



RESEARCH ARTICLE

REVISED Aortic flow is abnormal in HFpEF

[version 2; peer review: 2 approved, 1 approved with reservations, 1 not approved]

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Abstract**Aims**


Turbulent aortic flow makes the cardiovascular system less effective. It remains unknown if patients with heart failure with preserved ejection fraction (HFpEF) have disturbed aortic flow. This study sought to investigate advanced markers of aortic flow disturbances in HFpEF.

Methods

This case-controlled observational study used four-dimensional flow cardiovascular magnetic resonance derived, two-dimensional phase-contrast reformatted plane data at an orthogonal plane just above the sino-tubular junction. We recruited 10 young healthy controls (HCs),

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version 1 15 Dec 2023	✓ view	↑ ?		

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10 old HCs and 23 patients with HFpEF. We analysed average systolic aortic flow displacement (FD_{avg}), systolic flow reversal ratio (sFRR) and pulse wave velocity (PWV). In a sub-group analysis, we compared old HCs versus age-gender-matched HFpEF (N=10).

Results

Differences were significant in mean age ($P < 0.001$) among young HCs (22.9±3.5 years), old HCs (60.5±10.2 years) and HFpEF patients (73.7±9.7 years). FD_{avg}, sFRR and PWV varied significantly ($P < 0.001$) in young HCs (8±4%, 2±2%, 4±2m/s), old HCs (16±5%, 7±6%, 11±8m/s), and HFpEF patients (23±10%, 11±10%, 8±3). No significant PWV differences existed between old HCs and HFpEF. HFpEF had significantly higher FD_{avg} versus old HCs (23±10% vs 16±5%, $P < 0.001$). A FD_{avg} > 17.7% achieved 74% sensitivity, 70% specificity for differentiating them. sFRR was notably higher in HFpEF (11±10% vs 7±6%, $P < 0.001$). A sFRR > 7.3% yielded 78% sensitivity, 70% specificity in differentiating these groups. In sub-group analysis, FD_{avg} remained distinctly elevated in HFpEF (22.4±9.7% vs 16±4.9%, $P = 0.029$). FD_{avg} of >16% showed 100% sensitivity and 70% specificity ($P = 0.01$). Similarly, sFRR remained significantly higher in HFpEF (11.3±9.5% vs 6.6±6.4%, $P = 0.007$). A sFRR of >7.2% showed 100% sensitivity and 60% specificity ($P < 0.001$).


Conclusion

Aortic flow haemodynamics namely FD_{avg} and sFRR are significantly affected in ageing and HFpEF patients.

Keywords

Magnetic Resonance Imaging, Aortic Flow, Haemodynamics, HFpEF, Cardiac Output

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Any reports and responses or comments on the article can be found at the end of the article.

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Competing interests: PG is a clinical advisor for Pie Medical Imaging, Neosoft and Medis Medical Imaging; he provides consultancy to Edwards Lifesciences and Anteris. SEP provides Consultancy to Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada. All other authors have no competing interests to declare.

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REVISED Amendments from Version 1

The important changes made in this version include:

1. We have clarified how the diagnosis of HFpEF was made.
2. We have added internal validation of the agreement between 2D phase-contrast flow and 4D flow methods
3. We have corrected some typos and grammar.

Our results have not been changed or impacted and the message of the paper remains the same.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

2D	two-dimensional
4D	four-dimensional
CMR	cardiovascular magnetic resonance imaging
FD	flow displacement
FDs _{avg}	average systolic flow displacement
HCS	healthy controls
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVFP	left ventricular filling pressure
LVEF	left ventricular ejection fraction
PC	phase contrast
PWV	pulse wave velocity
sFRR	systolic flow reversal ratio
RA	rotational angle

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome in which patients have signs and symptoms of heart failure. The diagnosis of HFpEF has a significant negative impact on quality of life and a prognostic outcome comparable to those with heart failure with reduced ejection fraction (HFrEF)^{1,2}. The hallmark pathophysiology of HFpEF is high left ventricular (LV) filling pressure (LVFP) despite normal or near normal LV ejection fraction (LVEF; ≥ 50 per cent)³. The epidemiology of heart failure with preserved ejection fraction (HFpEF) is constantly evolving as the condition continues to be a significant global health concern, with a prevalence of 2–3% in the general population and up to 50% in the elderly population^{2,4}. There is a higher prevalence of hypertension, atrial fibrillation (AF), coronary artery disease (CAD), dyslipidemia, obesity, anaemia, diabetes mellitus, chronic kidney disease, and sleep-disordered breathing in these patients^{2,5,6}.

The aorta is subject to unique and complex flow dynamics, characterised by high flow rates, extreme pressure variations, and intricate flow patterns in both physiological and

pathological states⁷. The relationship between arterial stiffness and LV diastolic function is well established^{8–10}. Numerous studies have demonstrated and established quantitative aortic flow parameters such as flow displacement (FD) and flow reversal ratio (FRR) in pathological states such as aortopathy and aortic valve disease^{7,11–13}. Elevated systolic flow displacement (FD_{avg}), a marker of aortic flow eccentricity, causes turbulence within the ascending aorta. Any increase in FD leads to a rise in energy dissipation, which in turn reduces the efficiency of the cardiovascular system.

Additionally, any increase in systolic flow reversal ratio (sFRR) in the ascending aorta causes a loss of forward flow which is detrimental to the aortic conduit function, directly resulting in reduced peripheral perfusion and tissue oxygenation⁷. This intricate interplay between aortic haemodynamics and left ventricular function, referred to as ventricular-arterial coupling^{14–17}, remains insufficiently researched. Even though specific aetiological factors of HFpEF, for example, hypertension or diabetes, have been associated with aortic stiffness, it remains unknown if patients with HFpEF have aortic flow abnormalities described above, which can result in heightened cardiac workload, decreased cardiac output and compromised distal perfusion subsequently causing shortness of breath.

We hypothesise that patients with HFpEF have signs of abnormal aortic flow which compromises the aortic conduit function and results in more energy expenditure, making the cardiovascular system less efficient. Hence, the main objective of this study was to investigate aortic flow haemodynamics utilising four-dimensional (4D) flow cardiovascular magnetic resonance (CMR) imaging in patients with HFpEF and healthy controls.

Methods**Patient and Public Involvement**

The engagement of patients and the public was initiated at the project's inception through Norfolk and Suffolk Primary and Community Care Research Office (<https://nspccro.nihr.ac.uk/working-with-us/public-patient-and-carer-voice-in-research>). The PPI panel helped to make the study protocol patient friendly. PPI group provided insight into design of patient information sheet for the study. PPI group were in agreement that the research will produce open access research papers available to all to read.

Study cohort

We identified patients from the PREFER-CMR registry (**ClinicalTrials.gov: NCT05114785**). We enrolled 20 subjects into the healthy control (HC) group. The main inclusion criteria for the HCs were: > 18 years of age (<30 years for young HCs and, >50 years for old HCs) and no prior history of cardiovascular disease. We enrolled 23 patients with HFpEF. The main inclusion criteria for patients were over 18 years of age and a confirmed clinical diagnosis of HFpEF by clinical history of symptoms and signs, including CMR features of HFpEF (mainly raised left ventricular filling pressure >15mmHg)¹⁸. The exclusion criteria were limited to any CMR contraindication or fast atrial fibrillation (heart rate > 100 bpm) and high R-R variability.

Ethics approval and consent to participate

This study was conducted according to the principles outlined in the Declaration of Helsinki - Version 2013. The collection and management of data were approved by the National Research Ethics Service in the United Kingdom (21/NE/0149). A pragmatic opt-out informed consent was obtained from all subjects included in the study¹⁹.

Cardiovascular Magnetic Resonance protocol

CMR study was performed on a 1.5 Tesla Magnetom Sola Siemens system with a superconducting magnet (Siemens Healthineers AG, Erlangen, Germany). All patients were examined in the supine position, headfirst, using a respiratory sensor and electrocardiogram gating. Additionally, the scanner was equipped with a Biometric body with 18 coils.

The CMR protocol included baseline survey images and cines, gadolinium enhancement imaging, and 4D flow acquisition methods previously described by our group^{17,20–25}. If 4D flow was not available, two-dimensional phase contrast acquisition was done at an orthogonal plane just above the sino-tubular junction.

For standard cines, we acquired 30 phases throughout the cardiac cycle. Other cine acquisition parameters include TR: 2.71, TE: 1.13, field of view (FOV): 360×289.3mm² with Phase FOV – 80.4%, number of signal averages (NSA): 1, matrix: 224×180 [phase], bandwidth: 167.4 kHz, [930Hz/Px], flip angle: 80, slice thickness: 8 mm and Grappa acceleration with a factor of 2.

For 4D flow acquisition, the initial VENC setting was 150–200 cm/s for all HCs and HFpEF cases. For 4D flow, we acquired 30 phases throughout the cardiac cycle to keep the data consistent with cines. The acquired temporal resolution was 40 ms. Other 4D flow acquisition parameters include TR: 4.98, TE: 2.71, field of view (FOV): 200×256.3 mm², number of signal averages (NSA): 1, acquired voxel size = 3 × 3 × 3 mm³, bandwidth: 31.616 kHz, [494Hz/Px], flip angle: 5, and Grappa acceleration in the phase-encoding direction with a factor of 2 and slice direction of 1. The electrocardiogram was retrospectively gated with free breathing to avoid diastolic temporal blurring.

CMR analysis

All image analyses were post-processed with the in-house developed MASS research software (MASS; Version 2022-EXP, Leiden University Medical Center, Leiden, The Netherlands). A static reformatted plane was planned through the ascending aorta at the mid-main pulmonary artery level to generate a through-plane velocity encoded two-dimensional (2D) phase contrast (PC) data using 4D flow CMR data. This plane was treated as a two-dimensional phase contrast plane. Ascending aortic helical flow was defined as the flow swirling around the aortic centre line. Ascending aorta vortex flow was defined as any flow rotating on the long axis of the aorta near the inner curvature of the aortic root²⁶ (Figure 1). The following parameters we automatically derived based on the aortic contours:

- Aortic Forward Flow: This refers to the stroke volume during a cardiac cycle.

- Aortic maximum and minimum area are the largest and smallest cross-sectional area (respectively) computed in the ascending aorta during a cardiac cycle.
- Flow displacement systolic average (FDsavg): This is the distance between the vessel's central point and the centre-of-velocity of the forward flow, normalised to the vessel size during systole. It is presented as a percentage. The centre-of-velocity of the forward flow is computed as the mean location of pixels weighted by the velocity values within a defined aortic contour on a 2D Phase Contrast (PC) image.
- Rotational Angle signifies the angle formed by the line connecting the centre of forward flow velocity and the radius pointing at 12 o'clock position within the ascending aorta cross-section on every 2D PC image during cardiac cycle. RA was established at zero when the vector pointed at 12 o'clock and progressed clockwise to 180 degrees when pointing backward (6 o'clock position). This is sensitive to errors in negligible flow displacement as the position of the centre-of-velocity and vessel are at a close proximity. Therefore, a slight modification of the aortic contour can displace the location of the centre-of-velocity flow and significantly alter RA. To circumvent this effect, we chose a FD=12% threshold based on our bench testing.
- Systolic Forward and Backward Flows: These are obtained using per-pixel information. All positive velocities within the region of interest during systole were used to derive systolic forward flow. In contrast, all negative velocities within the same region were used to derive systolic negative flow.
- Systolic Flow Reversal Ratio Flow curves generated for each cardiac cycle. sFRR= systolic retrograde flow/systolic forward flow x 100%.
- Pulse Wave Velocity is the ratio of distance and transit time between ascending to descending aorta. A 3D image is created from parallel scout images of ascending, arch and descending aorta. 2D PC aortic flow plane matched to 3D images noting exact velocity measure points. Arch length is traced between these points. Transit time, calculated as the time difference between the points where the ascending and descending aorta flow waveforms reached half maximum of their peak velocities.

Statistical analysis

Data analyses were performed using MedCalc® Statistical Software, version 20.215 (MedCalc Software Ltd., Ostend, Belgium) and OriginPro, version 2023 (OriginLab Corporation, Northampton, MA, USA). Continuous variables are presented as the median along with the interquartile range (IQR). We treated data as non-parametric. To compare variables between the two groups, we employed the Mann-Whitney U test. For testing across three groups, we utilised the Kruskal-Wallis one-way ANOVA and followed it with a post-hoc analysis using the Conover method. To explore the independent association of

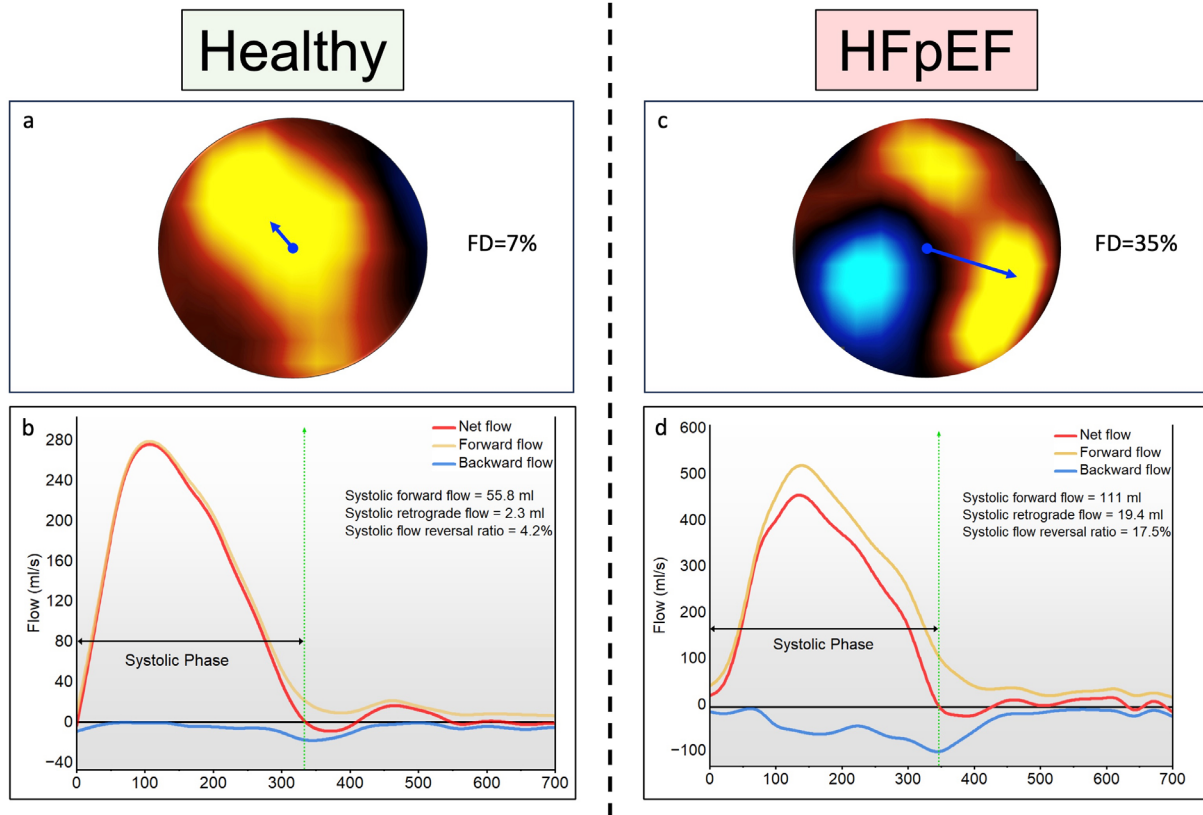


Figure 1. Central illustration of case examples from the study cohort. A and B – Flow mapping demonstrates normal predominantly laminar flow at peak systole in healthy individual with minimal flow reversal during systolic phases. **C and D** – Flow mapping a HFpEF patient demonstrating significant shift in flow displacement at peak systole. There is clear flow reversal observed (blue zone) at peak systole which is affecting aortic forward flow. This is quantified by FRR which is 17.5% during systole and can be noted on backward flow mapping (blue line) on the aortic flow curves.

all CMR indices, we used a partial correlation factor generated via the multiple regression method using all other CMR variables as covariates. To evaluate the ability of these blood flow parameters to distinguish HFpEF, we conducted Receiver Operator Characteristic (ROC) analysis and used Youden Index to determine cut-off values. We deemed statistical significance at a threshold of $P < 0.05$.

Study size

We used healthy young versus old systolic flow displacement data to derive the possible sample size to differentiate healthy old versus HFpEF cohorts. Factoring a mean difference of 8% and standard deviations of 4 and 5, to achieve an alpha of 0.05, we need to recruit at least 11 HFpEF patients and 6 elderly patients with a total sample size of 17 to achieve a power of $\beta = 0.20$. To further improve the diagnostic range, we planned to recruit > 20 HFpEF cases and at least 10 elderly healthy subjects.

Results

Study population

Patient characteristics are summarised in [Table 1](#). The study comprised 43 cases with comparable body surface area, of

which females accounted for 44%. These included ten individuals from the young HC group (females: 10%), another ten from the old HC group (females: 60%) and twenty-three HFpEF patients (females: 52%). The mean age was found to be significantly different in all three groups- younger HCs (22.9 ± 3.5 years) vs older HCs (60.5 ± 10.2 years; $P < 0.001$) vs HFpEF cohorts (73.7 ± 9.7 years; $P < 0.001$). The average age of HFpEF patients was found to be significantly older than that of old HCs ($P < 0.001$). Among the HFpEF patients, 16 (70%) had dyslipidemia, 12 (52%) had atrial fibrillation, 11 (48%) had hypertension, 8 (35%) had coronary artery disease, and 5 (22%) were diabetics.

Both the old controls and patients with HFpEF exhibited a notable decrease in aortic forward flow in comparison to young controls ($P = 0.02$) independent of gender and despite no significant variance in the left ventricular ejection fraction ([Table 2](#)). There was a significant rise in FD_{avg} in old controls and HFpEF in contrast to young controls with marked differences observed between these two groups as well ($16 \pm 5\%$ vs $23 \pm 10\%$, $P < 0.001$). Likewise, the sFRR significantly differed in all three groups ($P < 0.001$). Importantly, individuals

Table 1. Study demographics.

	Young HCs	Old HCs	HFpEF	P
Number recruited	10	10	23	
Demographics				
Age, years	22.9 ± 3.5	60.5 ± 10.2*	73.7 ± 9.7#	< 0.001
Female gender	1 (10)	6 (60)	12 (52)	0.076
BSA, m ²	1.9 ± 0.30	1.8 ± 0.20	1.93 ± 0.27	0.409
LV function				
LV mass, g/m ²	116 ± 19	77.6 ± 14*	117 ± 61#	0.005
LVEDV, ml/m ²	194 ± 43	146 ± 40*	146 ± 53	0.006
LVESV, ml/m ²	82 ± 29	55 ± 16*	62 ± 26	0.010
LVSV, ml/m ²	104 ± 35	84 ± 22*	77 ± 34	0.014
LV ejection fraction, %	56 ± 6	60 ± 9	56 ± 7	0.438
RV function				
RVEDV, ml/m ²	207 ± 49	144 ± 34*	144 ± 59	0.010
RVESV, ml/m ²	93 ± 30	56 ± 23*	58 ± 29	0.008
RVSV, ml/m ²	107 ± 39	80 ± 13	74 ± 38	0.066
RV ejection fraction, %	54 ± 5	58 ± 7	56 ± 14	0.276

Data were represented as median ± IQR (%). *BSA* body surface area, *EDV* end-diastolic volume, *ESV* end-systolic volume, *HCs* healthy cohorts, *HFpEF* heart failure with preserved ejection fraction, *LV* left ventricle, *RV* right ventricle, *SV* stroke volume.

*P<0.05 compared young HCs versus old HCs; #P<0.05 compared old HCs versus HFpEF.

Table 2. Aortic flow indices trend across the three groups.

	Young HCs	Old HCs	HFpEF	P
Number recruited	10	10	23	
Aortic flow parameters				
AO Forward Flow, ml	97±35	70±18*	70±19	0.02
AO Forward Flow indexed, ml/m ²	48±14	38±15*	36±10	0.01
AO Backward Flow, ml	2±1	1±4	2±3	0.86
AO Backward Flow indexed, ml	1±1	1±2	1±1	0.93
AO Max Area, mm ²	7±2	9±3	10±5	0.01
AO Min Area, mm ²	5±1	7±2*	8±4	<0.001
Flow Displacement systolic average, %	8±4	16±5*	23±10#	<0.001
Rotational Angle, °	0±0	-3±16	16±48#	0.04
Systolic Forward Flow, ml	90±37	66±18	77±27	0.15
Systolic Retrograde Flow, ml	2±1	4±4*	7±6#	<0.001
Systolic Flow Reversal Ratio, %	2±2	7±6*	11±10#	<0.001
Pulse Wave Velocity, m/s	4±2	11±8*	8±3	0.03

Data were represented as median ± IQR (%). *AO* aorta, *HCs* healthy cohorts, *HFpEF* heart failure with preserved ejection fraction.

*P<0.05 compared young HCs versus old HCs; #P<0.05 compared old HCs versus HFpEF.

with HFpEF exhibited significantly higher sFRR compared to old controls ($11\pm 10\%$ vs $7\pm 6\%$, $P<0.001$). These differences in FD_{avg} and sFRR in these two groups persisted regardless of the gender. Although the mean values of pulse wave velocity (PWV) in both old HCs and HFpEF were significantly higher than in controls, no significant differences were observed between these groups.

Association of aortic flow indices with age - young HCs vs old HCs

The mean age was significantly higher ($P<0.001$) in older HCs (60.5 ± 10.2 years) in comparison to younger HCs (22.9 ± 3.5 years). The indexed volumetric LV parameters were significantly reduced in old HCs, including indexed LV mass (77.6 ± 14 g/m² vs 116 ± 19 g/m², $P=0.005$), LV end-diastolic volume (EDV) (146 ± 40 ml/m² vs 194 ± 43 ml/m², $P=0.006$), LV end-systolic volume (ESV) (55 ± 16 ml/m² vs 82 ± 29 ml/m², $P=0.010$), and LV stroke volume (SV) (84 ± 22 ml/m² vs 104 ± 35 ml/m², $P=0.014$). The indexed aortic forward flow was significantly reduced in old HCs than young HCs (38 ± 15 ml/m² vs 48 ± 14 ml/m², $P=0.001$). Similarly, significant differences were observed in FD_{avg} ($16\pm 5\%$ vs $8\pm 4\%$, $P<0.001$), sFRR ($7\pm 6\%$ vs $2\pm 2\%$, $P<0.001$) and PWV (11 ± 8 m/s vs 4 ± 2 m/s, $P<0.001$) between the two groups (Table 1 & Table 2).

Flow reversal ratio systolic average (sFRR), a marker of vorticity and reduced aortic conduit function, and FD_{avg}, a marker of flow eccentricity, were independently associated with age ($P<0.001$ and $P<0.0001$, respectively) (Figure 2). sFRR was not significantly different between males and females ($6.3\pm 8.8\%$ vs $8.7\pm 5.3\%$, $P=0.21$). Similarly, there was no statistically significant difference in FD_{avg} between males and females ($15.5\pm 12\%$ vs $21.5\pm 10\%$, $P=0.066$).

On multiple regression analysis using Enter method aortic minimal area (partial $R=0.45$, $P=0.01$) and FD_{avg} (partial $R=0.41$, $P=0.03$) were the only two independent variables associated with age while factoring in all other CMR indices as covariates (Figure 3).

Aortic flow indices in Old HCs vs HFpEF

The FD_{avg} was significantly increased in HFpEF patients in comparison to old HCs ($23\pm 10\%$ vs $16\pm 5\%$, $P<0.001$) (Figure 4). Additionally, sFRR was significantly elevated in HFpEF group vs old HCs ($11\pm 10\%$ vs $7\pm 6\%$, $P<0.001$). The RA was observed to be distinctly higher in HFpEF patients when compared to old HCs ($16\pm 48^\circ$ vs $-37\pm 16^\circ$, $P=0.04$). However, there was no significant difference observed in the indexed aortic forward flow and PWV between these two groups.

A FD_{avg} of $>17.7\%$ showed 74% sensitivity and 70% specificity in differentiating between old controls and patients with HFpEF (AUC=0.71, $P=0.05$). Similarly, a sFRR of $>7.3\%$ showed 78% sensitivity and 70% specificity in distinguishing between old controls and HFpEF (AUC=0.76, $P=0.004$).

Aortic flow indices in Old HCs vs Age-gender-matched HFpEF

The differences in FD_{avg} and sFRR remained consistent and significant between HFpEF patients and old HCs when matched by age and gender. We observed a noticeable increase in FD_{avg} in age-gender matched HFpEF patients ($N=10$) vs old HCs ($22.4\pm 9.7\%$ vs $16\pm 4.9\%$, $P=0.029$) (Figure 5). Furthermore, sFRR was significantly elevated in age-gender-matched HFpEF patients vs old HCs ($11.3\pm 9.5\%$ vs $6.6\pm 6.4\%$, $P=0.007$). However, there was no significant difference observed in the indexed aortic forward flow, PWV and RA among these two groups. (Table 3).

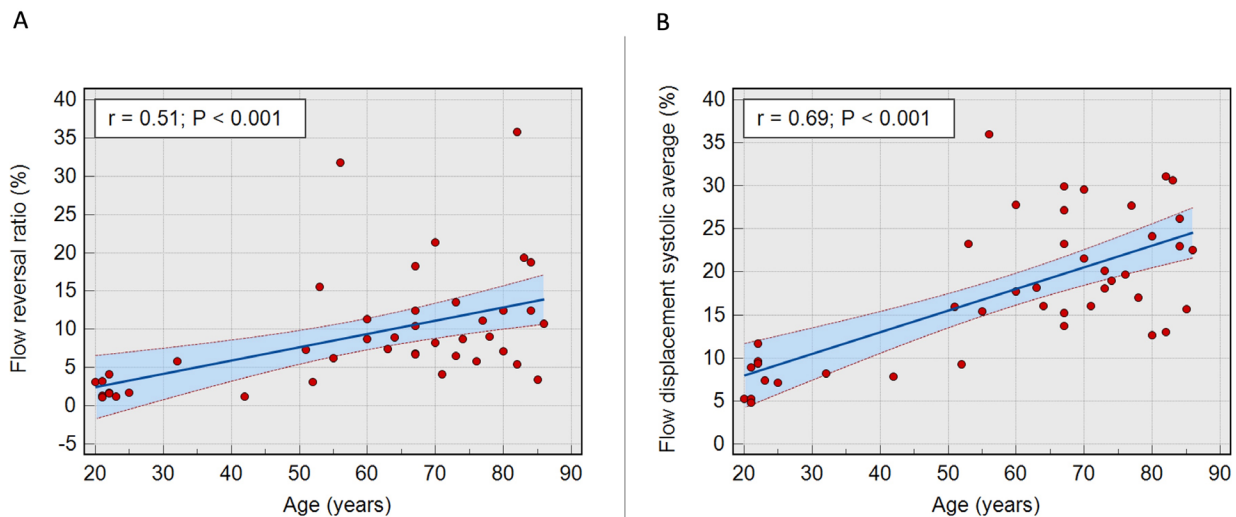


Figure 2. **A** - Scatter plot with 95% confidence interval illustrating a direct correlation between age and systolic flow reversal ratio ($P<0.001$). **B** - Scatter plot with 95% confidence interval illustrating a linear correlation between age and flow displacement systolic average ($P<0.001$).

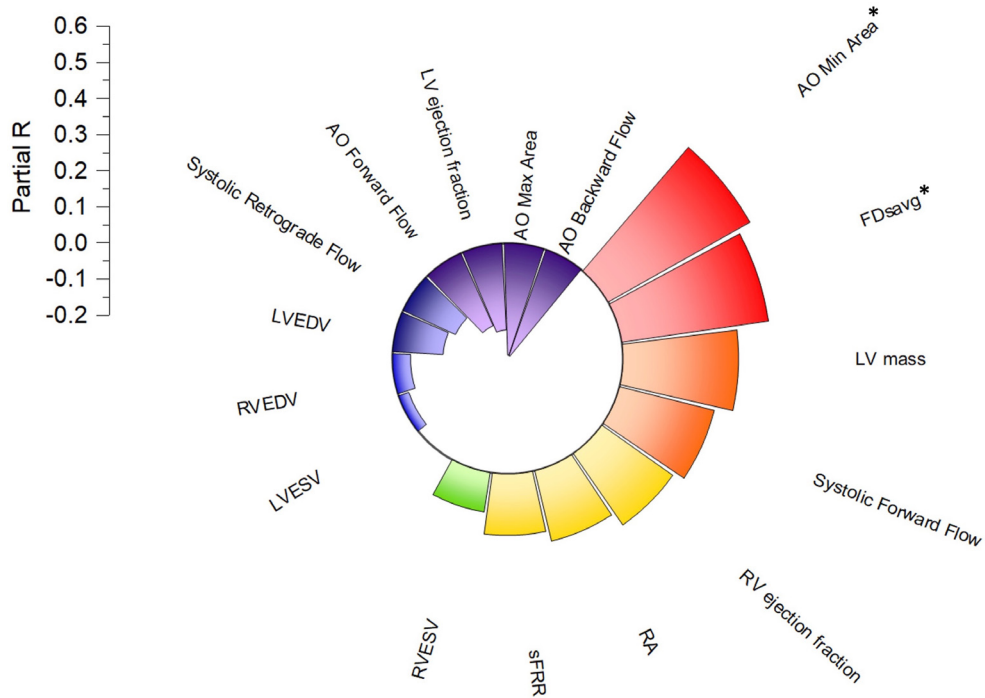


Figure 3. Radial bar plot illustrating a linear partial independent correlation of age with left ventricular and aortic flow parameters. Aortic minimum area (AO min area) and FDsavg have independent association to age of the whole study cohort and both increase with age.

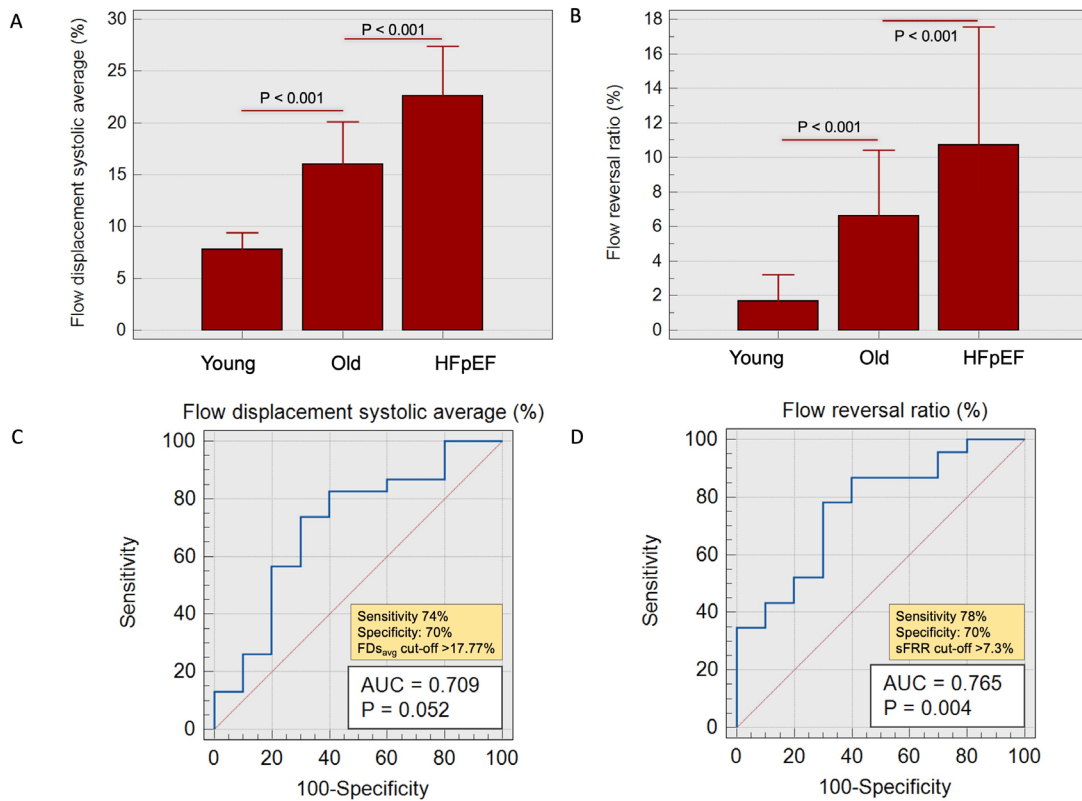


Figure 4. A - Bar charts demonstrating flow displacement systolic average trends in young vs old healthy cohorts vs HFpEF patients. **B** - Bar charts demonstrating systolic flow reversal ratio trends in young and old healthy cohorts and HFpEF patients. **C** and **D** - Receiver operating characteristic (ROC) with area under the curve demonstrating acceptable correlation in old HCs vs patients with HFpEF.

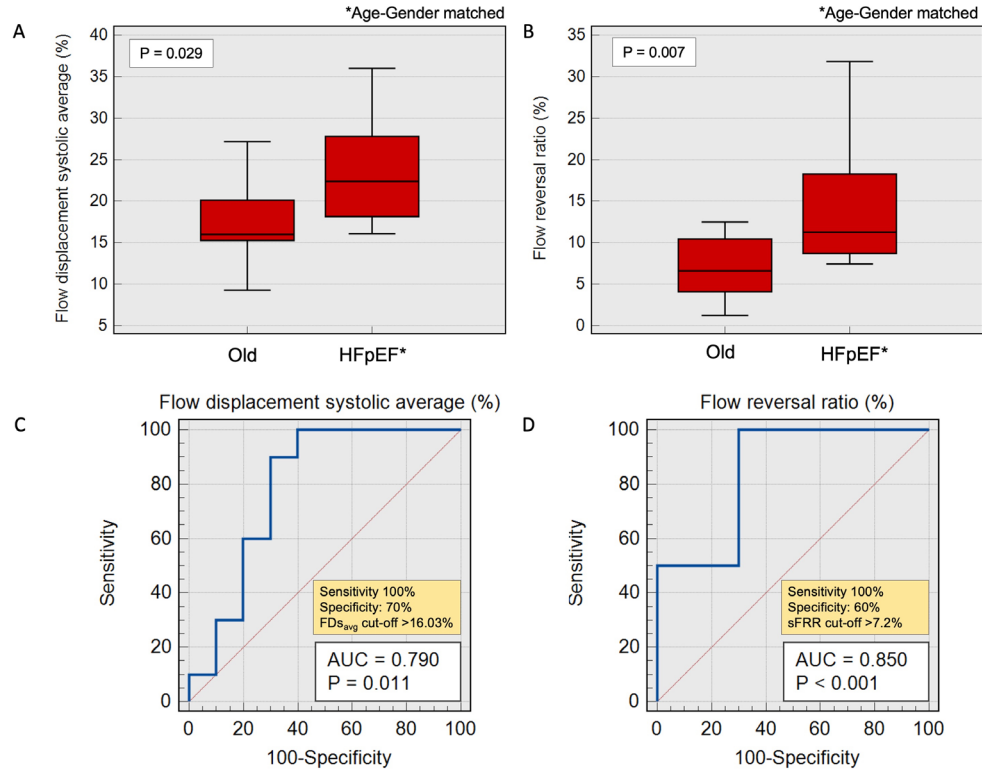


Figure 5. **A** – Bar charts demonstrating average systolic flow displacement trends in old healthy cohorts and age-gender-matched HFpEF patients. **B** - Bar charts demonstrating systolic flow reversal ratio trends in old healthy cohorts vs age-gender-matched HFpEF patients. **C** and **D** - Receiver operating characteristic (ROC) with area under the curve demonstrating acceptable correlation in old HCs vs patients with age-gender-matched HFpEF.

Table 3. Aortic flow indices in age-gender-matched old healthy cohort versus HFpEF.

	Old HCs N=10	HFpEF N=10	P-value
AO Forward Flow, ml	69.7±17.6	66.7±25.6	0.529
AO Forward Flow indexed, ml/m ²	38±15	35.1±11.4	0.529
AO Backward Flow, ml	1.1±3.6	2.1±2.8	0.436
AO Backward Flow indexed, ml	0.6±2.1	1±1.3	0.481
AO Max Area, mm ²	8.8±2.6	8.2±3.8	0.734
AO Min Area, mm ²	6.8±1.5	6.9±3.2	0.496
Flow Displacement systolic average, %	16±4.9	22.4±9.7	0.029*
Rotational Angle, °	-3.3±16.2	4.7±39.5	0.579
Systolic Forward Flow, ml	66.4±18	66.7±25.3	0.529
Systolic Retrograde Flow, ml	4.2±4.4	8.3±5.7	0.017*
Systolic Flow Reversal Ratio, %	6.6±6.4	11.3±9.5	0.007*
Pulse Wave Velocity, m/s	11±8.1	8.3±0.1	0.727

Data were represented as median ± IQR (%). AO aorta, HCs healthy cohorts, HFpEF heart failure with preserved ejection fraction.

*P<0.05 compared young HCs versus old HCs; #P<0.05 compared old HCs versus HFpEF.

A FD_{avg} exceeding 16% exhibited 100% sensitivity and 70% specificity in discerning age-gender matched HFpEF patients from old HCs (AUC=0.79, $P=0.01$). Correspondingly, a sFRR higher than 7.2% demonstrated a sensitivity of 100% and 60% specificity in distinguishing age-gender matched HFpEF patients from old HCs (AUC=0.85, $P<0.001$).

Two-dimensional phase-contrast versus four-dimensional phase-contrast reformatted plane

The coefficient of variation (CoV) between 4D flow derived and two-dimensional phase-contrast derived was 9.6% for FD_{avg} and for sFRR CoV was 10.6% with a within subject variation of only 0.7% ($P=0.26$).

Discussion

This study is one of the first to explore shifts in aortic flow hemodynamics within the ageing population and patients with HFpEF. A significant finding of this study is that both ageing and HFpEF demonstrate a rise in the systolic flow reversal ratio, which is a marker of aortic conduit function. This aortic flow biomarker, which also represents turbulent flow, exhibited marked disparities between old control group and age-gender-matched HFpEF patients. Moreover, FD_{avg} , an indicator of flow eccentricity in the ascending aortic root, increased progressively from young to old controls to HFpEF with marked differences between old controls and age-gender-matched HFpEF patients. Aortic forward flow also decreased in all respective groups despite no significant difference in left ventricular ejection fraction. We observed that the associations of sFRR and FD_{avg} were aligned with ageing rather than LV functional parameters. These CMR-derived aortic flow biomarkers have high sensitivity to detect HFpEF early in the disease process and contribute to improved phenotyping.

Mechanism underpinning Systolic Flow Displacement

Increased flow eccentricity in the aorta causes turbulence resulting in energy dissipation, requiring the heart to expend more energy to maintain sufficient blood flow making the cardiovascular system inefficient^{23,24,27,28}. The clinical utility of FD_{avg} as an independent biomarker has been established in predicting the rate of aortic growth in patients with bicuspid aortic valve (BAV) and aortopathy (with and without aortic valve disease)^{7,28-31}. We speculate that flow eccentricity, measured by FD_{avg} , develops due to left ventricular outflow tract remodelling and aortic remodelling due to an age-associated increase in afterload conditions on the ventricle³²⁻³⁴.

Mechanism underpinning Systolic Flow Reversal

Elevated sFRR, a marker of reduced aortic conduit function and increased vorticity, has been independently linked to aortic root dilatation³⁵ and shows a linear relationship with the severity of aortic stenosis³⁶. Barker *et al.*³⁶ demonstrated an FRR of >10% in patients with BAV and significant aortic stenosis. The systolic flow reversal ratio measures the retrograde flow of vorticity and represents areas of low-pressure development near the inner curvature of the aortic root due to pressure equalisation, which will plausibly happen if left ventricular filling pressures are high or if, during systolic contraction, the left ventricle is not able to generate enough mechanical force³⁷,

for example, after myocardial infarction. These underlying pathophysiological processes have been described in previous computational fluid dynamics simulation studies³⁸. In our HFpEF cohort, 48% of patients had systemic hypertension, and 35% had a previous myocardial infarction.

Our study is the first to show that abnormal aortic hemodynamics correlates with age and HFpEF without significant aortic valve disease. We observed that an sFRR level greater than 7.3% was found to have a sensitivity of 78% and specificity of 70% in distinguishing between old controls and HFpEF. Moreover, an FD_{avg} level greater than 18% had a sensitivity of 74% and specificity of 70% for the same differentiation. This study highlights that the mechanism of both flow eccentricity and flow turbulence is not only associated with the stenotic aortic valve. Interestingly, this study did not reveal any significant difference in PWV between old controls and HFpEF, contrary to previous studies^{39,40}.

Ageing signatures of CMR

Recently there has been a lot of interest in ageing-associated CMR signatures as ageing in itself is associated with cardiovascular outcomes. In a recent study by Shah, M. *et al.* (2023), machine learning was employed to forecast biological age by analysing multiple cardiovascular characteristics from CMR images and electrical data in 39,599 participants⁴¹. The study found that aging was associated with left ventricular and aortic stiffness, both of which emerged as a robust predictor of deviation from healthy cardiovascular aging and associated with range of cardiovascular outcomes. In addition, more recently, in a cohort of 169 healthy individuals, Zhao *et al.* have demonstrated how both FD_{avg} and sFRR are associated with exercise capacity assessed by peak oxygen uptake (PVO₂) from cardiopulmonary exercise testing ($r=-0.302$, $r=-0.219$ $PP<0.05$)⁴². With increase in both this aortic flow abnormalities, PVO₂ decreases. The findings from their research, along with our study, support the notion that breathlessness in patients with HFpEF is correlated with aortic flow abnormalities. With the growing literature, FD and sFRR analysis can be applied to 2D phase-contrast imaging, extending their applicability to wider and more diverse populations to define this causation better.

Clinical impact

Current echocardiogram models to estimate left ventricular filling pressure remain complex and factor in right heart haemodynamics, including tricuspid regurgitation velocity, which will get affected in the end-stage of HFpEF. An increase in right-sided pressure will result after the whole pulmonary vascular bed has been adversely remodelled, leading to a late diagnosis of HFpEF. The utility of 4D Flow CMR to quantify aortic flow hemodynamics (FD_{avg} and sFRR) could aid in the early diagnosis of HFpEF and sub-phenotyping patients with HFpEF. This is important as it will allow early pharmacological intervention and improve clinical outcomes. Moreover, FD_{avg} and FRR can be easily applied to 2D phase contrast CMR, making them widely applicable for more extensive studies. Future studies are required to evaluate the direct link between aortic flow physiology and exercise capacity. We must also establish how aortic flow influences left ventricular filling and central aortic pressures.

Limitations

While our observational and case-controlled study suggests that there may be a link between aortic flow abnormalities with ageing and HFpEF, it is important to note that the sample size used in this study was relatively small, which limits the generalisability and calls for further research with larger and more diverse cohort to draw definitive conclusions. There is a possibility of selection bias in the HFpEF cohort, and we may be identifying individuals who are much further down the temporal changes of ageing associated with HFpEF. Nevertheless, by doing age-matched comparison, we still are able to demonstrate patho-physiological step-up changes in different ages and diseased state. With no intervention currently available to improve aortic flow hemodynamics, our study is limited in establishing causality and restricts observations to only correlations. It is possible that other prevalent systemic risk factors in HFpEF, such as hypertension, obstructive sleep apnoea (OSA), diabetes, and obesity, could also contribute to changes in flow displacement and sFRR. Therefore, caution must be exercised when interpreting these findings as they may not represent the boarder population with HFpEF and age-related changes in the cardiovascular system.

Conclusion

Aortic flow haemodynamics, namely FD_{avg} and sFRR, are significantly affected in ageing and patients with HFpEF. Incorporating aortic flow haemodynamics assessment in

routine clinical practice may allow early and improved detection of HFpEF.

Ethics approval and consent to participate

This study was conducted according to the principles outlined in the Declaration of Helsinki - Version 2013. The collection and management of data were approved by the National Research Ethics Service in the United Kingdom (21/NE/0149).

Consent

All healthy controls gave informed consent. All patients were provided with clear information about the study. A pragmatic opt-out informed consent was obtained from all patients included in the study²⁰.

Data availability

The datasets generated and analysed during the current study are not publicly available. Access to the raw images of patients is not permitted since specialised post-processing imaging-based solutions can identify the study patients in the future. Data are available from the corresponding author upon reasonable request.

Acknowledgements

We acknowledge Rebecca Girling, Laura Staff and Victoria Underwood from Norfolk and Norwich University Hospitals for their constant support in managing the study.

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Jan Engvall 

Linköping University, Linköping, Sweden

I thank the editors for the opportunity to assess this manuscript which has received approval by 2 previous reviewers. The manuscript deals with aortic flow patterns in heart failure with preserved ejection fraction.

Title and Abstract

Title is OK. Abstract could contain AUC for the detection of HFpEF. It is easier to understand a combination of sensitivity and specificity than to grasp AUC, but then it is more common to report sensitivity at a specificity of 80% instead of reporting sensitivity at a specificity of 70%.

Methods

Patients in this study have been sourced from the PREFER-CMR registry in Norfolk and Norwich University Hospitals, initiated in 2022. The trial is registered in ClinicalTrials, but that entry has not been followed up. From the home page, it seems that 800 patients are included in the PREFER-CMR registry. All patients undergoing CMR at this institution are invited to participate in the registry. The standard CMR-study includes 4D-flow sequences, whenever possible. From the registry, various research questions can be addressed based on use of previously collected patient images and clinical data. In this particular study, 20 healthy controls (10 young=23 y.o., 10 old=61 y.o.) were selected from the registry in addition to 23 patients with a diagnosis of HFpEF (mean age 74 y.o.). A diagnosis of HFpEF was based on the presence of signs and symptoms of heart failure and certain CMR criteria previously developed by this group (fulfilling a regression equation that involves LA volume and LV mass indicating the probability of having LVFP >15 mm Hg). A better description of the diagnosis in the HFpEF patients has been asked for by a previous reviewer. However, the need for multiple inputs (echocardiographic findings, NT-pro-BNP levels), the difficulty in the diagnosis of HFpEF and the presence of diagnoses mimicking HFpEF has not been pursued by the authors in this text. Since the comparison of differences in 4D flow is highly dependent on the selection of the HFpEF group, the reader needs a more detailed description of patient selection.

The CMR method is well described but the authors fail to cite the features of quality control that

are recommended in the 2023 update of guidelines on CMR 4D-flow by Bissel et al, summarized in Table 3 of that publication (dr Garg is co-author). I lack e.g. a number on the reconstructed voxel size (acquired is 3x3x3 mm).

Systolic flow reversal in the ascending aorta is illustrated in Figure 1 but it could benefit the reader if anatomical directions were added to part a and c of the figure, e.g. anterior-posterior, lateral-septal. What is the meaning of flow reversal at peak systole in Figure 1? Is it part of excessive vortex development that could perhaps be related to a less pronounced Windkessel effect in older people, due to increased wall stiffness or reflected pressure waves? Could you try to illustrate vortex flow e.g. by a pathline analysis in the ascending aorta?

Results

A number of flow measures are given in Table 1 and Table 2. A comparison is performed between young and old healthy controls and with the HFpEF group. For young healthy compared to old/oldHFpEF, stroke volume is higher whether measured anatomically or from 4D/2D flow which is expected. Flow reversal is according to Table 1 and 2 rather small, but increases with age. In Table 2, the aortic area max/min is shown but the figures are very low 7/5 mm² for young healthy which corresponds to 2.5x2.5 mm diameter, which needs an explanation.

Discussion

Under the subheading "Mechanism underpinning Systolic Flow Reversal" the authors discuss pressure equalization and remodelling of the LVOT as an explanation for flow reversal, but do not discuss vorticity in relation to other features such as reflected pressure waves.

Under the subheading "Ageing signatures of CMR" the authors suggest that "breathlessness in patients with HFpEF is correlated with aortic flow abnormalities". The association might be true, but the mechanism causing breathlessness has to be sought elsewhere, e.g. in the stretch receptors of the pulmonary circulation.

In summary, this work is interesting but some questions remain as to the selection of the HFpEF patients and the quality control performed on the 4D-acquisition. There are also some questions as to aortic area in Table 2. I believe that citing the guideline paper of Bissel certifying that recommendations regarding quality control of scientific studies in CMR 4D-flow have been followed would strengthen the impact of the text.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: CMR ventricular function, CMR 4D-flow, Stress echocardiography, Transthoracic and transesophageal echocardiography, Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 15 January 2025

<https://doi.org/10.21956/wellcomeopenres.23435.r116687>

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Sungho Park 

University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

The authors have demonstrated the impact of aging and heart failure with preserved ejection fraction (HFpEF) on left ventricular (LV) function and aortic hemodynamics using cardiac MRI, 2D phase-contrast (PC), and 4D flow MRI techniques. This study introduces flow displacement and flow reversal ratio as novel biomarkers for understanding aging and HFpEF, which is highly interesting. However, several concerns need to be addressed before indexing.

First, turbulent flow is characterized by unsteady fluid motion and chaotic behavior. While swirling and retrograde flow can be features of turbulent flow, they are not direct markers as they may also appear in laminar flow. If the participants, including old healthy controls and individuals with HFpEF, demonstrate high peak velocities, this could support the presence of turbulent flow, which could be confirmed by calculating the Reynolds number. However, given that these participants do not appear to have valvular disease and show a decreasing trend in stroke volume (as indicated in Table 1), peak velocity might not be high enough to classify the aortic flow as turbulent. The authors should clarify the presence or absence of aortic valve disease, revise Figure 1c,d to better represent the data (as the current figures include an extreme forward flow case not consistent with the averages in Table 1), and verify the values or units in Table 1, as some markers seem not to be indexed. Based on these considerations, terms like "turbulent flow" and "energy dissipation"

might not be appropriate in the introduction and discussion sections, and alternative mechanisms or terminologies should be proposed.

Additionally, the authors mentioned that 2D PC MRI data was used when 4D flow data was unavailable, but the manuscript lacks sufficient details on this. It is important to specify how many 2D PC MRI datasets were used in each group and whether the sample sizes were adequate to compare results between 4D flow and 2D PC MRI. The sequence parameters for 2D PC MRI should also be detailed.

The study reported no significant differences in pulse wave velocity (PWV) between old healthy controls and individuals with HFpEF, highlighting discrepancies with previous studies. However, as the current study measured aortic PWV while previous studies often measured carotid-to-femoral PWV, it is plausible that aortic stiffening may not manifest in HFpEF, while carotid-to-femoral vasculature shows stiffening. The authors should clarify this distinction and provide insights into the underlying mechanisms behind these observations.

Numerous typographical errors remain in the manuscript and should be carefully addressed.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biomedical engineering; 4D flow MRI; MRI imaging

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 14 March 2024

<https://doi.org/10.21956/wellcomeopenres.23435.r76057>

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**Jonathan Bennett**

University College London, London, UK

The authors have clarified the selection criteria for HFpEF patients combining symptomatic status and recently developed CMR estimations of pulmonary capillary wedge pressure. Additionally, data has been provided comparing 2D and 4D measurements with a low in-subject variation and co-efficient of the mean.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiac magnetic resonance, aortic valve disease, HFpEF, aging, preventive cardiology, heart-brain interactions.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 01 March 2024

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Jonathan Bennett

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This article investigates age-related and heart failure with preserved ejection fraction (HFpEF) related differences in aortic flow dynamics. It aims to describe these variances by assessing novel markers of aortic flow hemodynamics using cardiac magnetic resonance (CMR) two-dimensional phase contrast flow measurements in young healthy controls, older healthy controls, and HFpEF patients.

Title and abstract:

The title is short and non-descriptive of the methods or type of abnormal flows detected – the authors could expand the title to give potential readers more insight into the article.

The abstract is clear and succinct and relates to the findings reported in the full manuscript.

The authors state the use of two-dimensional phase contrast CMR data as the method of acquisition in the abstract, however methods state that the data was derived from an initial 4D flow acquisition – the authors could be more specific in this respect.

Introduction:

The introduction is clear with its rationale for the study, having identified that aortic flow hemodynamics are abnormal in bicuspid aortic valve disease and that this relates to impaired aortic conduit function. The main objective for the study is clearly stated.

Methods:

The HFpEF cases were included based upon a confirmed diagnosis of HFpEF by CMR – the authors could expand on what would be considered diagnostic of HFpEF on CMR considering it is less commonly used compared to echocardiography. Also, an explicit statement of the symptomatic status of HFpEF patients for clarity.

The CMR protocol and analysis is well described. The authors expertly describe the various aortic hemodynamic parameters measured in bullet point form that is very useful for the reader.

The authors state that if 4D flow wasn't available 2D phase-contrast flow was used instead, some clarity regarding whether some patients had 2D phase-contrast compared with the 2D phase-contrast derived from 4D acquisition would be beneficial, and whether there was any analysis as to whether impact on results.

Figure 1 is clear in illustrating the methods.

Results:

The HFpEF group is reported as having 12 (52%) atrial fibrillations, and presumably the other groups all in sinus rhythm. It is not explicit as to what rhythm the HFpEF patients were in during image acquisition and the effect that this may have on the aortic flow haemodynamics – a statement on how atrial fibrillation was dealt with within the study would be useful.

The results section is clearly and logically presented taking the reader through the results of the main groups. The authors do further sub-group analysis of age-matching to confirm that aortic haemodynamic differences between these groups are unlikely to be a factor of age.

Figures are clear and well described.

Discussion:

The authors state that the aortic haemodynamics have a higher sensitivity to detect changes early in the HFpEF disease process – however it is unclear as to how they came to this conclusion and

what they would define as early HFpEF and whether this is how they would define their HFpEF cohort.

The limitations are well described and highlight the small sample sizes used in the study that limits the generalizability in the study, however considering the relatively novel nature of the measurements in these populations this study serves as a good starting point for future research.

Ethics:

No ethical issues noted.

Summary:

The authors present a well-described and analyzed comparison of aortic flow hemodynamics in three distinct cohorts, identifying potential future biomarkers. The methodology is robust, and writing style is clear, guiding the reader through the manuscript. They acknowledge limitations in sample size and address age differences between the cohorts.

Areas for clarification:

- Specific inclusion criteria for HFpEF via CMR, an uncommon technique for identifying HFpEF.
- Integration of atrial fibrillation within the HFpEF cohort into aortic flow measurements and its potential impact on results.
- Definition of "early HFpEF" and its relevance to the HFpEF group in this study.
- Clarification on whether all patients underwent 4D flow acquisition converted to 2D phase contrast or if some only had initial 2D phase contrast acquisition, and any analysis conducted to assess methodological differences.

Addressing these points will enhance the paper's value by providing early insights into potential biomarkers and mechanisms in HFpEF for future research in this critical field.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiac magnetic resonance, aortic valve disease, HFpEF, aging, preventive cardiology, heart-brain interactions.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Mar 2024

Pankaj Garg

Areas for clarification: The title is short and non-descriptive of the methods or type of abnormal flows detected – the authors could expand the title to give potential readers more insight into the article. **Author's Response:** We appreciate the reviewer's feedback regarding the brevity of the title. It is important to recognise that a concise title can serve as an effective attention-grabber, enticing readers to explore the content further. While the title provides an initial touchpoint, the article itself delves into comprehensive discussions on the methods employed and the various types of abnormal flows detected. By maintaining a succinct title, we encourage readers to engage with the full text, ensuring a deeper understanding beyond what an extended title might convey. Specific inclusion criteria for HFpEF via CMR, an uncommon technique for identifying HFpEF. **Author's Response:** We appreciate the reviewer's feedback regarding the initial manuscript. In response, we have provided additional clarity on the definition of Heart Failure with Preserved Ejection Fraction (HFpEF). Specifically, we now elaborate on the diagnostic criteria, which include a confirmed clinical diagnosis based on symptoms, signs, and Cardiovascular Magnetic Resonance (CMR) features associated with HFpEF (mainly raised left ventricular filling pressure >15mmHg). Notably, CMR features such as increased left atrial size and left ventricular hypertrophy serve as hallmarks of HFpEF. Importantly, the utilisation of a composite equation for left ventricular filling pressure through CMR enables more accurate assessments compared to traditional echocardiography indices) [PMID: 35512290]. Consequently, we have opted for CMR as the preferred diagnostic modality. We are sorry that the initial manuscript did not clarify this in detail. Integration of atrial fibrillation within the HFpEF cohort into aortic flow measurements and its potential impact on results. **Author's Response:** We appreciate the reviewer's attention to the details of our study. In response, we have provided further clarification regarding the inclusion criteria for patients with atrial fibrillation (AF). Specifically, we ensured that our study cohort consisted exclusively of AF patients with stable heart rates and good image quality. Patients with significant R-R variability were deliberately excluded to maintain consistency in our data. Regarding the impact of R-R variability, we acknowledge its potential to introduce temporal blurring during image acquisition, particularly during diastolic phases. However, we emphasise that the majority of the parameters proposed in our study are unlikely to be significantly affected by AF-related variability. Notably, the systolic phases remain less susceptible to this issue. Nevertheless, it is essential to recognise that the independent role of AF-associated hemodynamics and its specific impact on aortic flow indices warrant further investigation. Regrettably, our study remains underpowered to evaluate this aspect fully. We appreciate the reviewer's consideration of this limitation and will continue to explore this area in future research endeavours. Definition of "early HFpEF" and its

relevance to the HFpEF group in this study. **Author's Response:** We appreciate the thoughtful consideration of our study. The observed continuum in our cohort underscores an essential aspect: the older group studied is highly likely to develop symptoms associated with Heart Failure with Preserved Ejection Fraction (HFpEF) at some point. Our interpretation suggests that patients with the HFpEF syndrome experience an accelerated aging process within the cardiovascular system. This process manifests as reduced ventricular and aortic compliance, leading to subtle aortic flow abnormalities. Importantly, these abnormalities may already be evolving in older subjects who have not yet reached the critical symptomatic threshold. While intriguing, we acknowledge that our study does not establish a direct link between aortic flow abnormalities and associated comorbidities. Such an investigation remains beyond the scope of our current work. However, we recognise the potential clinical implications. The methods proposed in our study may serve as early indicators, hinting at the development of HFpEF. Future research endeavours should explore this link comprehensively, bridging the gap between aortic flow dynamics and clinical outcomes. Clarification on whether all patients underwent 4D flow acquisition converted to 2D phase contrast or if some only had initial 2D phase contrast acquisition, and any analysis conducted to assess methodological differences. **Author's Response:** We indeed carried out internal validation to check if 4D flow re-formatted plane flows at a level similar to 2D phase-contrast through-plane flows give similar results. In a randomly selected cohort of five cases where both data were available, we noted good agreement between 4D flow and 2D PC methods for FDs_{avg} and sFRR. This has now been added to the results section of the manuscript. This cross-validation allowed in some cases of HFpEF, where 4D flow was not available, for us to use the 2D PC.

Competing Interests: No competing interests were disclosed.

Reviewer Report 27 February 2024

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Nadir Elamin 

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This study is exceptional in its structure and presentation. The authors effectively introduced the topic of heart failure with preserved ejection fraction (HFpEF) and the significance of aortic flow. The hypotheses and objectives of the study were clearly outlined, making it easy to understand the purpose of the research. To enhance the introduction further, it would be beneficial to elaborate slightly on the methods used to evaluate aortic flow and provide illustrations of why echocardiography may not be suitable for intricate flow assessment.

The methodology section is well-organised and clearly defined, allowing for seamless navigation

between sections. The authors provided a comprehensive description of the study cohort and the standardised cardiovascular magnetic resonance (CMR) protocol, including image acquisition and data analysis. The different types of aortic flow assessments were also clearly defined in the methods section, and the statistical methods were well described, contributing to the reproducibility of the study.

The presentation of the results was clear and concise, with appropriate tables and figures used to support the findings. Nevertheless, incorporating a video comparing the aortic flow in the three groups would be beneficial. The authors effectively interpreted the results and integrated them with existing literature, highlighting the significance of aortic flow in HFpEF patients and older healthy control cohort. This advances our knowledge in both areas and provides opportunities for future research.

Overall, this study is of the highest quality, as evidenced by its coherent and well-organised structure. The paragraphs effectively summarised the objectives, and it is easy to create a list of bullet points from them. There are no grammatical or language errors that could impact the quality of the paper. This study will make a significant contribution to the literature on HFpEF patients, the innovative technology of CMR, and the importance of aortic flow in the aging population and patients with cardiovascular disease.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anti-thrombotic therapy, Cardiovascular disease, Percutaneous coronary and structural intervention, Heart failure, Hemodynamic of the heart and vascular system.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
