics were correlated ($p<0.01$ for both). Regarding the relationship of these parameters to LV-remodeling, whilst late-diastolic LV blood flow kinetic energy values are associated with adverse LV-remodeling parameters (e.g., absolute and relative change of LVEDV; 10%, 15%, 20% LV-remodeling), none of mitral inflow metrics showed relation to LV-remodeling. These findings exhibit a potential superior role for volumetric LV blood flow energetics over mitral inflow characteristics for pathophysiologic adaptation processes after MI and may be considered somewhat in line with the findings that LV blood flow energy assessment may demonstrate a stronger association with age than mitral inflow assessment (32).

4.3 Literature on the late-diastolic LV hemodynamics and LV-remodeling

The results of previous studies may also explain and indicate the relevance of late-diastolic energetics with remodeling. It was found that KE contribution from left atrial contraction is preferentially preserved by the ejection portion of LV volume (33). In another previous study, our research group observed that

wash-in of blood to the distal LV during late diastole is strongly associated with the presence of left ventricular thrombus formation after MI; which has already demonstrated the clinical significance of the post-MI late-diastolic LV blood flow energetics (34). Notably, a recent study demonstrated that the distribution of LV hemodynamic forces during diastole could even independently predict LV-remodeling, signifying the role of late-diastolic LV hemodynamics for post-MI LV-remodeling (19). The present longitudinal 4D flow CMR study adds to the clinical significance of late-diastolic energetics as it provides novel evidences that late-diastolic LV blood flow energetics may be linked with post-MI adverse remodeling.

4.4 LV blood flow in-plane KE proportion and LV-remodeling

Our research group has previously observed that post-MI patients with reduced LVEF have a higher in-plane proportion of KE within LV compared to preserved LVEF group (16). Progressive LV dysfunction and dilatation cause increased sphericity, which may transform the flow conditions within the cavity into a massive, swirling vortex (24). We have already mentioned in our previous work that this vortex flow includes transversal thrusts that will manifest as in-plane KE and may become increasingly prominent as the ventricle remodels. In our present study, patients with adverse LV-remodeling had a significantly higher in-plane proportion of KE within LV, and in-plane proportion of KE within LV demonstrated an association with LV-remodeling; yet this was not found independent in multivariable analyses. Future larger longitudinal studies are warranted to clarify the role of in-plane proportion of KE with LV-remodeling.

4.5 Predictive value of LV blood flow energetics and infarct characteristics for LV-remodeling

Furthermore, we observed that both LV blood flow A-wave KEi and CMR-derived infarct size are independently associated with at least 10% adverse LV-remodeling. However, only A-wave KEi showed an independent relation to at least 15% and 20% adverse LV-remodeling. These findings suggest that LV blood flow energetics may be informative for adverse LV-remodeling after MI, particularly for severe remodeling. In addition, using ROC analysis, we evaluated the diagnostic performances of LV blood flow KEi at A-wave and infarct size to predict adverse LV-remodeling. A-wave KEi had good diagnostic performance for all grades of remodeling. Particularly for severe adverse LV-remodeling, the diagnostic performance of A-wave KEi was noticeably superior to infarct size.

4.6 LV blood flow energetics, infarct characteristics, and LV-remodeling

Although it was shown that myocardial characteristics (e.g., infarct size) may be useful parameters for assessing LV-remodeling (4, 6, 35), recent studies have reported important limitations on the consistency of infarct characteristics to be associated with adverse LV-remodeling. One of the explanations might be that the post-STEMI infarct size quantification also incorporates acute-setting pathophysiological entities such as hyperemia, edema, and inflammation (6), which can hamper the link with LV-remodeling. The development of multiparametric models that factor in the flow dynamics to predict LV-remodeling are warranted for clinical use. Using 4D flow CMR, we have now identified threshold values of A-wave KEi that may be used in the future to predict various levels of adverse LV-remodeling. Once the 4D flow data are available, KE values for LV can be readily generated by segmentation of the LV using automated post-processing tools, and KE data can be derived through a short (e.g., 5 min) post-processing protocol. Employment of this approach may open opportunities for an enhanced prognostic stratification in STEMI patients.

4.7 Clinical characteristics and LV-remodeling

"Previous studies reported associations also between clinical factors, biomarkers, and LV-remodeling (36, 37). Reindl et al. observed significant associations between post-MI day 1, 2, and 3 heart rate measurements and LV-remodeling, whereas admission heart rate did not statistically differ (36). In our study, we registered only admission heart rate, and we found that, although patients with adverse LV-remodeling had a numerically higher admission heart rate, the difference was not statistically significant, in keeping with the literature (36). Moreover, we observed that the patients with adverse LV-remodeling had more frequent left anterior descending artery as the culprit, also in line with the literature (36, 38).

4.8 Clinical perspective and future directions

In parallel to the reduction in mortality rates in STEMI patients over the past two decades, an overall increase in the incidence of chronic heart failure has emerged, shifting the interest in outcome assessment (39, 40). The development of techniques that are capable of predicting LV-remodeling can help with preventing post-MI heart failure. Using the 4D flow CMR technique, this study provides novel insights into the relationship between 4D LV blood flow energetics in STEMI patients and adverse LV-remodeling, although the strength of the observed associations are not high and the exact

nature of post-MI flow changes have still to be uncovered. More LV blood flow hemodynamics-focused studies are needed to validate these findings and to assess whether these parameters can be translated into the clinic.

5. Limitations

This study has some limitations that need to be discussed. Although this study provides a unique observational longitudinal (3-month) assessment of CMR examination with a whole-heart 4D flow acquisition, the sample size of the study (n= 69) is relatively small, and the result of the study should be inferred with caution. Secondly, whilst the results are hypothesis generating, they are novel and if validated in further studies they may have implications for clinical practice. Thirdly, the results are only relevant for patients in sinus rhythm. Lastly, the temporal resolution of 4D-flow data acquisition (40 ms) may affect the quality of the KE assessment.

6. Conclusion

In patients with STEMI, infarct size and LV hemodynamics assessment by novel parameters of 4D LV blood flow energetics demonstrate a significant association with adverse LV-remodeling. Late-diastolic LV blood flow kinetic energy early after acute MI showed the potential to have an independent association with adverse LV-remodeling, particularly for severe forms.

Supplementary Data: Univariable analysis for association with the absolute change of LVEDV over 3-month; univariable analysis for association with at least 10%, 15%, and 20% LV-remodeling.

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Figure Legends

Figure 1: Comparison of LV ejection fraction and infarct characteristics

Comparison of ejection fraction and infarct characteristics between patients with and without adverse LV-remodeling. Data are shown as mean ± standard deviation, or median and interquartile range (Q1-Q3), or percentage.

Abbreviations: *LV, left ventricular; LVEDV, left ventricular end-diastolic volume; MVO, microvascular obstruction.*

Figure 2: Comparison of LV blood flow KEi

Comparison of LV blood flow KEi characteristics between patients with and without adverse LV-remodeling. Data are shown as mean and standard deviation.

Abbreviations: *LVEDV, left ventricular end-diastolic volume; KEi, kinetic energy indexed to LVEDV*

Figure 3: Correlation with LVEDV change

Relationship between LV blood flow characteristics, infarct size, and the absolute and relative LVEDV change over 3-month in the entire study cohort. The blue line indicates the regression line.

Abbreviations: *LVEDV, left ventricular end-diastolic volume; KEi, kinetic energy indexed to LVEDV.*

Figure 4: The prognostic abilities of KEi and infarct size

ROC curves of KEi and infarct size for diagnosing at least 10%, 15%, and 20% adverse LV-remodeling.

Abbreviations: *LV, left ventricular; LVEDV, left ventricular end-diastolic volume; KEi, kinetic energy indexed to LVEDV; ROC, receiver operator characteristic; CI, confidence interval.*

Graphical Abstract

The upper panel summarizes the established and novel potential CMR-derived contributors to adverse LV-remodeling. The bottom panel represents the late-diastolic LV blood flow KE maps on 4-chamber and 2-chamber views, LV blood flow KE curves, and mitral inflow curves for each identified adverse LV-remodeling level (mild: 10-15%, moderate: 15-20%, severe: >20%). With no adverse LV-remodeling, the level of kinetic energetics during late-diastole (A-wave) appears high compared to during early-diastole (E-wave). As LV-remodeling emerges and advances, the level of kinetic energetics during late-diastole (A-wave) reduces and becomes lower compared to during early-

diastole (E-wave). The reduction in LV blood flow energetics during late diastole (A-wave) is visually appreciated on KE maps. Concerning mitral inflow, a similar switch pattern is observed between early diastole and late diastole, as LV-remodeling emerges and advances.

Abbreviations: *LV, left ventricular; LVEDV, left ventricular end-diastolic volume; KEi, kinetic energy indexed to LVEDV.*

Tables

Table 1: Baseline characteristics

	No adverse LV-remodeling (n=45)	Adverse LV-remodeling (n=24)	P value
Age (years)	63±12	61±11	0.50
Male (No. %)	35 (78%)	20 (83%)	0.75
BMI (kg/m^2)	28±5	28±4	0.83
Hypertension (No. %)	13 (29%)	5 (21%)	0.46
Diabetes mellitus (No. %)	7 (16%)	2 (8%)	0.48
Hypercholesterolemia (No. %)	12 (27%)	5 (21%)	0.59
Smoking (No. %)	28 (62%)	10 (42%)	0.10
Heart rate (admission, bpm)	76±13	88±33	0.17
Systolic blood pressure (admission, mmHg)	140±28	141±38	0.92
Culprit artery (No. %)			
Left anterior descending artery	19 (42%)	19 (79%)	<0.01
Left circumflex artery	8 (18%)	2 (8%)	0.47
Right coronary artery	18 (40%)	3 (12%)	0.03
Multi-vessel disease (No. %)	6 (17%)	3 (14%)	0.81

Abbreviations: *LV, left ventricular; BMI, body mass index; BPM, beat per minute.;*

Table 2: LV volume, infarct, and mitral inflow characteristics

	No adverse LV-remodeling (n=45)	Adverse LV-remodeling (n=24)	P value
LV volume and infarct characteristics			
Mass (g)	119±30	133±32	0.08
End-diastolic volume (ml)	168±39	173±33	0.58
End-systolic volume (ml)	88±34	104±34	0.06
Stroke volume (ml)	80±16	69±15	<0.01
Ejection fraction (%)	49±9	41±11	<0.01
Infarct size (g/m^2)	8.2 [5.3-12.8]	14.0 [6.4-21.3]	0.04
MVO presence (%)	24 (53%)	17 (71%)	0.15
Anterior infarct (%)	18 (40%)	19 (79%)	<0.01
Mitral inflow metrics			
E-wave flow (ml/s)	325±105	325±100	0.98
A-wave flow (ml/s)	268±82	222±115	0.06
E/A (ratio)	1.4±1.2	2.3±2.8	0.14
Deceleration time (msec)	153±53	141±35	0.33

Abbreviations: *LV, left ventricular; MVO, microvascular obstruction; NA; not-applicable.*

Table 3: Univariable and multivariable linear regression analysis for association with the absolute change of LVEDV

	Univariable analysis			Multivariable analysis		
	β	95% CI	P value	β	95% CI	P value
KEi mean (per uJ/ml)	-1.73	(-3.75, 0.29)	0.09	ns		
KEi mean-systolic (per uJ/ml)	-1.52	(-3.02, -0.02)	0.05	ns		
KEi peak-systolic (per uJ/ml)	-0.99	(-1.96, -0.02)	0.05	ns		
KEi A-wave (per uJ/ml)	-1.28	(-2.41, -0.15)	0.03	-1.43	(-2.64, -0.22)	0.02
In-plane KE proportion (per %)	1.28	(0.11, 2.45)	0.03	ns		
Infarct size (per g/m^2)	1.07	(0.04, 2.10)	0.04	ns		
MVO presence (yes to no)	14.95	(0.71, 29.1)	0.04	ns		

ns = included in multivariable analysis (p <0.10 in univariable analysis) but removed from model in multivariable analysis (backward elimination procedure). Abbreviations: *LV, left ventricular; LVEDV, left ventricular end-diastolic volume.*

Table 4: Univariable and multivariable logistic regression analysis for association with adverse LV-remodeling

	Univariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Association with ≥10% LV-remodeling						
KEi mean (per uJ/ml)	0.85	(0.72, 1.02)	0.08	ns		
KEi peak (per uJ/ml)	0.95	(0.89, 1.00)	0.09	ns		
KEi mean-systolic (per uJ/ml)	0.88	(0.77, 1.00)	0.06	ns		
KEi A-wave (per uJ/ml)	0.90	(0.81, 0.99)	0.03	0.92	(0.83, 1.01)	0.09
In-plane KE proportion (per %)	1.09	(1.00, 1.20)	0.04	ns		
Mitral inflow A-wave (per ml/s)	0.99	(0.99, 1.00)	0.07	ns		
Infarct size (per g/m^2)	1.09	(1.01, 1.18)	0.02	1.08	(1.0, 1.17)	0.03
Association with ≥15% LV-remodeling						
KEi A-wave (per uJ/ml)	0.86	(0.77, 0.98)	0.02	0.86	(0.77, 0.98)	<0.01
In-plane KE proportion (per %)	1.09	(0.99, 1.21)	0.06	ns		
Infarct size (per g/m^2)	1.07	(0.99, 1.15)	0.08	ns		
Association with ≥20% LV-remodeling						
KEi mean (per uJ/ml)	0.77	(0.58, 1.00)	0.06	ns		
KEi peak (per uJ/ml)	0.91	(0.82, 0.99)	0.05	ns		
KEi mean-systolic (per uJ/ml)	0.81	(0.66, 1.00)	0.05	ns		
KEi peak-systolic (per uJ/ml)	0.90	(0.79, 1.01)	0.08	ns		
KEi peak-diastolic (per uJ/ml)	0.90	(0.82, 0.99)	0.05	ns		
KEi A-wave (per uJ/ml)	0.83	(0.71, 0.97)	0.02	0.83	(0.71, 0.97)	<0.01
In-plane KE proportion (per %)	1.11	(0.99, 1.25)	0.06	ns		

ns = included in multivariable analysis (p <0.10 in univariable analysis), but removed from model in multivariable analysis (backward elimination procedure). Abbreviations: *LV, left ventricular; LVEDV, left ventricular end-diastolic volume.*

Highlights

- This study reveals the association between left ventricular (LV) blood flow energetics and adverse LV-remodeling after myocardial infarction, for the first time.
- This relationship is most apparent with late-diastolic (A-wave) LV blood flow energetics.
- Of note, A-wave LV blood flow energetics may provide incremental value over infarct size as an indicator of severe adverse LV-remodeling.

Association of left ventricular flow energetics with remodeling after myocardial infarction: new hemodynamic insights for left ventricular remodeling

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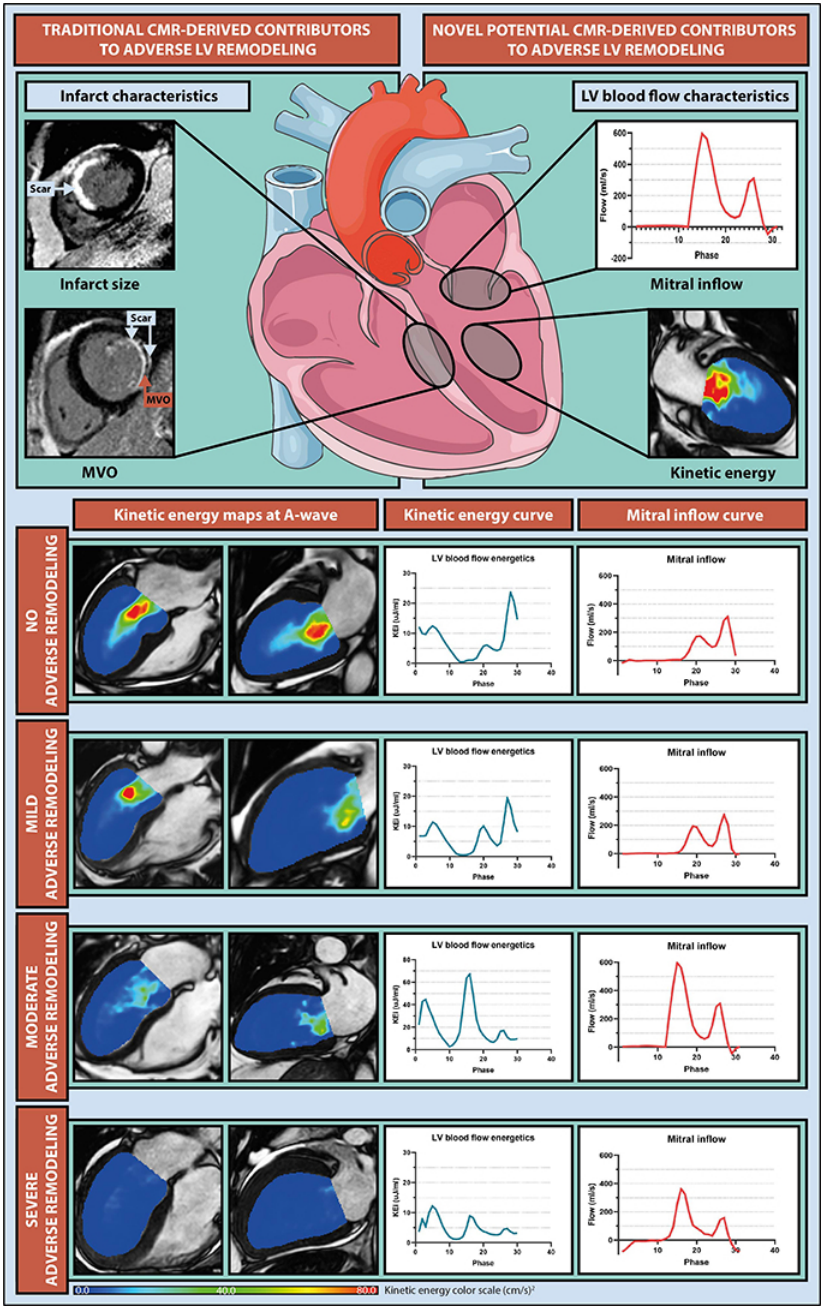


Graphics Abstract

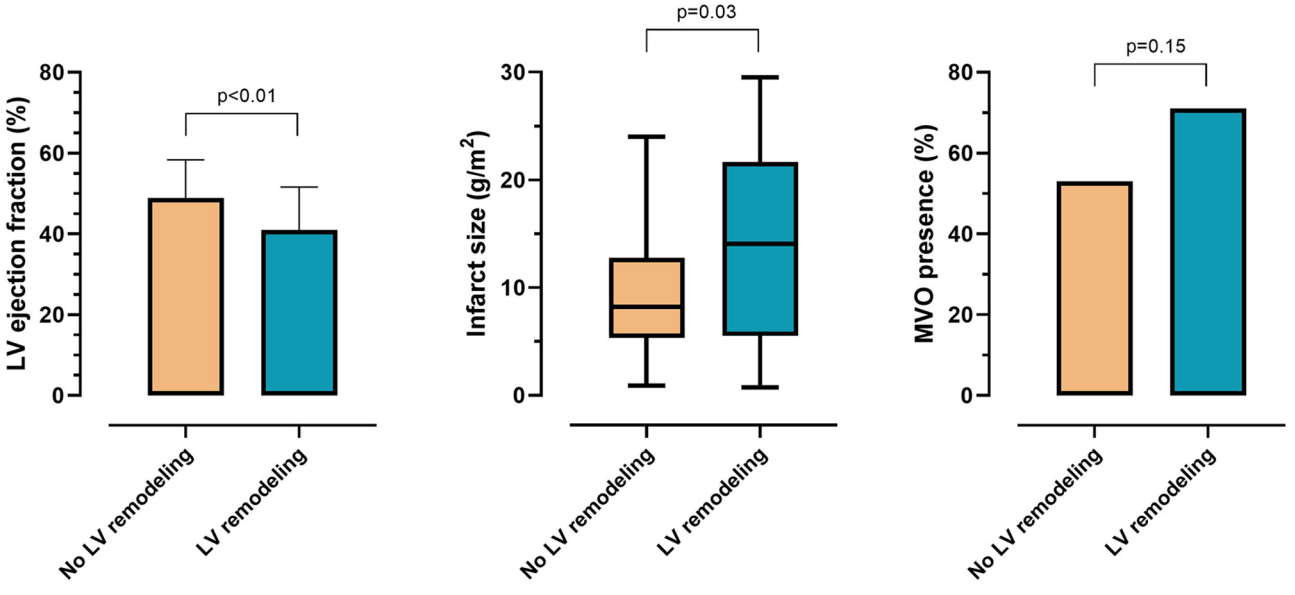
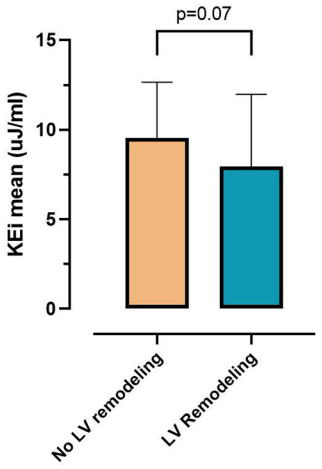

LV ejection fraction (%)
80
60
40
20
0
p<0.01
No LV remodeling
LV remodeling
Infarct size (g/m2)
30
20
10
0
p=0.03
No LV remodeling
LV remodeling
MVO presence (%)
80
60
40
20
0
p=0.15
No LV remodeling
LV remodeling

Figure 1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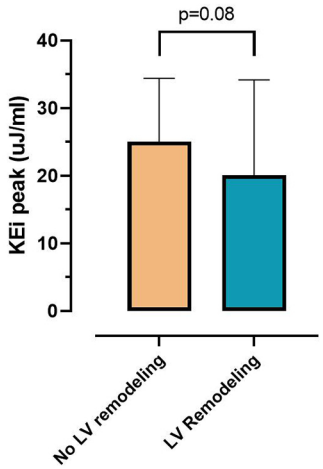
KEi mean (uJ/ml)
15
10
5
0
No LV remodeling
LV Remodeling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30
20
10
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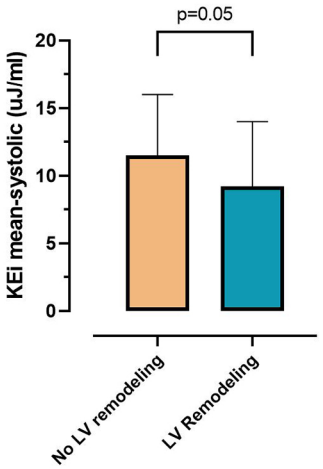
LV Remodeling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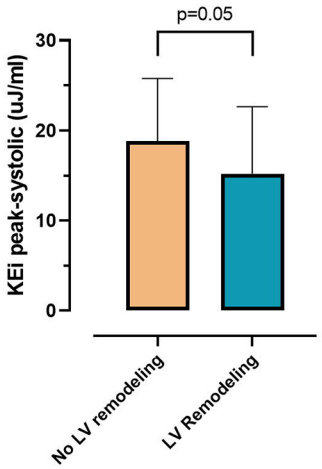
LV Remodeling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20
10
0
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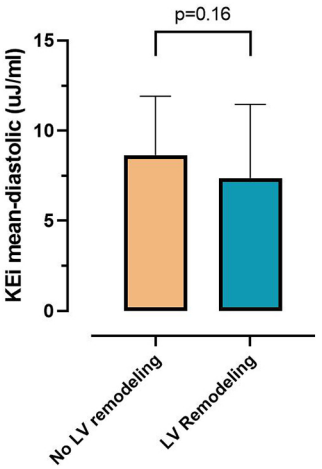
LV Remodeling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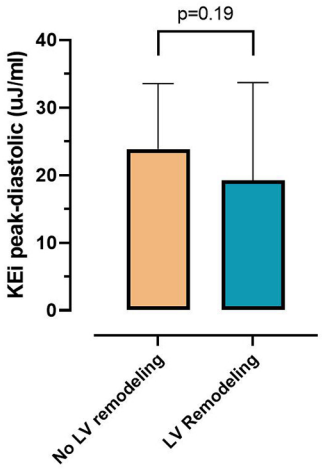
10
5
0
No LV remodeling
LV Remodeling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30
20
10
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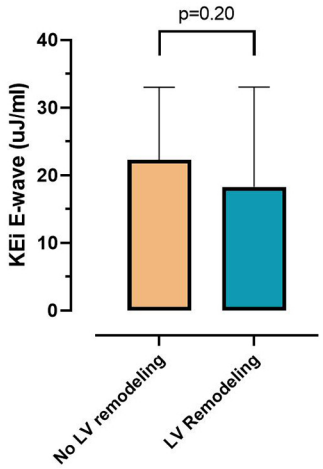
No LV remodeling
LV Remodeling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30
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10
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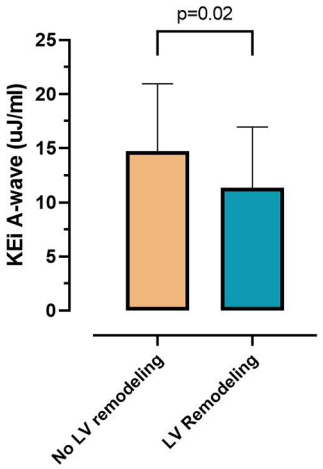
LV Remodeling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20
15
10
5
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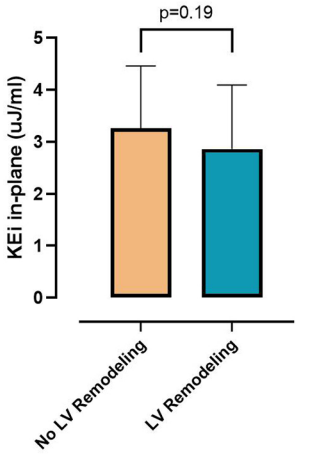
LV Remodeling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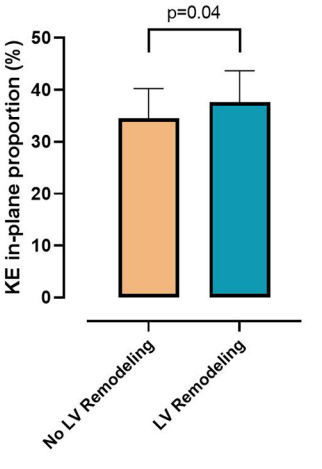
5
4
3
2
1
0
No LV Remodeling
LV Remodeling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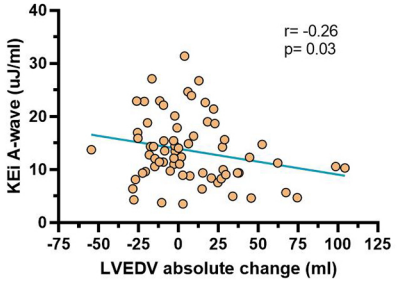
KE in-plane proportion (%)
50
40
30
20
10
0
No LV Remodeling
LV Remodeling

Figure 2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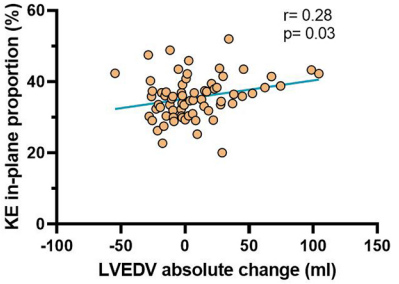
KEi A-wave (uJ/ml)
LVEDV absolute change (ml)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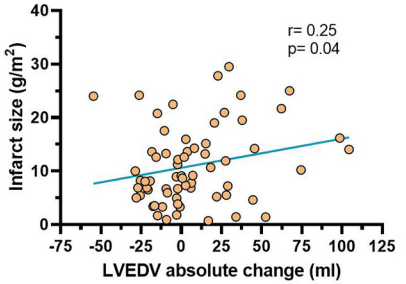
p= 0.03
KE in-plane proportion (%)
LVEDV absolute change (ml)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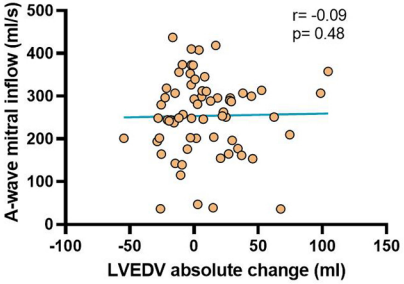
Infarct size (g/m2)
LVEDV absolute change (ml)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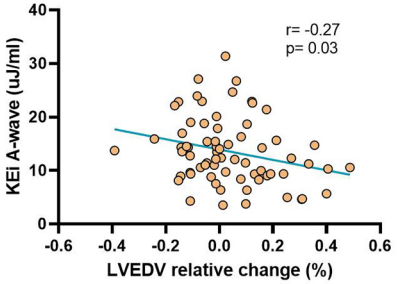
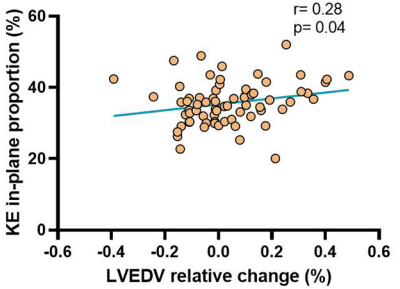
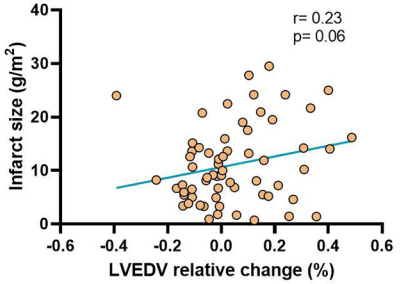
A-wave mitral inflow (ml/s)
LVEDV absolute change (ml)


r= -0.27
p= 0.03
KEi A-wave (uJ/ml)
LVEDV relative change (%)


r= 0.28
p= 0.04
KE in-plane proportion (%)
LVEDV relative change (%)


r= 0.23
p= 0.06
Infarct size (g/m2)
LVEDV relative change (%)

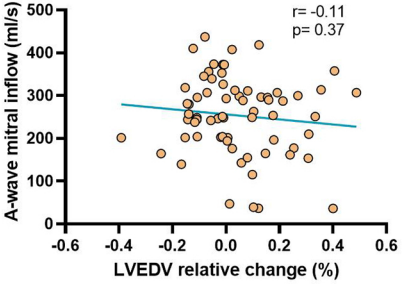

r= -0.11
p= 0.37
A-wave mitral inflow (ml/s)
LVEDV relative change (%)

Figure 3

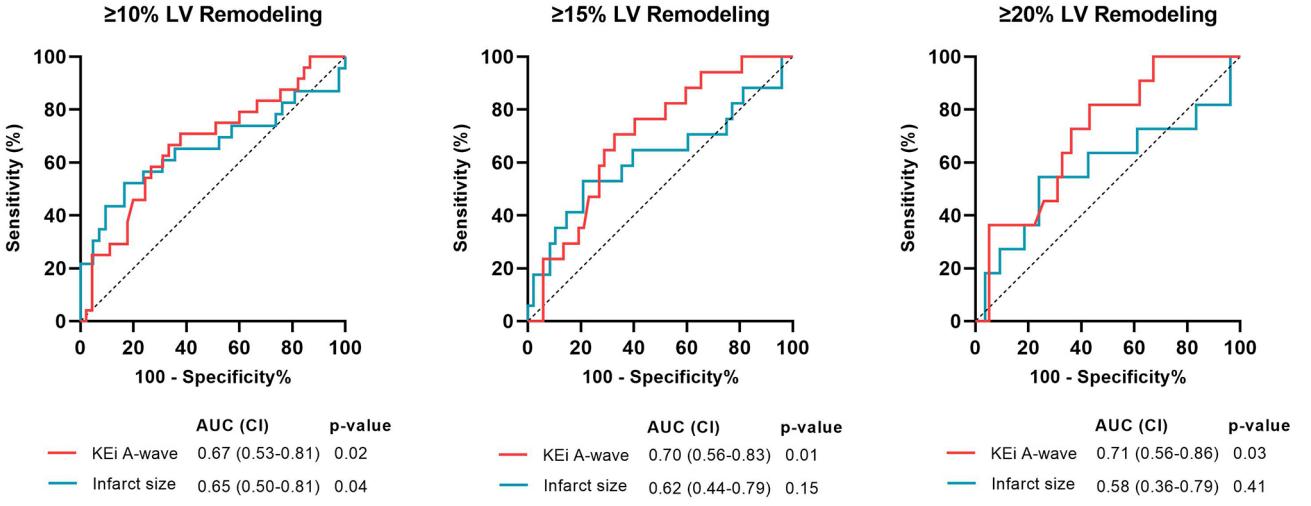

≥10% LV Remodeling
Sensitivity (%)
100 - Specificity%
AUC (CI) p-value
KEi A-wave 0.67 (0.53-0.81) 0.02
Infarct size 0.65 (0.50-0.81) 0.04
≥15% LV Remodeling
Sensitivity (%)
100 - Specificity%
AUC (CI) p-value
KEi A-wave 0.70 (0.56-0.83) 0.01
Infarct size 0.62 (0.44-0.79) 0.15
≥20% LV Remodeling
Sensitivity (%)
100 - Specificity%
AUC (CI) p-value
KEi A-wave 0.71 (0.56-0.86) 0.03
Infarct size 0.58 (0.36-0.79) 0.41

Figure 4