Repeated echocardiographic imaging of aortic stenosis: Real-life lessons

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Abstract

Background

Timing of aortic valve intervention is dependent on the accuracy and reproducibility of echocardiographic (ECHO) parameters. We aimed to assess haemodynamic subsets of aortic stenosis (AS), their change over time, and variability of ECHO parameters.

Method

This retrospective, longitudinal study compared sequential ECHO over 15 months to identify concordant or discordant aortic valve area (AVA) and mean pressure gradient (MPG).

Results

We included 143 patients with a mean age of 76.0 years. The median length of time between studies was 112 days (IQR 38-208). Initially participants were classified as 10 (7.0%) mild, 49 (34.3%) moderate and 84 (58.7%) severe AS. In 80 (55.9%) AVA and MPG were concordant; stroke volume index (SVi) was <35ml/m^2 in 53 (74.6%). AS severity was downgraded in 33 (23.1%) patients. MPG was most consistent and AVA was the least consistent between successive investigations (intraclass correlation coefficients R=0.86 and R=0.76, respectively). Even small variations in left ventricular outflow tract (LVOT) measurement of 1 standard deviation reclassified up to 67% of participants from severe to non-severe.

Conclusion

Almost half of patients with AS have valve area/gradient discordance. Variations in LVOT diameter measurement commensurate with clinical practice reclassified AS severity in up to 2/3 of cases. Change in AS severity should only be accepted following careful scrutiny of all available ECHO data.

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in high-income countries, and its prevalence is increasing as the population ages (1). Untreated, symptomatic AS has worse survival than many cancers, but timely aortic valve intervention returns the mortality curve to that normal for the population at large (2). Careful follow-up to allow appropriate timing of valve intervention is essential, in order to avoid adverse outcomes associated with advanced disease.

With the advent of percutaneous treatments for aortic valve disease, increasing numbers of patients are considered for intervention (3, 4) with a commensurate increase in the number of patients referred for echocardiographic (ECHO) surveillance of their AS. Recommendations for the ECHO follow-up of patients with aortic stenosis (AS) differ in the prescribed frequency of echocardiographic follow-up and are not always applied consistently (5).

The reproducibility and accuracy of repeated ECHO measurements is rarely reported or taken into account in 'routine' clinical practice; inter- or intra-observer variation may lead to misdiagnoses such as spurious worsening of haemodynamic parameters when different operators perform sequential scans. Accurate and reproducible ECHO measurements are particularly important in the current era, when the proliferation of AS haemodynamic subsets has markedly increased reliance on ECHO for clinical decision-making (6).

Our aims were: i) to ascertain the prevalence of haemodynamic subsets of AS in a 'real-world' practice, ii) to interrogate their trends of AS parameters on sequential transthoracic echocardiography (TTE), and iii) to model the clinical impact of LVOT measurement variability on grading the severity of AS.

Setting

Morriston Cardiac Centre is a tertiary academic institution with a catchment population of approximately 1,000,000 and performs approx. 18,000 TTEs/year. Echocardiograms and the corresponding reports are stored in digital format using a commercially available package (Change Healthcare, Nashville, TN, USA).

Methods

Inclusion and exclusion criteria

We retrospectively searched our digital ECHO database using as inclusion criteria: ‘study performed between 01/01/2019-31/03/2020’ **and** ‘indication for study = assessment of aortic stenosis (AS)’. We identified patients who had >1 study during this period, and retained for further analysis only those who had 2 or 3 studies, after ascertaining that the number of those with >3 exams was small. We excluded patient that had received frequent scans over a concentrated interval because of suspected or confirmed infective endocarditis. All patients had transthoracic echocardiographic (TTE) examinations according to the BSE minimum dataset for TTE (7). We assessed the values of, and sequential changes in: mean aortic valve (AV) gradient (MPG), peak AV velocity, AV area (AVA - by the continuity equation), stroke volume index (SVi) and left ventricular outflow tract (LVOT) diameter between successive examinations. We considered LVEF (cut-off 50%), SVi (35ml/m^2), AVA (1cm^2), MPG (40MM Hg) and PkV (4m/s) and, in accordance with the literature, identified four haemodynamic subsets of AS, according to AVA (cut-off 1cm^2) and MPG (cut-off 40 mm Hg). We classified AS severity using AVA: Mild - AVA >1.5 cm^2, moderate - AVA = 1-1.5 cm^2, and severe when <1cm^2 (8). We posited that, as the LVOT diameter is relatively fixed in a given patient even if the AS progresses, it can be used to test variability for repeated measurements.

We explored the potential clinical significance of variations in the measured LVOT diameter by calculating continuity AVA with the values at the extremes of the range of diameters measured sequentially, and identified the proportion of patients who would have been reclassified from severe to non-severe with the new LVOT values.

Statistics

Analyses were performed using IBM SPSS v. 25 (Chicago, IL, USA). Continuous numerical variables are presented as mean (±standard deviation (±SD)) and range. Non-normally distributed data are presented as median (±interquartile range (±IQR)). First and second ECHO studies were compared using paired samples 2-tailed t-tests, and first, second and third studies were compared using repeated measures ANOVA. Where parametric assumptions were not met, we used Wilcoxon Signed Rank test (1^{st} vs 2^{nd}) and Friedman's two-way ANOVA (1^{st} vs 2^{nd} vs 3^{rd}). The threshold for significance was set at $p<0.05$. We calculated the coefficient of variation and of repeatability of the echocardiographic measurements. The coefficient of repeatability (CR) was calculated as within-subject standard deviation (SW) x 2.77 ($\sqrt{2}*1.96$) (9). Dedicated software v. 2019b (Origin Lab, Northampton, MA, USA) was used to produce graphical representations of data. We assessed the variability of repeated measurements using Bland-Altman analysis and linear regression.

Results

We included 143 patients: 126 had two, and 17 had three ECHO studies. There were 68 females and 75 males, with a mean age of 76.0 years (±10.0). The median duration between study #1 and study #2 was 112 days (IQR 38-208, range 0-320). Table 1 shows the baseline characteristics and the absence of significant difference in mean ECHO parameters between first and second echo. At inclusion, there were 10 (7.0%) cases of mild, 49 (34.3%) of moderate and 84 (58.7%) severe AS.

Haemodynamic subsets

There were two 'concordant' subsets (severe AS, with AVA <1 cm^2 and MPG≥40mm Hg, and non-severe AS, with AVA ≥1 cm^2 and MPG ≤40mm Hg) and two 'discordant' subsets (one with AVA ≥1 cm^2 but with MPG >40mm Hg and a 'low-gradient AS' subset with AVA <1cm^2 and MPG≤40 mm Hg). There were only four patients in the subset with large area/high gradient. When comparing both subsets, SVi was significantly greater in 'concordant' as opposed to 'discordant' subsets (40.7 ml/m^2 [±11.4] versus 33.8 [± 10.9] p<0.0001, respectively) (Table 2). All other parameters were not significantly different, including LVEF (55.2% [±14.2] versus 55.4% [±12.8], respectively). Supplementary Table 1 shows the ECHO parameters of each subset and supplementary Table 2 displays these, as well as further haemodynamic subsets defined by each of the metrics used. LVEF binary class did not affect haemodynamic parameters, but MPG and PkV were different by both SVi and AVA cut-offs. Supplementary table 3 shows the proportion of patients within each haemodynamic subset.

Consistency between repeated measurements

There was no significant difference between the average measurements in those who had either 2 or 3 scans during the study period, and no overall trend was apparent across time. In 68 patients (47.5%) AVA decreased between the first and second ECHO, whereas in 75 (52.4%) patients AVA either stayed the same or increased. The group with decreasing AVA compared with the group in which AVA stayed the same or increased, was associated with a significant reduction in SVi between ECHO 1 and 2 (Δ-8.45 ml/m^2 versus Δ6.83 ml/m^2, respectively, p<0.0001). MPG and PkV were not significantly different.

Correlations between repeated measurements were highly significant but only moderate (Table 3). The best correlation between two successive measurements was for the mean transvalvular gradient (R = 0.86) and the worst for AVA (R = 0.76) with LVOT diameter in an intermediate position (R = 0.79).

Coefficients of variation and of repeatability for the echocardiographic parameters are given in supplementary Table 4. We assessed agreement between successive echocardiographic measures with Bland-Altman plots, obtaining absolute bias, 95% limits of agreement (LoA) and the proportion of measurement differences falling outside LoA. Bland-Altman plots for MG, AVA, LVOTd, LVOT VTI, PkV were produced (not shown). Absolute bias was small at: -0.54 (±8.6), 0.049 (±0.34), -0.004 (±0.20), -0.38 (±5.9), -4.7 (± 55.6), 0.0003 (±0.02), respectively. Percentages of measurement differences outside of the 95% LoA were consistent with each other at: 7.1%,6.2%, 5.4%, 5.3%, 7.4% and 8.2%, respectively. There was a tendency for greater disagreement with larger measurements particularly for MG and PkV. Despite this, there was an even spread of observations around the mean difference for all measures indicating no evidence of proportional bias.

Potential clinical impact of variation in LVOT diameter measurement

Repeated scanning led to a reclassification of the severity of the AS compared to the first scan in 54 patients (37.8%), downgraded in 33 (23.1%) and upgraded in 21 (14.7%) (Figure 1). Change in classification did not appear to be associated with age, sex or specific ECHO parameters (Supplementary Table 4). Supplementary Table 5 shows a comparison of the change in measured haemodynamic parameters by severity class between repeated measurements.

To model the impact of LVOT diameter, we added or subtracted the SD of the diameter, or the highest difference between sequential diameter measurements, to the diameter reported for each study. We calculated the proportion of patients whose AS severity would have been reclassified from severe (AVA<1cm^2) to non-severe (AVA $\geq$1cm^2) if LVOT diameter would have been measured as either bigger or smaller than the actual value (Table 4). The proportion of patients reclassified from severe to non-severe ranged from 20% to 67% according to the range of LVOT diameters used in the calculation.

Discussion

We found that in almost 50% of patients with aortic stenosis who had 2 TTE studies in a tertiary centre over the course of 15 months there was a decrease in the AVA of 0.22cm^2 (±0.16) (p<0.0001) between studies. Repeated scanning reclassified the AS severity (defined by AVA) of 54 (37.8%) patients. In 80 patients (55.9%) initial AVA and MPG were concordant, while the discordant scans were in patients with low-gradient AS, and there was a moderate-to-good correlation of repeated measurement of parameters used for calculating aortic valve area, including diameter of the LVOT. We demonstrated that variations in the measurement of the LVOT diameter well within the range encountered in clinical practice have a major impact on the classification of AS severity, with its corollary of potentially inappropriate or delayed surgical referral.

Further haemodynamic subset stratification demonstrated that LVEF, with a cut-off of 50%, did not result in significant differences between the metrics monitored, while SVi (35ml/m^2) and AVA (1cm^2) dichotomised observed MPG and PkV.

Clinical impact of variation in measurement

The assessment of the reproducibility, reliability and accuracy of echocardiographic measurements is an important component of the quality improvement of echo services (10). Repeated measurement of the LVOT diameter provided us with an opportunity to assess the reproducibility (11) of this linear measurement in our clinical practice. We found little variation of LVOT measurement in our lab, and demonstrated that variation within the limits of the standard deviation of the LVOT diameter measurement had a dramatic impact on the classification of AS severity. We focused on the LVOT diameter because it is a major contributor to discrepancies in the assessment of AS severity (12) and because (unlike gradients and areas, which may change during follow-up as the disease progresses) LVOT dimensions are generally static over time. To our best knowledge there is nothing published previously on the reproducibility of echo measurements in NHS, clinical non-research settings, and our data represent a step in this direction.

The downgrading of AS severity by continuity AVA in more than 1/5 of patients at a second ECHO study was unexpected. With the natural progression of AS we would expect either no change or worsening of AVA. We did not have global longitudinal strain data from enough patients to explore the possibility that this phenomenon reflected a subclinical change in LV systolic function.

Haemodynamic subsets of AS

Since the paper by Hachicha et al., which introduced the new entity of paradoxical low-flow, low gradient AS (14), the whole field has gained complexity, with the continued proliferation of multiple new indices and haemodynamic patient subsets (15) deemed to have prognostic relevance, although this approach has been questioned (16).

A common clinical problem is AS with low area but also with low gradient (17). If LVEF is depressed, the distinction between truly severe and pseudo-severe AS can often be made by low-dose Dobutamine stress echo (18). In the presence of a normal LVEF there may be paradoxical low-flow, low-gradient AS (14). Classifications depend on accurate echocardiographic measurements of multiple haemodynamic parameters, require elimination of alternative causes for symptoms, do not have universally accepted treatment implications, and even in the best laboratories, discrepancies in AS grading may occur, with puzzling clinical implications (19). The prevalence of each haemodynamic subset outside core echo labs is poorly characterised.

We describe the 'real world' prevalence of haemodynamic subsets of AS, defined by area, gradient, peak velocity and stroke volume index and show that LVEF (cut-off 50%) is not associated with different values of the haemodynamic metrics, whereas SVi and AVA dichotomise MPG and PkV.

Limitations

This work is retrospective and observational, but as such represents real-life practice. Although we did not have access to the clinical files to understand exactly the indication for the echo studies, the fact that in the majority of patients the severity of the AS appeared to have progressed suggests that the indication for echocardiographic surveillance of AS was correct and in keeping with the guidelines (13).

Conclusions

In a 'real world' setting, almost half of patients with AS have valve area/gradient discordance. AVA decreased in 45%, together with SVi. Small variations in LVOT diameter measurement reclassified AS severity in up to 2/3 of cases. In over a fifth of cases AS severity was downgraded by a follow-up scan. Clinical decisions should never be based solely on reported echocardiographic AS progression.

Declaration of Interest

None.

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CRediT Author Statement

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Table 1.

	1st Echo n = 143	2nd Echo n = 143	2nd Echo (>90 day interval) n = 89	Coefficient of Repeatability 1st echo vs. 2nd echo
Age		76.0 (±10.0)		
Sex (Male)		n = 75 (52.4%)		
Rhythm		Normal sinus rhythm: n = 76 Atrial fibrillation: n = 21 Sinus rhythm with bundle branch block: n = 16 Sinus bradycardia: n = 14 Other: n = 16		
Technical quality (Good or adequate visualisation)	n = 79 (55.2%)	n = 69 (48.3%)		
AV area (cm²)*	1.00 (0.76-1.20) [2.46]	1.05 (0.75-1.23) [2.65]	1.01 (0.78-1.23) [2.03]	0.542 (0.0161)
Mean Gradient (mmHg)*	25.9 (18.0-33.0) [54.4]	24.0 (18.0-33.0) [59.0]	26.1 (18.0-33.2) [59.0]	23.95 (0.694)
Peak velocity (mmHg/s)*	336 (288-390) [337]	324 (287-381) [337]	327 (288-393) [305]	154.09 (4.56)
Systolic Volume index (ml/m²)*	35.1 (30.6-44.1) [70.6]	36.2 (28.7-44.5) [66.5]	39.3 (30.3-45.1) [50.5]	16.43 (0.483)
LVOT Diameter (cm²)	2.05 (0.16) [0.52]	2.09 (0.21) [0.86]	2.08 (0.23) [1.45]	1.081 (0.0322)

Table 1. Mean (standard deviation) and [range] (*median (interquartile range) and [range]) for echocardiographic parameters of aortic stenosis at successive scans. Difference between values of echocardiographic parameters at 2 successive time points expressed as a mean. All comparisons compared with echo 1 are statistically non-significant. Coefficient of Repeatability (within-subjects SEM). Other rhythm includes ventricular paced rhythm, junctional rhythm and non-reported rhythms.

Table 2.

	Discordant	Concordant	P value
Age	76.8 (10.3)	76.1 (10.5)	>0.05
Sex	Male = 33 Female = 39	Male = 42 Female = 29	>0.05
LVOTd (cm)	1.98 (0.20)	2.12 (0.23)	>0.05
LVEF (%)	54.4 (12.8)	55.2 (14.2)	>0.05
SVi (ml/m^2)	33.8 (10.9)	40.7 (11.4)	<0.0001
MPG (mmHg)	27.1 (8.31)	27.8 (13.9)	>0.05
PkV (mmHg/s)	347 (54.8)	344 (77.7)	>0.05

Table 2. Comparison and associations of discordant (echo 1: AVA ≥1 cm^2, MPG >40 mm Hg and AVA <1 cm2, MPG ≤40 mm Hg) versus concordant and reclassified (changed AS classification of mild, moderate or severe from echo 1 to echo 2) versus non-reclassified severity subgroups. Abbreviations: LVOTd

– Left ventricular outflow tract diameter, LVEF – Left ventricular ejection fraction, SVi – Stroke volume index, MPG – Mean pressure gradient and PkV – peak velocity.

Table 3.

Parameter	Intra-class correlation coefficient (95% CI)	p-value
LVOT Diameter (cm)	0.787 (0.707 – 0.845)	<0.0001
Mean Gradient (mmHg)	0.859 (0.808 – 0.896)	<0.0001
AV area (cm^2)	0.757 (0.665 – 0.823)	<0.0001

Table 3. Correlation coefficients of repeated measurements in patients who had 2 echo studies. Abbreviations: LVOT – left ventricular outflow tract; AV – aortic valve.

Table 4.

Proportion of non-severe AS	Original AVA (continuity)	AVA R + 0.23	AVA R + 0.04	AVA R - 0.23	AVA R - 0.04
Unindexed n ≥1cm^2 (%)	62/146 (42%)	98/146 (67%)	67/146 (46%)	29/146 (20%)	57/146 (39%)
Indexed n ≥0.6cm^2 (%)	28/114 (25%)	61/114 (54%)	36/114 (32%)	11/114 (10%)	23/114 (20%)

Table 4. Impact of variation in the measurement of the LVOT diameter on classification of AS severity. R is the radius of the LVOT; 0.23 cm is the SD of the measurement of the diameter of the LVOT, and 0.04 cm is the largest difference between successive measurements of the LVOT diameter. AVA – Aortic valve area.