

# 'Weighing up the Load' – A Comparison of Cardiac Magnetic Resonance Methods to Assess Valvulo-Arterial Load in Patients with Aortic Stenosis

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## ABSTRACT

**Background and Aim:** The left ventricle (LV) faces a dual afterload in patients with aortic stenosis (AS) – both from the valve and vasculature. Together they form the global LV load. Two cardiac magnetic resonance (CMR) techniques have been described to quantify global LV load: (1) valvulo-arterial impedance instantaneous (ZVA-INS) and (2) valvulo-arterial load (VAL). The purpose of this study was to evaluate concordance (if any) between ZVA-INS and VAL. **Methods:** Twenty AS patients were compared (80 ± 9 years; 12 males; 80% severe). Aortic flow velocity data was obtained during breath-hold using through-plane PC Qflow imaging. ZVA-INS was determined as the relationship of aortic pressure and maximum aortic valve (AV) gradient to ascending aorta flow velocity in the time domain. VAL was determined as the relationship of aortic pressure to ascending aorta flow velocity in the frequency domain. Values from both methods were compared against total arterial compliance (TAC). **Results:** Global LV load was significantly higher when assessed by ZVA-INS (3990±1795 dynes.s.cm<sup>3</sup>) than VAL (946±318 dynes.s.cm<sup>3</sup>) (R=0.941; R<sup>2</sup>=0.886; F=109.2; P<0.01) due to the addition of maximum AV gradient. VAL was linearly related to TAC with no significant difference (R=0.313; R<sup>2</sup>=0.098; F=1.413; P=0.256). **Conclusion:** This study presents the first direct comparison of CMR methods to assess global LV load in patients with AS. We conclude a significant difference between ZVA-INS and VAL, but not between VAL and TAC. This relationship is most likely due to the addition of maximum AV gradient. **Key words:** Aortic stenosis, Arterial tonometry, Cardiac magnetic resonance, Valvulo-arterial impedance, Valvulo-arterial load, Ventriculo-arterial coupling.

## INTRODUCTION

Over the past decade, there has been renewed focus on methods to quantify global left ventricular (LV) load in patients with aortic valve stenosis (AS) owing to the rapid uptake of transcatheter aortic valve replacement (TAVR). Valvulo-arterial impedance ( $Z_{VA}$ ) is the most readily accessible method using transthoracic echocardiography (TTE).<sup>[1]</sup> Despite the accessibility of TTE limitations include: i) the potential for underestimation of flow velocity due to misalignment of the Doppler signal with flow direction; ii) the risk of underestimation of left ventricular outflow tract (LVOT) diameter due to inadequate quality and/or positioning of the imaging plane, and; iii) measurement variability related to manual tracing of flow velocity contours.<sup>[2]</sup> These limitations may significantly alter the performance of TTE to accurately quantify load in patients with AS.

Advances in Cardiac Magnetic Resonance (CMR) techniques have made it possible to measure load non-invasively in patients with AS. Two techniques have been described - valvulo-arterial impedance

instantaneous ( $Z_{VA-INS}$ ) and valvulo-arterial load (VAL).  $Z_{VA-INS}$  is measured by acquiring aortic flow velocities above the valve and within the LVOT, and by carotid arterial tonometry (AT) after CMR exam.  $Z_{VA-INS}$  is calculated by the addition of LV pressure change (from end-diastolic foot to time of 95% of peak aortic flow), maximum AV gradient and expressed as the relationship to 95% of peak aortic flow (Figure 1).<sup>[3,4]</sup> VAL is measured by acquiring aortic flow velocities in the ascending aorta at the level of the main pulmonary artery (MPA), and by radial AT simultaneously during CMR exam. Aortic pressure and volume flow waveforms are deconstructed into component harmonics for frequencies up to 8 to 10Hz.<sup>[5]</sup>

To our knowledge, direct comparison of  $Z_{VA-INS}$  and VAL has not previously been performed. VAL has the advantage of: i) allowing simultaneous acquisition of pressure, flow and volume data; ii) accounts for the multiple flow velocity profiles seen in AS, and iii) estimates load in the frequency domain - a more

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difficult method of assessment, but one that has a stronger basis in the physical sciences.<sup>[3-7]</sup>

The aim of this study was to assess concordance (if any) between  $Z_{VA-INS}$  and VAL for the estimation of global LV load in patients with known AS for the first time. We also investigated any relationship between these indices and total arterial compliance (TAC) – a validated estimate of compliance of the arterial tree.

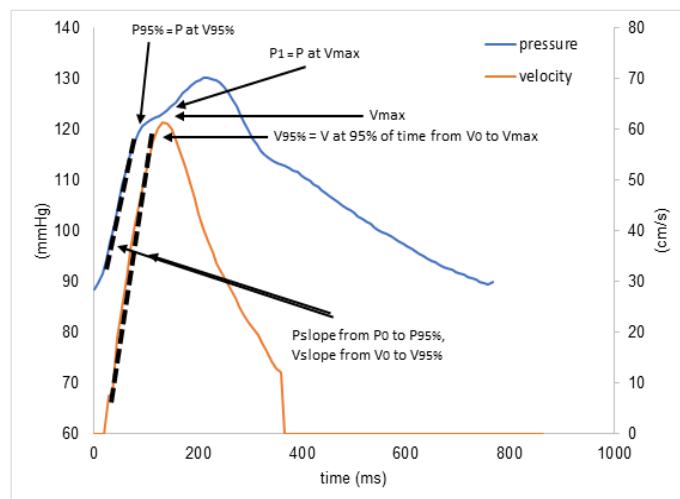
## MATERIALS AND METHODS

### Study Population

Twenty patients with AS (mean age  $80 \pm 9$  years; 12 males) were studied using a simultaneous CMR/AT and blood pressure measurement protocol.<sup>[5]</sup> Patients were excluded if there was inadequate or insufficient data to perform both  $Z_{VA-INS}$  and VAL analysis. All patients had previously provided written, informed consent and all studies were approved by the Local Hospital Research Ethics Committee.

### Arterial Tonometric Pressure Acquisition

Blood pressure was obtained via a brachial cuff sphygmomanometer during CMR scanning. AT was performed using a standalone (operator-independent) CMR compatible wrist tonometer bracelet, custom modified from a Millar SPT-301 high fidelity arterial tonometer (Millar Instruments, Houston, Texas).<sup>[8]</sup> The bracelet was fitted to the patient's wrist before scanning occurred. Once a stable pressure trace was obtained, the bracelet was left *in situ* for the duration of the CMR study and recording of tonometric pressure commenced. Using the SphygmoCor 8.1 system (AtCor Medical, Sydney, Australia) off-line, AT was calibrated to brachial sphygmomanometer cuff Systolic Pressures (SP) and Diastolic Pressures (DP), averaged over 10 cardiac cycles, and then converted to aortic pressure waveforms using a validated transfer function described previously.<sup>[9-15]</sup>



**Figure 1:** The aortic flow velocity and pressure waveform. Schematic representation of the aortic flow velocity and pressure waveform for estimation of ZVA-INS. ZVA-INS was calculated by the LV pressure change from end-diastolic foot to time of 95% of peak flow (P0 to P95%), maximum transvalvular aortic pressure gradient calculated by PC MR, and LVOT velocity encoded from curve (V95%, V at 95% of time from V0% to V95%). LV: Left ventricular; LVOT: Left ventricular outflow tract; MR: Magnetic resonance; ZVA-INS: Valvulo-arterial impedance-instantaneous.

## Cardiac Magnetic Resonance Image and Flow Acquisition

Cardiac magnetic resonance studies were performed with a 1.5T magnet with dedicated phased-array cardiac coil during successive end-expiratory breath-holds simultaneously with wrist bracelet tonometry (Siemens Magnetom, Erlangen, Germany). Steady state free precession (SSFP) images covering the entire LV volume were first acquired using a standard protocol. In addition, SSFP images were acquired during breath-hold perpendicular to the ascending aorta. Average scan parameters were: TR/TE of 3.4/1.4ms, flip angle 50°, views per segment 6, slice thickness 6mm, pixel spacing 0.76mm, acquisition matrix 224x192 and temporal resolution 10ms. Ascending aortic flow velocity data was obtained during breath-hold perpendicular at the level of the MPA using through-plane phase-contrast (PC Qflow) imaging (Figure 2). Average scan parameters were: TR/TE of 4.3-4.6/2.1-2.7 ms, flip angle 15°, slice thickness 8mm, pixel size 1.25-2.05mm, acquisition matrix of 256x208, views per segment 2, effective temporal resolution 17ms. AV mean and peak gradient were measured directly above the valve. Average encoding velocity was Venc 2m/s for LVOT acquisitions and Venc 5.5m/s for aortic valve acquisitions, but PC acquisition was repeated with higher Venc Blood pressures in the event of aliasing. Measurement of aortic cross-sectional area (CSA) was performed at the level of the MPA.<sup>[5]</sup> All CMR analyses were performed using CVI 42 (Circle Cardiovascular Imaging, Calgary, Canada) (Figure 2).

### Hemodynamic Data Analysis

Valvulo-arterial impedance instantaneous ( $Z_{VA-INS}$ ) was estimated as:

$$Z_{VA-INS} = \Delta P_{-Q95} + \text{Max}G_{-NET} \div \Delta Q_{-95},$$

where  $\Delta P_{-Q95}$  represents the LV pressure change from its end-diastolic foot to time of 95% of peak flow,  $Q_{-95}$  is estimated from the LVOT velocity encoded flow curve, and  $\text{Max}G_{-NET}$  represents the maximum AV gradient calculated by PC MR while taking into account pressure recovery, expressed as steady state in the time domain (Figure 1).<sup>[3]</sup>

Valvulo-arterial load (VAL) was estimated as:

$$\text{VAL} = \frac{P_n}{Q_n} e^{i(\theta_n - \phi_n)}$$

where  $P_n$  represents derived central aortic pressure,  $Q_n$  represents aortic flow velocity product at the MPA level, and represents both the harmonic component of pressure and phase of impedance. Impedance spectrum quantification was performed by deconstructing aortic pressure and flow waveforms into component harmonics for frequencies up to 8 to 10 Hz using a fast Fourier transformation (FFT).<sup>[4,5,7]</sup>

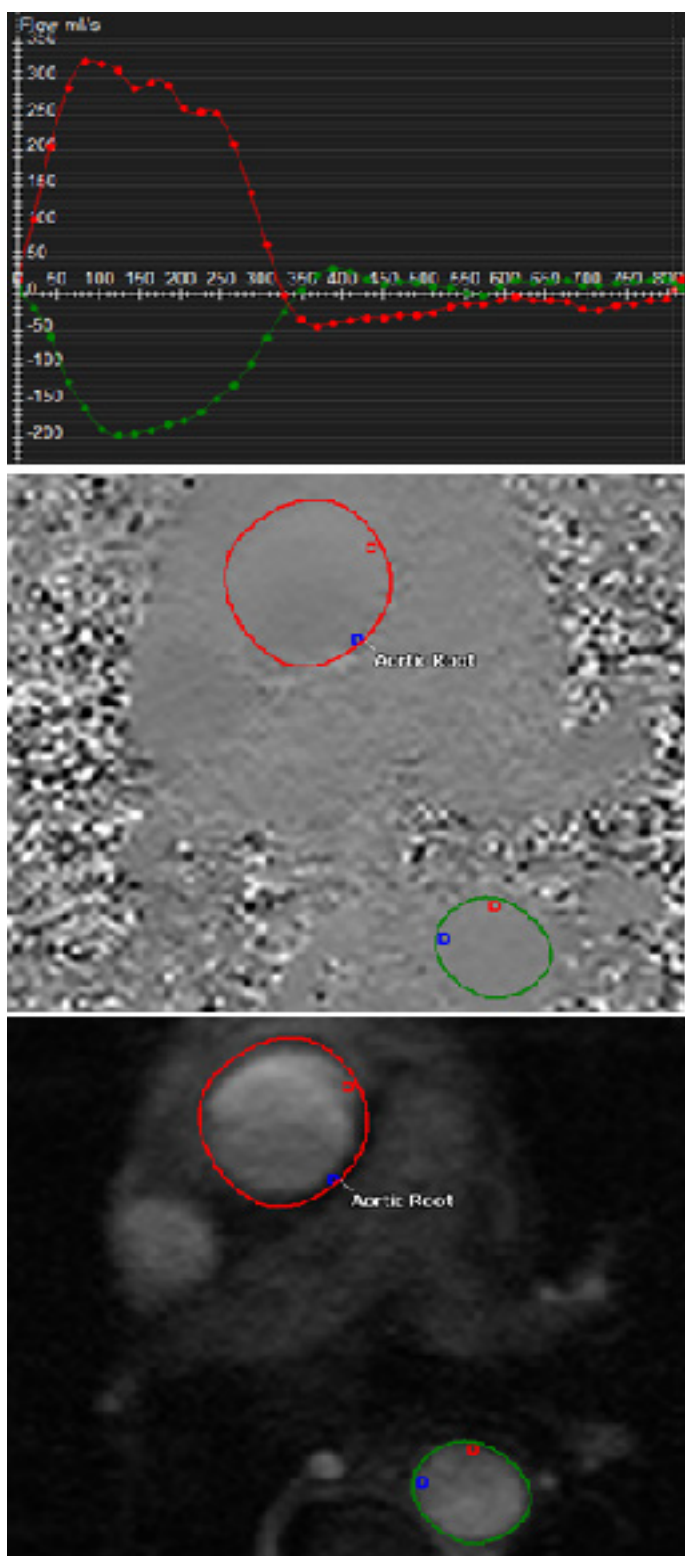
Total arterial compliance (TAC) is a validated estimate of the compliance of the large, elastic central arteries as well as the small muscular peripheral arteries. It has previously been demonstrated to be an important determinant of cardiovascular function and risk.<sup>[16]</sup> For the purpose of this study, we used the stroke volume/pulse-pressure method which is widely accepted as an index of normal or abnormal compliance.<sup>[16]</sup> TAC was estimated as:

$$\text{TAC} = \text{SV} \div \text{PP} \times 1330,$$

where SV represents stroke volume obtained by PC flow and volumetric assessment (expressed as the average), PP represents AT derived central aorta systolic pressure minus diastolic aorta pressure, and 1330 is the conversion unit.

### Intra-Observer and Inter-Observer Variability

All CMR measurements were performed by 2-blinded independent observers experienced in the technique and expressed as an average. Volumetric and flow measurement using the VAL technique and



**Figure 2:** Representative CMR left ventricular outflow tract aortic flow velocity in AS.

CMR Qflow flow velocity mapping of ascending (red) / descending (green) aorta at the level of the main pulmonary artery demonstrating a delayed time to peak velocity, with turbulent post-stenotic flow observed at peak, and flow velocity falling from this first peak to the zero level greater than 300ms.

AS: Aortic stenosis; CMR: Cardiac magnetic resonance; LVOT: Left ventricular outflow tract; MPA: Main pulmonary artery.

observers has previously been demonstrated to be extremely reproducible, with intraclass correlation coefficients approaching 1 for both intra- and inter-operator variability for both volume and flow measurement respectively (intra-operator 0.997 and 0.994; inter-operator 0.994 and 0.996;  $p < 0.001$ ).<sup>[4]</sup> As pressure acquisition was operator independent, it follows that pressure-volume and pressure-flow assessments using simultaneous AT and CMR were also reproducible.

### Statistical Analysis of Data

All normally distributed descriptive data are reported as mean and standard deviation. After identification of an overall significant difference, all possible pairwise comparisons were made, and a Tukey adjustment was applied to control the overall type I error rate. A one sample T-test was used to compare means. Correlation of numerical variables was assessed by linear regression, Scatter and Bland-Altman plots. A Spearman's rho calculation was performed to identify any correlation between VAL,  $Z_{VA-INS}$ , TAC and other variables. Data analysis was performed with SPSS-24 (IBM Corporation, Armonk, New York).

## RESULTS

Twenty patients (mean age  $80 \pm 9$  years; 12 males) were studied by CMR, AT and blood pressure. Baseline patient characteristics are reported in Table 1. Study patients were elderly ( $80 \pm 9$  years), overweight (body mass index  $28 \pm 7 \text{kg/m}^2$ ) and had a pre-existing history of hypertension on anti-hypertensive therapy in 60% (12/20) of cases. Severe AS was present in 80% of patients, 11 patients had nil/trivial concomitant aortic regurgitation (AR), whilst the remaining 9 had mild AR.

### Hemodynamic Parameters Including Load Estimation

CMR and AT-derived parameters are reported in Table 2. The mean AV gradient was  $37 \pm 13 \text{mmHg}$ , the peak AV gradient was  $68 \pm 22 \text{mmHg}$  and the planimeted AVA was  $0.9 \pm 0.2 \text{cm}^2$ . Peak LVOT velocity in the ascending aorta was  $32 \pm 12 \text{cm/sec}$ . AT-derived central systolic pressure (SP) was  $132 \pm 20 \text{mmHg}$ , diastolic pressure (DP) was  $77 \pm 8 \text{mmHg}$  and pulse pressure (PP) was  $55 \pm 19 \text{mmHg}$ .

Simultaneous pressure-flow and volume-flow analysis permitted quantification of  $Z_{VA-INS}$  and VAL.  $Z_{VA-INS}$  was  $3990 \pm 1795 \text{dyne.s.cm}^{-3}$  by linear-flow and  $442 \pm 120 \text{dyne.s.cm}^{-5}$  by volume-flow. VAL values were significantly lower ( $946 \pm 318 \text{dyne.s.cm}^{-3}$  by linear-flow;  $106 \pm 33 \text{dyne.s.cm}^{-5}$  by volume-flow;  $P < 0.01$ ). No relationship was observed between  $Z_{VA-INS}$  and VAL ( $r = 0.941$ ;  $r^2 = 0.886$ ;  $F = 109.2$ ;  $P < 0.001$ ) (Tables 1 and 2; Figures 3 and 4).

Derived SV and PP data permitted quantification of TAC. TAC was  $1072 \pm 419.4 \text{dyne.s.cm}^{-3}$ . A positive linear relationship was observed between VAL and TAC (Figure 4;  $r = 0.313$ ;  $R^2 = 0.098$ ;  $F = 1.413$ ;  $P = 0.256$ ) but not between  $Z_{VA-INS}$  and TAC (Table 3; Figure 4;  $r = 0.886$ ;  $R^2 = 0.786$ ;  $F = 47.645$ ;  $P < 0.001$ ).

### Correlation between Valvulo-Arterial Impedance, Load and Other Variables

A Spearman's rho analysis was performed to assess correlation between VAL,  $Z_{VA-INS}$  and variables thought to be related to increased global LV load. Increased VAL was found to be associated with raised SBP ( $P < 0.01$ ,  $r = 0.83$ ) and advanced age ( $P = 0.04$ ,  $r = 0.51$ ). Increased  $Z_{VA-INS}$  was found to be associated with LV ejection fraction (EF) ( $P = 0.03$ ,  $r = 0.58$ ), peak aortic valve gradient ( $P = 0.01$ ,  $r = 0.66$ ) and mean aortic valve gradient ( $P = 0.02$ ,  $r = 0.60$ ).



## DISCUSSION

The present study is the first direct comparison of CMR techniques to measure global LV load in patients with AS. Our findings can be summarized as follows: i) VAL estimates pulsatile arterial load using frequency domain analysis; ii)  $Z_{VA-INS}$  estimates steady state load using time domain analysis; iii) global LV load was significantly higher when assessed by  $Z_{VA-INS}$  than VAL and iv) there was a positive linear relationship between VAL and TAC but not  $Z_{VA-INS}$ . We attribute these findings, largely, to the addition of maximum AV gradient in the case of  $Z_{VA-INS}$ .

### Clinical Significance of Increased Load in Patients with Aortic Valve Stenosis

Ventricular function in patients with AS is impeded both by restricted aortic flow and arterial stiffening. Although  $Z_{VA-INS}$  and VAL are recently described indices,<sup>[3,5]</sup> increased  $Z_{VA}$  by TTE has previously been demonstrated to be a useful prognostic indicator of morbidity and mortality in asymptomatic patients with severe AS, symptomatic

patients with moderate AS, and in patients with paradoxical low-flow low-gradient AS.<sup>[17,18]</sup> Similarly, increased  $Z_{VA}$  is an independent predictor of myocardial systolic dysfunction in patients with anywhere from mild to severe AS.<sup>[19]</sup> This study demonstrated increased load (whether it be VAL or  $Z_{VA-INS}$ ) to be associated with hypertension ( $P < 0.01$ ), advanced age ( $P = 0.04$ ), impaired LV contractility (LVEF  $P = 0.03$ ; LVGLS  $P = 0.05$ ) and increased aortic transvalvular pressure gradients (peak gradient  $P = 0.01$ ; mean gradient  $P = 0.02$ ) as we might have expected.

### Redefining Load in Patients with Aortic Valve Stenosis

Calculation of load in patients with AS has undergone significant evolution over the past decade as physiologists and clinicians have sought to re-integrate knowledge of the physical sciences into load estimation using advanced imaging techniques. By definition, impedance of the systemic circulation expresses the relationship between pulsatile pressure and flow in an artery and is defined as:

$$z = P \div Q,$$

Where Z represents impedance, P represents pressure and Q represents flow. It is determined by relating corresponding frequency components of arterial pressures and flow waves acquired simultaneously in that artery site. It forms a graph of modulus (amplitude of pressure divided by amplitude of flow) and phase (time delay between flow and pressure represented as an angle) plotted against frequency.<sup>[20]</sup> Despite its widespread use in patients with AS, neither the commonly used TTE measure ( $Z_{VA}$ ) or  $Z_{VA-INS}$  represent pulsatile arterial load. Both indices may more accurately be described as steady state load. In this respect,

**Table 1: Baseline pre-operative demographic characteristics of study population.**

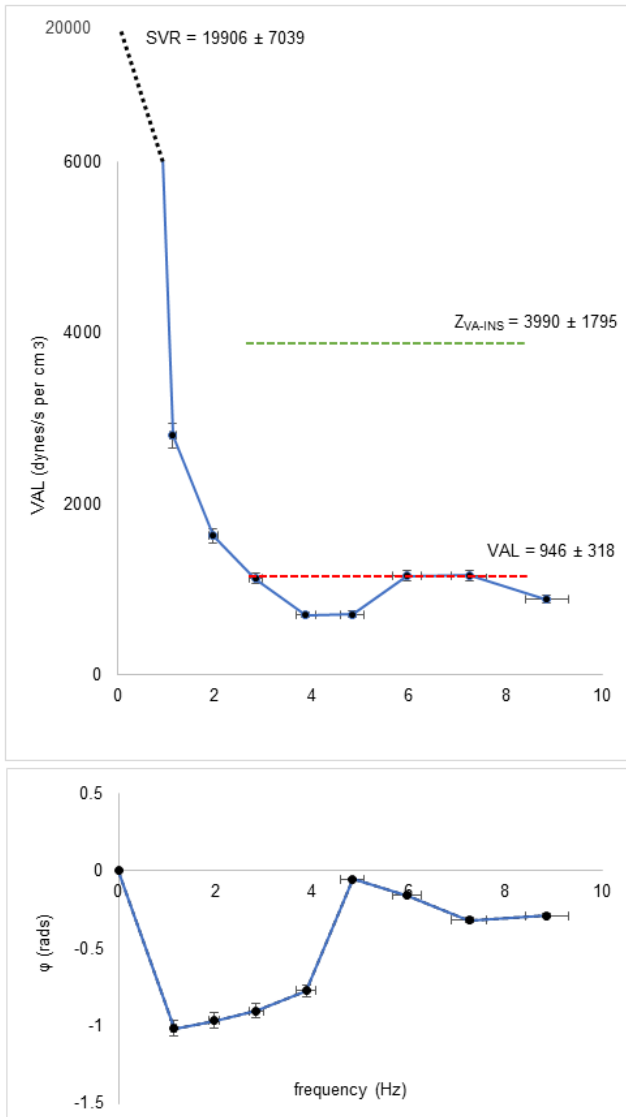
Elderly AS	Mean±SD (n=20)
Age, mean years ± SD	80 ± 9
Sex	
Male, n (%)	12 (60%)
Height (cm)	166 ± 11
Weight (kg)	78 ± 21
Body mass index (kg/m <sup>2</sup> )	28 ± 7
Body surface area (Dubois m <sup>2</sup> )	1.9 ± 9.3
Brachial SBP (mmHg)	140 ± 20
Brachial MBP (mmHg)	86 ± 16
Brachial DBP (mmHg)	75 ± 8
Central SP (mmHg)	132 ± 20
Central DP (mmHg)	77 ± 8
Central PP (mmHg)	55 ± 19
Heart rate (bpm)	70 ± 13
Cardiovascular history	
Atrial fibrillation	6 (50%)
NYHA class 3-4	14 (70%)
Hypertension	12 (60%)
Coronary artery disease	7 (35%)
AS mechanism	
Bicuspid, n (%)	2 (10%)
Degenerative, n (%)	18 (90%)
Medications	
ACE inhibitors, n (%)	11 (55%)
Beta-blockers, n (%)	8 (40%)
Digoxin, n (%)	1 (5%)
Diuretics, n (%)	8 (40%)

AS: Aortic valve stenosis; ACE: Angiotensin converting enzyme; DP: Diastolic pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure; NYHA: New York Heart Association; PP: Pulse pressure; SBP: Systolic blood pressure; SD: Standard deviation; SP: Systolic pressure.

**Table 2: Comparison of  $Z_{VA-INS}$  and VAL values.**

	$Z_{VA-INS}$ Mean±SD (n=20)	VAL Mean±SD (n=20)	P value	Reference range
<b>LV function</b>				
LV EF ± SD (%)	65 ± 14	65 ± 14	0.30	≥55 %
SV (L/min)	77 ± 18	77 ± 18	N/A	50-100mL
CO (L/min)	5.7 ± 1.5	5.7 ± 1.5	1.0	4-8L/min
<b>Aortic valve, n</b>				
Maximum velocity (cm/S)	32 ± 12	32 ± 12	N/A	<290 cm/S
Mean gradient (mmHg)	37 ± 13	37 ± 13	N/A	<25 mmHg
Aortic valve area (cm <sup>2</sup> )	0.9 ± 0.2	0.9 ± 0.2	N/A	>2.0 cm <sup>2</sup>
Aortic diameter (cm <sup>2</sup> )	9.2 ± 3.0	9.2 ± 3.0	N/A	
<b>Global LV load, n</b>				
Global LV load determination (dyne.s.cm <sup>-3</sup> )	3990 ± 1795	946 ± 318	<0.01	
Linear				
Global LV load determination (dyne.s.cm <sup>-5</sup> )	442 ± 120	222 ± 122	<0.01	700-1500 dyne.s.cm <sup>-5</sup>
Volume				
TAC (dyne.s.cm <sup>-3</sup> )	1483 ± 1034	1483 ± 1034	N/A	

AT: Arterial tonometry; AVA: Aortic valve area; CMR: Cardiac magnetic resonance; CO: Cardiac output; LV: Left ventricular; SD: Standard deviation; SVR: Systemic vascular resistance; TAC: Total arterial compliance; VAL: Valvulo-arterial load;  $Z_{VA-INS}$ : Valvulo-arterial impedance instantaneous.

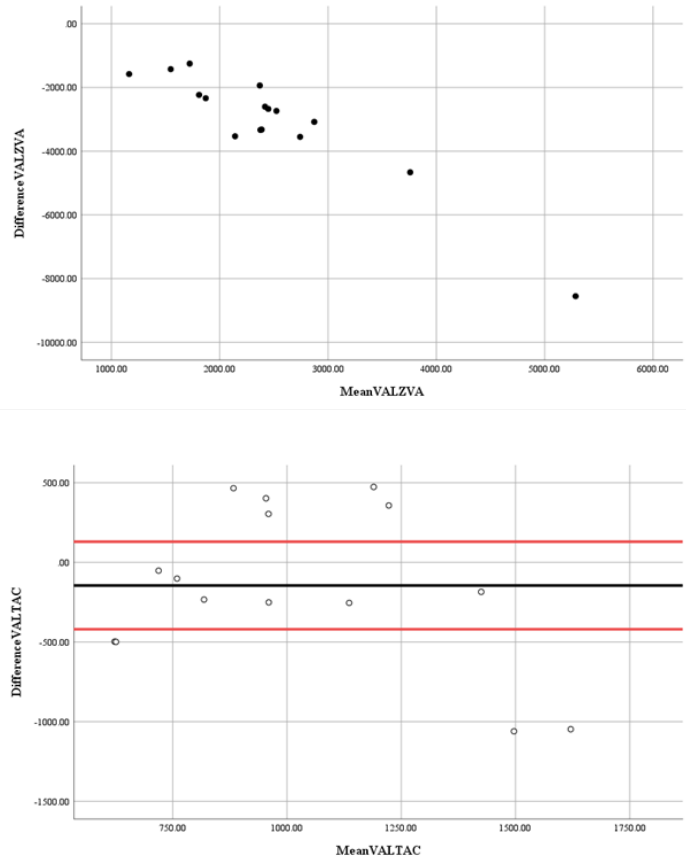


**Figure 3:** Ensemble average of ZVA-INS and VAL-derived load. Ensemble average of ZVA-INS and VAL-derived pulsatile and steady state load in study patients showing elevated VAL and SVR compared to what might be expected in healthy age-matched controls. AT: Arterial tonometry; CMR: Cardiac magnetic resonance; SVR: Systemic vascular resistance; VAL: Valvulo-arterial load; ZVA-INS: Valvulo-arterial impedance-instantaneous.

simultaneous CMR-derived methods performed in the frequency domain represent a significant advancement as they have the ability to i) measure pulsatility of the systemic circulation; ii) do not require any assumption of aortic geometry, and; iii) provide high fidelity measurements including aortic flow velocity, pressure and global LV load.<sup>[3-5,7]</sup>

### Estimation of Aortic Flow Velocity and Transvalvular Pressure Gradient

Measurement of aortic flow velocity by CMR poses different challenges, mainly related to the size and placement of voxels relative to a narrow jet. In patients with AS, especially in bicuspid aortic valve patients, measurement is routinely performed at the LVOT or just above the valve.<sup>[21,22]</sup> Flow measurement in the LVOT or directly above the AV, where complex flow is less prominent is thought to provide a more accurate



**Figure 4:** Correlation between ZVA-INS, VAL and TAC.. Bland-Altman plot relationship between ZVA-INS and VAL in 20 subjects showed a consistent bias between ZVA-INS and VAL, whereby ZVA-INS was consistently higher than VAL. Bland Altman relationship between VAL and TAC in 20 subjects showed a positive relationship ( $R = 0.313$ ;  $R^2 = 0.098$ ;  $F = 1.413$ ;  $P = 0.256$ ). AT: Arterial tonometry; CMR: Cardiac magnetic resonance; SVR: Systemic vascular resistance; TAC: Total arterial compliance; VAL: Valvulo-arterial load; ZVA-ins: Valvulo-arterial impedance-instantaneous.

measurement of forward flow. On the other hand, at the level of the MPA, the stenotic jet shows arguably its most important eccentricity and turbulence with consecutive voxel dephasing. This may lead to an underestimation of forward flow but better accounts for the multiple eccentric flow profiles that are typically observed in patients with AS. In this respect, the two techniques are fundamentally different –  $Z_{VA-INS}$  acquires LVOT flow at the level of the LVOT, whereas VAL acquires flow at the level of the MPA in the ascending aorta.<sup>[3,5]</sup>

### Estimation of Valvulo-Arterial Impedance and Load

Valvulo-arterial load was significantly higher when assessed by  $Z_{VA-INS}$  than VAL ( $P < 0.001$ ). Whereas Soulat, *et al.* proposed  $Z_{VA-INS}$  as the ratio between the total arterial pressure (summation of tonometric pressure as a surrogate for central aortic pressure and the maximum pressure gradient across the aortic valve) and aortic flow, VAL is measured as the combined global valvular and arterial load.<sup>[5]</sup> AS and systemic hypertension represent elevated impedances in series. Aortic valve hemodynamics are inherently coupled to the systemic arterial vasculature. Therefore, estimation of AV gradient is dependent on both arterial pressure and flow in relation to the systemic circulation.<sup>[23]</sup>

**Table 3: Individual comparison of  $Z_{VA-INS}$ , VAL and TAC.**

Individual Patient	VAL (dyne.s.cm <sup>-3</sup> )	VAL (dyne.s.cm <sup>-5</sup> ) CMR/AT	$Z_{VA-INS}$ (dyne.s.cm <sup>-3</sup> )	$Z_{VA-INS}$ (dyne.s.cm <sup>-5</sup> )	TAC (dyne.s.cm <sup>-3</sup> )
A	1401.47	162.87	3338.95	387.80	2026.88
B	966.36	115.46	4517.34	539.71	1263.16
C	1008.82	54.68	9562.20	518.28	871.41
D	708.62	73.74	4042.48	420.65	650.00
E	374.09	62.56	1953.32	326.64	935.09
F	1115.74	125.65	3720.37	418.97	875.25
G	701.62	86.09	3039.69	372.97	807.2
H	1111.74	134.11	3785.20	456.60	744.94
I	725.39	77.92	4048.72	434.88	752.84
J	693.01	140.29	2926.46	592.40	1085.45
K	1155.16	123.29	3892.27	415.39	1517.43
L	834.53	102.02	2260.60	276.36	952.66
M	1097.06	123.54	2348.33	264.45	703.35
N	1332.41	104.50	4412.86	346.11	1855.96
O	1426.53	157.45	6090.08	672.19	1034.11
Mean	946.22	105.98	3990.39	441.79	1071.70
SD	318.22	33.41	1795.28	119.90	419.84

AT: Arterial tonometry; CMR: Cardiac magnetic resonance; TAC: Total arterial compliances; VAL: Valvulo-arterial load;  $Z_{VA-INS}$ : Valvulo-arterial impedance instantaneous.

Summation of these resistances (as in the case of  $Z_{VA}$  and  $Z_{VA-INS}$ ) may lead to an overestimate.<sup>[24]</sup> Secondly, inconsistencies in the measurement of AV gradient on TTE, and more recently CMR, are well described.<sup>[25]</sup> A recent meta-analysis found CMR methods to be heterogenous with varying algorithms and lower absolute values.<sup>[25]</sup> Finally, when compared to healthy age-matched controls using the same technique, lower aortic peak flow velocity and higher load was observed in patients with AS.<sup>[4,7]</sup> This finding is reassuring as low peak flow velocity is typically observed in patients with advanced age and aortic root dilatation, whilst elevated VAL relates to the contributory effects of conduit vessel stiffness and valvular stenosis.

### Time versus Frequency Domain Analysis in Aortic Valve Stenosis

Whilst global LV load is often calculated in the time domain (based on an approach introduced by Dujardin, *et al.*),<sup>[26]</sup> calculation of impedance in the time domain is based on the assumption that pressure and flow are linear and measured simultaneously at the same location.<sup>[6]</sup> This is not the case in AS. Frequency domain analysis is a more common method of load assessment and has a stronger basis in the physical sciences, albeit more difficult to apply.<sup>[6]</sup> VAL allows for pressure-flow analysis using frequency domain analysis of the aortic pressure and flow velocity waveforms. Impedance spectrum quantification is performed by deconstructing aortic pressure and flow waveforms into their component harmonics for frequencies up to 8 to 10 Hz.<sup>[4,5,27]</sup> This technique, aside from being well founded in the physical sciences, represents a significant advancement in the assessment of load in patients with AS better accounts for pulsatile arterial load and thus any alteration in haemodynamic loading conditions.

### Limitations of the Study

This is a small comparative cohort study. It is possible that the presence of AS could have altered the CMR flow characteristics in the proximal aorta and affected estimation of aortic pressure from radial pressure to a degree. We did not perform carotid tonometry, four-dimensional flow, nor did we challenge patients with loading alterations during the test to assess the response of the 2 methods, in an attempt to limit study duration. Study recruitment could have been improved with a cardiac technician to check MRI-compatible devices before and after CMR, and to monitor pacing function during the scan.

### CONCLUSION

The left ventricle faces a dual afterload in patients with AS – a valvular load due to the AS, and an arterial load consequent of aortic stiffening in the presence of hypertension and age. Together they form the global LV load. Quantification of load, whether it be VAL or  $Z_{VA-INS}$ , is of renewed interest as clinicians seek to better understand the interaction between ventricular and arterial performance in patients with AS. Although traditional TTE methods are well described, newer CMR-derived methods have the ability to determine ‘gold standard’ afterload in combination with ‘gold standard’ contractility, representing a more accurate method of load assessment. Whilst  $Z_{VA-INS}$  is a more straightforward method to apply, VAL may be better suited to the physiological nuances of AS as it measures pulsatile arterial load. Further studies are needed to investigate the relationship of such hemodynamic indices with clinical outcomes, in order to guide management.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**LV:** Left Ventricle; **AS:** Aortic Stenosis; **CMR:** Cardiac Magnetic Resonance; **(Z VA-INS):** Valvulo-Arterial Impedance Instantaneous; **VAL:** Valvulo-Arterial Load; **AV:** Aortic Valve; **TAC:** Total Arterial Compliance; **TAVR:** Transcatheter Aortic Valve Replacement; **TTE:** Transthoracic Echocardiography; **LVOT:** Left Ventricular Outflow Tract; **MPA:** Main Pulmonary Artery; **SSFP:** Steady State Free Precession; **FFT:** Fast Fourier Transformation.

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