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Longitudinal Changes in Left Ventricular Blood Flow Kinetic Energy After Myocardial Infarction: Predictive Relevance for Cardiac Remodeling

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Background: Four-dimensional (4D) flow cardiac magnetic resonance (cardiac MR) imaging provides quantification of intracavity left ventricular (LV) flow kinetic energy (KE) parameters in three dimensions. ST-elevation myocardial infarction (STEMI) patients have been shown to have altered intracardiac blood flow compared to controls; however, how 4D flow parameters change over time has not been explored previously.

Purpose: Measure longitudinal changes in intraventricular flow post-STEMI and ascertain its predictive relevance of long-term cardiac remodeling.

Study Type: Prospective.

Population: Thirty-five STEMI patients (M:F = 26:9, aged 56 ± 9 years).

Field Strength/Sequence: A 3 T/3D EPI-based, fast field echo (FFE) free-breathing 4D-flow sequence with retrospective cardiac gating.

Assessment: Serial imaging at 3–7 days (V1), 3-months (V2), and 12-months (V3) post-STEMI, including the following protocol: functional imaging for measuring volumes and 4D-flow for calculating parameters including systolic and peakE-wave LVKE, normalized to end-diastolic volume (iEDV) and stroke volume (iSV). Data were analyzed by H.B. (3 years experience). Patients were categorized into two groups: preserved ejection fraction (pEF, if EF > 50%) and reduced EF (rEF, if EF < 50%).

Statistical Tests: Independent sample t-tests were used to detect the statistical significance between any two cohorts. $P < 0.05$ was considered statistically significant.

Results: Across the cohort, systolic KE_{sv} was highest at V1 (28.0 ± 4.4 μ J/mL). Patients with rEF retained significantly higher systolic KE_{sv} than patients with pEF at V2 (18.2 ± 3.4 μ J/mL vs. 6.9 ± 0.6 μ J/mL, $P < 0.001$) and V3 (21.6 ± 5.1 μ J/mL vs. 7.4 ± 0.9 μ J/mL, $P < 0.001$). Patients with pEF had significantly higher peakE-wave KE_{iEDV} than rEF patients throughout the study (V1: 25.4 ± 11.6 μ J/mL vs. 18.1 ± 9.9 μ J/mL, $P < 0.03$, V2: 24.0 ± 10.2 μ J/mL vs. 17.2 ± 12.2 μ J/mL, $P < 0.05$, V3: 27.7 ± 14.8 μ J/mL vs. 15.8 ± 7.6 μ J/mL, $P < 0.04$).

Data Conclusion: Systolic KE increased acutely following MI; in patients with pEF, this decreased over 12 months, while patients with rEF, this remained raised. Compared to patients with pEF, persistently lower peakE-wave KE in rEF patients is suggestive of early and fixed impairment in diastolic function.

Evidence Level: 1

Technical Efficacy: Stage 3

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Myocardial infarction (MI) remains one of the leading causes of morbidity and mortality worldwide. Despite advancements in various imaging modalities, left ventricular ejection fraction (LVEF) measured via transthoracic echocardiography remains the most popular method for risk-stratifying patients post-MI and guiding heart failure treatment. Previous

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studies have shown that impaired diastolic recovery following MI is a predictor of major adverse cardiac events (MACE).^{1,2} Four-dimensional flow (4D flow) cardiac magnetic resonance (cardiac MR) imaging provides quantification of intra-cavity LV flow kinetic energy (KE) in three dimensions at different time points in the cardiac cycle.^{3–7} This allows for the assessment of the different flow components of both systolic and diastolic function.

The effects of cardiovascular disease on 4D flow have been studied by various authors. Stoll et al studied 4D flow hemodynamics in patients with dilated cardiomyopathy and ischemic heart disease. They demonstrated that the degree of derangement in KE parameters correlated with ventricular dilatation, brain natriuretic peptide (BNP) levels, performance on 6-minute walk tests and patient symptoms, highlighting that 4D flow parameters could provide additive value in monitoring heart failure therapy and predicting prognosis.⁸ In a separate study, Garg et al demonstrated acute MI patients to have lower peak E-wave KE than controls, pointing to an early loss of diastolic function.⁹ Most studies to date however have measured 4D flow at single time points and longitudinal studies focusing on serial changes through the convalescent period following MI are lacking.^{4,8,9}

A detailed understanding of the intraventricular flow dynamics in relation to cardiac remodeling and their potential clinical predictive relevance for cardiac remodeling will be clinically important to help early patient stratification and management.

Therefore, the aim of this study was to perform serial 4D flow measurements in patients following ST-elevation myocardial infarction (STEMI), with the following objectives: 1) investigate longitudinal changes in LV systolic KE; 2) investigate change in LVKE in preserved ejection fraction (EF) vs. reduced EF; and 3) investigate the associations between acute 4D markers and longitudinal LVEF recovery.

Methods

The study protocol was approved by the institutional research ethics committee and complied with the Declaration of Helsinki; all patients gave written informed consent for their participation. (NIHR 33963, REC 17/YH/0062).

Study Population

“First event” STEMI patients were prospectively recruited from a single tertiary center. Study inclusion criteria were 1) MI as defined by current international guidelines¹⁰; 2) revascularization via percutaneous coronary intervention (PCI) within 12 hours after onset of symptoms; and 3) no contraindications to MR. Exclusion criteria were 1) previous revascularization procedure (coronary artery bypass grafting or PCI); 2) known cardiomyopathy; 3) severe valvular heart disease; and 4) hemodynamic instability lasting longer than 24 hours

following PCI and contraindication. Acute clinical management followed contemporary guidelines.¹⁰

MR Protocol and Image Acquisition

The study protocol included an MR scan within 3–7 days of index presentation (V1), a second scan at 3 months (V2) and a third scan at 12 months (V3). Cardiac MR examinations were performed on a 3.0 T Philips scanner (Philips Healthcare, Best, the Netherlands); the imaging protocol included full LV coverage by functional cine cardiac MR and late gadolinium enhanced (LGE) imaging. Cardiac MR examinations were performed on a 3.0 T Philips Achieva TX system (Philips) equipped with a 32-channel cardiac-phased array receiver coil, MultiTransmit technology and high-performance gradients with $G_{max} = 80$ mT/m and slew rate = 100 mT/m/msec. A full blood count, including hematocrit was measured at the time of intravenous cannulation.

Survey images were used to plan vertical long-axis, horizontal long-axis, three-chamber (LV outflow tract) views and the LV volume contiguous short-axis stack. Cine imaging used a balanced steady-state free precession (bSSFP) pulse sequence (echo time [TE]/repetition time [TR]/flip angle 1.3 msec/2.6 msec/40°, spatial resolution $1.6 \times 2.0 \times 10$ mm, typical temporal resolution 25 msec, slice thickness 8 mm, and 30 phases per cardiac cycle). Modified Look-Locker inversion recovery (MOLLI) to determine the T1-inversion time. LGE imaging was done at 15-minute from gadolinium-based contrast injection, using phase sensitive inversion recovery (PSIR) spoiled gradient echo (GE) sequence (SENSE factor 1.7, typical TE/TR of 3.0/6.1 msec, flip angle of 25°, slice thickness of 10 mm and with Look-Locker scout determined T1-inversion time), and whole-heart 4D flow.

4D Flow Acquisition

An unnavigated free-breathing 4D flow data acquisition was planned in the trans-axial plane while ensuring complete ventricle coverage. A 3D echo-planar imaging (EPI)-based, fast field echo (FFE) sequence was used with retrospective cardiac gating; 30 phases were reconstructed across the cardiac cycle. Sequence parameters were as follows: acquired voxel size = $3 \times 3 \times 3$ mm³, reconstructed voxel size = $2.23 \times 2.23 \times 3$ mm³, field of view (FOV) = 400×300 mm², repetition time (TR) = 8.1 msec, echo time (TE) = 3.5 msec, flip angle = 10°, number of signal averages = 1, Velocity encoding (VENC) = 150 cm/sec, EPI factor (k-space profiles/excitations) = 5. The MRI scanner performed reconstruction via 4-point encoding; Maxwell correction methods were applied for compensating the effects of concomitant gradient terms. Before further processing, phase contrast data were visually reviewed to ensure no velocity aliasing artifacts were present.¹¹

Image Analysis

All 4D flow images were analyzed by H.B. (3 years of experience), who analyzed LV flow KE mapping for all patients and

visits. All other MR images were analyzed by A.D. (6 years of experience), which included volumetric assessment, tissue characterization for infarct size and microvascular obstruction (MVO) for all patients and visits. Both investigators were blinded to the time point, other clinical data such as EF and long-term clinical outcomes.

LV Blood Flow Parameters

Data analysis was undertaken using the research software tool MASS (Leiden University Medical Center, Leiden, The Netherlands). Cine short-axis segmentation was used to define the boundaries of the region for LV blood flow parameter estimation. Prior to these calculations, spatial misalignment between the cine short-axis stack and 4D flow data were corrected by rigid registration as previously described.¹² Specific details for how the endocardial delineations are used to derive the kinetic energy mapping results have been reported previously.⁹ The biomarkers derived from analysis of the 4D flow datasets are summarized in Table 1. In keeping with previous publications, KE parameters were subsequently normalized to left ventricular end diastolic volume (LVEDV) and presented as kinetic energy indexed to end diastolic volume (KE_{iEDV}).⁹ Additionally, in order to account for serial changes in LVEDV following STEMI, KE parameters were normalized to LVSV and also presented as kinetic energy indexed to systolic volume (KE_{iSV}).

Standard Cardiac MR Analysis for LV Function and LGE

Cine and LGE data were analyzed using cvi42 software (Circle Cardiovascular Imaging Inc, Calgary, Canada) to derive LV

volumes and EF. On LGE images, a threshold of 5 standard deviations (SD) above the remote myocardial tissue signal intensity was used to detect and quantify the amount of infarcted myocardium. The extent of infarction both in grams and LV mass percentage was quantified using computer-assisted planimetry. MVO was defined as dark zones within an area of LGE at 15 minutes post administration.

Subgroup Analysis

Following LVEF analysis of the V1 scan, patients were categorized into the two following groups: patients with $LVEF \geq 50\%$ were classified as preserved ejection fraction (“pEF”), while patients with $LVEF < 50\%$ were categorized as reduced ejection fraction (“rEF”). Patients in the rEF group were further subdivided into mildly impaired, and moderate-to-severely impaired systolic function in line with the European Society of Cardiology (ESC) guidelines for heart failure.¹³

In order to assess changes in flow dynamics in relation to LV recovery over time, following LVEF analysis at V3, patients were categorized into three groups: group 1 (“unchanged pEF” group) included patients (8/35 patients) who had preserved EF throughout, group 2 (“recovered” group) included patients (10/35 patients) who had reduced EF on acute scan which recovered to within normal limits ($EF \geq 50\%$) by V3, and group 3 (“impaired EF” group) included patients (17/35 patients) whose EF remained impaired ($<50\%$) at V3.

Intraobserver/Interobserver Variability

For interobserver variability, H.B. (3 years of experience) and A.D. (6 years of experience) analyzed all data from 10 study patients separately, blinded to each other’s analysis. For intraobserver variability, HB re-analyzed 10 randomly selected data sets more than a month later. Variability was assessed using Bland–Altman plots.

Statistical Analysis

Statistical analysis was performed using SPSS® statistics 26.0 (International Business Machines, Armonk, New York, USA). Normality was assessed through the Shapiro–Wilk test. Standard clinical parameters are presented as mean $\pm$ standard deviation. Quantitative flow imaging parameters are expected to be nonparametric⁹ are presented as median and interquartile ranges (IQR). For two-group comparison, the Students t-test was used for parametric data and a Mann–Whitney U test for nonparametric data. One-way analysis of variance (ANOVA) with Turkey’s post hoc or Kruskal–Wallis test with post hoc Duns multiple comparison tests were performed with Bonferroni correction for normally and non-normally distributed multiple groups respectively. Categorical data were compared using χ^2 tests. A P -value <0.05 was considered statistically significant.

TABLE 1. Description of Left Ventricular Kinetic Energy Flow Parameters

Parameter	Description
Average KE	The average KE of LV flow for the complete cardiac cycle
Minimal KE	The minimal KE of the LV flow at any time point during the complete cardiac cycle
Systolic KE	The average KE of the LV flow during systole
Diastolic KE	The average KE of the LV flow during diastole
PeakE-wave KE	The peak KE of the LV flow during early diastolic filling
PeakA-wave KE	The peak KE of the LV flow during late diastolic filling

All KE parameters were normalized to LVEDV (presented as KE_{iEDV}) and LVSV (presented as KE_{iSV}).⁹

Results

Demographic Characteristics

Thirty-five STEMI patients (M:F = 26:9, aged 56 ± 9 years) completed all 3 scans (Table 2). At V1, 16 patients (46%) presented with an inferior STEMI; across the study population EF was $45 \pm 8\%$ with a mean infarct size of 12 ± 9 g. Out of the 35 patients, 25 patients (71%) had a reduced EF at V1. By V2, mean EF was significantly improved to $51 \pm 8\%$ and did not show any significant further change at V3 ($50 \pm 10\%$, $P < 0.87$). The mean infarct size significantly reduced to 8 ± 7 g at V2 and also did not undergo further change by V3 (7 ± 6 g, $P < 0.99$) (Table 3). Out of the

whole cohort, nine patients (26%) had hypertension. Statistical analysis between hypertensive and nonhypertensive patients showed no significance in flow parameters (average KE_{iEDV} $P = 0.14$, systolic KE_{iEDV} $P = 0.08$).

Longitudinal Changes in LV Systolic KE in all STEMI Patients

Acutely, the average LV systolic KE_{iEDV} was 10.0 ± 4.7 $\mu J/mL$; however, this decreased significantly by visit 2 (7.5 ± 4 $\mu J/mL$) and did not undergo further significant change by V3 (8.1 ± 3.0 $\mu J/mL$, $P = 0.79$) (Table 3). When normalizing for LVSV, the same pattern was observed; mean KE_{iSV} decreased significantly between V1 and V2 (KE_{iSV} 28.0 ± 4.4 $\mu J/mL$ vs. 17.7 ± 3.4 $\mu J/mL$) but did not change significantly between V2 and V3 (KE_{iSV} 17.7 ± 3.4 $\mu J/mL$ vs. 19.2 ± 5.1 $\mu J/mL$, $P = 0.09$).

Change in LVKE in Preserved EF vs. Reduced EF

At V1, patients with rEF had significantly lower peakE-wave KE_{iEDV} than patients with pEF (rEF 18.1 ± 9.9 $\mu J/mL$ vs. pEF 25.4 ± 11.6 $\mu J/mL$) (Table 4) (Figure 1). This was most evident at V3, when comparing patients with moderate-to-severely impaired systolic function (peakE-wave KE_{iEDV} , 12.2 ± 4.8 $\mu J/mL$) with patients with pEF (peakE-wave KE_{iEDV} , 27.7 ± 4.1 $\mu J/mL$) (Fig. 2b).

Longitudinally, peakE-wave KE_{iEDV} in patients with rEF trended downwards and reduced from 18.1 ± 9.9 to 15.8 ± 7.6 $\mu J/mL$ by V3. Meanwhile in the pEF group, peakE-wave KE_{iEDV} demonstrated an upward trend, reaching 27.7 ± 14.8 $\mu J/mL$ by V3, which was significantly higher than the rEF group (Table 4). Left ventricular end-diastolic volume (LVEDVi) tended to increase in the rEF group between V1 and V3 (from 78 ± 13 to 87 ± 18 mL/m^2 , $P = 0.23$) while remaining relatively fixed in the pEF group (67 ± 7 to 67 ± 10 mL/m^2 , $P = 0.79$). When peakE-wave KE was normalized for SV, peak E-wave KE_{iSV} remained significantly higher in rEF patients at V2 (36.1 ± 6.8 vs. 24.7 ± 2.3 $\mu J/mL$). By V3, rEF patients had higher peak-E KE_{iSV} albeit the difference was not statistically significant (24.1 ± 5.6 vs. 20.8 ± 2.4 $\mu J/mL$, $P = 0.06$).

At V1, LV systolic KE_{iEDV} was significantly higher in the pEF group than rEF (12.9 ± 2.9 vs. 8.9 ± 3.5 $\mu J/mL$). In both groups, systolic KE_{iEDV} gradually decreased over the three scans, but it is worth noting that patients with rEF also had significantly higher LVEDVi at all three scans. When corrected for SV, systolic KE at V1 was not significantly different between the two groups (pEF: 27.6 ± 2.8 $\mu J/mL$ vs. rEF 29.0 ± 6.2 $\mu J/mL$, $P = 0.13$). Additionally, in patients with pEF, systolic KE_{iSV} significantly decreased by 3 months (27.6 ± 2.8 to 6.9 ± 0.6 $\mu J/mL$), meanwhile in patients with rEF, it remained relatively raised, significantly higher than pEF patients at

TABLE 2. Patient Demographics

Patient Characteristics	All (N = 35)
Age (years)	56 ± 9
Sex	26:9 (M:F)
Height (cm)	170 ± 7
Weight (kg)	80 ± 10
Body surface area	1.9 ± 0.1
Risk factors (No (%))	
Smoker	10 (29)
Hypertension	9 (26)
Diabetes	7 (20)
Family history	12 (34)
Peripheral vascular disease	2 (6)
Presenting characteristics	
Culprit coronary artery (No (%))	
Left anterior descending	13 (37)
Left circumflex	6 (17)
Right coronary artery	16 (46)
Mean time from onset of symptoms to balloon (minutes)	263 ± 188
Treatment (No (%))	
Aspirin	35 (100)
Adenosine diphosphatase receptor antagonist (Ticagrelor)	35 (100)
Angiotensin converting enzyme (ACE) inhibitor	35 (100)
Beta-blocker	35 (100)

TABLE 3. Cardiac MR Parameters

	V1 (N = 35)	V2 (N = 35)	V3 (N = 35)	P-value (V1-2)	P-value (V2-3)	P-value (V1-3)	ANOVA
Standard cardiac MR clinical parameters							
LVEDV (mL)	146 ± 28	154 ± 33	158 ± 38	0.3	0.67	0.16	0.36
LVEDVi (mL/m ²)	75 ± 13	79 ± 15	81 ± 18	0.39	0.55	0.12	0.28
LVESVi (mL/m ²)	81 ± 23	77 ± 27.3	81 ± 33	0.51	0.64	0.93	0.81
SVi (mL/m ²)	67 ± 15	76 ± 15	77 ± 15	0.01	0.77	0.004	0.01
EF (%)	45 ± 8	51 ± 8	50 ± 10	0.01	0.87	0.01	0.01
IS (%)	19.1 ± 14.4	13.7 ± 10.2	11.8 ± 9.5	0.07	0.42	0.02	0.02
IS (g)	12 ± 9	8 ± 7	7 ± 6	0.02	0.99	0.03	0.01
MVO (g)	0.7 ± 1.2	–	–	–	–	–	–
LV KE parameters derived from 4D flow (μJ/mL)							
FullRR average	1358 ± 562	933 ± 232	929 ± 445	<0.001	0.26	<0.001	<0.001
Minimal	139 ± 117	105 ± 46	127 ± 75	<0.001	0.02	0.08	0.004
Systolic	1868 ± 568	968 ± 502	1141 ± 542	<0.001	0.02	<0.001	<0.001
Diastolic	1049 ± 513	933 ± 234	888 ± 336	0.005	<0.001	<0.001	<0.001
PeakE-wave	2939 ± 1035	2379 ± 744	1972 ± 642	<0.001	<0.001	<0.001	<0.001
PeakA-wave	2382 ± 1396	1483 ± 744	1612 ± 874	<0.001	0.001	0.001	<0.001
LV KE _{iEDV} parameters derived from 4D flow (μJ/mL)							
FullRR average	8.5 ± 1.9	7.5 ± 3.6	7.4 ± 2.9	0.02	0.94	0.03	0.03
Minimal	1.1 ± 0.5	0.9 ± 0.4	0.9 ± 0.5	0.15	0.86	0.24	0.31
Systolic	10 ± 4.7	7.5 ± 4.0	8.1 ± 3.0	0.005	0.79	0.01	0.01
Diastolic	8.1 ± 3.8	6.9 ± 3.6	7.4 ± 3.6	0.25	0.99	0.2	0.37
PeakE-wave	19.3 ± 11.2	18.3 ± 11.7	17 ± 13.6	0.51	0.52	0.15	0.38
PeakA-wave	16.7 ± 8.0	13.4 ± 8.4	13.7 ± 8.8	0.11	0.78	0.19	0.24
LV KE _{iSV} parameters derived from 4D flow (μJ/mL)							
FullRR average	17.9 ± 2.8	14.9 ± 2.9	12.9 ± 3.4	<0.001	0.02	<0.001	0.05
Minimal	1.9 ± 0.3	1.9 ± 0.4	1.5 ± 0.4	0.98	<0.001	<0.001	<0.001
Systolic	28.0 ± 4.4	17.7 ± 3.4	19.2 ± 5.1	<0.001	0.09	<0.001	0.07
Diastolic	12.9 ± 2.1	13.4 ± 2.6	9.8 ± 2.6	0.68	<0.001	<0.001	<0.001
PeakE-wave	39.4 ± 6.2	35.1 ± 6.8	21.3 ± 5.7	0.03	<0.001	<0.001	<0.001
PeakA-wave	18.9 ± 3.0	22.7 ± 4.4	23.5 ± 6.3	<0.001	0.23	<0.001	0.30
LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume indexed for BSA; LVESVi = left ventricular end-systolic volume indexed for BSA; SVi = stroke volume indexed for BSA; EF = ejection fraction; IS = infarct size; MVO = microvascular obstruction. Standard Cardiac MR clinical parameters are presented as mean ± standard deviation. LV KE _{iEDV} and LV KE _{iSV} parameters are presented as median ± inter-quartile range. <i>P</i> < 0.05 is deemed significant.							

TABLE 4. Preserved and Reduced EF

	pEF (N = 10)			rEF (N = 25)			pEF vs. rEF		
	V1	V2	V3	ANOVA	V1	V2	V3	ANOVA	P-value (V1) P-value (V2) P-value (V3)
Standard cardiac MR parameters									
LVEDV (mL)	132 ± 23	136 ± 29	131 ± 23	0.87	152 ± 28	161 ± 33	168 ± 38	0.23	0.04 0.04 0.001
LVEDVi (mL/m ²)	67 ± 7	70 ± 10	67 ± 10	0.79	78 ± 13	82 ± 15	87 ± 18	0.19	0.003 0.007 <0.001
LVESVi (mL/m ²)	61 ± 13	58 ± 13.8	53 ± 10	0.38	89 ± 21	85 ± 28	91 ± 33	0.69	<0.001 0.001 <0.001
SVi (mL/m ²)	71 ± 13	73 ± 17.7	77 ± 15	0.64	65 ± 15	77 ± 14	77 ± 15	0.005	0.26 0.52 0.94
EF (%)	54 ± 3	57 ± 5	59 ± 5	0.03	42 ± 6	48 ± 8	47 ± 9	0.01	<0.001 <0.001 <0.001
IS (%)	13.3 ± 14.3	6.7 ± 6.8	5 ± 5.8	0.15	21.5 ± 14.0	16.5 ± 10.0	14.1 ± 9.2	0.07	0.13 0.01 0.01
IS (g)	5.5 ± 5.7	2.6 ± 3.1	2.3 ± 2.6	0.16	14.2 ± 8.8	9.9 ± 7.4	8.7 ± 6.5	0.03	0.01 0.02 0.005
MVO (g)	0.3 ± 0.9	–	–	–	0.9 ± 1.3	–	–	–	0.19 – –
Residual CD (n,%)	3 (30)	–	–	–	8 (32)	–	–	–	– – –
LV KE parameters (μJ/mL)									
FullRR average	1551 ± 626	881 ± 650	1091 ± 649	0.02	1268 ± 298	1047 ± 243	1134 ± 299	0.002	0.03 0.24 0.17
Minimal	160 ± 144	72 ± 102	94 ± 70	0.12	136 ± 33	115 ± 48	146 ± 69	0.025	0.13 0.24 0.005
Systolic	1936 ± 851	637 ± 645	949 ± 579	0.001	1875 ± 455	1272 ± 414	1472 ± 365	<0.001	0.32 0.001 <0.001
Diastolic	1294 ± 484	927 ± 660	1169 ± 709	0.24	976 ± 222	982 ± 285	921 ± 279	0.484	<0.001 0.10 0.09
PeakE-wave	3728 ± 2038	3002 ± 2991	3769 ± 2213	0.51	2665 ± 863	2433 ± 1960	1681 ± 801	0.004	<0.001 0.004 <0.001
PeakA wave	2496 ± 937	987 ± 1453	1481 ± 1321	0.09	2399 ± 1447	1906 ± 540	2177 ± 577	0.199	0.39 0.04 0.006
LV KE _{iEDV} parameters (μJ/mL)									
FullRR average	10.0 ± 3.2	8.3 ± 5.4	9 ± 2.4	0.34	8.3 ± 2.6	7.5 ± 2.0	7.3 ± 2.2	0.22	0.09 0.64 0.19
Minimal	1.0 ± 0.4	0.9 ± 0.5	0.8 ± 0.2	0.42	1.1 ± 0.5	0.9 ± 0.3	1 ± 0.6	0.58	0.95 0.47 0.27
Systolic	12.9 ± 2.9	9.1 ± 5.7	8.7 ± 4.3	0.06	8.9 ± 3.5	7.3 ± 3.2	7.9 ± 3.5	0.08	0.02 0.31 0.4
Diastolic	8.4 ± 3.2	7.6 ± 5	8.5 ± 3.1	0.85	7.6 ± 4.0	6.7 ± 3.1	6.8 ± 3.5	0.58	0.65 0.42 0.31
PeakE-wave	25.4 ± 11.6	24.0 ± 10.2	27.7 ± 14.8	0.92	18.1 ± 9.9	17.2 ± 12.2	15.8 ± 7.6	0.41	0.03 0.05 0.04

TABLE 4. Continued

	pEF (N = 10)			rEF (N = 25)			pEF vs. rEF		
	V1	V2	V3	ANOVA	V1	V2	V3	ANOVA	P-value (V1) P-value (V2) P-value (V3)
PeakA wave	17.5 ± 5.6	13.2 ± 9.7	15.1 ± 10.7	0.60	16.7 ± 8.7	13.4 ± 8.2	12.9 ± 6.8	0.31	0.53 0.77 0.74
LV KE _{isv} parameters (μJ/mL)									
FullRR	22.1 ± 2.2	8.9 ± 0.8	7.8 ± 0.9	<0.001	18.6 ± 4.0	15.4 ± 2.9	14.6 ± 3.4	<0.001	0.005 <0.001 <0.001
average									
Minimal	2.3 ± 0.2	0.9 ± 0.1	1.1 ± 0.1	<0.001	2.0 ± 0.4	2.0 ± 0.4	1.6 ± 0.4	<0.001	0.20 <0.001 <0.001
Systolic	27.6 ± 2.8	6.9 ± 0.6	7.4 ± 0.9	<0.001	29.0 ± 6.2	18.2 ± 3.4	21.6 ± 5.1	<0.001	0.13 <0.001 <0.001
Diastolic	18.4 ± 1.9	10.4 ± 0.9	8.1 ± 0.9	<0.001	13.4 ± 2.9	13.8 ± 2.6	11.1 ± 2.6	<0.001	<0.001 <0.001 <0.001
PeakE-wave	42.3 ± 4.3	24.7 ± 2.3	20.8 ± 2.4	<0.001	40.8 ± 8.8	36.1 ± 6.8	24.1 ± 5.6	<0.001	0.46 <0.001 0.06
PeakA-wave	35.6 ± 3.6	12.8 ± 1.2	12.4 ± 1.5	<0.001	19.7 ± 4.2	23.4 ± 4.4	26.5 ± 6.2	<0.001	<0.001 <0.001 <0.001

LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume indexed for BSA; LVESVi = left ventricular end-systolic volume indexed for BSA; SVi = stroke volume indexed for BSA; EF = ejection fraction; IS = infarct size; MVO = microvascular obstruction; pEF = preserved ejection fraction; rEF = reduced ejection fraction. Standard Cardiac MR clinical parameters are presented as mean ± standard deviation. LV KE_{EDV} and LV KE_{isv} parameters are presented as median ± inter-quartile range. pEF includes patients with an EF > 50% at visit 1 and rEF includes patients with an EF < 50% at visit 1.

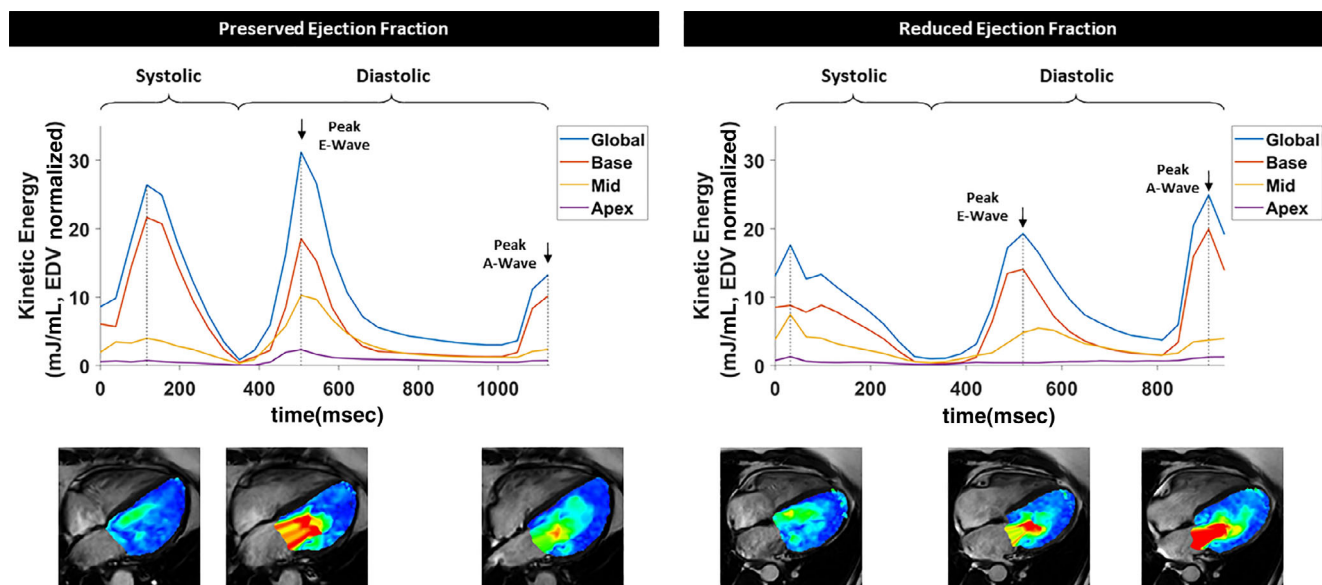


FIGURE 1: Shows representative kinetic energy curves throughout the cardiac cycle of 2 separate patients, acquired at (12 months [V3]). The left panel shows a patient with preserved ejection fraction (pEF), while the panel on the right shows a patient with reduced ejection fraction (rEF). Flow vectors at peak-systole, PeakE-wave and PeakA-wave indexed for EDV for each patient is shown underneath. The patient with rEF has higher systolic KE_{iEDV} , lower peakE-wave KE_{iEDV} and higher peakA-wave KE_{iEDV} .

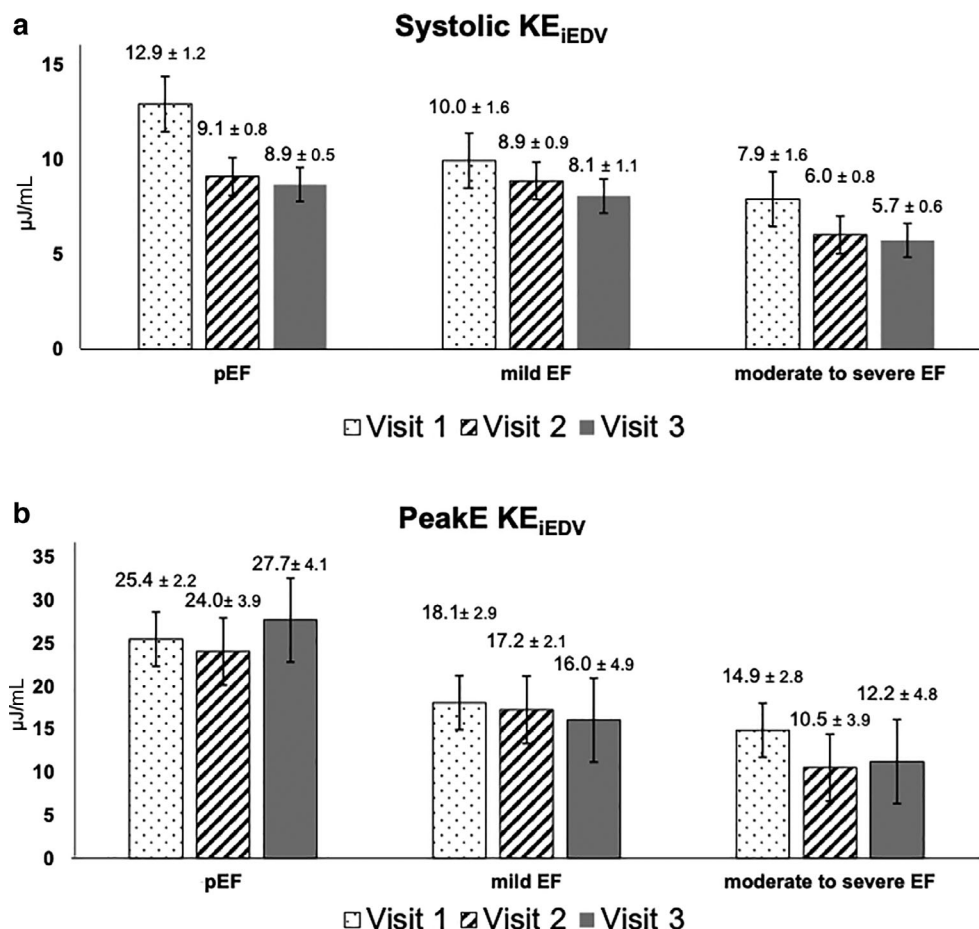


FIGURE 2: Shows systolic (a) and peak E (b) left ventricular kinetic energy (KE) parameters indexed for end-diastolic volume at the three visits for different grades left ventricular impairment: preserved ejection fraction (pEF), mildly impaired (mild EF) and moderate-to-severely impaired EF. Systolic KE is significantly lower in mild EF and moderate-to-severely impaired EF groups than the pEF group ($P < 0.02$ and $P < 0.03$, respectively). Patients with pEF have higher peak-KE at all three visits than mild EF and moderate-to-severely impaired EF patients.

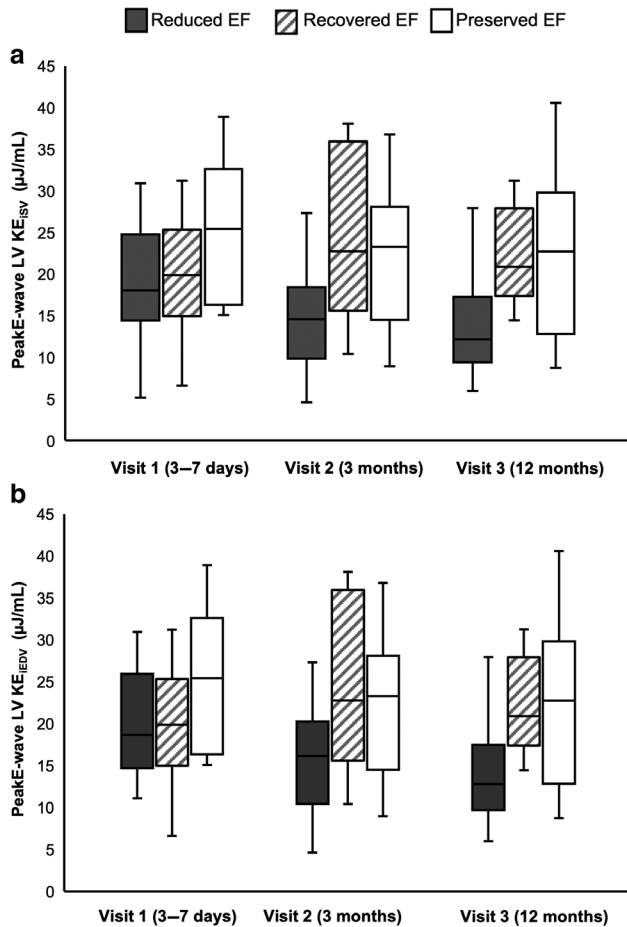


FIGURE 3: Shows longitudinal changes in peakE-wave indexed for EDV (a) and SV (b) between patients with preserved EF (>50%), recovered EF (<50% at V1 which improved to >50% at V3) and impaired EF (<50%) across three visits. Patients in reduced EF group underwent longitudinal reductions in PeakE-wave kinetic energy (KE) over 12 months (ANOVA $P < 0.01$).

V2 (rEF: 18.2 ± 3.4 vs. pEF 6.9 ± 0.6 $\mu\text{J/mL}$) and V3 (21.6 ± 5.1 vs. 7.4 ± 0.9 $\mu\text{J/mL}$).

Longitudinal Associations Between 4D Flow Parameters and LVEF Recovery

By V3, 17 out of the 35 (49%) patients had an impaired EF (<50%). Characteristics of these 17 patients included: two hypertension, one type 1 diabetes mellitus, one type 2 diabetes mellitus, six cardiovascular family history, and 12 smoking history (seven current smokers and five ex-smokers). Retrospective analysis showed that this group had significantly lower peakE-wave KE_{iEDV} at V1 (18.1 ± 7.9) than patients with unchanged pEF (25.4 ± 12.7) and recovered EF (19.9 ± 9.8) (Fig. 3). By V2, the recovered EF (group 2) group showed a significant increase in peakE-wave KE_{iEDV} (19.9 ± 9.8 vs. 20.9 ± 8.6).

Discussion

4D Flow analysis offers unique insights into changes in both systolic and diastolic function following STEMI. This study

compared longitudinal changes in flow KE parameters over three time points in first-event STEMI patients. The main findings from this study are 1) across the entire cohort, systolic KE significantly decreased over the first 3 months with no change detected between 3 and 12 months; 2) compared with patients with preserved EF, patients with acutely reduced EF had lower peakE-wave KE, which also decreased further over 12 months, likely signifying longitudinal decline in diastolic function; 3) among patients with acutely reduced EF, those who experienced a serial increase in peakE-wave KE over the first 3 months also showed an improvement in LVEF, highlighting the importance of diastolic recovery in long-term outcomes.

Changes in Systolic KE Occur Within 3 Months post-MI

The average LV systolic KE_{iEDV} in patients (10.0 ± 4.7 $\mu\text{J/mL}$) was higher than previously reported values in acute MI patients by our group (9.2 ± 3.8 $\mu\text{J/mL}$), but all 35 patients showed a decrease in systolic KE over the first 3 months between V1 and V2.⁹ Left ventricular remodeling is a key process initiated following MI, which is known to take place over weeks to months dependent on factors including size, location, and transmurally of infarct. Previously, Garg et al. demonstrated systolic KE is decreased in MI patients compared to controls; however, this was inclusive of both acute and chronic MI patients.⁹ Results show that systolic KE was highest acutely following MI (systolic $\text{LVKE}_{\text{iEDV}}$ 10.0 ± 4.7 $\mu\text{J/mL}$ systolic LVKE_{iSV} 28.0 ± 4.4 $\mu\text{J/mL}$); even higher than the controls in Garg et al ($\text{LVKE}_{\text{iEDV}}$ 9.2 ± 3.8 $\mu\text{J/mL}$),⁹ but this steadily decreased over the 3 months and remained stable over the following 9 months. Previous authors have noted that owing to the acute loss in regional contractility, LV preload and wall stress are increased acutely following MI.^{9,11} Increased wall stress is a powerful stimulant for the sympathetic adrenergic system, triggering the release of catecholamines, activation of the renin-angiotensin-aldosterone system and the production of atrial and brain natriuretic peptides.¹⁴ The cumulative effects of these adaptive responses mediate an increase in heart rate and contractility in order to preserve cardiac output¹⁵ and could explain the increased systolic and diastolic KE during the acute scan of these results compared to previously published control data.

Interestingly when indexing values for SV, results show that patients with pEF at V1 experience a serial reduction in systolic KE over time, which may reflect successful physiological adaptation of dealing with the extra pre-load; meanwhile in patients with rEF, the systolic KE remains persistently higher. This may explain why patients with larger infarcts and lower EF following STEMI are at higher risk of developing adverse remodeling.

Assessment of Diastolic Function Using 4D Flow

Systolic impairment following MI has been documented and is known to be a prognostic marker of long-term adverse outcomes.¹⁶ Given that diastolic function, that is, myocardial relaxation is now also recognized as an “active” phase of the cardiac cycle,¹⁷ it stands to reason that ischemic injury could also impair diastolic function; however, evidence of this in current literature is relatively sparse.² 4D flow MR has the ability to assess not only systolic but also diastolic LV function throughout the full cardiac cycle. Results from this study suggest that, just like systolic function, diastolic function is also immediately impaired following MI, especially in patients with reduced EF, as evidenced by the lower peak-E velocities. Due to its practicality, echocardiography remains the most feasible way for assessing both systolic and diastolic function following STEMI, and MR is reserved for patients where accurate estimation of LV volumes, scar size and transmural flow is required. These results highlight that the addition of 4D flow sequences to standard Cardiac MR protocols can help provide supplementary information of diastolic function.

Future Clinical Applications

The results from this study have demonstrated that 4D flow analysis can detect subtle changes in diastolic function following MI in both patients with rEF and pEF. As discussed above, most significant changes in LV flow occur within the first 3 months following MI; this could provide a timeframe for rehabilitation and treatment as well as follow up and progression. LV dilatation following MI contributes to possible development of heart failure. The use of 4D flow could provide investigative mechanisms to assess the impact of existing and novel pharmacological intervention on this process. Further studies are needed to establish whether changes in intracardiac flow can be altered by medical therapy.

Limitations

The small sample size of 35 participants was obtained from a single center and were scanned using a single vendor at a single field strength. Future studies should aim to increase cohort numbers from multiple centers in order to increase study results generalizability. Taking into account the exclusion criteria, results from this study cannot be applied to patients with significant valvopathy, cardiomyopathies, and congenital heart disease.

Conclusion

LV KE flow parameters can be used to assess both systolic and diastolic function post-MI. Longitudinal trends seen in this study suggests systolic KE is increased acutely following MI; in patients with pEF, this decreases over the following 3 months, while in patients with rEF, it remains raised. Patients with rEF also have reduced LV in-flow in early-diastole, signifying impaired LV relaxation, which also worsens

over time. Given the prognostic relevance of impaired diastolic recovery, we demonstrate how 4D flow can provide additive value in monitoring heart failure therapy following MI.

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