IJC Heart & Vasculature 32 (2021) 100705

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Impact of increased augmentation index and valvuloarterial impedance on symptom recovery after aortic valve replacement for severe aortic stenosis

Dylan R. Jones [a,b,*], Derek P. Chew [a,b], Matthew J. Horsfall [a,b], Ajay R. Sinhal [b], Majo X. Joseph [b], Robert A. Baker [a,b], Jayme S. Bennetts [a,b], Joseph B. Selvanayagam [a,b], Andrew E. Russell [b], Carmine G. De Pasquale [a,b], Sam J. Lehman [a,b]

[a] Flinders University, Adelaide, SA, Australia
[b] Flinders Medical Centre, Adelaide, SA, Australia

ARTICLE INFO

Article history:
Received 7 September 2020
Received in revised form 5 December 2020
Accepted 12 December 2020

Keywords:
Aortic stenosis
Aortic valve replacement
TAVR
Symptoms
Augmentation index
Valvuloarterial impedance

ABSTRACT

Background: Aortic stenosis (AS) is a common valvular disorder with a large symptomatic burden resulting from increased myocardial workload due to valvular obstruction. The contribution of increased afterload from arterial stiffness on symptoms is uncertain. The purpose of this analysis was to determine the symptomatic impact of arterial stiffness as determined by Applanation Tonometry.

Methods: Eighty-eight patients with severe AS undergoing intervention with transcatheter aortic valve replacement (TAVR) (n = 65) or surgical aortic valve replacement (SAVR) (n = 23) were prospectively enrolled. Symptoms were recorded using the NYHA Class, Kansas City Cardiomyopathy Questionnaire (KCCQ) and a 6 min walk test (6MWT) at baseline, and 1- and 6-months post intervention. Pulse Wave Analysis (PWA) using Applanation Tonometry was performed at all reviews, including the augmentation index (AIx).

Results: Patients undergoing TAVR were older, with worse renal function and lower aortic valve areas, but were otherwise similar. There was no significant difference between the augmentation index of our AS population compared with an age matched reference population (p = 0.89).

Symptoms significantly improved after intervention according to NYHA Class, KCCQ and 6MWT. Additionally, with adjustment, the initial augmentation index correlated with the final KCCQ (Coeff. = −0.383, p = 0.02) and NYHA Class (Coeff. = 0.012, p = 0.03) and a baseline AIx value in the top quartile resulted in a significantly worse final KCCQ (95.1 v 85.2, p = 0.048) relative to the bottom 3 quartiles.

Conclusions: According to our analysis, an elevated baseline AIx is associated with a poorer symptomatic recovery after aortic valve intervention and so is worthy of consideration when assessing potential symptomatic benefit.

1. Introduction

Severe aortic stenosis (AS) is a common valvular heart condition in elderly patients and is associated with significant symptoms and poor prognosis if left untreated. Symptoms are largely a manifestation of increased left ventricular (LV) afterload, resulting in increased myocardial wall stress, and myocardial oxygen demand [1] as well as increased left sided filling pressure, leading to heart failure. Aortic valve replacement (AVR) reduces the valvular gradient in patients with severe aortic stenosis and therefore decreases afterload and myocardial wall stress, and results in improved symptoms, quality of life (QOL) and survival [2–6]. However, not all patients achieve the same symptomatic or QOL benefit from AVR. As symptoms and QOL scores gain increased relative importance in advanced age, determining who is likely to achieve the greatest symptomatic benefit from this procedure is of importance.

There is a strong association between the presence of aortic stenosis and reduced arterial compliance as both are a manifestation of the degenerative atherosclerotic process common in advanced age [1]. One mechanism by which patients may remain symptomatic is that despite a reduction in the valvular gradient

* Corresponding author at: Department of Cardiology, Flinders Medical Centre, Bedford Park, SA 5042, Australia.
E-mail address: dylan.jones@flinders.edu.au (D.R. Jones).

https://doi.org/10.1016/j.ijcha.2020.100705
2352-9067/

after the procedure, excess LV afterload remains due to ongoing arterial stiffness [7,8]. Therefore, the symptom complex in these patients is likely due to a combination of exposure of the LV to both the valvular load caused by the aortic transvalvular gradient and the arterial load caused by reduced systemic arterial compliance.

The central augmentation index (AIx) is a measure of arterial stiffness derived by measuring the augmented pressure waveform in the ascending aorta divided by pulse pressure [9]. This reflection wave returns during diastole in healthy individuals, resulting in an insignificant peak central arterial pressure, but in a stiffer arterial system, the systolic pressure wave is rapidly reflected within a less compliant vascular system, and augments the late systolic pressure, increasing the peak central arterial pressure [10] and therefore systolic myocardial afterload. This component of LV afterload is theoretically less dependent on the transaortic gradient and may potentially predict an ongoing symptomatic state after the aortic valve gradient is reduced by either surgical or transcatheter aortic valve replacement. The correlation between baseline AIx and symptoms following AVR has not been described.

An estimate of combined LV haemodynamic load is provided by the valvuloarterial impedance (Zva), which takes into account both the valvular and vascular afterload [8]. This parameter has previously been shown to be associated with mortality after transcatheter aortic valve replacement (TAVR) [7], but its relationship with symptom improvement is unclear.

The purpose of this analysis was to determine the relationship between baseline Zva and AIx and symptoms after aortic valve intervention as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), New York Heart Association (NYHA) Class and 6 Minute Walk Test (6MWT).

2. Methods

2.1. Patient population

Patients with severe, symptomatic aortic stenosis (AS) expected to undergo treatment with TAVR or surgical aortic valve replacement (SAVR) were prospectively enrolled after informed consent on presentation to the Structural Heart Disease Clinic or the Pre-Operative Assessment Clinic at Flinders Medical Centre, a large tertiary teaching hospital, between September 2016 and April 2018. Further follow up continued until December 2018.

2.2. Definition of severe AS and echocardiographic parameters

The patient population was identified as having severe AS if any of the following echocardiographic criteria were achieved: Aortic valve (AV) mean gradient $\geq$ 40 mmHg; AV peak velocity $\geq$ 4.0 m per second (m/s); AV area (AVA) $\leq$ 1.0 cm^2; or dimensionless performance index (DPI) $\leq$ 0.25, as per the criteria outlined in the joint statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography [11], or if they were clinically judged to have severe AS and were planned for AVR.

2.3. Baseline demographics and patient assessment

Patients were assessed pre-procedurally, at early review, 4–6 weeks post-procedurally, and at late review, 6–8 months post-procedurally, as determined by the patient's treating cardiologist.

At the initial assessment, demographic details were recorded, as well as height and weight, and relevant clinical history. A medication history and any ECG abnormalities were taken at all 3 visits. Relevant pathology including haematology, biochemistry and Troponin T and N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) if available were documented at the first and final visit. The pre-procedural echocardiogram was also documented, and haemodynamic information was recorded, as well as at the early and late reviews.

Pre-procedural symptoms were recorded using the New York Heart Association (NYHA) Classes of Heart Failure [12] and the Kansas City Cardiomyopathy Questionnaire (KCCQ) [13], as validated in this population by Arnold et al. [14]. These symptom tools were repeated at early and late review to determine degree and timing of symptomatic recovery. Objective symptoms were also recorded at all 3 visits, when patient mobility allowed, using a 6-minute walk test (6MWT) [15]. Gait speed over 4 m recorded in the first two 25 m laps. Frailty was assessed using the Hopkins Frailty Assessment (HFA) [16] pre-procedurally and at the late review.

Lastly, Pulse Wave Analysis (PWA) using the Applanation Tonometry method was performed at all 3 reviews using the Sphygmocor Applanation Tonometry device [17] (Fig. 1). Heart rate and systolic and diastolic blood pressure were recorded allowing calculation of mean arterial pressure and pulse pressure. Using the Sphygmocor device, record was made of Central Aortic Pressure, Central Aortic Pulse Pressure and Central Augmentation Pressure in mmHg, as well as Central Augmentation Index standardized to a heart rate of 75 bpm (%), Ejection Duration (ms) and Subendocardial Viability Ratio (%).

Procedural information was recorded including type of AV intervention (SAVR or TAVR, including which access approach), the date of the procedure, the Society of Thoracic Surgeons (STS) risk scores [18,19] at the time of procedure, including the Mortality and the Mortality and Morbidity scores, and the Transcatheter Valve Therapy (TVT) TAVR [20] in-hospital mortality score. Deaths, ICU admissions, and any perioperative complications including myocardial infarction (MI), cerebrovascular accident (CVA), conduction disease requiring a permanent pacemaker (PPM) and bleeding, as defined by the Valve Academic Research Consortium (VARC) [21] were documented.

2.4. Outcomes

For this analysis, outcomes were compared between symptomatic recovery as measured by the KCCQ Overall Summary (KCCQ-OS) Score and haemodynamic assessment using PWA.

KCCQ-OS is scored from 0 to 100, with higher numbers indicating a lower symptom burden. Recovery was measured as a continuous variable by change in baseline KCCQ-OS score to final score, and also using Relative Change in KCCQ, defined as the change in the KCCQ-OS Score divided by the baseline KCCQ-OS Score, allowing a higher weighting for patients who changed more significantly from a very symptomatic baseline relative to those who had little symptomatic change from an already high baseline KCCQ-OS Score.

The primary haemodynamic assessment used was the Central Augmentation Index (AIx), measuring the degree to which the peak of a measured pressure wave is over and above the peak of the incident pressure wave due to the addition of the reflected pressure wave. The AIx is dependent on the timing and magnitude of the reflected waveform and is influenced by the compliance and structure of vessels distal to the site of measurement [17].

The augmentation index can vary depending on several factors, including age, gender and height, therefore an augmentation index reference value was used to standardise our patients, and the variance between the calculated augmentation index and the reference augmentation index was determined. The formula for the augmentation reference index used was $AIx = 79.20 + 0.63\ (age) - 0.002\ (age^2) - 0.28\ (heart\ rate) - 0.39\ (height)$ for men and $AIx = 56.28 + 0.90\ (age) - 0.005\ (age^2) - 0.34\ (heart\ rate) - 0.24\ (height)$ for women, according the analysis by Janner et al. [22].

We also analysed differences in blood pressure, heart rate, ejection duration, subendocardial viability ratio (SEVR), defined as

Fig. 1. The Sphygmocor Applanation Tonometry device. https://atcormedical.com/wp-content/uploads/2019/09/XCEL_System.jpg.

diastolic to systolic pressure–time integral ratio, a measure of the balance between coronary perfusion and arterial load, and the valvuloarterial impedance (Zva), which is the measured impediment to blood ejection due to the combined resistive forces of both the valvular obstruction and the reduced arterial compliance.

Study data were collected and managed using REDCap electronic data capture tools hosted at the South Australian Health and Medical Research Institute (SAHMRI) [23,24].

The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/16/SAC/168), and all aspects comply with the Declaration of Helsinki.

2.5. Statistical analysis

Continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequencies and proportions. Correlations between two different variables were reported as probabilities of the variable being obtained by chance and undertaken using Spearman's rho test. Adjustment for comorbidities was undertaken using a linear regression model. Analysis of differences between the same variable over time were reported as probabilities of the variable being obtained by chance and undertaken using the Wilcoxon signed-rank test.

All reported P-values were 2-sided, and statistical significance was set at $P < 0.05$. Statistical analysis, and the production of tables and figures were undertaken using STATA IC 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

3. Results

3.1. Patient characteristics

Within the study period, 158 patients were prospectively enrolled for potential inclusion. Of these, 91 patients proceeded to aortic valve intervention within the study period with 65 patients treated with TAVR, 23 patients treated with SAVR (including 7 with concomitant coronary artery bypass grafting) and 3 patients with BAV alone. BAV only patients were excluded from the analysis, and the SAVR and SAVR with grafts groups were combined.

Patients undergoing TAVR were significantly older, with worse renal function, lower aortic valve areas and higher STS scores but were otherwise similar. Applanation tonometry data were then analysed, and the groups were compared. There were no significant differences between groups but a trend towards a lower AIx reference value in the SAVR group, which is age dependent. The variance from the AIx reference value was not different between groups. Baseline symptoms were also assessed to determine if any differences existed between groups. There was a non-significant trend towards a higher baseline symptom burden with TAVR compared with SAVR, and a significantly lower unadjusted 6MWT distance. Baseline patient data are summarised in Table 1.

3.2. Applanation Tonometry and symptoms

Since the procedural groups were similar, they were then combined for the primary analysis. Due to concerns regarding heterogeneity between TAVR and SAVR groups, a subgroup excluding

Table 1
Baseline patient characteristics, echocardiographic data, Applanation Tonometry values and symptom scores by procedure.

	Overall (N = 88)	TAVR (N = 65)	SAVR (N = 23)	p-value
Demographics and comorbidities				
Age, median (IQR)	84 (79, 87)	86 (82, 88)	72 (65, 83)	**<0.001**
Female Gender, n (%)	33 (38%)	26 (40%)	7 (30%)	0.42
BMI, median (IQR)	27.4 (24.6, 30.6)	27.3 (24.3, 29.3)	28.8 (24.8, 34.0)	0.15
NT-proBNP (ng/mL), median (IQR)	1307 (680, 3142)	1568 (748, 5214)	492 (295, 2299)	0.099
EGFR (mL/min/1.73 m^2), median (IQR)	64 (50.5, 74.5)	60 (48, 69)	71 (61, 83)	**<0.001**
Prior HF, n (%)	10 (11%)	7 (11%)	3 (13%)	0.77
Prior HTN, n (%)	70 (80%)	54 (83%)	16 (70%)	0.17
Prior IHD, n (%)	46 (52%)	35 (54%)	11 (48%)	0.62
Prior CVA, n (%)	21 (24%)	15 (23%)	6 (26%)	0.77
Prior COPD, n (%)	10 (11%)	8 (12%)	2 (9%)	0.64
Prior PVD, n (%)	16 (18%)	14 (22%)	2 (9%)	0.17
Mitral Valve Disease – Mod/Sev, n (%)	4 (5%)	4 (6%)	0 (0%)	0.22
Prior Diabetes, n (%)	23 (26%)	17 (26%)	6 (26%)	0.99
Prior AF/Flutter, n (%)	30 (34%)	24 (37%)	6 (26%)	0.35
Prior CABG, n (%)	18 (20%)	14 (22%)	4 (17%)	0.67
HFA Score, median (IQR)	1 (1, 3)	2 (1, 3)	1 (1, 3)	0.42
STS Score (%), median (IQR)	2.7 (2.0, 4.0)	3.0 (2.4, 4.4)	1.9 (0.9, 2.6)	**<0.001**
Echocardiographic data				
EF (%), median (IQR)	59 (49, 63.7)	58 (48, 63.7)	60 (50, 64)	0.75
AV Mean Gradient (mmHg), median (IQR)	45.25 (39.1, 52.2)	43.4 (38.8, 51)	47.2 (40.7, 57.2)	0.19
AV Area (cm^2), median (IQR)	0.8 (0.63, 0.94)	0.75 (0.61, 0.91)	0.9 (0.72, 1)	**0.029**
AV Peak Velocity (m/s), median (IQR)	4.40 (4.10, 4.70)	4.38 (4.00, 4.65)	4.50 (4.10, 4.90)	0.32
DPI, median (IQR)	0.23 (0.18, 0.27)	0.23 (0.17, 0.27)	0.225 (0.2, 0.28)	0.62
E/e', median (IQR)	15.2 (12.0, 20.9)	16 (12.0, 20.9)	14 (13.0, 18.5)	0.66
Left Atrial Area (cm^2), median (IQR)	25.3 (22.0, 28.1)	25.4 (22.0, 28.0)	25.2 (21.0, 28.3)	0.87
Applanation Tonometry data				
Systolic BP (mmHg), median (IQR)	152 (136, 166)	153 (135, 167)	150 (143, 160)	0.60
Diastolic BP (mmHg), median (IQR)	81 (70, 87)	79 (70, 87)	84 (75, 86)	0.48
MAP (mmHg), median (IQR)	104 (95, 112)	103 (94, 111)	104 (100, 112)	0.73
Pulse Pressure (mmHg), median (IQR)	70 (60, 83)	76 (61, 85)	66 (56, 75)	0.21
Heart Rate (bpm), median (IQR)	68 (60, 80)	68 (60, 80)	66 (59, 78)	0.71
Central Arterial Pressure (mmHg), median (IQR)	142 (127, 157)	142 (127, 158)	139 (133, 152)	0.84
Central Pulse Pressure (mmHg), median (IQR)	59 (48, 72)	60 (50, 73)	55 (46, 61)	0.13
Augmentation Pressure (mmHg), median (IQR)	22 (15, 29)	22 (16, 30)	21 (12, 25)	0.3
AIx (%), median (IQR)	36 (26, 42)	36 (28, 42)	34 (23, 43)	0.85
Ejection Duration (ms), median (IQR)	37 (33, 41)	38 (34, 42)	36 (33, 41)	0.61
SEVR (%), median (IQR)	132 (113, 154)	130 (111, 152)	144 (120, 158)	0.19
Zva, median (IQR)	4.3 (3.8, 5.4)	4.4 (3.9, 5.6)	3.9 (3.6, 4.3)	0.1
AIx Reference Value (%), median (IQR)	31.9 (27.6, 36.1)	32.8 (29.2, 36.7)	30.1 (23.8, 35.9)	0.053
AIx Variance, median (IQR)	2.98 (-6.28, 10.12)	3.22 (-6.80, 9.45)	0.18 (-2.86, 10.27)	0.51
Symptom scores				
KCCQ-OS, median (IQR)	60.2 (40.8, 76.7)	55.9 (39.1, 70.4)	69.9 (49.2, 85.4)	0.085
NYHA Class, median (IQR)	3 (2, 3)	3 (2, 3)	2 (2, 3)	0.19
6MWT Distance (m), median (IQR)	384 (284, 432)	336 (270, 404)	420 (394, 480)	**0.002**

*TAVR = Transcatheter aortic valve replacement, SAVR = Surgical aortic valve replacement, IQR = Interquartile range, N = Number, BMI = Body mass index, BNP = B-type natriuretic peptide, EGFR = Estimated Glomerular Filtration Rate, HF = Heart Failure, HTN = Hypertension, IHD = Ischaemic Heart Disease, CVA = Cerebrovascular Accident, COPD = Chronic Obstructive Pulmonary Disease, PVD = Peripheral Vascular Disease, AF = Atrial fibrillation, CABG = Coronary artery bypass grafting, HFA = Hopkins frailty assessment, EF = Ejection Fraction, AV = Aortic valve, DPI = Dimensionless performance index, BP = Blood pressure, MAP = Mean arterial pressure, AIx = Augmentation index, SEVR = Subendocardial viability ratio, Zva = Valvuloarterial impedance, KCCQ-OS = Kansas City Cardiomyopathy Questionnaire – Overall Summary, NYHA = New York Heart Association, 6MWT = Six-Minute walk test.

surgically managed patients was also analysed. We first determined whether aortic stenosis significantly altered the augmentation pressures by comparing the augmentation index of our group prior to intervention with the augmentation reference value. There was no significant difference between groups (35.5% v 32.0%, p = 0.134 for the entire cohort and 34.3% v 32.6%, p = 0.303 for the TAVR only subgroup), indicating that aortic stenosis does not significantly alter AIx.

Next we determined whether the applanation tonometry variables analysed correlated significantly with patient symptoms at baseline, as measured by the KCCQ, the NYHA class or the 6MWT using Spearman's rho test. The baseline KCCQ only correlated significantly with diastolic blood pressure, but the NYHA class correlated significantly with heart rate, AIx, and the ejection duration. The 6MWT did not correlate significantly with any of the AT variables at baseline.

A regression analysis was performed to adjust for age, gender and prior COPD, the comorbidity most likely to contribute to non-cardiac dyspnoea. The results were similar, with significant correlations between NYHA class and heart rate, ejection duration and AIx, and the addition of SEVR. The KCCQ no longer correlated with any variables, but the 6MWT now significantly correlated with the Pulse Pressure. These correlations are summarised in Table 2.

In the TAVR only subgroup, with the adjusted analysis the results were similar, with baseline NYHA class correlating with heart rate (Coeff. 0.014, p = 0.041), the augmentation index (Coeff. 0.018, p = 0.012), ejection duration (Coeff. 0.036, p = 0.024) and subendocardial viability ratio (Coeff. −0.006, p = 0.032), and the 6 Minute Walk Test now correlated with Zva (Coeff. 21.48, p = 0.047). No other correlations reached significance.

3.3. Symptoms after AV intervention

Symptoms were then compared over time, between baseline, 1 month after valve intervention and 6 months after valve inter-

Table 2
Unadjusted and adjusted correlation between baseline haemodynamic parameters and baseline symptom scores.

Factor	KCCQ Score	NYHA Class	6MWT Distance
Unadjusted			
Systolic BP, median (Rho, (p))	−0.065, (0.56)	0.112, (0.32)	0.074, (0.60)
Diastolic BP, median (Rho, (p))	0.249, **(0.02)**	−0.018, (0.87)	−0.017, (0.90)
MAP, median (Rho, (p))	0.099, (0.38)	0.087, (0.44)	0.017, (0.90)
Pulse Pressure, median (Rho, (p))	−0.145, (0.09)	0.091, (0.42)	0.084, (0.55)
Heart Rate, median (Rho, (p))	−0.120, (0.28)	0.234, **(0.03)**	−0.077, (0.58)
Central Arterial Pressure, median (Rho, (p))	−0.043, (0.70)	0.098, (0.38)	0.055, (0.69)
Central Pulse Pressure, median (Rho, (p))	−0.188, (0.09)	0.121, (0.280)	−0.012, (0.93)
Augmentation Pressure, median (Rho, (p))	−0.137, (0.220)	0.108, (0.33)	−0.022, (0.87)
AIx, median (Rho, (p))	−0.167, (0.13)	0.243, **(0.03)**	−0.082, (0.55)
Ejection Duration, median (Rho, (p))	−0.061, (0.58)	0.221, **(0.046)**	−0.048, (0.73)
SEVR, median (Rho, (p))	0.122, (0.27)	−0.201, (0.07)	0.066, (0.64)
Zva, median (Rho, (p))	−0.011, (0.92)	0.148, (0.18)	0.118, (0.40)
Adjusted for age, gender and COPD			
Systolic BP, median (Coeff, (p))	0.086, (0.41)	−0.001, (0.75)	0.939, (0.09)
Diastolic BP, median (Coeff, (p))	0.298, (0.10)	0.002, (0.73)	−0.211, (0.83)
MAP, median (Coeff, (p))	0.235, (0.16)	<0.001, (0.97)	0.630, (0.47)
Pulse Pressure, median (Coeff, (p))	−0.015, (0.91)	−0.002, (0.54)	1.561, **(0.02)**
Heart Rate, median (Coeff, (p))	−0.223, (0.25)	0.014, **(0.02)**	−0.360, (0.72)
Central Arterial Pressure, median (Coeff, (p))	0.097, (0.36)	−0.002, (0.61)	0.811, (0.15)
Central Pulse Pressure, median (Coeff, (p))	−0.071, (0.61)	−0.001, (0.83)	1.427, (0.06)
Augmentation Pressure, median (Coeff, (p))	−0.176, (0.40)	0.002, (0.73)	1.86, (0.11)
AIx, median (Coeff, (p))	−0.261, (0.18)	0.014, **(0.02)**	1.382, (0.23)
Ejection Duration, median (Coeff, (p))	−0.290, (0.51)	0.030, **(0.02)**	1.451, (0.53)
SEVR, median (Coeff, (p))	0.090, (0.23)	−0.005, **(0.03)**	−0.404, (0.34)
Zva, median (Coeff, (p))	−1.098, (0.49)	0.051, (0.29)	11.183, (0.23)

*KCCQ = Kansas City Cardiomyopathy Questionnaire – Overall Summary, NYHA = New York Heart Association, 6MWT = Six-Minute walk test, BP = Blood pressure, MAP = Mean arterial pressure, AIx = Augmentation index, SEVR = Subendocardial viability ratio, Zva = Valvuloarterial impedance.

vention. Symptoms significantly improved for all groups. This is demonstrated in Fig. 2. We were concerned that further intervention group heterogeneity could be present due to differences in symptomatic recovery time between TAVR and SAVR, so we compared median KCCQ symptom scores at 1 month and found no significant difference between TAVR and SAVR (87.5 v 83.6, p = 0.809).

Additionally, using a Wilcoxon signed-rank test, no significant differences were noted between baseline and at 6 months for E: e' (z = 0.57, p = 0.57) or NTproBNP (z = 0.14, p = 0.89), but left atrial area was larger (z = 2.28, p = 0.02).

3.4. Applanation Tonometry after AV intervention

AT values were then compared between baseline, 1 month post intervention and 6 months post intervention. The AIx reduced significantly, as did the ejection duration and, as expected due to the valvular improvement, the Zva. The SEVR increased significantly. This is demonstrated in Table 3. AIx and ejection duration correlated strongly with each other (rho 0.378, p = 0.002).

In the TAVR only subgroup, the AIx reduction trended towards, but did not reach, significance (z = 1.513, p = 0.13). The ejection duration (z = 2.984, p = 0.003), and the Zva (z = 2.592, p = 0.010) reduced significantly, and the SEVR increased significantly (z = -2.662, p = 0.008), as with the entire cohort.

3.5. Predicting symptoms based on initial AT

We then did an analysis to investigate whether final symptoms using KCCQ, NYHA, 6MWT Distance and the Relative KCCQ, could be predicted based on initial AT values. The only significant correlation was between initial diastolic BP and the relative KCCQ (rho = −0.28, p = 0.04). This correlation strengthened slightly when adjusting for age, gender and prior COPD (Coeff. = −0.02, p = 0.02). Additionally, with adjustment the final Overall KCCQ correlated with initial HR (Coeff. = −0.34, p = 0.03), AIx (Coeff. = −0.38, p = 0.02) and Zva (Coeff. = −3.22, p = 0.01). NYHA Class also correlated with the initial AIx (Coeff. = 0.01, p = 0.02). Baseline AIx, however, did not correlate with the relative change of KCCQ at 6 months.

In the TAVR only subgroup, when adjusted, the initial diastolic BP again correlated with the relative KCCQ (Coeff. = −0.017, p = 0.015), and the initial Zva correlated with the Final KCCQ (Coeff. = −3.767, p = 0.005). The correlations between baseline AIx, and Final KCCQ and NYHA Class were lost (p = 0.162 and p = 0.111, respectively).

We then wished to determine whether the final AT and the final symptoms correlated with each other and found that when adjusted for age, gender and prior COPD, only Zva significantly correlated with the final 6MWT distance, but the AIx trended towards significance for the Final Relative KCCQ, designed to be weighted towards those with the largest change from the lowest baseline. These data are demonstrated in Table 4.

Lastly, we wished to determine whether a specific initial AIx value could be found which resulted in a significant reduction in symptomatic recovery. We tested the median and the highest quartile of initial AIx against the final KCCQ-OS.

Using the median AIx of 35.5%, there was no significant difference in the KCCQ-OS at 6 months between patients with a value above and below this mark (94.95 v 87.5, p = 0.290). However, using the highest quartile of AIx in our population of 42%, we found a significant difference in the final KCCQ-OS (95.1 v 85.2, p = 0.046).

If including only TAVR treated patients, the final KCCQ-OS score were similar (95.1 v 87.2), but this did not reach significance with the reduced power (p = 0.118).

4. Discussion

Predicting symptomatic outcomes can be difficult, especially in the elderly population who may have competing causes for dyspnoea. This ability would be especially useful in the elderly severe aortic stenosis population for whom symptomatic benefit is the main driver behind intervention, rather than prolonging life. This

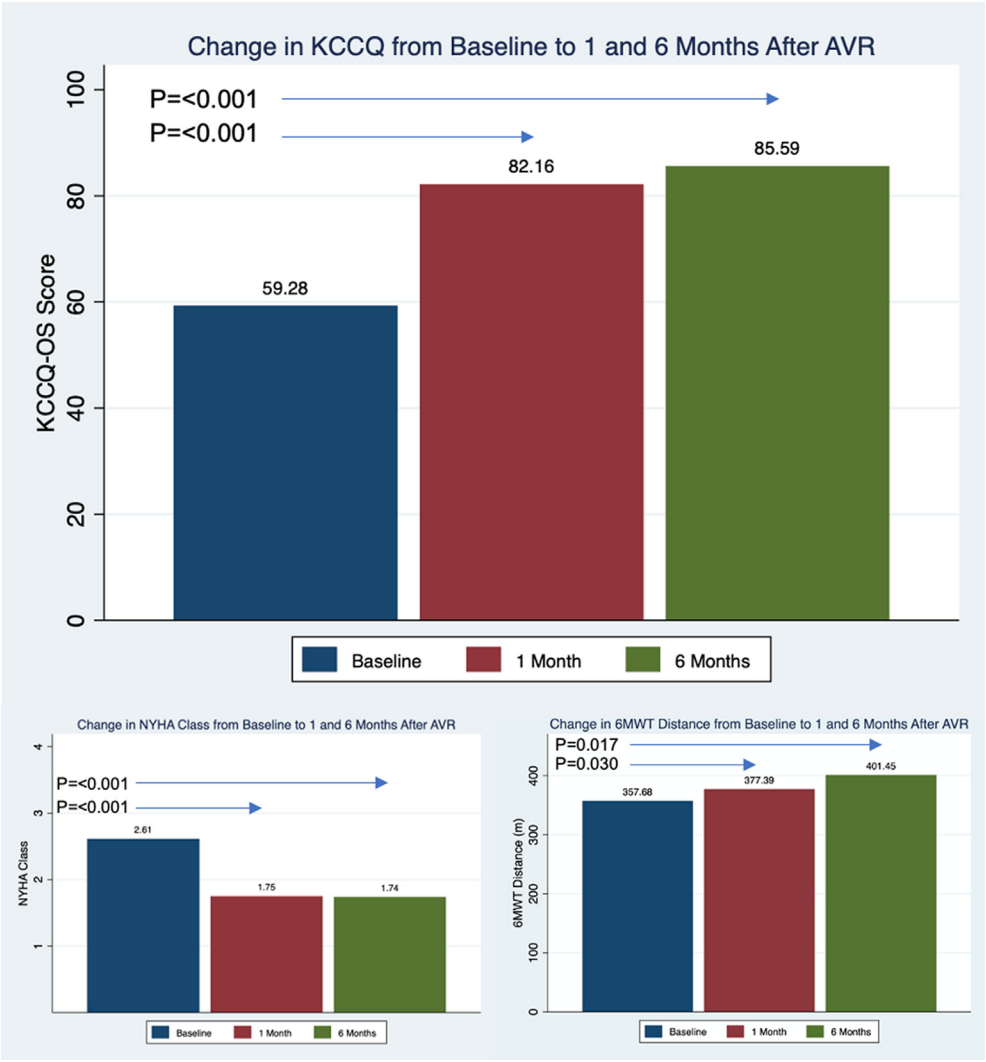

Fig. 2. Change in symptom status from baseline to 1 and 6 months after AV intervention with TAVR or SAVR. *AVR = Aortic Valve Replacement, KCCQ(-OS) = Kansas City Cardiomyopathy Questionnaire (– Overall Summary), NYHA = New York Heart Association, 6MWT = Six-Minute walk test.

Table 3
Change in Applanation Tonometry values at baseline and early and late post intervention.

Factor	Baseline	1 Month Post	6 Months Post	p-value
Systolic BP (mmHg), median (IQR)	152 (136, 166)	150 (134, 165)	150 (133, 164)	0.64
Diastolic BP (mmHg), median (IQR)	80 (70, 87)	74 (64, 82)	81 (73, 86)	0.41
MAP (mmHg), median (IQR)	104 (95, 112)	100 (88, 110)	102 (94, 111)	0.50
Pulse Pressure (mmHg), median (IQR)	70 (60, 83)	76 (62, 88)	72 (55, 86)	0.94
Heart Rate (bpm), median (IQR)	68 (60, 80)	66 (62, 82)	69 (61, 79)	0.54
Central Arterial Pressure (mmHg), median (IQR)	141 (127, 157)	134 (121, 156)	136 (119, 152)	0.27
Central Pulse Pressure (mmHg), median (IQR)	59 (48, 71	60 (48, 73)	59 (41, 71)	0.46
Augmentation Pressure (mmHg), median (IQR)	22 (14, 30)	16 (11, 27)	20 (10, 26)	0.08
AIx (%), median (IQR)	35.5 (26.5, 42.5)	27.5 (19, 34)	31 (23, 37)	**0.048**
Ejection Duration (ms), median (IQR)	37 (33, 42)	34 (31, 37)	35 (32, 39)	**0.01**
SEVR (%), median (IQR)	133 (113, 156)	144 (123, 167)	144 (125, 159)	**0.01**
Zva, median (IQR)	4.3 (3.8, 5.6)	3.6 (2.8, 4.7)	3.7 (3.2, 4.5)	**<0.001**
AIx Variance	3.0 (-6.3, 10.1)	−5.6 (-12.3, 0.4)	−0.9 (-9.3, 7.7)	0.08

*BP = Blood pressure, MAP = Mean arterial pressure, AIx = Augmentation index, SEVR = Subendocardial viability ratio, Zva = Valvuloarterial impedance.

analysis intended to examine whether a simple, inexpensive, non-invasive bedside investigation could assist in making this determination.

As has been previously reported, symptoms improved with intervention for aortic stenosis, by both surgical and transcatheter approaches. The timing of symptomatic recovery was also relatively similar, with no difference in symptom scores noted between groups at 1 month. Zva also significantly improved, since it is a composite variable representing both valvular and arterial resistance. Although the valvular obstruction has been relieved, the arterial stiffness component remains, which can also be represented by AIx, a measure of arterial stiffness leading to increased

Table 4
Adjusted correlation between baseline and final Applanation Tonometry and final symptoms.

	Final KCCQ	Final NYHA	Final 6MWT	Final Relative KCCQ
Baseline AT				
Systolic BP, median (Coeff., (p))	−0.032, (0.72)	−0.001, (0.80)	0.646, (0.45)	−0.003, (0.46)
Diastolic BP, median (Coeff., (p))	−0.045, (0.77)	−0.002, (0.68)	0.749, (0.52)	−0.015, **(0.01)**
MAP, median (Coeff., (p))	−0.052, (0.72)	−0.002, (0.70)	0.875, (0.44)	−0.010, (0.05)
Pulse Pressure, median (Coeff., (p))	−0.024, (0.83)	<-0.001, (0.98)	0.385, (0.72)	0.003, (0.40)
Heart Rate, median (Coeff., (p))	−0.342, **(0.03)**	0.006, (0.26)	0.745, (0.54)	<0.001, (0.99)
Central Arterial Pressure, median (Coeff., (p))	−0.024, (0.79)	−0.001, (0.80)	0.161, (0.85)	−0.004, (0.30)
Central Pulse Pressure, median (Coeff., (p))	−0.028, (0.82)	<0.001, (0.96)	0.128, (0.91)	0.004, (0.34)
Augmentation Pressure, median (Coeff., (p))	−0.160, (0.37)	0.007, (0.23)	−0.398, (0.80)	0.001, (0.92)
AIx, median (Coeff., (p))	−0.383, **(0.02)**	0.012, **(0.03)**	−0.205, (0.88)	−0.004, (0.48)
Ejection Duration, median (Coeff., (p))	−0.481, (0.18)	0.001, (0.92)	2.001, (0.44)	−0.001, (0.92)
SEVR, median (Coeff., (p))	0.086, (0.17)	−0.001, (0.66)	−0.131, (0.77)	−0.002, (0.52)
Zva, median (Coeff., (p))	−3.219, **(0.01)**	0.016, (0.71)	8.808, (0.44)	−0.038, (0.45)
Final AT				
Systolic BP, median (Coeff, (p))	0.088, (0.40)	<0.001, (0.93)	0.404, (0.58)	−0.001, (0.77)
Diastolic BP, median (Coeff, (p))	−0.216, (0.28)	0.011, (0.10)	0.403, (0.79)	−0.011, (0.15)
MAP, median (Coeff, (p))	−0.027, (0.88)	0.006, (0.31)	0.649, (0.63)	−0.007, (0.31)
Pulse Pressure, median (Coeff, (p))	0.185, (0.11)	−0.003, (0.39)	0.371, (0.65)	0.002, (0.62)
Heart Rate, median (Coeff, (p))	−0.135, (0.37)	0.002, (0.70)	0.467, (0.73)	0.002, (0.66)
Central Arterial Pressure, median (Coeff, (p))	0.089, (0.41)	<0.001, (0.90)	0.341, (0.66)	−0.004, (0.38)
Central Pulse Pressure, median (Coeff, (p))	0.208, (0.10)	−0.004, (0.38)	0.288, (0.74)	>-0.001, (0.88)
Augmentation Pressure, median (Coeff, (p))	0.443, (0.06)	−0.006, (0.44)	1.549, (0.33)	−0.012, (0.16)
AIx, median (Coeff, (p))	0.143, (0.53)	0.003, (0.71)	1.295, (0.40)	−0.016, (0.06)
Ejection Duration, median (Coeff, (p))	−0.144, (0.72)	<0.001, (0.94)	0.460, (0.89)	−0.012, (0.43)
SEVR, median (Coeff, (p))	−0.023, (0.69)	<0.001, (0.86)	0.094, (0.81)	<0.001, (0.75)
Zva, median (Coeff, (p))	−3.556, (0.15)	0.073, (0.36)	−38.509, **(0.04)**	0.035, (0.70)

*KCCQ = Kansas City Cardiomyopathy Questionnaire – Overall Summary, NYHA = New York Heart Association, 6MWT = Six-Minute walk test, BP = Blood pressure, MAP = Mean arterial pressure, AIx = Augmentation index, SEVR = Subendocardial viability ratio, Zva = Valvuloarterial impedance.

arterial pressure during systolic contraction, and therefore myocardial workload and symptoms. Additionally, the NYHA class, but not the KCCQ score or the 6MWT distance were shown to correlate at baseline with the AIx, but not Zva. The AIx was also one of the few AT variables shown to significantly decrease with intervention. Other variables that significantly changed included the ejection duration, the SEVR and the Zva, which all can be explained mechanistically by relief of the valvular obstruction and improved transvalvular flow. One hypothesis is that it is the reduced ejection duration post intervention which leads to a modification and hence reduction in the peak reflected pressure wave which causes the increased augmentation pressure as demonstrated by the strong statistical correlation between the AIx and ejection duration. This, in addition to the increased coronary perfusion time as demonstrated by the SEVR, could both, in theory, improve symptoms.

The baseline AIx, prior to intervention, also significantly correlated with the final adjusted KCCQ and NYHA, indicating that a higher AIx could potentially predict the final symptomatic outcome, although the relative change in KCCQ did not correlate.

Interestingly, it was found that a baseline AIx value of 42% and higher correlated with a significantly worse symptomatic benefit as measured by the 6 month KCCQ-OS, indicating it is patients in the top quartile of AIx who are most at risk of a poor outcome.

In a subgroup analysis including only TAVR treated patients, performed due to concerns regarding differences in baseline demographics, there were no differences between the AIx value and the age, gender and body size predicted reference values, as with the entire cohort. The correlations between baseline symptoms and AT values were also similar to the entire cohort. The changes in AT values after intervention were also similar to the entire cohort, except the AIx reduction now trended towards, but did not reach, significance, likely due to reduced power. The significant correlations seen in the entire group between baseline AIx, and Final KCCQ and NYHA class were also lost in the TAVR only subgroup, although a trend existed, again likely due to a reduction in power, as well as the significant difference in symptoms at the highest AIx quartile.

Potential limitations to this analysis include the relatively small sample size and the heterogenous intervention population. This was exacerbated for the TAVR only subgroup, making definitive correlations difficult, however, we were able to show that the intervention groups were similar and that the major differences in the intervention groups were accounted for by the adjustments made in the AIx calculation, namely age. The AIx can also vary between different body types and genders, which we attempted to overcome by comparing with validated reference values. Also due to the small population it was difficult to adjust for many comorbidities, and so it was decided to focus on COPD, which is most likely to contribute to persistent symptoms post intervention.

Applanation tonometry warrants further investigation in a larger dataset as it could potentially be a very simple but useful tool to assist in assessing expected symptomatic benefit post severe aortic stenosis intervention in the elderly.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] B.A. Carabello, Introduction to aortic stenosis, Circ. Res. 113 (2) (2013) 179–185.
[2] M.B. Leon, C.R. Smith, M. Mack, D.C. Miller, J.W. Moses, L.G. Svensson, et al., Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery, N. Engl. J. Med. 363 (17) (2010) 1597–1607.
[3] A. Cribier, H. Eltchaninoff, A. Bash, N. Borenstein, C. Tron, F. Bauer, et al., Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description, Circulation 106 (24) (2002) 3006–3008.
[4] R.S. Craig, B.L. Martin, J.M. Michael, D.C. Miller, W.M. Jeffrey, G.S. Lars, et al., Transcatheter versus surgical aortic-valve replacement in high-risk patients, N. Engl. J. Med. 364 (23) (2011) 2187–2198.
[5] B.L. Martin, R.S. Craig, J.M. Michael, R.M. Raj, G.S. Lars, K.K. Susheel, et al., Transcatheter or surgical aortic-valve replacement in intermediate-risk patients, N. Engl. J. Med. (2016).

[6] M.J. Mack, M.B. Leon, V.H. Thourani, R. Makkar, S.K. Kodali, M. Russo, et al., Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients, N. Engl. J. Med. 380 (18) (2019) 1695–1705.
[7] S. Katsanos, K.H. Yiu, M.A. Clavel, J. Rodes-Cabau, D. Leong, F. van der Kley, et al., Impact of valvuloarterial impedance on 2-year outcome of patients undergoing transcatheter aortic valve implantation, J. Am. Soc. Echocardiogr. 26 (7) (2013) 691–698.
[8] M. Briand, J.G. Dumesnil, L. Kadem, A.G. Tongue, R. Rieu, D. Garcia, et al., Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment, J. Am. Coll. Cardiol. 46 (2) (2005) 291–298.
[9] D.C. James, P.M. Barry, M.D. Anthony, Use of radial artery applanation tonometry and a generalized transfer function to determine aortic pressure augmentation in subjects with treated hypertension, J. Am. Coll. Cardiol. 32 (5) (1998) 1214–1220.
[10] E. Patvardhan, K.S. Heffernan, J. Ruan, M. Hession, P. Warner, R.H. Karas, et al., Augmentation index derived from peripheral arterial tonometry correlates with cardiovascular risk factors, Cardiol. Res. Pract. 2011 (2011) 253758.
[11] H. Baumgartner, J. Hung, J. Bermejo, J.B. Chambers, T. Edvardsen, S. Goldstein, et al., Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European association of cardiovascular imaging and the American society of echocardiography, J. Am. Soc. Echocardiogr. 30 (4) (2017) 372–392.
[12] M. Dolgin, A. New York Heart, C. Criteria, Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston; New York: Little Brown; 1994.
[13] C.P. Green, C.B. Porter, D.R. Bresnahan, J.A. Spertus, Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure, J. Am. Coll. Cardiol. 35 (5) (2000) 1245–1255.
[14] S.V. Arnold, J.A. Spertus, Y. Lei, K.B. Allen, A.K. Chhatriwalla, M.B. Leon, et al., Use of the Kansas City Cardiomyopathy Questionnaire for monitoring health status in patients with aortic stenosis, Circ. Heart Fail. 6 (1) (2013) 61–67.
[15] V. Bittner, D.H. Weiner, S. Yusuf, W.J. Rogers, K.M. McIntyre, S.I. Bangdiwala, et al., Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction, SOLVD Investigators. JAMA. 270 (14) (1993) 1702–1707.
[16] L.P. Fried, C.M. Tangen, J. Walston, Frailty in older adults evidence for a phenotype, Frailty in older adults evidence for a phenotype, 2001.
[17] M. Butlin, A. Qasem, Large artery stiffness assessment using sphygmocor technology, Pulse (Basel) 4 (4) (2017) 180–192.
[18] J.M. Brennan, F.H. Edwards, Y. Zhao, S.M. O'Brien, P.S. Douglas, E.D. Peterson, et al., Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007, Circulation 126 (13) (2012) 1621–1629.
[19] K. Hemmann, M. Sirotina, S. De Rosa, J.R. Ehrlich, H. Fox, J. Weber, et al., The STS score is the strongest predictor of long-term survival following transcatheter aortic valve implantation, whereas access route (transapical versus transfemoral) has no predictive value beyond the periprocedural phase, Interact. Cardiovasc. Thorac. Surg. 17 (2) (2013) 359–364.
[20] C. Reiff, S. Gurevich, S. Bertog, P. Sorajja, R. Kelly, S. Garcia, Validation of STS/ACC TVT-TAVR score in veterans undergoing transcatheter aortic valve replacement, J. Invasive Cardiol. 30 (12) (2018) 447–451.
[21] S. Stortecky, G.G. Stefanini, T. Pilgrim, D. Heg, F. Praz, F. Luterbacher, et al., Validation of the valve academic research consortium bleeding definition in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation, J. Am. Heart Assoc. 4 (10) (2015) e002135.
[22] J.H. Janner, N.S. Godtfredsen, S. Ladelund, J. Vestbo, E. Prescott, Aortic augmentation index: reference values in a large unselected population by means of the SphygmoCor device, Am. J. Hypertens. 23 (2) (2010) 180–185.
[23] P.A. Harris, R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, et al., The REDCap consortium: Building an international community of software platform partners, J. Biomed. Inform. 95 (2019) 103208.
[24] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inform. 42 (2) (2009) 377–381.