This is a repository copy of Validation of four-dimensional flow cardiovascular magnetic resonance for aortic stenosis assessment.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/162607/

Version: Published Version

Article:
Archer, G.T., Elhawaz, A., Barker, N. et al. (13 more authors) (2020) Validation of four-dimensional flow cardiovascular magnetic resonance for aortic stenosis assessment. Scientific Reports, 10 (1). 10569. ISSN 2045-2322

https://doi.org/10.1038/s41598-020-66659-6

Reuse
This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:
https://creativecommons.org/licenses/

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.
Validation of four-dimensional flow cardiovascular magnetic resonance for aortic stenosis assessment

Gareth T. Archer1-2, Alaa Elhawaz3, Natasha Barker3, Benjamin Fidock1, Alexander Rothman3, R. J. van der Geest1, Rod Hose1,6, Norman Briffa1,2, Ian R. Hall2, Ever Grech2, Malenka Bissell4, Abdallah Al-Mohammad4, Thomas A. Treibel5, Andrew J. Swift1,6, James M. Wild1,6 & Pankaj Garg1,6✉

The management of patients with aortic stenosis (AS) crucially depends on accurate diagnosis. The main aim of this study was to validate the four-dimensional flow (4D flow) cardiovascular magnetic resonance (CMR) methods for AS assessment. Eighteen patients with clinically severe AS were recruited. All patients had pre-valve intervention 6MWT, echocardiography and CMR with 4D flow. Of these, ten patients had a surgical valve replacement, and eight patients had successful transcatheter aortic valve implantation (TAVI). TAVI patients had invasive pressure gradient assessments. A repeat assessment was performed at 3–4 months to assess the remodelling response. The peak pressure gradient by 4D flow was comparable to an invasive pressure gradient (54 ± 26 mmHg vs 50 ± 34 mmHg, P = 0.67). However, Doppler yielded significantly higher pressure gradient compared to invasive assessment (61 ± 32 mmHg vs 50 ± 34 mmHg, P = 0.0002). 6MWT was associated with 4D flow CMR derived pressure gradient (r = 0.45, P = 0.01) and EOA (r = 0.54, P < 0.01) but only with Doppler EOA (r = 0.45, P = 0.01). Left ventricular mass regression was better associated with 4D flow derived pressure gradient change (r = 0.64, P = 0.04). 4D flow CMR offers an alternative method for non-invasive assessment of AS. In addition, 4D flow derived valve metrics have a superior association to prognostically relevant 6MWT and LV mass regression than echocardiography.

Aortic stenosis (AS) is the most common left-sided heart valve disease, and with an ageing population, the incidence is set to double over the next 20 years1. Once patients with severe AS develop symptoms and reduction in heart function, two-year mortality can reach 50% if the valve is not replaced. Timing of intervention depends on an accurate assessment of not only symptoms but also of AS severity. Transthoracic echocardiography (TTE) is the first-line test for the assessment of AS severity, left ventricular (LV) function and haemodynamics24. However, it is well-established that TTE has limitations – the approximation of blood flow as a single streamline by continuous-wave Doppler TTE overestimates valvular pressure gradients compared to invasive measurements3-6. This is because of the approximation of blood flow as a single streamline by continuous-wave Doppler TTE. In addition, the effective orifice area (EOA) is calculated using the continuity equation which includes many geometric and physiological assumptions, in particular, the measurement of left ventricular outflow tract diameter is a significant source of error7. If there is diagnostic uncertainty or when there is a discrepancy between non-invasive and the clinical assessment of AS severity, guidelines recommend invasive cardiac catheterization for haemodynamic assessment in symptomatic patients8.

Cardiovascular magnetic resonance (CMR) imaging already offers a reference method for monitoring longitudinal changes in LV remodelling response in patients with AS8. Four-dimensional (4D) flow CMR is an emerging tool which allows quantifying cross-sectional x/y/z planner velocities over the complete cardiac cycle9. It has the advantage of identifying the true peak velocity across the three-dimensional aortic sinus and also circumvents

1Department of Infection, Immunity & Cardiovascular Disease, University of Sheffield, Sheffield, UK. 2Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. 3Division of Image Processing, Leiden University Medical Centre, Leiden, The Netherlands. 4Division of Biomedical Imaging, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK. 5Institute for Cardiovascular Sciences, University College London, London, UK. 6Insigneo institute of in-silico medicine, University of Sheffield, Sheffield, United Kingdom. ✉e-mail: p.garg@sheffield.ac.uk
many of the issues of echocardiographic measurement such as Doppler misalignment, as well as flow and geometric assumptions. Being able to identify where the maximum velocity occurs in a three-dimensional (3D) space is a major advantage not only over Doppler TTE but also the current standard two-dimensional (2D) phase-contrast CMR methods for AS assessment – which is recognised to underestimate velocities\(^\text{10,11}\).

Moreover, it allows quantification of the EOA using the peak velocity plane, which coincides with the vena contracta, identified by an evaluation of the whole three-dimensional aortic sinus flow. However, there are many unknowns for wider adoption of these methods for AS assessment. Firstly, validation of peak velocity assessment by 4D flow CMR for estimating peak pressure drop across the aortic valve is lacking against the reference invasive method. Secondly, EOA calculation using the peak velocity plane (vena contracta) on 4D flow CMR has not been validated. Thirdly, it remains unclear if 4D flow CMR would offer any incremental benefit over Doppler TTE.

Thus, the main aims of this study were: (1) to validate the 4D flow CMR peak velocity assessment against the reference invasive pressure drop assessment, (2) to validate the 4D flow CMR velocity plane derived EOA against Doppler TTE derived EOA, (3) investigate if 4D flow CMR aortic valve assessment offers any better association to exercise tolerance evaluated by the six-minute walk test (6MWT) when compared to Doppler TTE, and (4) in the cohort with follow-up imaging studies, evaluate which measures are associated with LV remodelling.

Methods

**Study population.** This was a prospective, single-centre, sub-study of the EurValve programme (http://www.eurvalve.eu/). We recruited 18 patients with suspected severe aortic stenosis on echocardiography from the heart valve clinic. All patients who underwent 4D flow CMR prior to any valve intervention were also invited for post valve intervention follow-up 4D flow CMR and TTE at 3–4 months.

The inclusion criteria was clinically severe AS. The exclusion criteria were: moderate or severe aortic regurgitation, significant other valve diseases, coronary artery disease requiring coronary artery bypass grafting surgery, limited pre- and post-intervention imaging data, any MRI contraindications or the inability to complete a six-minute walk test (6MWT).

**Ethics.** This study was sponsored by the Sheffield Teaching Hospitals NHS Foundation Trust and approved by the National Research Ethics Service (17/LO/0283) in the UK. Written informed consent was obtained from all patients before participation. The study complied with the Declaration of Helsinki.

**Echocardiography.** All echocardiograms were performed according to the British Society of Echocardiography guidelines for TTE examination\(^\text{12}\). Grading of aortic stenosis was performed as per the ESC guidelines using mean, and peak gradients and EOA was calculated by the continuity equation\(^\text{17}\). Patients received TTE examination before valve intervention (3–4 months prior to the invasive study), and a follow-up TTE was undertaken at 3–4 months.

**Invasive pressure gradient assessment.** Invasive pressure gradients were obtained in all patients undergoing transcatheter aortic valve implantation (TAVI) as part of routine care prior to and post valve implantation. Cardiac catheterisation was performed using standard techniques via the femoral artery\(^\text{13}\). Seven-French pigtail catheters were placed in both the ascending aorta and the LV cavity, and simultaneous pressures were recorded\(^\text{14}\). The analysis was performed by the Xper CardioFlex system (Philips Healthcare, The Netherlands). Peak to peak pressure gradient was determined in millimetres of mercury (mmHg). This method is well established and has been used to define the natural history of AS and symptomatic development.

**CMR.** CMR was performed on a 3 Tesla Philips Healthcare Ingenia system equipped with a 28-channel coil and Philips dStream digital broadband MR architecture technology. Patients received CMR examination before valve intervention (3–4 months prior to the invasive study) and a follow-up CMR study was done in 3–4 months.

**CMR protocol.** The CMR protocol included a baseline survey, cines (vertical long axis, horizontal long axis, short-axis contiguous left-ventricle volume stack 3-chamber (LVOT-views) and aortic valve view cines). Cine images were acquired during end-expiratory breath-hold with a balanced steady-state free precession (bSSFP), single-slice breath-hold sequence. The number of LV short-axis slices varied according to the size of each patient's heart.

Cine images had a spatial resolution of 2.5 \(\times\) 2.5 mm\(^2\), interpolated to 1.56 \(\times\) 1.56 mm\(^2\), and a slice thickness of 10 mm with contiguous slices for the short axis stack. Other imaging parameters were 30 phases, echo time (TE) = 1.5 ms, repetition time (TR) = 3.05 ms, flip angle = 45°, the field of view (FOV) was 400 mm, and SENSE factor 2–3.

**Four-dimensional flow CMR acquisition.** For the 4D flow CMR acquisition, the initial VENC setting was estimated from TTE peak velocity and tested using a through-plane two-dimensional phase contrast acquisition. Further increments were added until aliasing disappeared across the aortic valve. Field-of-view was planned to cover the whole heart, aortic valve and ascending aorta. The 4D flow sequence used echo-planar imaging (EPI) acceleration factor of 5 with no respiratory gating. This sequence has been validated by previous studies for vascular flow quantification in humans at both 1.5 T and 3 T field strengths\(^\text{15,16}\). Other standard scan parameters were: acquired voxel size = 3 x 3 x 3 mm, reconstructed voxel size = 1.5 x 1.5 x 1.5 mm, echo time (TE) = 3.5 ms, repetition time (TR) = 10 ms, flip angle 10°, the FOV 340 x 340 and 30 cardiac phase.

Data pre-processing was done on the scanner to correct for phase offset errors such as eddy currents, Maxwell effects, and encoding errors related to gradient field distortions to avoid impairment of the measurements and inaccuracies in flow quantification\(^\text{17,18}\).
CMR image analysis. All images were post-processed and analysed using offline research software called MASS (Version 2019 EXP, Leiden University Medical Centre, Leiden, The Netherlands). Left ventricular volumes, EF, and mass were calculated according to standard methods.

Four-dimensional flow CMR pressure gradient assessment. All three-phase directions were screened for aliasing artefact, and if present, this was manually corrected using established phase unwrapping methods. Any spatial misalignment with cine superimposition was manually corrected throughout the cardiac cycle prior to any quantification. The precise location of the maximum velocity \( V_{\text{max}} \) in the aorta during systole was identified in the 4D flow data set and the velocity recorded in a similar method to Donati et al.

Steps taken to identify the peak trans-valvular velocity were as follows:
1. Firstly, a valvular plane was identified and tracked throughout the cardiac cycle (orange line in the supplementary video 1).
2. Several multi-planar slices 3/4 mm apart were done above the valve to assess the quality of the flow curves in the region of vena-contracta.
3. The reformatted plane with the highest velocity and no artefact was selected. This was at the level of the vena contracta above the level of the valve.

Post valve intervention assessment is demonstrated in the supplementary online video. The maximum velocity determined in the 3D velocity data was used to determine the peak pressure drop by the simplified Bernoulli equation \( \Delta P = 4(V_{\text{max}})^2 \).

Four-dimensional flow CMR effective orifice area (EOA) assessment. For EOA estimation, we applied the Bernoulli principles and the law of conservation of flow at the level of vena contracta across all systolic phases where the valve is maximally open. Time-resolved flow and velocity data were recorded, and as flow = area * velocity, EOA was estimated using the following equation:

\[
\text{EOA} = \frac{\text{Flow}}{V_{\text{max}}} \\
\]

Acceleration of the blood through the valve in early systole and the deceleration of blood prior to valve closure was recorded. An estimate of EOA was acquired using a line of best fit for the linear relationship of flow and the velocity at the vena contracta and calculating the gradient of that line (Fig. 1). Velocities at different flow rates throughout the systolic phases were recorded and used to reduce noise from the data, which may be higher if the EOA was calculated from one data point.

Six-minute walk test. The six-minute walk test (6MWT) was carried out according to the guidelines outlined by the American Thoracic Society. All tests were performed by the same clinician at the same location to avoid bias. None of the patients included had limiting arthropathy or airways disease.

Statistical analysis. Statistical analysis was carried out with IBM SPSS Statistics version 25 software. Continuous measurements are presented as median with interquartile ranges (IQR). Normality of data was assessed by the Shapiro–Wilk test. Given the non-normal distribution of the data, a paired non-parametric two-tailed test (Wilcoxon signed-rank test) was used for paired analysis. Mann-Whitney test was used for all
Results

Demographic characteristics. Eighteen patients completed the full study protocol. Of these, eight patients underwent TAVI and ten patients surgical aortic valve replacement (SAVR). SAVR patients were younger than TAVI patients (68 ± 8 vs 82 ± 11, P = 0.01), and the 6MWT was better in SAVR patients than in TAVI (409 ± 182 meter vs 318 ± 96 meter, P = 0.02). A total of 6 post-operative patients (1 SAVR, 5 TAVI) declined to come back for research CMR scan. A full summary of the demographic data of the patients is shown in Table (1). Online Supplementary Table 1 provides detail on the type of replaced valve.

Invasive pressure gradient validation. From the whole cohort, eight pre-intervention patients and three post-intervention patients received invasive catheter evaluation. The peak pressure gradient by 4D low CMR was comparable to the invasive pressure gradient (54 ± 26 mmHg vs 50 ± 34 mmHg, P = 0.67). In contrast, Doppler TTE significantly overestimated the pressure gradient across the aortic valve when compared with invasive study (61 ± 32 mmHg vs 50 ± 34 mmHg, P = 0.0002) (Fig. 2). In addition, there was significant bias (−18.6 mmHg, P < 0.01) by Doppler TTE to estimate the peak pressure gradient (Fig. 3). Both Doppler TTE and 4D low CMR derived pressure gradients demonstrated association with the corresponding invasive assessment (r = 0.95, P < 0.01; r = 0.63, P = 0.04). Using a cut-off of 64 mmHg peak pressure gradient for defining severe AS, the invasive assessment was more in agreement with 4D low CMR (weighted Kappa = 0.25, 95% CI −0.39 to 0.89) than Doppler TTE (weighted Kappa = 0.16, 95% CI −0.16 to 0.47). Online Supplementary Table 2 details per patient recordings.

EOA validation. Both 4Dflow and Doppler TTE derived EOAs were comparable (1.1 ± 0.5 cm² versus 1.2 ± 0.4 cm², P = 0.10, bias = −0.01, P = 0.10) (Fig. 4). In addition, the 4D flow derived EOA demonstrated a good correlation with Doppler TTE derived EOA (Fig. 5) for both pre-/post valve intervention cases.

Association to 6MWT. There was a significant negative correlation observed between 6MWT and 4D low CMR derived peak pressure gradient (r = −0.45, P = 0.01), 6MWT was also significantly associated with 4D flow CMR derived EOA (r = 0.54, P = 0.002) (Table 2, Fig. 5). However, the Doppler TTE derived peak pressure gradient did not demonstrate any significant correlation with 6MWT. Doppler-derived EOA showed good correlation to 6MWT (0.45, P = 0.01).

| | Patients chosen for TAVI (n = 8) | Patients chosen for SAVR (n = 10) | P |
|---|---|---|---|
| Age (years) | 82 ± 11 | 68 ± 8 | 0.01 |
| Sex (Female) | 8 (100%) | 6 (60%) | 0.05 |
| Height (cm) | 1.6 ± 0.035 | 1.7 ± 0.13 | 0.08 |
| Weight (Kg) | 55.8 ± 27.25 | 79.9 ± 8 | 0.15 |
| BMI (kg/m²) | 23.35 ± 9.75 | 28.1 ± 4.4 | 0.32 |
| SysBP (mmHg) | 150.5 ± 14 | 156.5 ± 25 | 0.63 |
| DiaBP (mmHg) | 70.5 ± 15 | 76 ± 14 | 0.45 |
| HR (bpm) | 63.2 ± 11 | 64.85 ± 11 | 0.94 |
| HDL | 1 (12.50%) | 0 (0%) | 0.26 |
| DM | 2 (25%) | 2 (20%) | 0.81 |
| Hypertension | 7 (87.50%) | 5 (50%) | 0.10 |
| Creatinine | 68.5 ± 20 | 79.5 ± 26 | 0.25 |
| ARB blocker | 0 (0%) | 1 (10%) | 0.57 |
| ACEi | 2 (25%) | 1 (10%) | 0.41 |
| Beta blocker | 2 (25%) | 2 (20%) | 0.81 |
| Ca channel blocker | 3 (37.50%) | 3 (30%) | 0.74 |
| Loop diuretics | 3 (37.50%) | 1 (10%) | 0.18 |
| Peak PG TTE (mmHg) | 77.6 ± 27.5 | 64.6 ± 22.3 | 0.12 |
| Mean PG TTE (mmHg) | 40 ± 11 | 32 ± 8 | 0.22 |
| 6MWT (m) | 318 ± 96 | 409 ± 182 | 0.02 |
| NYHA | 2 (25%) | 2 (20%) | 0.81 |

Table 1. Study demographics as per the final procedure the patient had. For all continuous variables, P-value was done using Mann-Whitney test. For all categorical variables, P-value was calculated using chi-squared test.
Association with NYHA functional status. There was no significant correlation between the NYHA classification and all parameters used in this study except for pressure gradient and EOA. Doppler TTE and 4D flow CMR pressure gradients were found to have a significant positive correlation with NYHA classification ($r = 0.74$, $P < 0.05$).
P < 0.001; r = 0.56, P = 0.001 respectively), Whereas, Doppler TTE and 4D flow CMR EOAs were found to be negatively associated with NYHA classification (r = −0.74, P < 0.001, r = −0.51, P = 0.003 respectively).

**Association with relative LV mass change.** Spearman’s correlations were computed to determine if there were any significant relationships between the relative LV mass change and the relative change in other imaging parameters. The correlation appears to be statistically significant with the relative 4D flow CMR pressure gradient

|                       | NYHA | 6MWT |
|-----------------------|------|------|
|                       | R*   | P    | R*   | P    |
| 6MWT (m)              | −0.099 | 0.60 |      |      |
| **Haemodynamic parameters** |      |      |      |      |
| BP systolic (mmHg)    | 0.08  | 0.67 | 0.23 | 0.20 |
| BP diastolic (mmHg)   | 0.18  | 0.34 | 0.26 | 0.14 |
| HR (bpm)              | −0.02 | 0.92 | −0.27| 0.22 |
| **CMR functional parameters** |      |      |      |      |
| LVEDV (mL)            | 0.15  | 0.45 | 0.36 | 0.05 |
| LVESV (mL)            | 0.13  | 0.52 | 0.24 | 0.19 |
| LV mass (g)           | 0.33  | 0.08 | 0.13 | 0.49 |
| LV SV (mL)            | 0.14  | 0.46 | 0.36 | 0.05 |
| MR EF (%)             | −0.10 | 0.60 | −0.23| 0.22 |
| **Aortic valve assessment** |      |      |      |      |
| Peak PG_{TTE} (mmHg)  | 0.74  | <0.01| −0.26| 0.16 |
| EOA_{TTE} (cm²)       | −0.74 | <0.01| 0.45 | 0.02 |
| Peak PG_{4D} (mmHg)   | 0.56  | <0.01| −0.45| 0.02 |
| EOA_{4D} (cm²)        | −0.51 | <0.01| 0.54 | <0.01|

Table 2. Correlation between CMR derived metrics with both qualitative symptom burden (NYHA functional class) and exercise tolerance measured by the 6MWT. *Spearman's rho correlation coefficient.
Larger studies are needed to evaluate our proposed methods in these challenging cases of aortic stenosis. Velocity through the aortic valve, we speculate that it is still relevant in slow low, low gradient aortic stenosis.

assumptions made by Doppler TTE. As this method is the gradient of the linear regression line between low and comprehensive assessment of AS. EOA is relatively preload independent when compared to peak velocity assessment — EOA derived by 4D low CMR described in this study is not subject to the geometric assumptions made by Doppler TTE. In addition, we describe and validate a novel EOA measurement in pre-/post-aortic valve intervention against Doppler TTE. Importantly, we note that only for 4D flow CMR, both pressure gradient and EOA demonstrated association to exercise tolerance quantified by the 6MWT. Lastly, 4D flow CMR derived peak pressure gradient demonstrated association to LV mass regression at three-months.

Pressure gradient assessment. Previous studies have demonstrated a discordance between the invasive and Doppler TTE peak pressure gradient assessment and that Doppler methods overestimate the peak pressure drop. Many reasons for this overestimation have been proposed. Firstly, due to the inherent differences between Doppler pressure gradient method, which provides a maximum instantaneous pressure gradient at one-time point versus the invasive method that provides the peak-to-peak gradient which occurs at two different time points, can lead to this overestimation. Secondly, if the gain setting on the Doppler scale is set high, it can lead to overestimation of peak velocity. Other reasons include human errors associated with the Doppler method. The 4D flow CMR methods described in this study also relies on the maximum instantaneous pressure gradient but did not result in any overestimation. In fact, for defining severe AS, 4D flow CMR demonstrated pressure gradient was more consistent with the invasive method. Reduction in overestimation could be because the peak velocity plane was spatially identified by velocity vector visualisation. This technique is not routinely applied in Doppler TTE as peak velocity assessment is made by continuous-wave Doppler, which summarises all velocities in one direction.

Similar to our study, previous work by Allen et al. have demonstrated a systematic bias between Doppler and 4D flow CMR for the assessment of peak velocity assessment in patients with AS. They showed Doppler to overestimate peak velocities. On the contrary, Nordmeyer et al. have previously demonstrated that 4D flow assessment results in significantly higher peak transvalvular flow velocities (3.12 m/s versus 2.78 m/s, P < 0.05) in stenotic lesion when compared to Doppler. However, the majority of patients in their study (56%) were with pulmonary stenosis, where Doppler alignment remains challenging. Furthermore, their patient population was different from our study. They mainly studied younger patients (26 ± 10 years old) with bi-cuspid aortic valve disease leading to complex eccentric jets in the aortic root, which are difficult to align by uni-directional encoded ultrasound imaging methods. Hence, it is more likely that ultrasound methods will underestimate true peak velocity in their study cohort. Similar to Nordmeyer et al. study, Gabbour et al. demonstrated that 4D flow resulted in significantly higher peak velocity than echocardiography in younger patients with various congenital heart diseases. Both these studies imply that 4D flow derived peak velocity assessment is possibly superior to echocardiographic methods in complex aortic valve stenotic lesions. Our study provides complementary, supportive data that 4D flow derived peak pressure gradients across the aortic valve in mainly degenerative aortic stenosis is reliable and is in agreement with the invasive assessment.

Effective orifice area assessment. EOA assessment offers complementary information when making a comprehensive assessment of AS. EOA is relatively preload independent when compared to peak velocity assessment. In addition, the novel EOA derived by 4D flow CMR described in this study is not subject to the geometric assumptions made by Doppler TTE. As this method is the gradient of the linear regression line between flow and velocity through the aortic valve, we speculate that it is still relevant in slow low, low gradient aortic stenosis. Larger studies are needed to evaluate our proposed methods in these challenging cases of aortic stenosis.

Severity of aortic stenosis and functional capacity. One of the most important clinical aspects to determine the timing of aortic valve intervention is symptom onset. This can be assessed subjectively by the NYHA functional class or more quantitatively by the 6MWT. More recently, studies have demonstrated that 6MWT predicts clinical outcomes and already, in some centres, the 6MWT is now part of the routine assessment for patients referred for TAVI. In this study, it was noteworthy that it was only for 4D flow CMR, both pressure gradient and EOA were associated with both NYHA functional class and more importantly, with the 6MWT. A better association to the 6MWT may concur with enhanced prognostication for patients with aortic stenosis than Doppler TTE derived pressure gradients.

Table 3. Association of relative LV mass change to relative change in other imaging markers pre-/post aortic valve intervention. The relative pressure gradient change pre/post valvular intervention, determined by 4D flow CMR correlated with the relative change of LV mass. *Spearman’s rho correlation coefficient.

| Parameter                        | r*   | P     |
|----------------------------------|------|-------|
| LV EF (%)                        | 0.27 | 0.40  |
| Peak PG(TE) (mmHg)               | 0.64 | 0.04  |
| EOA4Dlow (cm²)                   | 0.25 | 0.45  |
| Peak PG(TTE) (mmHg)              | 0.56 | 0.06  |
| EOA(TTE) (cm²)                   | -0.08| 0.79  |
Positive LV remodelling post intervention. It is well established that after aortic valve intervention, the LV mass regresses with decrease in afterload. LV mass regression is independently associated with improved long-term survival. It is plausible to expect a proportionate decrease in afterload, or the pressure gradient across the aortic valve and LV mass post aortic valve replacement. In this study, LV mass regression demonstrated a slightly better correlation to 4D flow CMR derived pressure gradient change - again suggesting its superiority over the standard methods of assessment.

Limitations. This study had several limitations. One key limitation is the small number of patients recruited to the study. At most, this study offers hypothesis-generating data for future larger studies, which are needed to further validate our findings. However, it is still plausible to conclude that 4D flow CMR offers an alternative non-invasive method to quantify AS and its severity. 4D flow CMR is currently not widely available and requires a significant acquisition and post-processing competence, but streamlining and simplification would facilitate clinical adoption. During the 4D flow acquisition, respiratory navigation was omitted, which may have had an impact on the accuracy of derived velocity parameters. However, studies that carried out a head-to-head comparison of whole-heart 4D flow CMR have demonstrated that for quantification of intra-cardiac flow, both respiratory navigated and non-respiratory navigated 4D flow CMR acquisitions are comparable. Another limitation that could influence the quality of the velocity profile is a low temporal resolution (40 ms). Other confounding factors include variation in the heart rate and physiological conditions between the two acquisitions.

Clinical perspective. Many of the standard methods used in the assessment of AS have been shown to have inherent inaccuracies. This includes both the non-invasive Doppler TTE and invasive assessment. Importantly, discordance between EOA and the pressure gradient to grade the severity of AS can further the confusion. It is clinically desirable to have more non-invasive tools to reduce the clinical dilemma and make an affirmative diagnosis and grading of AS. This study demonstrates that the non-invasive, non-contrast 4D flow CMR can not only provide a clinically relevant measurement of pressure gradient and EOA, but also that these metrics have enhanced association with the prognostically relevant 6MWT in patients with AS. In this study, the accuracy of 4D flow CMR pressure gradient assessment was slightly better than Doppler TTE when compared against the reference invasive methods. However, the precision was slightly lower with 4D flow CMR pressure gradient. Hence, the results from this study suggest that in patients where Doppler TTE is inconsistent with symptoms and has discordant results, 4D flow CMR could help in clinical decision making for deciding on aortic valve intervention.

Conclusion
4D flow CMR offers an alternative method for non-invasive assessment of aortic stenosis. In addition, 4D flow CMR derived valve metrics have a superior association to prognostically relevant 6MWT and LV mass regression than TTE. Future larger studies are warranted to investigate the clinical benefit of using 4D flow CMR derived AS severity to make clinical decisions.

Ethics approval and consent to participate. This study was sponsored by the Sheffield Teaching Hospitals (STH) NHS Foundation Trust and approved by the National Research Ethics Service (17/LO/0283) in the UK.

Consent for publication. Written informed consent was obtained from all patients before participation.

Data availability
Please contact author for data requests.

Received: 24 December 2019; Accepted: 18 May 2020;
Published online: 29 June 2020

References
1. Nkomo, V. T. et al. Burden of valvular heart diseases: a population-based study. The Lancet 368, 1005–1011 (2006).
2. Baumgartner, H. et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Rev. Esp. Cardiol. Engl. Ed. 71, 110 (2018).
3. Nishimura, R. A. et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. J. Am. Coll. Cardiol. 63, e57–e183 (2014).
4. Parame swarman, A. C., Reisner, D. & Amanullah, A. Discrepancy between gradients derived by cardiac catheterization and by Doppler echocardiography in aortic stenosis: how often does pressure recovery play a role? Echocardiogr. Mt. Kisco N Y 26, 1000–1005; quiz 999 (2009).
5. Svezack, D. M., Almuti, K., Ostfeld, R., Bello, R. & Gordon, G. M. Routine adjustment of Doppler echocardiographically derived aortic valve area using a previously derived equation to account for the effect of pressure recovery. J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 21, 34–37 (2008).
6. Donati Fabrizio et al. Beyond Bernoulli. Circ. Cardiovasc. Imaging 10, e005207 (2017).
7. Baumgartner, H. et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 22, 1–235; quiz 101–102 (2009).
8. Cardiovascular MR Manual. (Springer International Publishing, 2015).
9. van der Geest, R. J. & Garg, P. Advanced Analysis Techniques for Intra-cardiac Flow Evaluation from 4D Flow MRI. Curr. Radiol. Rep. 4, 38 (2016).
10. Markl, M. et al. Advanced flow MRI: emerging techniques and applications. Clin. Radiol. 71, 779–795 (2016).
11. Adrians, B. P. et al. Clinical assessment of aortic valve stenosis: Comparison between 4D flow MRI and transthoracic echocardiography. J. Magn. Reson. Imaging MRI https://doi.org/10.1002/jmri.26847 (2019).
12. Wharton, G. et al. A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. Echo Res. Pract. 2, G9–G24 (2015).
13. Seldinger, S. I. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta Radiol. 39, 368–376 (1953).
14. Chopard, R. et al. Invasive assessment of doubtful aortic stenosis by measuring simultaneous transaortic gradient with a pressure wire. Am. J. Cardiol. 111, 1772–1777 (2013).
15. Garg, P. et al. Comparison of fast acquisition strategies in whole-heart four-dimensional flow cardiac MR: Two-center, 1.5 Tesla, phantom and in vivo validation study. J. Magn. Reson. Imaging 47, 272–281 (2017).
16. Zhang, J.-M. et al. Comparison of Image Acquisition Techniques in Four-Dimensional Flow Cardiovascular MR on 3 Tesla in Volunteers and Tetralogy of Fallot Patients. Conf. Proc. Annul. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf. 2018, 1115–1118 (2018).
17. Lorenz, R. et al. Influence of Eddy Current, Maxwell and Gradient Field Corrections on 3D Flow Visualization of 3D CINE PC-MRI Data. Magn. Reson. Med. Off. J. Soc. Magn. Reson. Med. Soc. Magn. Reson. Med. 72, 33–40 (2014).
18. MacDonald, M. E., Forkert, N. D., Pike, G. B. & Frayne, R. Phase Error Correction in Time-Averaged 3D Phase Contrast Magnetic Resonance Imaging of the Cerebral Vasculature. PLOS ONE 11, e0149930 (2016).
19. Schulz-Menger, J. et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. J. Cardiovasc. Magn. Reson. 15, 35 (2013).
20. Ghiglione, D. & Pritt, M. Two-Dimensional Phase Unwrapping: Theory, Algorithms, and Software. (1998).
21. Nayak, K. S. et al. Cardiovascular magnetic resonance phase contrast imaging. J. Cardiovasc. Magn. Reson. 17, 71 (2015).
22. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am. J. Respir. Crit. Care Med. 166, 111–117 (2002).
23. Baumgartner, H., Stefenelli, T., Niederberger, J., Schima, H. & Maurer, G. ‘Overestimation’ of catheter gradients by Doppler ultrasound in patients with aortic stenosis: a predictable manifestation of pressure recovery. J. Am. Coll. Cardiol. 33, 1655–1661 (1999).
24. Abbas, A. E. & Pibarot, P. Hemodynamic characterization of aortic stenosis states. Catheter. Cardiovasc. Interv. Off. J. Soc. Card. Angiogr. Interv. 93, 1002–1023 (2019).
25. Lui, E. Y. L., Steinman, A. H., Cobbold, R. S. C. & Johnston, K. W. Human factors as a source of error in peak Doppler velocity measurement. J. Vasc. Surg. 42, 972–979 (2005).
26. Allen, B. D. et al. Thoracic aorta 3D hemodynamics in pediatric and young adult patients with bicuspid aortic valve. J. Magn. Reson. Imaging JMRI 42, 954–963 (2015).
27. Nordmeyer, S. et al. Four-dimensional velocity-encoded magnetic resonance imaging improves blood flow quantification in patients with complex accelerated flow. J. Magn. Reson. Imaging JMRI 37, 208–216 (2013).
28. Gabbour, M. et al. 4-D flow magnetic resonance imaging: blood flow quantification compared to 2-D phase-contrast magnetic resonance imaging and Doppler echocardiography. Pediatr. Radiol. 45, 804–13 (2015).
29. Abdul-Jawad Altisent, O. et al. Predictors and Association With Clinical Outcomes of the Changes in Exercise Capacity After Transcatheter Aortic Valve Replacement. Circulation 136, 632–643 (2017).
30. Ali, A. et al. Enhanced left ventricular mass regression after aortic valve replacement in patients with aortic stenosis is associated with improved long-term survival. J. Thorac. Cardiovasc. Surg. 142, 285–291 (2011).
31. Kanski, M. et al. Whole-heart four-dimensional flow can be acquired with preserved quality without respiratory gating, facilitating clinical use: a head-to-head comparison. BMC Med. Imaging 15 (2015).
32. Dumesnil, J. G. & Yoganathan, A. P. Theoretical and practical differences between the Gorlin formula and the continuity equation for calculating aortic and mitral valve areas. Am. J. Cardiol. 67, 1268–1272 (1991).

Acknowledgements
We thank the staff of the MRI unit at the University of Sheffield in facilitating all the CMR scans. In addition, we thank all the staff at the Cardiothoracic Department, Sheffield Teaching Hospitals NHS Foundation Trust for their support and help during this study. This work was supported in part by EurValve (European Union funding) (Personalised Decision Support for Heart Valve Disease), Project Number: H2020 PHC-30–2015, 689617. AR was supported by Clinical Research Career Development Fellowships from the Wellcome Trust (206632/Z/17/Z), AS was supported by the Wellcome Trust (205188/Z/16/Z). PG was supported by the Academy of Sciences Starter Grant (SGLO181/1100). Imaging infrastructure was supported by MRC and BHF funding MR/M008894/1.

Author contributions
G.T.A. recruited and supervised C.M.R. and T.T.E. studies for the project. G.T.A. and R.H. proposed the novel method of E.O.A. assessment. A.E., N.B. and B.F. supported recruitment, data entry and management. P.G., R.H., N.B. organised the study. A.R., I.H. and E.G. supported invasive assessment and input in haemodynamic assessment. A.J.S. and P.G. provided clinical reports and assessment. J.M.W. provided intellectual and infrastructure support. R.V.G. provided the software for C.M.R. evaluation. A.A.M., M.B. and T.A.T. provided critical input into the content and discussion regarding the findings of the study. The manuscript, figures and tables were drafted and revised by P.G. All authors took part in critical review and drafting of the manuscript and have read and approved the final manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41598-020-66659-6.
Correspondence and requests for materials should be addressed to P.G.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
