

4D Flow Component Reveals Left Ventricular Function In Atrial Fibrillation

Chengchen Zhao

Zhejiang University School of Medicine

Guanzhong Chen

Zhejiang University School of Medicine

Chunna Jin

Zhejiang University School of Medicine

Jianzhong Sun

Zhejiang University School of Medicine

Meixiang Xiang (✉ xiangmxhz@163.com)

Zhejiang University School of Medicine <https://orcid.org/0000-0003-0255-6056>

Research Article

Keywords: Cardiovascular magnetic resonance, echocardiogram, 4D flow, flow component, systolic function, diastolic function, atrial fibrillation

Posted Date: February 3rd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1307383/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose: Applying cardiovascular magnetic resonance (CMR) 4D flow to evaluate left ventricular systolic and diastolic function in atrial fibrillation (AF).

Methods: In this study, from May 2021 to October 2021, 26 AF patients and 15 healthy participants were recruited and underwent multiparametric CMR and echocardiogram scans before discharge. The CMR protocol incorporated an assessment of 4D flow, cardiac function. Notably, the AF patients maintained irregular heart rhythm during the CMR scan. The 4D flow components were compared with echocardiogram results.

Results: AF patients had a lower proportion of direct flow (33.5% (8.43; 47.5) in AF vs. 69.1% (63.4; 74.4) in healthy), higher delayed ejection ($24.1 \pm 12\%$ in AF vs. $14.7 \pm 6.8\%$ in healthy), retained inflow (32.5% (24.6; 36.9) in AF vs. 14.5% (12.5; 18.2) in healthy) and residual volume (4.73% (1.47; 15.0) in AF vs. 0.62% (0.46; 1.62) in healthy). A high correlation was observed between flow EF and CMR EF ($R=0.78$, $P<0.001$) in AF patients. The mean bias among the methods was higher for flow EF than CMR EF (24.86%). Multivariable linear regression showed that the correlation between retained inflow and E/e' ($\beta=0.152$, $P=0.048$) remained significant when adjusted for confounders. Direct flow ($\beta= -0.170$, $P=0.038$) and retained inflow ($\beta=0.350$, $P=0.024$) significantly correlated with the Minnesota Living with Heart Failure Questionnaire score.

Conclusion: CMR 4D flow component revealed a significantly different flow pattern in AF patients compared with healthy participants and provided de novo flow biomarker indicating LV systolic function (direct flow and flow EF) and diastolic function (retained inflow).

Introduction

Worldwide, atrial fibrillation (AF) is the most common arrhythmia in adults, associated with high morbidity and mortality[1]. A critical biomarker- left ventricular ejection fraction (LVEF), predicts the survival of patients with AF and the effect of catheter ablation[2, 3]. Conventionally, LVEF is derived from echocardiography in clinical practice[4]. Although echocardiographic grading scales are well established, allowing the evaluation of left ventricular diastolic function in sinus rhythm[5, 6], assessing diastolic abnormalities in AF remains clinically challenging and often disregarded due to its irregular beating pattern.

Cardiac magnetic resonance (CMR) is the gold standard for the evaluation of cardiac structural and functional abnormality[7]. An emerging strategy called 4D flow CMR enables the acquisition of complexing blood flow in three directions simultaneously within a period of time[8]. It obviates the need in conventional 2D phase-contrast CMR flow, which manually aligns single velocity-encoding direction with target flow signals. The previous study had proved that 4D flow evaluated left atrium (LA) and left atrium appendage blood flow dynamics; results correlated strongly with transesophageal echocardiography velocities ($r= 0.41$, $P <0.05$) and stasis ($r= -0.39$, $P <0.05$) in the context of AF rhythm[9]. However, few

studies reported ventricular function evaluation in AF rhythm through 4D flow. A technique named flow component showed much advanced practical meaning in normal and disease states[10, 11]. It enables visualization of three multidimensional images of flow that allow quantification of intraventricular blood flow; it may reflect changes in left ventricle (LV) configuration, myocardial function, and pressure distribution within the disease, eventually associated with LV function[12].

This study aims to evaluate the efficacy of 4D flow MRI and flow component in the context of atrial fibrillation and explore its association with left ventricular systolic and diastolic function.

Method

Participant

Patients admitted to the hospital from May 1st, 2021, to October 20th, 2021, were enrolled in this research. Patients were eligible if they were diagnosed with atrial fibrillation. CMR scan was performed when patients maintained AF rhythm. The exclusion criteria included younger than 18 years old, inability to be placed in a magnetic resonance image (MRI) scanner due to body mass, pacemaker, and severe renal abnormality (glomerular filtration rate < 30 mL/min/1.73 m²), hemodynamically unstable. Persistent AF was defined as AF heart rhythm lasting longer than seven days; Paroxysmal AF was defined as AF rhythm lasting shorter than seven days; Additionally, healthy participants were recruited as reference. All subjects provided written informed consent. The institutional review board approved the study.

Echocardiogram And Clinical Data Collection

The echocardiogram was performed on a EPIQ7 system with an X5-1 matrix transducer (Philips Medical Systems, Andover, MA). Echocardiogram parameters, including LA dimension (defined as the largest diameter of LA in parasternal long-axis view), echo EF (Simpson bi-plane mode using apical four-chamber and two-chamber view) was measured. E/e', E, Septal e, tricuspid regurgitation velocity, LA volume index was measured according to recommendations of the American Society of Echocardiography and the European Association of Echocardiography. CHA2DS2-VASc score was calculated to assess the stroke risk level. HAS-BLED score was calculated to assess the bleeding risk level. Laboratory results in AF patients were acquired before discharge, including serum creatine, alanine aminotransferase (ALT), hemoglobin (Hb), brain natriuretic peptide (BNP), N-terminal pro-B type natriuretic peptide (NT-proBNP). The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is used to evaluate the quality of life and symptom burden of patients[13, 14].

Cmr Protocol

All CMR scan were practiced on a 3.0T magnetic resonance system (uMR 790, United Imaging Healthcare, Shanghai, China). Cardiac volumes and function were assessed using balanced steady-state

free precession cine images with retrospective ECG gating during a breath-hold. The average temporal resolution was 45.6 ms. A stack of short-axis planes (8 mm thickness) and three long-axis planes (2-, 3-, and 4-chamber) were obtained using the following imaging parameter: TR (repetition time) = 2.85 ms, TE (echo time) = 1.32 ms, flip angle = 55°, and resolution = 1.82 × 1.73 mm. T1 mapping was performed with a modified Look-Locker inversion recovery sequence with a 5(3)3-scheme. Native T1 images were acquired from 3 short-axis slices (basal, mid, and apical).

4D flow acquisitions were performed according to recommendation [8]. It adopted a retrospectively ECG triggered, respiratory navigator gated, 3-dimensional, 3-directional, time-resolved phase-contrast, Spoiled gradient echo pulse sequence. Temporal resolution = 40 ms, repetition time = 20.8 ms, echo time = 2.86 ms, flip angle = 8°, voxel size = 3 × 3 × 5 mm³, velocity encoding = 150 cm/s, scanning time ranged from 8-15 minutes.

Image Analysis

Two experienced clinicians analyzed the CMR data using Cvi42 version 5.13.2 (Circle Cardiovascular Imaging Inc., Calgary, Canada). LA and LV functions were analyzed offline. Left ventricular (LV) volumes (LV end-diastolic volume (EDV), LV end-systolic volume (ESV), stroke volume (SV), and cardiac output (CO)), LV mass index, and CMR EF (derived from LV) were measured and analyzed by standard volumetric techniques through short-axis cine images. Cardiac strain analysis included global longitudinal strain (GLS, %), global radial strain (GRS, %), and global circumference strain (GCS, %). GLS was derived from two-, three-, and four-chamber views, whereas GRS and GCS parameters, were derived from the short-axis stack.

The 4D flow datasets were imported into the Cvi42 version 5.13.2 (Circle Cardiovascular Imaging Inc., Calgary, Canada) for further analysis. Images were corrected for background offset errors and velocity aliasing artifacts. For semiautomatic (valve tracking) analysis, the three-chamber view of cine images from the study was used as the reference for aortic valve and mitral valve tracking. The valve contours on each phase of the 4D Flow series were corrected manually. Isovolumetric relaxation phase was set as the interval between closing of aortic valve and opening of mitral valve. The position of pathlines at end-systole divides them into four functional flow components as described previously [15, 16]: '(1) direct flow: blood flow that enters and exits the LV in the analyzed cardiac cycle; (2) retained inflow: blood flow that enters the LV but does not exit during the analyzed cycle; (3) delayed ejection flow: blood flow that starts within the LV and exits during the analyzed cycle; and (4) residual volume: blood flow that remains in the LV for at least two cardiac cycles' (Figure 1). Each component volume was calculated as a proportion of the total end-diastolic volume. Ejection fraction derived from 4D flow, namely flow EF, was calculated as the equation displayed: flow EF = direct flow + delayed ejection.

Statistical analysis

Categorical and consecutive data were presented as number (%), mean \pm standard deviation (normal distribution), or median \pm quartile (non-normal distribution). Differences between means were tested by the unpaired t-test or Kruskal-Wallis test as appropriate. Pearson correlation was used to assess the correlation between variables. Statistical significance was defined as $P < 0.05$. Univariate and Multivariable linear regression was carried out to investigate the association of flow component with diastolic function and MLHFQ. Statistical analysis was performed using the R package.

Result

Baseline characteristics

A total of 41 subjects were recruited for our study, including 26 AF patients and 15 healthy volunteers. One patient and one healthy participant was excluded due to poor 4D flow data quality. Baseline characteristics including demographics, clinical characteristics, echocardiogram data, and CMR data were listed in Table 1 and Table 2. The mean age of the AF group was 70.0 years [57.0; 75.0], and 17 (68%) were male. The mean age of the healthy participant group was 28.5 years [26.2; 50.0], and 10 (71.4%) were male. The mean CHA₂DS₂-VaSc score of the AF group was 2.6 ± 1.5 . The echocardiogram results revealed an enlarged LA dimension (4.4 cm [3.9; 5.1]) of the AF group compared with the healthy participant group. CMR data showed that the AF group had a higher LA volume than healthy participants (97.6 ml [67.1; 132.0]) vs. 48.1 ml [41.4; 53.3]; $P < 0.001$). There were no significant differences in sex, body mass index, and heart rate between groups.

Changes in flow component

Flow visualizations in the systolic phase, the diastolic phase, and the interval between the diastolic and the systolic phase were shown in Figure 2, demonstrating a distinct flow component pattern in an AF patient compared with a healthy participant. AF patients had a lower proportion of direct flow (33.5% [8.43; 47.5] in AF vs. 69.1% [63.4; 74.4] in healthy). Evidently, a significant difference in delayed ejection ($24.1 \pm 12\%$ in AF vs. $14.7 \pm 6.8\%$ in healthy), retained inflow (32.5% [24.6; 36.9] in AF vs. 14.5% [12.5; 18.2] in healthy) and residual volume (4.7% [1.5; 15.0] in AF vs. 0.62% [0.5; 1.6] in healthy) were observed (Table 2).

Flow component and LV systolic function

According to the particle tracing, the flow component in LV was divided into four parts. Flow EF derived from the flow component was calculated. Pearson analysis revealed that direct flow positively correlated with CMR EF ($R=0.81$, $P < 0.001$), SV ($R=0.61$, $P < 0.001$), CO ($R=0.44$, $P=0.005$), and echo EF ($R=0.60$, $P < 0.001$); direct flow negatively correlated with LVEDV ($R=-0.39$, $P=0.014$), LVESV ($R=-0.68$, $P < 0.001$) and BNP ($R=-0.54$, $P=0.044$). Similarly, flow EF positively correlated with CMR EF ($R=0.86$, $P < 0.001$), SV ($R=0.66$, $P < 0.001$), CO ($R=0.46$, $P=0.003$), and echo EF ($R=0.68$, $P < 0.001$); Flow EF negatively correlated with LVEDV ($R=-0.46$, $P=0.003$), LVESV ($R=-0.78$, $P < 0.001$), BNP ($R=-0.79$, $P < 0.001$), and NT-proBNP ($R=-0.50$, $P=0.015$) (Figure 4).

Subgroup analysis was conducted in AF and healthy participants separately. Pearson analysis was performed to assess the correlation between direct flow, flow EF and CMR EF. For direct flow and CMR EF, a borderline ($R=0.52$, $P=0.058$) and significant positive correlation ($R=0.72$, $P<0.001$) were observed in healthy volunteers and AF patients respectively. For flow EF and CMR EF, high correlation was both observed in healthy volunteers ($R=0.59$, $P=0.028$) and AF patients ($R=0.79$, $P<0.001$).

Flow component and LV diastolic function

Echocardiogram results showed that retained inflow significantly correlated with left ventricular diastolic function parameters (E/e' ($R=0.51$, $P<0.001$), Septal e' ($R=-0.52$, $P<0.001$), tricuspid regurgitation velocity ($R=0.34$, $P=0.003$)) (Figure 3). Besides, the association between retained inflow and LA function (LA volume ($R=0.46$, $P=0.003$), LA EF ($R=-0.60$, $P<0.001$)), left ventricle function (LVEF ($R=-0.75$, $P<0.001$), LVEDV ($R=-0.42$, $P=0.007$), LVESV ($R=0.63$, $P<0.001$)) was observed; the association between retained inflow and age reached a borderline P-value ($R=0.31$, $P=0.053$) (Figure 3). Multivariable linear regression showed that correlation between retained inflow and E/e' ($\beta=0.151\pm 0.007$, $P=0.0476$) remained significant when adjusted for age, HR, LA volume index, and gender in AF patients (Table 3).

Flow component and symptom burden

The symptom burden and quality of life was evaluated with MLHFQ. The mean (SD) MLHFQ score of AF patients was 12.6 ± 8.9 (Table 1). Univariate linear regression analysis showed that direct flow and retained inflow were significantly correlated with MLHFQ ($\beta=-0.143$, $P=0.045$ and $\beta=0.319$, $P=0.025$, respectively). Besides, direct flow and retained inflow remained significantly correlated with MLHFQ when adjusted for age and gender. ($\beta=-0.170$, $P=0.038$ and $\beta=0.350$, $P=0.024$, respectively)

Discussion

The results of our study demonstrated several important findings regarding the diagnostic value of 4D flow component measurements in patients with AF. First, we found significantly reduced direct flow and added delayed ejection, retained inflow, and residual volume in AF patients compared with healthy participants. These results suggested that patients with AF had specific flow patterns, which were important indicators of ventricle function, both diastolic and systolic. Second, two new biomarkers, namely flow EF and direct flow derived from 4D flow correlated with CMR EF and biomarkers derived from CMR, echocardiogram, and serum sample. Third, we found that retained inflow related to diastolic function (E/e') and remained significant after adjusting for confounders. Finally, direct flow and retained inflow associated with symptom burden and quality of life in AF patients.

Flow Component In Systolic Function

Cardiac magnetic resonance is generally considered as the gold standard to assess the systolic function by traditionally measuring the parameters such as LVEF, myocardial strain, and stroke volume[17].

However, accurate assessment of systolic function in patients with atrial fibrillation is still challenging due to the beat-to-beat irregularity and elevated ventricular rate. Unlike traditional evaluation technologies, 4D flow CMR enables to comprehensively evaluate the intracardiac flow in three directions throughout the cardiac cycle[18].

It is also reported that 4D flow technology may potentially measure cardiac function among atrial fibrillation patients. In the previous study, Kim et al.[19] used 4D flow CMR to compare hemodynamics in 30 healthy controls and 50 paroxysmal atrial fibrillation patients. In Kim's study, compared with the control group, the ratio of direct flow was lower in the paroxysmal atrial fibrillation group ($44.5 \pm 11.2\%$ vs. $50.0 \pm 12.2\%$), while the delayed ejection was higher ($21.6 \pm 5.6\%$ vs. $18.6 \pm 5.7\%$). In our study, flow components significantly differed between the atrial fibrillation group and the healthy controls, with the lower direct flow and a higher ratio of the other three. However, it is worth noting that Kim et al. performed the analysis in the paroxysmal atrial fibrillation patients with sinus rhythm. In our study, we carried out the 4D flow CMR among the patients maintaining AF rhythm during the CMR scan, which may be helpful to gain insight into the hemodynamics change during AF. Moreover, we also found that the flow EF strongly correlates with the other confirmed systolic-related parameters, CMR EF and SV. Our analysis indicated that 4D flow component analysis, especially this new parameter flow EF, may serve as a biomarker of LV systolic function in AF patients.

Flow EF seemed much higher than clinical defined EF, which might originated from flow separation and visualization method. Our measurement in healthy participants (Direct flow $69.1[63.4;74.4]\%$, Delayed ejection $14.7 \pm 6.8\%$) were analogous to Kim et al.[19] (Direct flow $50.0 \pm 12.2\%$, Delayed ejection $18.6 \pm 5.7\%$). Zhao et al.[20] reported a different level of flow component (Direct flow $35 \pm 5\%$, Delayed ejection $17 \pm 4\%$) using MASS (Leiden University Medical Center, Leiden, The Netherlands). We admitted that our healthy participant were selectively younger and had a higher heart rate during CMR scan, which might increase LV EF.

Flow Component In Diastolic Function

We observed an association between retained inflow and left ventricular diastolic function (E/e'). Echocardiogram recommendations suggested parameters including E/e' , LA volume index, and tricuspid regurgitation velocity[21]. Kuo et al.[22] reported lower E/e' (10.3 ± 5.01 , $P < 0.001$) in the best GLS group among AF patients. Doukky et al.[23] reported that E/e' predicted LA thrombus (OR 1.13(1.06-1.20), $P < 0.001$). Defining a diastolic function in the context of AF is quite challenging due to its irregular beating pattern. 4D flow-derived parameters may provide additional clinical evidence in the evaluation of diastolic function. Schäfer et al.[24] tested 4D flow in COPD patients and proved that tricuspid valve e' , tricuspid valve A, and 6-minute walking test correlated with LV peak early diastolic vorticity (Analysis was based on 4D Flow dataset). Browning et al.[25] reported that peak spatially integrated vorticity derived from 4D flow might reflect right ventricular diastolic function. In the present study, we found a significant correlation between retained inflow and diastolic function parameters (E/e' , Septale e' , LA volume index) in all

subjects; in the AF group, this correlation remained significant after adjusted for confounders including demographics and cardiac function. It is worth mentioning that retained inflow describes the blood flow dynamics in the diastolic phase[12]. Hence the association between retained inflow and diastolic function was expected. Moreover, advanced methodology, including kinetic energy, has the potential to analyze cardiac function[20, 26].

Age And Sex Difference In Flow Component

Age and sex may introduce a difference in flow component analysis. We had relatively balanced sex and body mass index; however, age was not perfectly matched. We introduced multivariable linear regression to balance these demographic characteristics, including age and sex, and we witnessed similar results. A multicenter study of CMR 4D flow demonstrated that sex differences in retained inflow, residual volume was evident; however, age difference regarding flow components was not evident[20].

Limitation

This study had limitations. First, it was a single-center, small sample study, with an age difference between the AF and healthy groups. Hence, we adopted multivariable linear regression to adjusted age confounders and compared with previous study[11] to explore the age influence on flow component. Small sample size limited linear regression model effect. Second, 4D flow was sensitive to noise, arrhythmia, and motions; besides, a respiratory navigator was not applied in acquiring these data, which may cause artifacts. We excluded participants with low image quality. Our CMR protocol followed the recommendations, of which the stability of 4D flow was confirmed [8]. Third, cine images derived from CMR were accompanied by artifacts due to arrhythmia, influencing the accuracy of LV function evaluation. Therefore, we adopted echocardiogram results parameters as a supplement.

Conclusion

In conclusion, the CMR 4D flow component revealed a significantly different flow pattern in AF patients than healthy participants and provided a de novo flow biomarker indicating LV function. 4D flow-derived EF may reflect LV systolic function, and retained inflow may be associated with diastolic function in AF patients. These biomarkers may serve as a meaningful tool, enabling observation of dynamic changes in AF patients and symptom burden. At the same time, CMR 4D Flow visualizes more versatile, comprehensive, and minor modifications in intra-cardiac flow than echocardiogram (regardless of 2D or 3D). Larger studies are warranted to determine the clinical implications of our findings ultimately.

Declarations

Funding

This study was supported by Provincial and Ministry Joint Major Projects of National Health Commission of China (WKJ-ZJ-1703 to Meixiang Xiang) and The Key Research and Development Program of Zhejiang Province (2020C03118 to Meixiang Xiang)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Chengchen Zhao and Guanzhong Chen and Chunna Jin. The first draft of the manuscript was written by Chengchen Zhao and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Zhejiang University Medical School Second Affiliated Hospital Institutional Review Board. All subjects gave written informed consent in order to participate.

Consent for publication

The authors affirm that human research participants provided informed consent for publication of the images in Figure.

References

1. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JJ, Ellinor PT, Ezekowitz MD, Field ME, Furie KL et al (2019) 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 140(2):e125–e151
2. Al HS, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, MacDonald MR, Petrie MC, Cantillon D, Tarakji KG et al (2015) Catheter Ablation for Atrial Fibrillation in Heart Failure Patients: A Meta-Analysis of Randomized Controlled Trials. *JACC Clin Electrophysiol* 1(3):200–209
3. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J et al (2018) Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 378(5):417–427
4. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 16(3):233–270

5. Sitges M, Ajmone MN, Cameli M, D'Andrea A, Carvalho RF, Holte E, Michalski B, Podlesnikar T, Popescu BA, Schulz-Menger J et al (2021) EACVI survey on the evaluation of left ventricular diastolic function. *Eur Heart J Cardiovasc Imaging* 22(10):1098–1105
6. Nagueh SF, Smiseth OA, Appleton CP, Byrd BR, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P et al (2016) Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 29(4):277–314
7. Leiner T, Bogaert J, Friedrich MG, Mohiaddin R, Muthurangu V, Myerson S, Powell AJ, Raman SV, Pennell DJ (2020) SCMR Position Paper (2020) on clinical indications for cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 22(1):76
8. Dyverfeldt P, Bissell M, Barker AJ, Bolger AF, Carlhäll CJ, Ebbers T, Francios CJ, Frydrychowicz A, Geiger J, Giese D et al (2015) : 4D flow cardiovascular magnetic resonance consensus statement. *In* 17:72
9. Markl M, Lee DC, Furiasse N, Carr M, Foucar C, Ng J, Carr J, Goldberger JJ (2016) Left Atrial and Left Atrial Appendage 4D Blood Flow Dynamics in Atrial Fibrillation. *Circ Cardiovasc Imaging* 9(9):e4984
10. van der Geest RJ, Garg P (2016) Advanced Analysis Techniques for Intra-cardiac Flow Evaluation from 4D Flow MRI. *Curr Radiol Rep* 4:38
11. Juffermans JF, Minderhoud S, Wittgren J, Kilburg A, Ese A, Fidock B, Zheng YC, Zhang JM, Blanken C, Lamb HJ et al (2021) : Multicenter Consistency Assessment of Valvular Flow Quantification With Automated Valve Tracking in 4D Flow CMR. *JACC Cardiovasc Imaging*
12. Bolger AF, Heiberg E, Karlsson M, Wigström L, Engvall J, Sigfridsson A, Ebbers T, Kvitting JP, Carlhäll CJ, Wrane B (2007) Transit of blood flow through the human left ventricle mapped by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 9(5):741–747
13. Rector TS, Kubo SH, Cohn JN (1993) Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *AM J CARDIOL* 71(12):1106–1107
14. Napier R, McNulty SE, Eton DT, Redfield MM, AbouEzzeddine O, Dunlay SM (2018) Comparing Measures to Assess Health-Related Quality of Life in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 6(7):552–560
15. Eriksson J, Bolger AF, Ebbers T, Carlhäll CJ (2013) Four-dimensional blood flow-specific markers of LV dysfunction in dilated cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 14(5):417–424
16. Eriksson J, Carlhäll CJ, Dyverfeldt P, Engvall J, Bolger AF, Ebbers T (2010) Semi-automatic quantification of 4D left ventricular blood flow. *J Cardiovasc Magn Reson* 12(1):9
17. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M, Salerno M, Teague SD, Valsangiacomo-Buechel E, van der Geest RJ et al (2020) Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. *J Cardiovasc Magn Reson* 22(1):87

18. Westenberg JJ, Danilouchkine MG, Doornbos J, Bax JJ, van der Geest RJ, Labadie G, Lamb HJ, Versteegh MI, de Roos A, Reiber JH (2004) Accurate and reproducible mitral valvular blood flow measurement with three-directional velocity-encoded magnetic resonance imaging. *J Cardiovasc Magn Reson* 6(4):767–776
19. Kim H, Sheitt H, Wilton SB, White JA, Garcia J (2021) Left Ventricular Flow Distribution as a Novel Flow Biomarker in Atrial Fibrillation. *Front Bioeng Biotechnol* 9:725121
20. Zhao X, Tan RS, Garg P, Chai P, Leng S, Bryant J, Teo L, Ong CC, Geest R, Allen JC et al (2021) Impact of age, sex and ethnicity on intra-cardiac flow components and left ventricular kinetic energy derived from 4D flow CMR. *INT J CARDIOL* 336:105–112
21. Sanchis L, Andrea R, Falces C, Poyatos S, Vidal B, Sitges M (2018) Differential Clinical Implications of Current Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. *J Am Soc Echocardiogr* 31(11):1203–1208
22. Kuo JY, Chang SH, Sung KT, Chi PC, Liao JN, Chao TF, Su CH, Yeh HI, Hung CL (2020) Left ventricular dysfunction in atrial fibrillation and heart failure risk. *ESC Heart Fail* 7(6):3694–3706
23. Doukky R, Garcia-Sayan E, Patel M, Pant R, Wassouf M, Shah S, D'Silva O, Kehoe RF (2016) Impact of Diastolic Function Parameters on the Risk for Left Atrial Appendage Thrombus in Patients with Nonvalvular Atrial Fibrillation: A Prospective Study. *J Am Soc Echocardiogr* 29(6):545–553
24. Schäfer M, Humphries S, Stenmark KR, Kheifets VO, Buckner JK, Hunter KS, Fenster BE (2018) 4D-flow cardiac magnetic resonance-derived vorticity is sensitive marker of left ventricular diastolic dysfunction in patients with mild-to-moderate chronic obstructive pulmonary disease. *Eur Heart J Cardiovasc Imaging* 19(4):415–424
25. Browning JR, Hertzberg JR, Schroeder JD, Fenster BE (2017) : 4D Flow Assessment of Vorticity in Right Ventricular Diastolic Dysfunction. *Bioengineering (Basel)*4(2)
26. Kaur H, Assadi H, Alabed S, Cameron D, Vassiliou VS, Westenberg J, van der Geest R, Zhong L, Dastidar A, Swift AJ et al (2020) : Left Ventricular Blood Flow Kinetic Energy Assessment by 4D Flow Cardiovascular Magnetic Resonance: A Systematic Review of the Clinical Relevance. *J Cardiovasc Dev Dis*7(3)

Tables

Table1 Demographic and clinical characteristics

	Atrial fibrillation	Healthy participant	P
	N=25	N=14	
Sex (male)	17 (68.0%)	10 (71.4%)	0.999
Age (years)	70.0 [57.0; 75.0]	28.5 [26.2; 50.0]	<0.001
Height (cm)	166.6 ±6.2	168.8 ±7.2	0.153
Weight (kg)	63.0 [57.0; 72.0]	67.0 [62.0; 74.2]	0.529
Body mass index (kg/m ²)	23.0 [21.3; 25.3]	22.6 [21.1; 25.2]	0.953
Heart rate (bpm)	72.0 [64.0; 87.0]	65.5 [62.0; 68.0]	0.076
Systolic BP (mmHg)	124.8 ±18.7	114.1 ±10.8	0.029
Diastolic BP (mmHg)	73.0 [65.0; 81.0]	68.0 [58.5; 73.0]	0.076
BNP (pg/ml)	282.4 [103.7; 510.5]		
NT-proBNP (pg/ml)	783.0 [514.0; 1563.5]		
Serum creatine (mmol/l)	75.6 ±17.9		
Alanine aminotransferase (mmol/l)	18.0 [14.0;32.0]		
Hb (g/l)	137.3 ±21.2		
CHA2DS2-VASc	2.6 ±1.5		
HAS-BLED			
0	6 (24.0%)		
1	11 (44.0%)		
2	7 (28.0%)		
3	1 (4.00%)		
Hypertension	14 (56.0%)		
Coronary artery disease	9 (36.0%)		
Diabetes	2 (8.00%)		
Chronic obstructive pulmonary disease	2 (8.00%)		
Thyroid disease	2 (8.00%)		
MLHFQ	12.6 ±8.9		

Presented as mean ±standard deviation, median [IQR]or n (%).

BP blood pressure; BNP brain natriuretic peptide; NT-proBNP N-terminal pro-B type natriuretic peptide.

Table2 Echocardiogram and cardiovascular magnetic resonance parameters

	Atrial fibrillation	Healthy participant	P
	N=25	N=14	
Echocardiogram			
LV EF(%)	56.0 [40.0;65.3]	59.0 [56.5;61.5]	0.455
LA dimension(cm)	4.4 [3.9;5.1]	3.3 [3.1;3.5]	<0.001
E/e'	11.1 [9.1;14.7]	8.46 [8.2;9.5]	<0.001
E-wave(cm/s)	95.4 ±28.8	91.5 ±15.2	0.585
Septal-e(cm/s)	7.9 ±2.6	10.8 ±1.68	<0.001
Tricuspid regurgitation velocity(cm/s)	228.0 [187.0;282.0]	0 [0;0]	<0.001
LA volume index	48.7 [39.8;84.1]	28.8 [25.7;30.6]	<0.001
Cardiac magnetic resonance			
LA volume(ml)	97.6 [67.1;132.0]	48.1 [41.4;53.3]	<0.001
LA EF(%)	21.9 [15.5;33.8]	59.0 [56.1;62.7]	<0.001
LA strain	6.6 [4.9;11.3]	33.7 [26.9;39.8]	<0.001
LV EF(%)	44.5 [23.5;51.2]	62.2 [58.5;67.3]	<0.001
LV end-diastolic volume(ml)	153.7 [119.3;208.3]	131.3 [110.3;157.5]	0.364
LV end-systolic volume(ml)	79.5 [57.9;131.0]	51.2 [35.2;66.7]	0.002
Stroke volume(ml)	53.5 ±20.1	83.2 ±14.3	<0.001
Myocardium mass(g)	81.9 [75.3;112.5]	69.9 [63.6;95.8]	0.121
Cardiac output(ml/min)	3914.1 ±1468.1	5613.4 ±1344.6	0.001
LV GCS	-12.9 [-16.7;-8.3]	-18.9 [-20.7;-18.2]	<0.001
LV GRS	18.3 ±9.4	34.7 ±5.7	<0.001
LV GLS	-12.0 ±4.4	-18.3 ±2.0	<0.001
Native T1(ms)	1186.0 [1164.7;1251.7]	1169.3 [1154.0;1175.0]	0.056
Direct flow(%)	33.5 [8.4;47.5]	69.1 [63.4;74.4]	<0.001
Delayed ejection(%)	24.1 ±12.0	14.7 ±6.8	0.004
Retained inflow(%)	32.5 [24.6;36.9]	14.5 [12.5;18.2]	<0.001
Residual volume(%)	4.7 [1.7;15.0]	0.6 [0.4;1.6]	0.001
Flow EF(%)	61.4[37.3;70.2]	84.8 [80.4;86.9]	<0.001

Presented as mean \pm standard deviation, median [IQR] or n (%).

LV left ventricle; EF ejection fraction; LA left atrial; GCS global circumference strain; GRS global radial strain; GLS global longitude strain.

Table 3 Linear regression of retained flow and E/e' in different model

Variables	Univariate analysis			Multivariate analysis		
	Beta	95% CI	P	Beta	95% CI	P
Retained inflow(%)	0.122	-0.025 - 0.269	0.099	0.152	0.002 - 0.301	0.048*
Age(years)	-0.038	-0.210 - 0.134	0.655	-0.034	-0.205 - 0.137	0.683
Heart rate(bpm)	-0.043	-0.122 - 0.036	0.273	-0.060	-0.146 - 0.027	0.166
LA volume index(ml/m ²)	0.038	0.001 - 0.074	0.044	0.032	-0.005 - 0.070	0.086
Sex(male)	0.005	-4.110 - 4.120	0.998	0.156	-3.759 - 4.072	0.934

Table 4 Linear regression of direct or retained flow component and MLHFQ

Variables	Univariate analysis			Multivariate model 1			Multivariate model 2		
	Beta	95% CI	P	Beta	95% CI	P	Beta	95% CI	P
Direct flow(%)	-0.143	-0.282 - -0.004	<0.001	-0.170	-0.328 - -0.011	0.038			
Retained inflow(%)	0.319	0.045 - 0.593	0.025				0.350	0.050 - 0.649	0.024
Age(years)	<0.001	-0.339 - 0.340	0.997	0.157	-0.194 - 0.507	0.363	0.124	-0.207 - 0.455	0.445
Sex(male)	1.860	-6.182 - 9.902	0.637	0.758	-6.943 - 8.458	0.840	1.154	-6.365 - 8.673	0.753

Figures

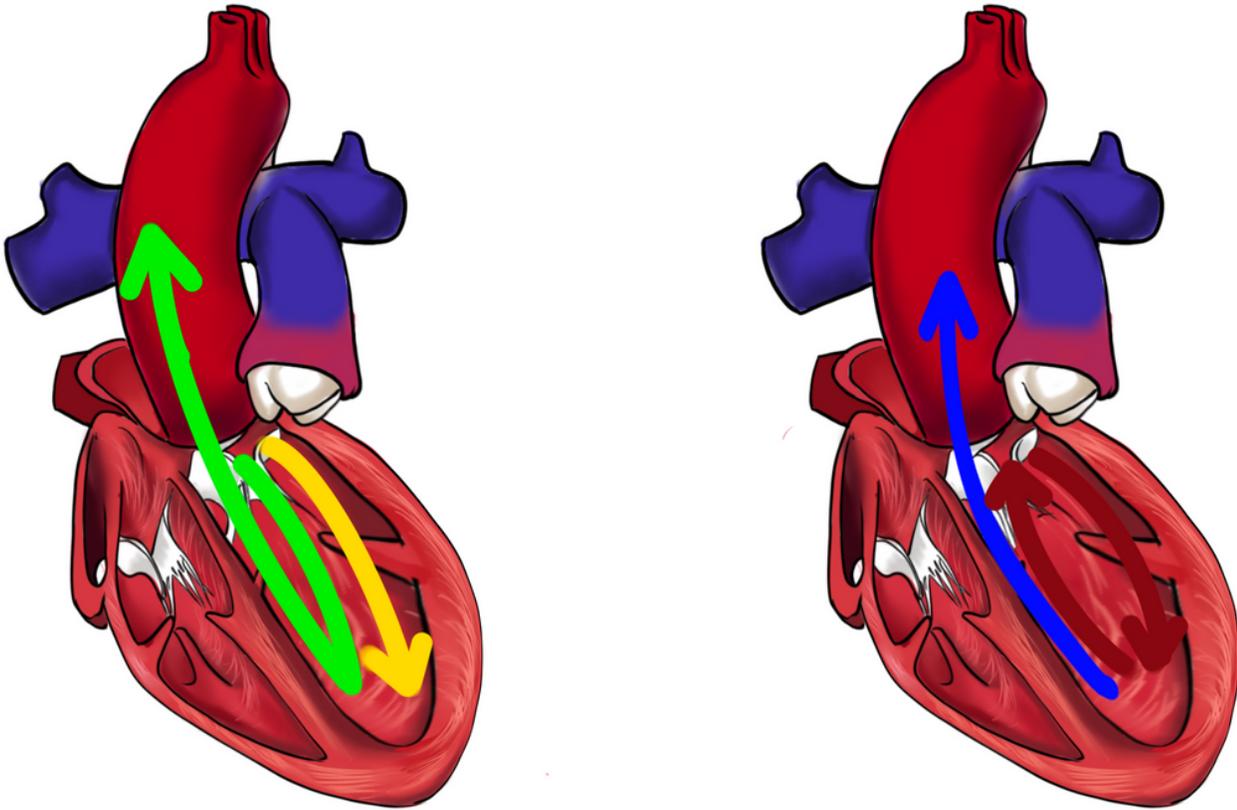


Figure 1

Illustration of flow component

LV blood volume is separated into four components. Direct flow is a part of inflow that enters ventricle during diastole, exits during systole (green line). Retained inflow is another part of inflow that remains in the ventricle during the systole (yellow line). Delayed ejection is a part of LV volume during diastole that exits during systole (blue line). Residual volume stays in the ventricle for more than one cycle (red line). LV left ventricle.

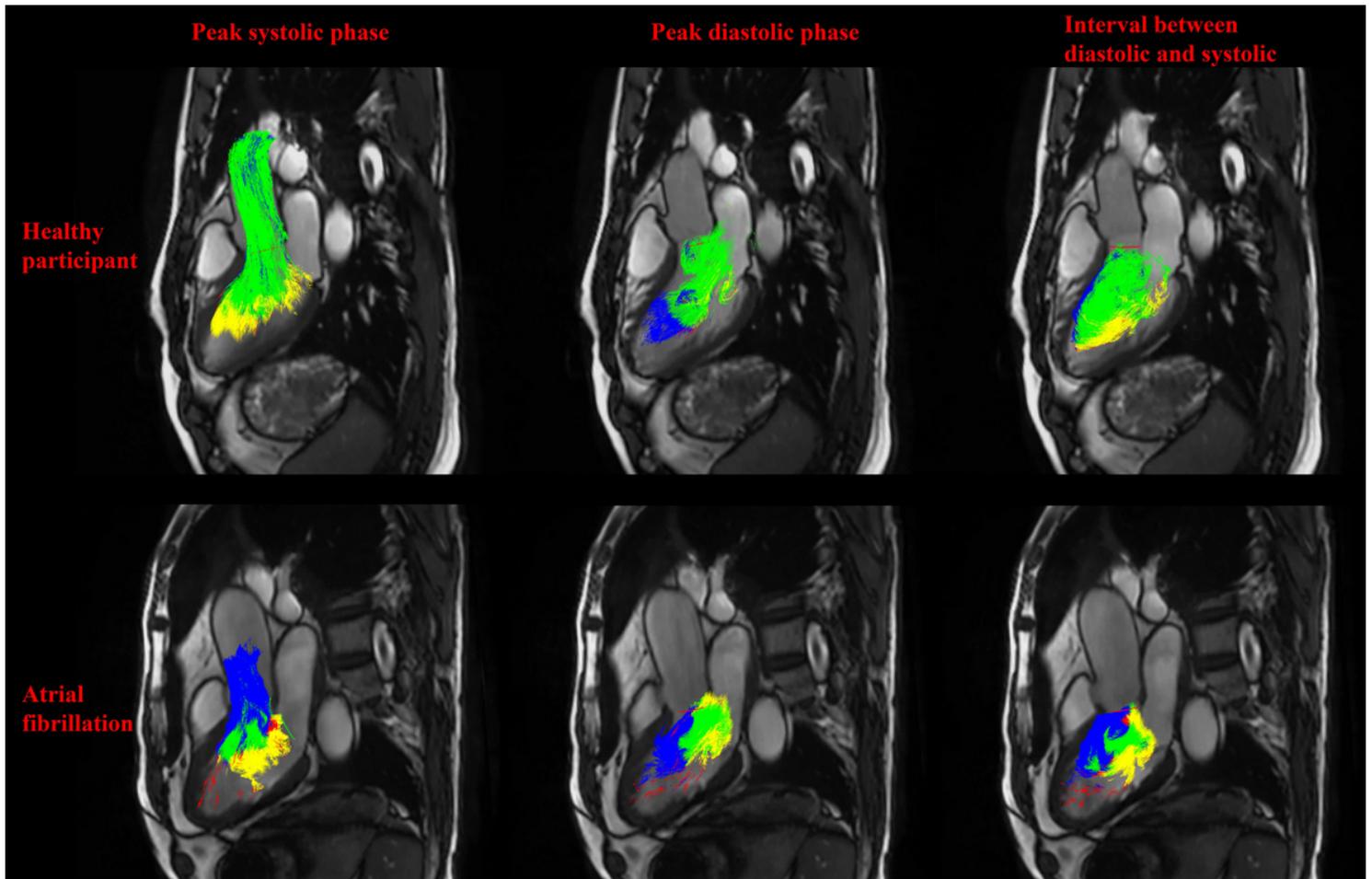


Figure 2

Flow component visualization of a AF patient and a healthy participant

Images of flow components in peak systole, peak diastolic and interval between them, captured from a healthy participant (top row) and an atrial fibrillation patient (bottom row). Direct flow was marked with green lines. Retained inflow was marked with yellow lines. Delayed ejection was marked with blue lines. Residual volume was marked with red lines.

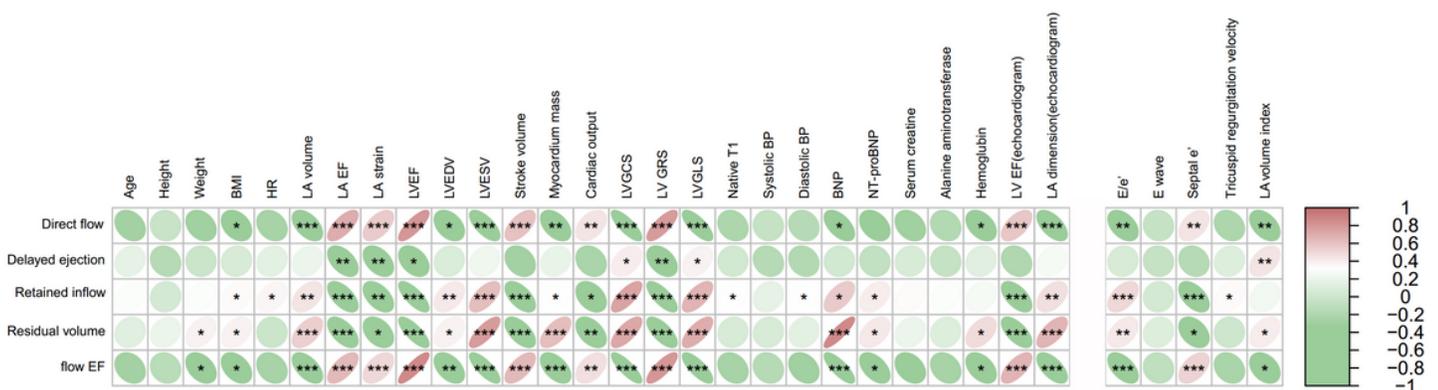


Figure 3

Heat map of correlation between factors

Heat map of flow components and clinical factors and ventricle function. Red dot represented a positive correlation. Green dot represented a negative correlation. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Parameters derived from echocardiogram were illustrated.

LV left ventricle; EF ejection fraction; LA left atrial; GCS global circumference strain; GRS global radial strain; GLS global longitudinal strain; BP blood pressure; BNP brain natriuretic peptide; NT-proBNP N-terminal pro-B type natriuretic peptide.

Figure 4

Direct flow and flowEF compare with LVEF in healthy volunteers and AF patients A&B, correlation of direct flow and LVEF. C&D, correlation of flow EF and LVEF. Direct flow and flow EF was derived from 4D flow. LVEF was derived from cine images EF ejection fraction. LV, left ventricle; EF, ejection fraction.