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Validation of time-resolved, automated peak trans-mitral velocity tracking: Two center four-dimensional flow cardiovascular magnetic resonance study

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ABSTRACT

Objective: We aim to validate four-dimensional flow cardiovascular magnetic resonance (4D flow CMR) peak velocity tracking methods for measuring the peak velocity of mitral inflow against Doppler echocardiography.
Method: Fifty patients were recruited who had 4D flow CMR and Doppler Echocardiography. After transvalvular flow segmentation using established valve tracking methods, peak velocity was automatically derived using three-dimensional streamlines of transvalvular flow. In addition, a static-planar method was used at the tip of mitral valve to mimic Doppler technique.
Results: Peak *E*-wave mitral inflow velocity was comparable between TTE and the novel 4D flow automated dynamic method (0.9 ± 0.5 vs 0.94 ± 0.6 m/s; $p = 0.29$) however there was a statistically significant difference when compared with the static planar method (0.85 ± 0.5 m/s; $p = 0.01$). Median A-wave peak velocity was also comparable across TTE and the automated dynamic streamline (0.77 ± 0.4 vs 0.76 ± 0.4 m/s; $p = 0.77$). A significant difference was seen with the static planar method (0.68 ± 0.5 m/s; $p = 0.04$). E/A ratio was comparable between TTE and both the automated dynamic and static planar method (1.1 ± 0.7 vs 1.15 ± 0.5 m/s; $p = 0.74$ and 1.15 ± 0.5 m/s; $p = 0.5$ respectively). Both novel 4D flow methods showed good correlation with TTE for *E*-wave (dynamic method; $r = 0.70$; $P < 0.001$ and static-planar method; $r = 0.67$; $P < 0.001$) and A-wave velocity measurements (dynamic method; $r = 0.83$; $P < 0.001$ and static method; $r = 0.71$; $P < 0.001$). The automated dynamic method demonstrated excellent intra/inter-observer reproducibility for all parameters.
Conclusion: Automated dynamic peak velocity tracing method using 4D flow CMR is comparable to Doppler echocardiography for mitral inflow assessment and has excellent reproducibility for clinical use.

Abbreviations: 3D, Three-dimensional; 4D, Four-dimensional; MR, Magnetic Resonance; CMR, Cardiac Magnetic Resonance; TTE, Transthoracic Echocardiography; LA, Left Atrium; LV, Left Ventricle; LVOT, Left Ventricular Outflow Tract; MV, Mitral Valve; CoV, Coefficient of Variation; 4DFD, 4D flow dynamic method; 4DFS, 4D flow static planar method.

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1. Background

Mitral inflow peak velocity measurements are an integral part of standard transthoracic echocardiography (TTE) and are used as a surrogate for left ventricular (LV) filling pressures [1]. Mitral *E*-wave velocity, A-wave velocity and E/A ratio are the most widely used haemodynamic parameters, indicative of the passive and active filling of blood through the mitral valve into the left ventricle [1,2]. Mitral inflow peak *E*-wave velocity results from the left atrial (LA)-LV pressure gradient during early diastole and is affected by alterations in the rate of LV relaxation and LA pressure. Peak A-wave velocity results from the LA contraction and associated LA-LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function. The use of peak mitral inflow velocities for LV filling pressure assessment is still clinically recommended by guidelines in mainly patients with reduced ejection fraction [3].

Four-dimensional (4D) flow time-resolved phase-contrast cardiac magnetic resonance (CMR) with retrospective valve-tracking can provide a more comprehensive and multidirectional assessment of peak blood flow velocities across cardiac valves [4–9]. Previous studies have identified good agreement between 4D flow CMR and the reference method for peak flow velocity assessment, namely pulse-wave doppler TTE [5–7]. Four-dimensional flow CMR can overcome many of the limitations of Doppler TTE and may improve the accuracy of transvalvular peak velocity quantification [2,10–13]. Despite the promising capabilities of 4D flow CMR technology, its use in clinical practice has been hampered by lengthy post-processing times and the lack of validated software tools to accurately quantify flow velocities. Software solutions using automated pipelines to extract peak velocity information in three-dimensional space from the transvalvular valvular flow streamlines (dynamic automated method) and using a static plane (static planar method) at the level of mitral valve leaflet tips, mimicking the methods applied using Pulse wave Doppler are currently under development. The motivation for this work is that it would reduce operator dependence in peak velocity assessment through the mitral valve. This may enhance the reproducibility, which is clinically important.

Therefore, the primary objective of this study is to develop and validate an automated pipeline to derive time-resolved peak mitral inflow velocity using 3D streamlines generated through the mitral valve annular plane against Doppler TTE. We also aim to investigate its reproducibility.

2. Methods

2.1. Study cohort

For this study, we retrospectively recruited 50 patients were from the multicentre EurValve project (http://www.eurvalve.eu/) at Sheffield, UK ($n = 32$) and from Norfolk and Norwich University Hospital, Norwich ($n = 18$). The inclusion criteria for this study at both sites were that all patients underwent 4D flow CMR and standard Doppler echocardiography. The exclusion criteria were limited to any MRI contraindications. Only patients who were stable as out-patients were recruited.

2.2. Ethics

The prospective EurValve programme was approved by the National Research Ethics Service (17/LO/0283) in the UK. Written informed consent was obtained from patients. At Norwich, the study was approved as an audit and observational retrospective study (2020/21–075). Consent was waived. The study complied with the Declaration of Helsinki.

2.3. Echocardiography

All echocardiograms were performed according to the British Society of Echocardiography guidelines for TTE examination [14]. Pulsed-wave doppler TTE was used to measure peak *E*-wave (early-filling) and peak A-wave (late-filling during atrial contraction) flow velocities and the E/A ratio later derived from these two variables. Measurements were taken at the level of the tips of the mitral valve leaflets.

2.4. Cardiovascular magnetic resonance

At Sheffield, CMR was performed on a 3 Tesla Philips Healthcare Ingenia system equipped with a 28-channel coil and Philips dStream digital broadband MR architecture technology. At Norwich, CMR was done on a 3 Tesla Discovery 750w GE system (GE Healthcare, Milwaukee, WI, USA) equipped with an 8-channel cardiac coil.

2.5. CMR protocol

The CMR protocol included a baseline survey and cines. Cine images were acquired during end-expiratory breath-hold with a balanced steady-state free precession (bSSFP), single-slice breath-hold sequence. Long axis cine SSFP in two-chamber, three-chamber and four-chamber views were also acquired. The number of LV short-axis slices varied according to the size of each patient's heart.

2.6. Four-dimensional flow CMR acquisition

For the 4D flow CMR acquisition, the initial VENC setting was 150–200 cm/s for all cases. Generic MRI parameters were similar on both Philips and GE systems. Field-of-view was planned to cover the whole heart, aortic valve and ascending aorta. On the Philips system, an echo-planar imaging (EPI) acceleration factor of 5 with no respiratory gating was used. On the GE system, HYPERKAT acceleration with a factor of 6 was used. Other standard scan parameters were: field-of-view = 340 mm × 340 mm, acquired voxel size = 3 × 3 × 3 mm^3, reconstructed voxel size = 1.5 × 1.5 × 1.5 mm^3, echo time (TE) = 3.5 ms, repetition time (TR) = 10 ms, flip angle = 10°, and 30 cardiac phases.

Data pre-processing was done using CAAS software (Pie Medical Imaging) to correct for phase offset errors resulting from eddy currents, and encoding errors related to gradient field distortions to minimise inaccuracies in flow quantification.

2.7. 4D flow cardiac magnetic resonance analysis

Transvalvular 4D flow analysis through the mitral valve and peak velocity quantification was performed on CAAS MR (Prototype version 5.2; Pie Medical Imaging, Maastricht, Netherlands). Assessment of the peak velocity of mitral inflow was performed as per the analysis protocol described in Fig. 1. Mitral inflow velocities were recorded using 4D flow CMR by two novel methods on CAAS, namely the automated dynamic and static planar pipelines.

2.8. Automated dynamic method and static planar method

Automated retrospective valve-tracking on long-axis four-chamber orthogonal cine views was carried out using CAAS MR software during image post-processing. This was performed using recently published and well-established methods [15–17] (Figs. 1 and 2). After manual correction of any misalignment between the 4D flow CMR data and the cine images, automated tracking of mitral inflow allowed for careful isolation of transvalvular forward flow through only the mitral valve and into the left ventricle during diastole. To avoid the detection of blood flow not passing through the mitral valve, such as left ventricular outflow tract (LVOT) velocities or aortic regurgitant velocities, we carefully analysed the mitral flow velocity map throughout the cardiac cycle to ensure only mitral forward flow was included (Fig. 2 - Image B). This was done by manually contouring the high-signal phase-contrast in the region of interest representing mitral inflow and ensuring the

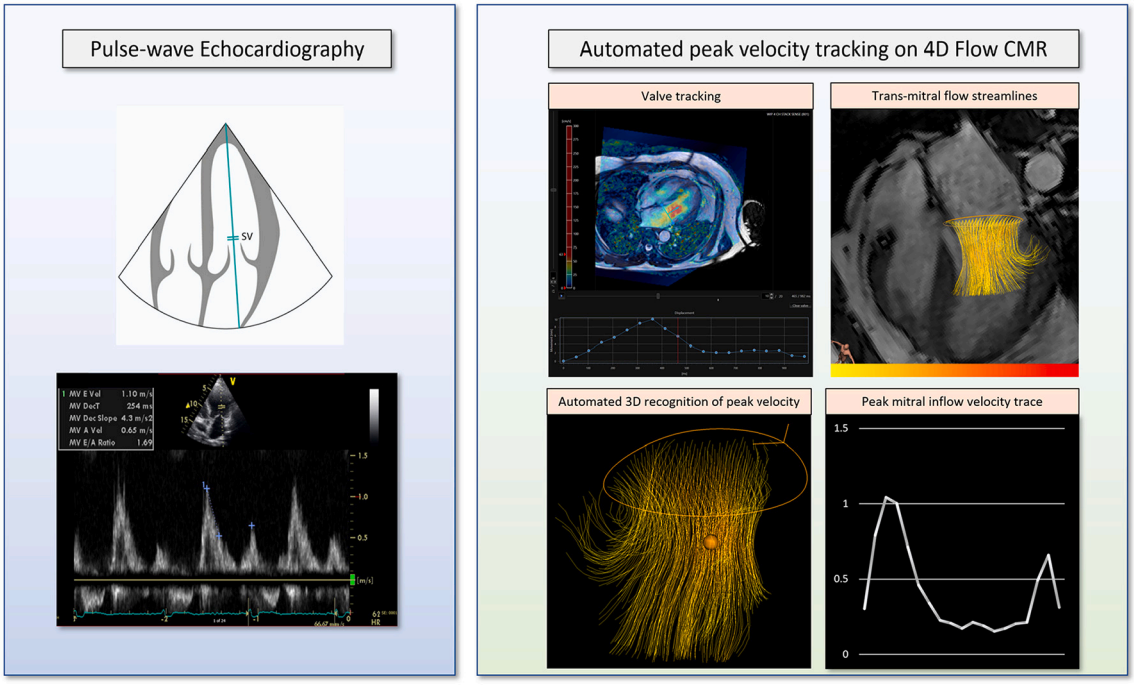

Fig. 1. Peak velocity measurements with Pulse-wave Transthoracic Echocardiography (Left) and 4D flow CMR using automated peak velocity tracking (Right). Left Image: Doppler echocardiography used to interpret *E*-wave and A-wave velocities readings.
Right Image: Illustration of the semi-automated valve tracking process performed using well-established techniques (top-left). *Trans*-mitral 3D streamlines are generated by the software solution demonstrating mitral inflow (top-right). Automated three-dimensional recognition of transvalvular peak velocity demonstrated by the 'yellow sphere' embedded within streamlines (bottom-left). Peak mitral inflow velocity trace is generated to extrapolate *E*-wave and A-wave velocity readings (bottom-right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

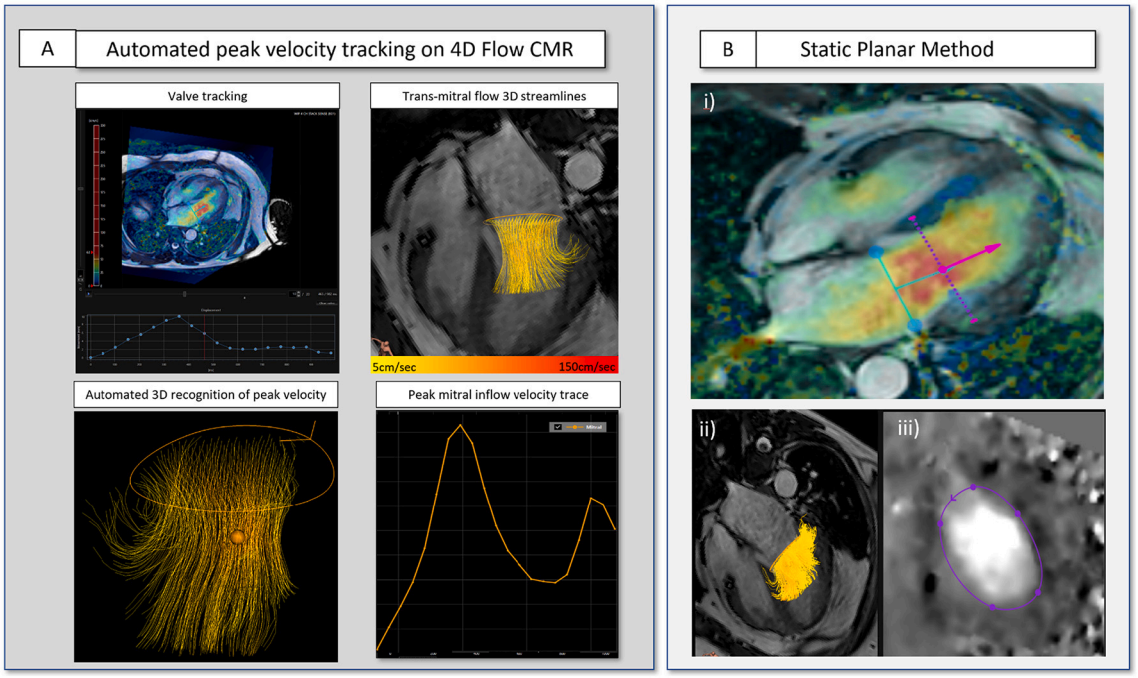

Fig. 2. Mitral inflow peak velocity tracking on CAAS MR using two novel methods: A) Automated dynamic method and B) static-plane method. Image A (Top-left) Semi-automated mitral valve-tracking schematics - the two attachments of the mitral valve leaflets are manually selected at a single point in the cardiac cycle. The software performs automated tracking of the valve in motion throughout the cardiac cycle. 3D streamlines produced showing mitral inflow. Automated peak velocity tracking is indicated by a yellow sphere within the streamlines. 4-chamber orthogonal long-axis cine view showing mitral inflow as 3D streamlines on 4D flow CMR during diastole (Top-right) (Bottom-left). Peak velocity tracings demonstrating E-wave and A-wave velocity peaks (Bottom-right). Image B (Top image) Static method using the alternative plane to illustrate colour-coded 4D flow CMR. Mitral inflow velocity detection (purple arrow). (Bottom-left) Mitral forward flow shown as 3D streamlines on 4D flow CMR. (Bottom-right) 4D flow CMR velocity mapping of mitral flow showing the contour (purple ring) which is manually adjusted to outline the region of mitral inflow depicted as the hyperdense opacity.

exclusion of blood flow that was not indicative of mitral inflow. Next, the software produced 3D streamlines within the contoured area to allow 3D visualization of mitral inflow (Fig. 1) (Fig. 2). The software then identifies the peak velocity with the streamlines for the complete cardiac cycle (Fig. 2). Adjustment of spacing between the streamlines can be performed to allow better identification of the automated peak velocity area at the tip of the mitral valve leaflets. It is widely accepted that the peak velocity across the mitral valve is situated at the tips of the mitral valve leaflets. In some cases, during post-processing, the software's automated 3D recognition capabilities detected the area of peak velocity to be more distal to the mitral valve leaflets and nearer the apex of the ventricle. When this occurred during data collection, the terminal length setting of streamlines was adjusted to ensure the peak velocity readings were taken from the correct anatomical site where, physiologically, the highest mitral inflow velocity would be expected to occur. Alterations to streamline settings were kept to a minimum and were performed in only seven of the cases during post-processing. Once the operators (P·N. and C.G.C.) were satisfied with the automated 3D velocity tracking of the area of peak velocity, peak *E*-wave and A-wave velocities were recorded (Fig. 1) (Fig. 2 - Image A). The 4D flow CMR post-processing times took, on average, 6–8 min per case.

For the second technique, namely the static planar method, we defined a static reformatted phase-contrast plane at the level of the tip of the mitral valve leaflets. (Fig. 2). Using the velocity mapping image (Fig. 2) mitral inflow was contoured manually at each phase of the cardiac cycle to ensure only inflow velocities were recorded. Peak velocity readings in the static method were taken by recording the maximum velocity in the reformatted plane.

2.9. Reproducibility testing

For intra-observer tests, P·N. (an academic research doctor with 6-months training in advanced CMR) repeated the analysis in 30 cases after 3 months. For inter-observer tests, both of the above post-processing protocols were repeated by a second investigator C.G.C. (a cardiology academic clinical fellow with 3-years' experience in advanced CMR) in a subgroup of 30 randomly selected cases from both centres.

2.10. Statistical analysis

Data analyses were performed using SPSS statistics (version 20.0, IBM, Chicago, Illinois, USA) by P·N. and P.G. Normal distribution was tested using Shapiro-Wilk test. Parametric continuous variables were expressed as mean ± standard deviation (SD), and, non-parametric as median ± inter quartile range (IQR). Categorical baseline variables were stratified into two groups; patients with left ventricular ejection fractions of above and below 50%. Categorical variables were compared using the Chi-squared test. Independent variables were compared using Annova or Mann-Whitney test. Wilcoxon test was performed to compare mitral inflow parameters measured by TTE and the 4D flow CMR methods. Correlations between the two imaging modalities were evaluated using Pearson's correlation coefficient and reported with 95% confidence intervals. Bland-Altman plots were constructed to evaluate agreement between TTE and the two 4D flow CMR methods. Reproducibility analyses were performed for intra-observer and inter-observer data and were reported by the coefficient of variation using the logarithmic method. A *p*-value of <0.05 was deemed to be statistically significant.

3. Results

Demographic data for the 50 subjects are displayed in Table 1. The age of our sample cohort ranged from 30 to 88 years of age. The median age (with inter quartile range) of the cohort was 69 ± 16 years-old in patients with a preserved ejection fraction and 71 ± 19 years-old in patients with a reduced ejection fraction. A total of 46% (23 of 50) of the sample population were male, and 84% (42 of 50) of the patients were in sinus rhythm at the time of CMR and TTE image acquisition. The mean time difference between CMR and TTE was 1.7 months. The 4D flow acquisition took 8 ± 4mins. For automated dynamic 4D flow analysis it took us 4 ± 3 min and for the 4D flow static planar method it took us 4 ± 2 min.

Table 1
Demographic variables expressed as mean ± SD (non-parametric data as median ± IQR) or n (%).

N = 50	LVEF ≥ 50% (*N* = 33)	LVEF < 50% (*N* = 17)	*P*-value
Age (years) ± IQR	69 ± 16	71 ± 19	0.65*
BSA (m^2) ± SD	1.75 ± 0.19	1.92 ± 0.15	**0.005**#
Male, n (%)	11 (33.3)	12 (70.6)	**0.012***
Sinus rhythm, Yes - n (%)	30 (90.9)	12 (70.6)	0.063*
Diabetes Mellitus, n (%)	5 (15.2)	5 (29.4)	0.232μ
Hypertension, n (%)	14 (42.4)	4 (23.5)	0.187μ
Previous Myocardial infarction, n (%)	2 (6.1)	0 (0)	0.3μ
Smoker, n (%)	10 (30.3)	10 (58.8)	0.051μ
NYHA I, n (%)	19 (57.6)	12 (70.6)	**0.046**μ
NYHA II, n (%)	13 (39.4)	2 (11.8)	
NYHA III, n (%)	1 (3.0)	3 (17.6)	
Beta-blockers, n (%)	12 (36.4)	2 (11.8)	0.066μ
Loop diuretics, n (%)	3 (9.1)	2 (11.8)	0.765μ
Other diuretics, n (%)	4 (12.1)	3 (17.6)	0.594μ
Calcium-channel antagonists, n (%)	2 (6.1)	1 (5.9)	0.98μ
Angiotensin-receptor antagonists, n (%)	3 (9.1)	1 (5.9)	0.692μ
Angiotensin-converting enzyme inhibitors, n (%)	6 (18.2)	4 (23.5)	0.654μ

* Mann-Whitney test.
\# Annova (one way analysis of variance).
μ Chi-squared test.

The study findings are summarised in Table 2. No significant difference was found between Doppler TTE and 4D Flow CMR measurements of median *E*-wave velocity using the novel dynamic automated

Table 2
Baseline variables comparing patients with reduced ejection fraction and preserved ejection fraction.

CMR Baseline Data	LVEF ≥ 50%		LVEF < 50%		*P*-values
	Mean/ median	SD/ IQR	Mean/ median	SD/ IQR	
LVEDV (ml)	140	43	178	34	0.003
LVESV (ml)	52	25	107	21	<0.001
LVSV (ml)	87	21	71	20	0.012
LV mass (g)*	108	51	111	81	0.91
TTE Mitral *E*-Wave Velocity (m/s) *	0.84	0.36	1.10	0.41	0.08
TTE Mitral A-Wave Velocity (m/s) *	0.75	0.46	0.84	0.31	0.83
TTE Mitral E/A Ratio*	1.00	0.60	1.25	0.85	0.08
4DF Dynamic Mitral E-wave Velocity (m/s) *	0.86	0.57	1.08	0.62	0.99
4DF Dynamic Mitral A-wave Velocity (m/s) *	0.76	0.39	0.78	0.56	0.96
4DF Dynamic Mitral E/A Ratio*	1.15	0.50	1.20	0.50	0.57
4DF Static Planar Mitral E-Wave Velocity (m/s) *	0.83	0.57	0.95	0.44	0.95
4DF Static Planar Mitral A-wave Velocity (m/s) *	0.64	0.40	0.77	0.52	0.58
4DF Static Mitral E/A Ratio *	1.20	0.50	1.05	0.70	0.55

* Mann-Whitney test (presented as Median ± IQR).

streamline (0.9 ± 0.5 m/s vs 0.94 ± 0.6 m/s respectively; $p = 0.29$). However, a significant difference between median E-wave velocities was observed with TTE compared to the static planar method (0.85 ± 0.5 m/s; $p = 0.01$).

Similarly, no significant difference was found between median A-wave velocity readings in TTE and the dynamic automated CMR method (0.77 ± 0.4 m/s vs 0.76 ± 0.4 m/s respectively; $p = 0.77$). However, the static planar method showed a significant difference to median A-wave velocity measured by TTE (0.68 ± 0.5 m/s; $p = 0.04$).

Median E/A ratio was consistent across TTE and both the automated

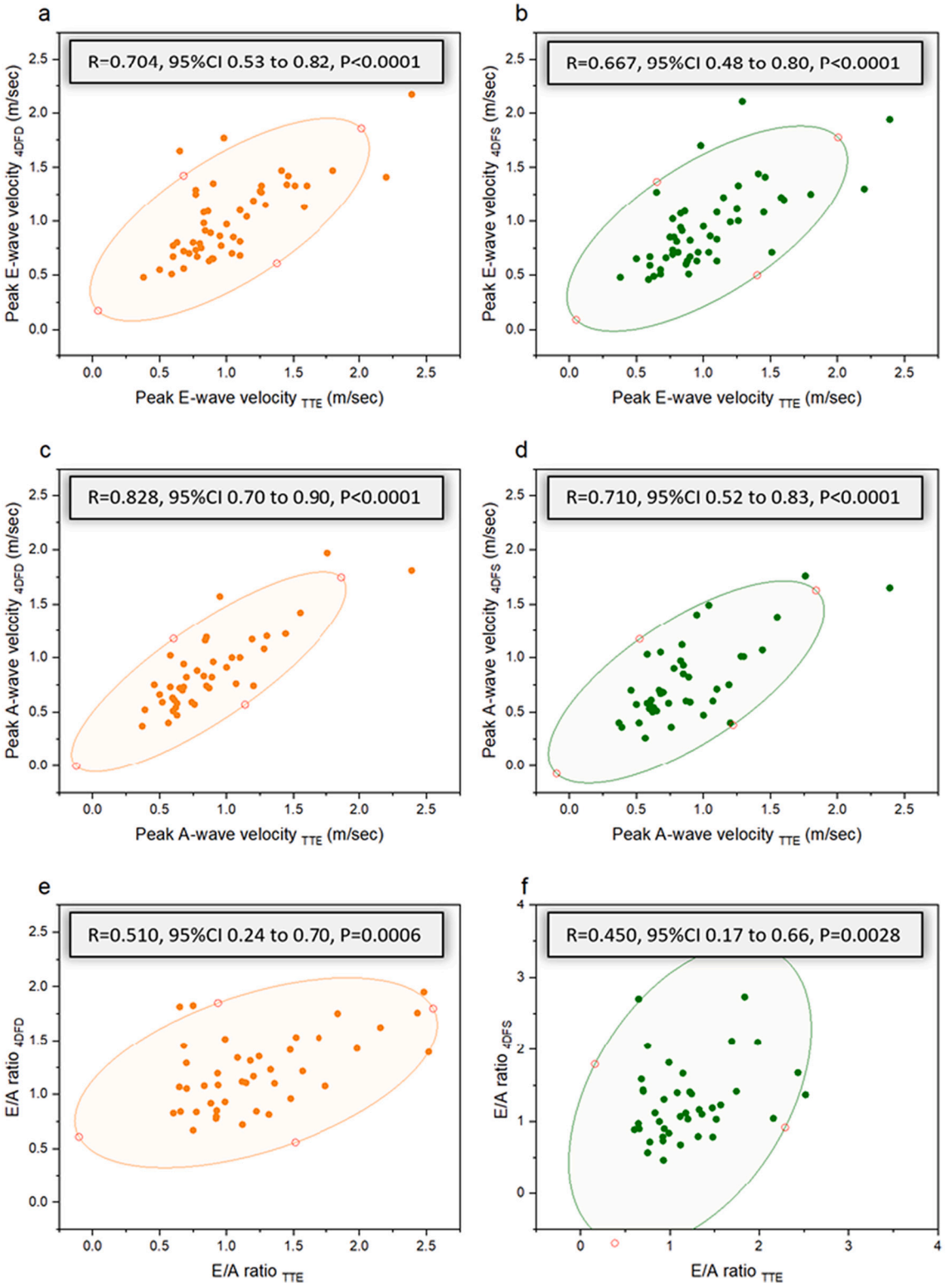

Fig. 3. Scatter plots demonstrating correlations between Transthoracic echocardiography peak mitral inflow velocity readings and 4D flow Cardiac Magnetic Resonance peak velocity measurements. Ellipses: 95% confidence interval of scatter plots.
4DFD – 4D flow dynamic, 4DFS – 4D flow static planar.

dynamic 4D flow CMR method (1.1 ± 0.7 vs 1.15 ± 0.5 respectively; $p = 0.74$) and the static planar method (1.15 ± 0.5; $p = 0.5$). Fig. 4 illustrates the comparison in mitral inflow velocities between Doppler TTE and the two 4D flow CMR methods.

3.1. Correlation

Mitral inflow peak velocity quantification by 4D flow CMR strongly correlated with Doppler TTE, when using the automated dynamic method for *E*-wave ($r = 0.70$; $p < 0.001$) and A-wave ($r = 0.83$; $p < 0.001$) velocity measurements (Fig. 3) (Table 3). We also observed a significant correlation using the static planar method for measuring E-wave ($r = 0.67$; $p < 0.001$) and A-wave velocity ($r = 0.71$; $p < 0.001$). Modest correlations in E/A ratio measurements were observed between TTE and both the automated dynamic method ($r = 0.51$; $p < 0.001$) and the static planar method ($r = 0.45$; $p = 0.003$) on 4D flow CMR.

3.2. Bland Altman analysis

The Bland-Altman plots in Fig. 4 illustrate the agreement between Doppler TTE and both the automated dynamic and static planar 4D flow CMR methods in all three measured parameters of peak velocity mitral inflow. Mean bias in E-wave velocity between TTE and the dynamic 4D flow CMR method was 0.01 m/s; 95% limits of agreement −0.57 - 0.60 m/s ($p = 0.77$) whilst for the static planar 4D flow method there was a significant mean bias of 0.09 m/s; 95% limits of agreement −0.53 - 0.72 m/s ($p = 0.04$).

Mean bias in A-wave velocity between TTE and dynamic 4D flow CMR method was 0.00 m/s; 95% limits of agreement −0.44 - 0.44 m/s ($p = 0.99$) whilst for the static planar 4D flow method there was a statistically significant mean bias of 0.10 m/s; 95% limits of agreement −0.47 - 0.66 m/s ($p = 0.04$).

Mean bias in E/A ratio between TTE and dynamic 4D flow CMR method was 0.02 m/s; 95% limits of agreement −0.87 - 0.91 m/s ($p = 0.76$) whilst for the static planar 4D flow method mean bias was −0.13 m/s; 95% limits of agreement −1.58–1.31 m/s ($p = 0.25$).

3.3. Reproducibility analysis

Table 4 displays the results of the repeatability analyses of the automated dynamic and static planar 4D flow CMR methods.

3.4. Intraobserver repeatability analyses

Intraobserver and interobserver repeatability analyses were performed on a subgroup of 30 randomly selected cases. The intraobserver coefficient of variation for *E*-wave and A-wave velocity measurements using the dynamic automated method was 2.8% and 2.3% respectively. Intraobserver coefficient of variation for E/A ratio was 4.5%.

The intraobserver coefficient of variation for *E*-wave and A-wave velocity measurements using the static planar method was 6.7% and 7.4% respectively. The intraobserver coefficient of variation for E/A ratio was 4.7% indicating excellent intraobserver reliability for all mitral inflow parameters in both 4D flow methods.

3.5. Interobserver repeatability analyses

The interobserver coefficient of variation for *E*-wave and A-wave velocity using the dynamic automated method was 2.3% and 7.2% respectively. Interobserver coefficient of variation for E/A ratio was 7.2% indicating excellent interobserver reliability for all mitral inflow parameters in both 4D flow methods.

The interobserver coefficient of variation for E-wave and A-wave velocity using the static planar method was 14.0% and 16.0% respectively. The interobserver coefficient of variation for E/A ratio was 15.7%.

3.6. Inter-site comparison

The mean of the differences between TTE derived mitral inflow peak velocities and dynamic 4D flow derived mitral inflow peak velocities were comparable between Sheffield and Norwich (E-wave: 0.22 ± 0.24 m/s versus 0.17 ± 0.18 m/s, $p = 0.5$; A-wave: 0.22 ± 0.24 m/s versus 0.17 ± 0.18 m/s, $p = 0.5$). Similarly, was the case of comparison with static planar method between Sheffield and Norwich (E-wave: 0.26 ± 0.23 m/s versus 0.22 ± 0.21 m/s, $p = 0.6$; A-wave: 0.22 ± 0.21 m/s versus 0.14 ± 0.19 m/s, $p = 0.2$).

4. Discussion

In this study, we evaluated the agreement between Doppler TTE and two novel 4D flow CMR methods for the quantification of peak mitral inflow velocities. The main findings of this two-centre validation study are that mitral inflow velocity assessment by the dynamic automated streamline 4D flow CMR method is comparable to standard Doppler pulse-wave TTE. In addition, both 4D flow CMR methods for peak mitral inflow assessment demonstrated excellent intraobserver and interobserver reproducibility. To the best of our knowledge, this is the first study of its kind to demonstrate two 4D flow CMR methods with such a high degree of reproducibility.

Diastolic heart failure is the impairment of ventricular relaxation and stiffening, affecting its ability to fill adequately. Its mechanism and management are less understood compared to its systolic counterpart; however, it is associated with significant morbidity and mortality, with the E/A ratio having been shown to be a reliable predictor of adverse outcomes in such patients [18]. Accurate quantification of transmitral peak velocities is essential in the assessment of LV filling pressures and diastolic function in patients with heart failure and can offer significant

Table 3
Table of findings comparing and correlating mean mitral inflow velocity measurements by transthoracic echocardiography (TTE) and 4D flow CMR adopting the automated dynamic and static planar methods. (**Median ± IQR**) *Wilcoxon test.

	Transthoracic Echocardiography	4D flow dynamic	4D flow static planar	P-values (TTE vs Dynamic)	P-values (TTE vs Static planar)
Mitral Valve E-wave Velocity (m/s)	0.9 ± 0.5	0.94 ± 0.6	0.85 ± 0.5	0.29*	**0.01***
Mitral Valve A-wave Velocity (m/s)	0.77 ± 0.4	0.76 ± 0.4	0.68 ± 0.5	0.77*	**0.04***
Mitral Valve E/A Ratio	1.1 ± 0.7	1.15 ± 0.5	1.15 ± 0.5	0.74*	0.5*
TTE versus 4D flow dynamic	Correlation	P-values	TTE versus 4D flow Static planar	Correlation	P-values
MV E-wave peak velocity (m/s)	R = 0.70	p < 0.001	MV E-wave peak velocity	R = 0.67	p < 0.001
MV A-wave peak velocity (m/s)	R = 0.83	p < 0.001	MV A-wave peak velocity	R = 0.71	p < 0.001
MV E/A ratio	R = 0.51	P < 0.001	MV E/A ratio	R = 0.45	p = 0.003

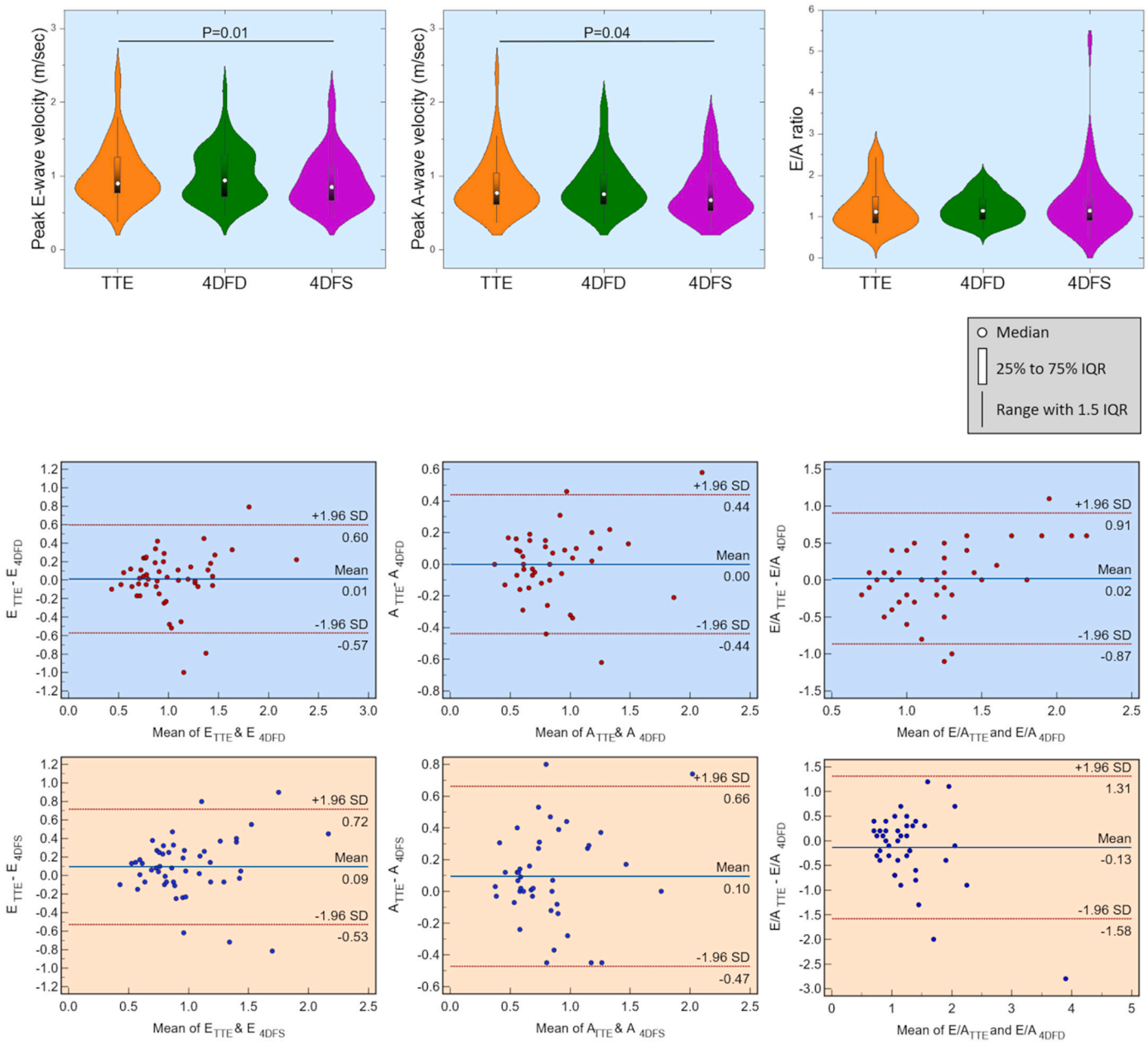

Fig. 4. (a) Violin plots illustrating the comparison of mitral inflow velocities between Doppler TTE, Automated dynamic CMR method and Static planar CMR method. (b) and (c) Bland-Altman plots demonstrating the degree of agreement between TTE and the two novel methods employed using 4D flow CMR to measure the mitral inflow velocity parameters; *E*-wave, A-wave and E/A ratio.
4DFD – 4D flow dynamic, 4DFS – 4D flow static planar.

prognostic value. Echocardiography is non-invasive, safe and widely accessible and remains a valuable tool in routine cardiac examinations for transmitral flow velocity assessment. A number of studies have validated the accuracy of transthoracic echocardiography in the measurement of LV filling pressures and diastolic function, in comparison to invasive left heart catheterisation [2] and advocate its routine clinical use. Whilst echocardiography is a familiar and widely available modality, the accuracy and precision of its use is largely operator-dependent, with its reliability suffering from limited acoustic windows, inappropriate probe location, angulation, and respiratory motion artefact. A recent meta-analysis of 27 studies comparing invasive LV filling pressures to echocardiography suggests TTE metrics are only moderately associated with invasive measurement [2]. CMR imaging is typically used in practice in the setting of heart failure, to investigate myocardial viability in cases of infarction or myocardial structure such as with myocardial fibrosis or infiltration [19–22]. It is also used in cases where echocardiography is unable to provide sufficient information such as in patients with poor acoustic windows. CMR could be an adjunct imaging modality to assess LV diastolic function in cases where echocardiography is not suited or unable to provide sufficient information.

The 4D flow CMR method circumvents many of the limitations associated with echocardiography, having the ability to provide detailed imaging due to its high spatial and temporal resolution. The recent developments in 4D flow CMR and the emerging role of CMR have galvanised research interest in this imaging modality as a promising alternative to echocardiography in diastolic function evaluation. 4D flow CMR offers a time-resolved component and is not restricted to the assessment of the static two-dimensional acquired phase-contrast plane. However, a validated software module that accurately measures

Table 4
Table demonstrating repeatability analyses for 4D flow CMR streamlines with coefficients of variation [95% confidence intervals].

	Intraobserver CoV* (%)	Interobserver CoV* (%)
4D flow Automated Dynamic – Mitral E-wave velocity	2.8%	2.3%
4D flow Automated Dynamic – Mitral A-wave velocity	2.3%	7.2%
4D flow Automated Dynamic – E/A ratio	4.5%	7.2%
4D flow Static Planar – Mitral E-wave velocity	6.7%	14.0%
4D flow Static Planar – Mitral A-wave velocity	7.4%	16.0%
4D flow Static Planar – E/A ratio	4.7%	15.7%

* Coefficient of Variation.

transvalvular haemodynamics is yet to be developed and validated for routine use. A number of studies have investigated the accuracy and reproducibility of mitral forward flow velocity measurements using 4D flow CMR processes against TTE [23–25]; however, these studies have only demonstrated a moderate agreement between phase-contrast CMR and Doppler echocardiography. The differences between the findings of the previous studies and this study could be explained by the significantly lower mean age in their study's sample group [23] and as such, any differences in velocity measurements and systematic bias may be influenced by age-related structural and functional haemodynamic changes [11]. Previous literature on 4D flow CMR have evaluated processes that have proven time-consuming and user-dependent, due to the need for manual detection of the mitral valve leaflets at each phase of the cardiac cycle. This is reflected in the significant interobserver variability seen in a previous study [26]. This study offers a single method with an automated component, which could offset some of these limitations.

Our study demonstrated strong correlations and excellent agreement between the automated dynamic streamline and echocardiography with no significant difference observed between median peak *E*-wave velocity and A-wave velocity measurements. This was consistent with the good correlation and agreement reported in a previous study by Rathi et al. [27] using phase-contrast CMR imaging. The E/A ratio was consistent across TTE and the automated dynamic method. In addition, our study was able to demonstrate a lower degree of bias in E/A ratio measurements between both the automated dynamic and static planar CMR methods and TTE (bias = 0.02 and − 0.13 respectively) than in the previously mentioned study (bias = −0.29). The alternative static planar method tended to systematically underestimate median E-wave and A-wave velocity readings, which is consistent with the findings in the aforementioned study [27]. The static planar method tended to overestimate the E/A ratio compared to TTE, however, this was not statistically significant. The wider limits of agreement seen using the static planar method suggests inferior accuracy to the automated dynamic streamline. Despite this, the degrees of bias observed in both 4D flow CMR methods were small. It is therefore unlikely to be clinically relevant in the grading of diastolic dysfunction severity in clinical practice. Median A-wave velocity using the automated dynamic method showed the strongest correlation with echocardiography, whilst the E/A ratio measured using the static planar method showed the weakest correlation. Overall, the correlation between echocardiography and 4D flow CMR was strongest with the automated dynamic streamline as opposed to the static planar method. We speculate that the automated dynamic method showed greater accuracy and agreement than the alternative static planar method, due to its capabilities to automatically track the mitral valve throughout each phase of the cardiac cycle, allowing for minimal manual intervention and subjectivity. This is further supported by the excellent and superior interobserver and intraobserver reproducibility observed in the automated dynamic streamline compared to the static planar method. The automated dynamic method is capable of systematically producing accurate velocity readings when compared to the reference Doppler TTE. The semi-automated valve-tracking, peak velocity and mitral inflow streamline detection capabilities of the automated method likely explains the superior accuracy and reproducibility in the measurement of *E*-wave and A-wave velocities. These data reinforce the findings in recent validation studies of 4D flow CMR that indicate it is a reliable tool for clinicians in LV diastolic assessment [17,23,28]. It would be of interest to replicate this study in a larger sample population to validate these findings.

4.1. Clinical translation and future direction

Mitral inflow velocity assessment by echocardiography has not translated as a biomarker of LV filling pressure in clinical trials because of operator dependence in acquiring these measurements. The enhanced reproducibility of our novel dynamic 4D flow CMR method, coupled with the shorter post-processing time needed, makes it a viable clinical tool for the assessment of mitral inflow velocities in clinical trials using LV diastolic function as a target for therapy. It is worth noting that the shorter post-processing times of the automated dynamic method would also benefit clinical use, especially in cases where repeated assessments are desired. Finally, current standard CMR multi-parametric protocols do not include LV diastolic assessment as an integral part of routine assessment. This study paves the way for integrating advanced CMR methods for routine assessment of LV diastolic function, which further makes CMR a one-stop test for not only sub-phenotyping the etiology of heart failure, but also assessing LV filling pressure.

4.2. Limitations

We acknowledge this study presents some limitations. Echocardiography and CMR were not performed at the same time with an average time difference of 1.7 months between TTE and CMR. This may introduce haemodynamic variation and could explain the wider limits of agreement reported in our Bland-Altman analysis. However, this time difference was consistent across all included cases. Manual selection of the mitral valve leaflets for valve-tracking and the manual adjustment of contour lines on velocity mapping can introduce user-dependent variability and is an inherent limitation of CMR. Future developments could involve automated detection of the valve leaflet insertions, which may eliminate this limitation and further improve reliability. Interstudy reproducibility analyses were not performed and could be useful in further evaluating the validity of our findings.

5. Conclusion

Automated dynamic peak velocity tracing method using 4D flow CMR is comparable to Doppler echocardiography for mitral inflow assessment and has excellent reproducibility for clinical use. Future studies are warranted to explore the diagnostic and prognostic advantages of both techniques for mitral inflow assessment in patients with diastolic dysfunction.

Conflict of interest

Dr. P. Garg is a clinical advisor for Pie Medical Imaging and Medis Medical Imaging.

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Author contributions

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