

Ageing, hypertension and aortic valve stenosis – Understanding the series circuit using cardiac magnetic resonance and applanation tonometry

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ABSTRACT

Background: Aortic stenosis (AS) is no longer considered to be a disease of fixed left ventricular (LV) afterload, but rather, functions as a series circuit, with important contributions from both the valve and vasculature. Patients with AS are typically elderly, with hypertension and a markedly remodelled aorta. The arterial component is sizeable, and yet, quantifying this to-date has been difficult to determine. We compared measurement of aortic pressure, flow and global LV load using a cardiac magnetic resonance (CMR)/applanation tonometry (AT) technique to uncouple ventriculo-arterial (VA) interactions.

Methods: 20 healthy elderly patients and 20 with AS underwent a CMR/AT protocol. CMR provided LV volume and aortic flow simultaneously with AT pressure acquisition. Aortic pressure was derived by transformation of the AT waveform. Systemic vascular resistance (SVR) and global LV load were determined as the relationship of pressure to flow in the frequency domain. Values from both cohorts were compared.

Results: AS patients were older ($p < 0.01$) albeit with no significant difference in brachial or central aortic pressure. SVR (14228 vs 19906 dyne s.cm⁻³; $p = 0.02$) and load (740 vs 946 dyne s.cm⁻³; $p = 0.02$) were higher in patients with AS, whilst aortic peak flow velocity was lower (38 vs 58 cm/s; $p < 0.01$).

Conclusions: Quantification of aortic pressure, flow velocity and global LV load using a simultaneous CMR/AT technique is able to demonstrate the progressive effects of hypertension and aortic stiffening with advanced age and valvular stenosis. This technique may help to better identify future patients at risk of VA coupling mismatch after correction of AS.

1. Background

With ageing, the central elastic aorta progressively dilates, elongates and becomes tortuous with stiffened walls [1]. Characteristic age-related changes in aortic flow velocity, pressure waveform and vascular load (VL) of the ascending aorta are now well described. Stiffening of the aorta increases the speed of propagation of the pressure pulse wave along the central arteries, which results in an earlier return of reflected waves. The shift in timing of the reflected wave augments the peak systolic pressure (SP) in the proximal aorta during systole and increases the central pulse pressure (PP). Increased SP, in turn, increases

the afterload on the heart, whilst lower diastolic pressure (DP) may reduce coronary perfusion.

The pathophysiology of adverse outcomes in patients with aortic stenosis (AS) relates to an imbalance between the global increase in left ventricular (LV) load, whether it be of valvular or vascular origin, and LV reserve at rest and during exercise. Although severity of AS has a predominant impact on structural and functional LV alterations, hypertension and increased arterial load also play a role. The prevalence of hypertension was found to be greater than 75% in a series of older patients with AS [2,3] and has been demonstrated to negatively impact upon LV remodelling, function and survival [4,5] by increasing arterial

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stiffness and, in turn, the global LV afterload. Approximately 1 in 10 patients who undergo transcatheter aortic valve implantation (TAVI) experience a worsening of symptoms or re-hospitalization for heart failure at 5-years [6] - this is presumed due to unrecognised ventriculo-arterial (VA) coupling mismatch.

After relief of valvular stenosis with surgery or TAVI, the LV load is transferred to the stiff arterial tree [7] manifesting clinically as blood pressure elevation. Traditionally, normalisation of pressure gradient across the valve is widely considered to be a marker of short-term therapeutic success, however, a reduction in global LV load may be a better marker of long-term therapeutic success. To reduce LV load optimally requires treatment of hypertension with blood pressure lowering agents. This may be challenging in patients with AS. Antihypertensive treatment for asymptomatic AS patients and a BP of $\geq 140/90$ mmHg ($\geq 160/90$ mmHg in patients >80 years) is generally recommended [8]. No such guidelines exist for the management of symptomatic patients, and as such, general guidelines for hypertension in adult patients are variably applied.

Recent studies of ascending aortic impedance as an estimation of afterload have utilized non-invasive pressure from carotid or radial arterial tonometry (AT) and flow velocity from the ascending aorta on cardiac magnetic resonance (CMR) [9–12] to estimate global LV load. For the purposes of this study, vascular load (VL) refers to the measurement of global LV load in healthy elderly patients, whilst valvulo-arterial load (VAL) refers to the measurement of global LV load in patients with known AS. Both measurements use established high-fidelity AT and CMR pressure and flow techniques to provide a measure of the steady and pulsatile components of global LV load, and are described in further detail below [12].

In the present study, we first sought to compare ascending aortic flow velocity and pressure waveforms in healthy older adults and those with AS using a simultaneous CMR/AT technique. With this data, we then estimated SVR and global LV load in healthy older adults and those with AS to uncouple VA interactions.

2. Methods

2.1. Study population

We studied 20 healthy volunteers (12 males) free from overt cardiovascular disease, aged from 64 to 79 years [9]. All were asymptomatic and had no history of cardiovascular disease, hypertension, diabetes, drug therapy and all had a normal electrocardiogram. They also had normal LV function according to screening echocardiography (ejection fraction [EF] greater than 55%) with normal valvular function. We compared this with 20 patients (12 males) studied with known AS, aged from 60 to 89 years [12]. Patients with AS were excluded if they had significant ($\geq 2+$) concomitant mitral or aortic regurgitation or an implantable cardiac device. Baseline patient characteristics are reported in Table 1. All patients provided written, informed consent and all studies were approved by the local hospital research ethics committee.

2.2. Arterial tonometry hemodynamics

Blood pressure was measured with brachial cuff sphygmomanometer during CMR scanning. Arterial tonometry was performed simultaneously with CMR study [10]. Radial AT was performed with the use of a standalone (operator independent) CMR wrist bracelet tonometer modified from a Millar Instruments SPT-301 tonometer (Millar Instruments, Houston, TX, USA) [13]. Using the SphygmoCor 8.1 system (AtCor Medical, Sydney, Australia) off-line, radial tonometric pressure waveform was calibrated to brachial sphygmomanometer cuff SP and DP, averaged over 10 cardiac cycles, and then converted to aortic pressure waveforms using a validated transfer function. This technique has been used with ease in healthy volunteers [9] and CMR-indicated patients [10,12], to permit high-fidelity measurement of aortic

Table 1

Baseline pre-operative demographic characteristics of study population.

	Healthy elderly Mean [SD] (n = 20)	Elderly AS Mean [SD] SCO(n = 20)	P value
Age, mean years \pm SD	68 \pm 6	80 \pm 9	p < 0.01
Sex			
Male, n (%)	12 (60%)	12 (60%)	p = N/S
Height (cm)	170 \pm 11	166 \pm 11	p = 0.58
Weight (kg)	73 \pm 12	78 \pm 21	p = 0.70
Body mass index (kg/m ²)	25 \pm 4	28 \pm 7	p = 0.23
Body surface area (Dubois m ²)	1.8 \pm 0.2	1.9 \pm 0.3	p = 0.27
Brachial SBP (mmHg)	125 \pm 19	140 \pm 20	p = 0.06
Brachial MBP (mmHg)	99 \pm 14	86 \pm 16	p = 0.10
Brachial DBP (mmHg)	77 \pm 11	75 \pm 8	p = 0.27
Central SP (mmHg)	127 \pm 18	132 \pm 20	p = 0.06
Central DP (mmHg)	79 \pm 11	77 \pm 8	p = 0.10
Central PP (mmHg)	47 \pm 10	55 \pm 19	p = 0.27
Heart rate (bpm)	67 \pm 11	70 \pm 13	p = 0.32
Cardiovascular history			
Atrial fibrillation	N/A	6 (50%)	N/A
NYHA class 3–4	N/A	14 (70%)	N/A
Hypertension	N/A	12 (60%)	N/A
Coronary artery disease	N/A	7 (35%)	N/A
AS mechanism			
Bicuspid, n (%)	N/A	2 (10%)	N/A
Degenerative, n (%)	N/A	18 (90%)	N/A
Medications			
ACE inhibitors, n (%)	N/A	11 (55%)	N/A
Beta-blockers, n (%)	N/A	8 (40%)	N/A
Digoxin, n (%)	N/A	1 (5%)	N/A
Diuretics, n (%)	N/A	8 (40%)	N/A

Abbreviations AS, aortic valve stenosis; ACE, angiotensin converting enzyme; DP, diastolic pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; N/A, not applicable; N/S, non significant; NYHA, New York Heart Association; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation; SP, systolic pressure.

end-systolic pressure and other indices.

2.3. Cardiac magnetic resonance image acquisition

All participants underwent CMR imaging with a 1.5 T magnet with dedicated phased-array cardiac coil during successive end-expiratory breath-holds (Signa HDx; GE Healthcare, Waukesha, USA and 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 3.4/1.4 ms, flip angle 50°, views per segment 6, slice thickness 6 mm, pixel spacing 0.76 mm, acquisition matrix 224 \times 192 and temporal resolution 10 ms. Ascending aorta flow velocity data was obtained during breath-hold perpendicular to the ascending aorta at the level of the main pulmonary artery (MPA) using through-plane phase-contrast (Qflow) imaging (Fig. 1). Average scan parameters were: TR/TE of 4.3–4.6/2.1–2.7 ms, flip angle 15°, slice thickness 8 mm, pixel size 1.25–2.05 mm, acquisition matrix of 256 \times 208, views per segment 2, effective temporal resolution 17 ms. Aortic valve mean and peak gradient were measured in the stenotic jet directly above the valve.

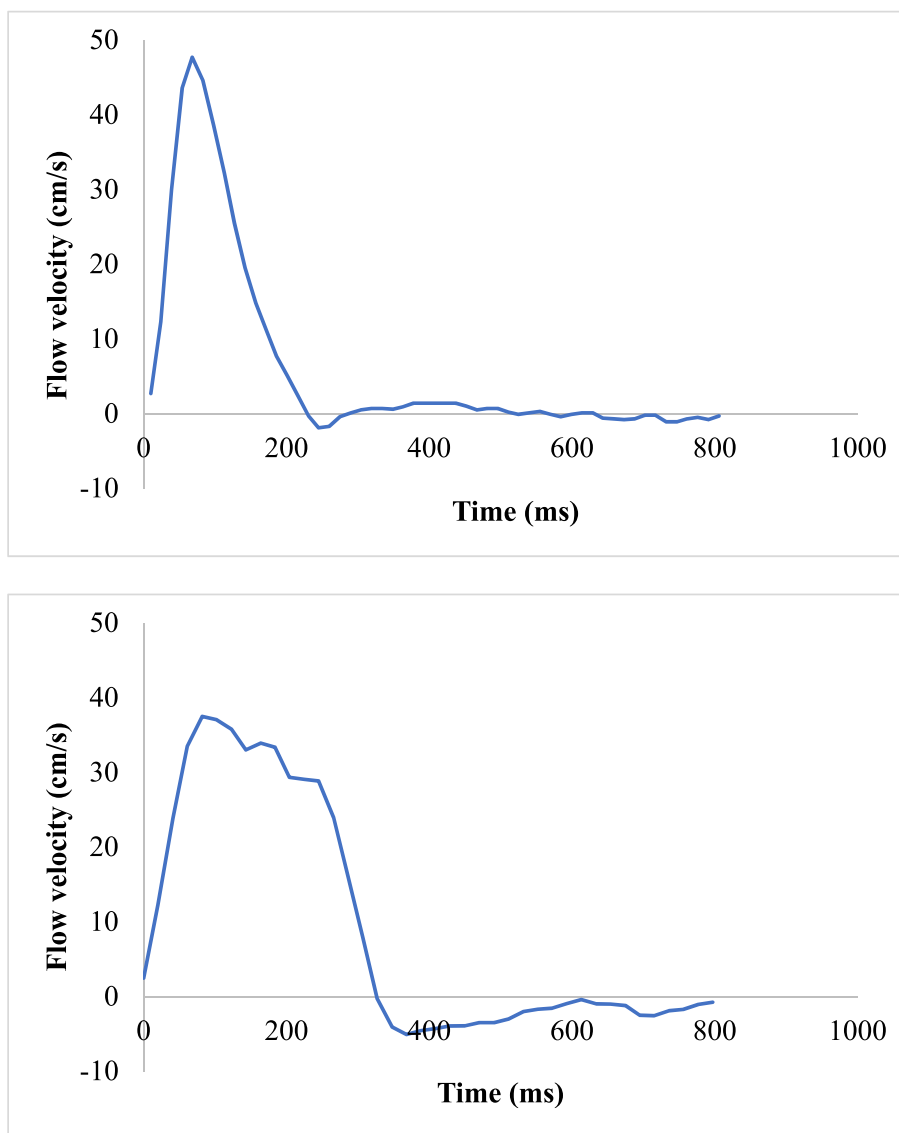


Fig. 1. Representative cardiac magnetic resonance-derived aortic flow velocity waves in a healthy subject (top) and a patient with aortic valve stenosis (bottom).

Encoding velocity (V_{enc}) was adapted to the maximum velocity but was typically V_{enc} 2 m/s for ascending aorta acquisitions and V_{enc} 5.5 m/s for aortic valve acquisitions in patients with AS. Measurement of aortic cross-sectional area (CSA) was also performed at the level of the MPA [12]. All CMR analyses were performed using CVI 42 (Circle Cardiovascular Imaging, Calgary, Canada).

2.4. Haemodynamic data analysis

Global LV load was derived from the simultaneous relationship between aortic pressure and flow velocity. Data obtained formed 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 [14–17]. This technique been described in detail previously [9,10,12] and was expressed as:

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

where Z represents global LV load (otherwise known as aortic characteristic impedance), P_n represents derived central aortic pressure, Q_n represents aortic flow velocity product at the MPA level, and $e^{i(\theta_n - \phi_n)}$ represents both the harmonic component of pressure and phase of

impedance [12]. Global LV load was expressed as vascular load (VL) in healthy older adults with no known AS and valvulo-arterial load (VAL) in patients with AS. The latter term, VAL, acknowledges the inherent contributions of valvular stenosis to load estimation as well as the interdependence between pressure gradient and systemic load [18]. Systemic vascular resistance was measured as the input impedance modulus at steady state (0 Hz) whilst global LV load (whether it be VL or VAL) was estimated as the average magnitude of impedance modulus between 2 and 9 Hz, and expressed as linear (dyne s.cm^{-3}) and volume flow (dyne s.cm^{-5}) [1,19].

2.5. Statistical analysis

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 Fisher's exact test and Mann Whitney U test were used to compare descriptive statistics. A Linear Regression model was used to control for SP differences and a Spearman's rho calculation was performed to identify any correlation with VL and VAL. Data analysis was performed with SPSS-24 (IBM Corporation, Armonk, New York).

3. Results

Individual patient characteristics are summarised in Table 1. The AS cohort was older (68 ± 6 years versus 80 ± 9 years; $p < 0.01$), albeit with no significant difference in heart rate, EF or stroke volume on study day.

3.1. Cardiac magnetic resonance

A representative CMR-derived ascending aortic flow velocity waveform in a healthy elderly subject and a patient with AS is shown in Fig. 1. In healthy elderly patients, the aortic flow velocity waves typically showed a steep rise from foot to a single systolic peak at around 100 ms, with flow velocity falling from first peak to end of systole between 150 and 300 ms, and then fluctuating around zero throughout the diastolic period (Fig. 1). In elderly patients with AS, aortic flow velocity waves showed a delayed time to peak velocity at around 150 ms, with turbulent flow typically observed at peak, and flow velocity falling from this first peak to end of systole greater than 300 ms as a consequence of longer ejection duration (333 ms versus 343 ms; $p = 0.05$) (Fig. 1). The average peak flow velocity was significantly lower in patients with AS than healthy elderly patients (58 versus 38 cm/s; $p < 0.01$) (Table 2).

3.2. Arterial tonometry

All healthy elderly patients were free of cardiovascular disease including hypertension, whilst 12 (60%) AS patients had a pre-existing hypertension on blood pressure lowering therapy. In healthy elderly patients, the central SP was 127 ± 18 mmHg, DP was 79 ± 11 mmHg and the central PP was 47 ± 10 mmHg. In patients with AS, central SP (132 ± 20 mmHg; $p = 0.06$), DP (77 ± 8 mmHg; $p = 0.10$) and PP (55 ± 19 mmHg; $p = 0.27$) values were all higher than healthy elderly patients, albeit not statistically significant.

Table 2
Comparison of VL and VAL values.

	Healthy elderly VL Mean \pm SD (n = 20)	Elderly AS VAL Mean \pm SD (n = 20)	P value	Reference range
LV function				
LV EF \pm SD (%)	65 ± 6	65 ± 14	N/A	$\geq 55\%$
SV (mL/beat)	81 ± 32	77 ± 18	$p = 0.13$	60-100 mL/beat
Aortic flow velocity, n				
Peak flow velocity (cm/S)	58 ± 26	38 ± 7	$p < 0.01$	40-70 cm/S
Mean AV gradient (mmHg)	N/A	37 ± 13	N/A	< 25 mmHg
Aortic valve area (cm ²)	N/A	0.9 ± 0.2	N/A	> 2.0 cm ²
Aortic CSA at MPA level (cm ²)	7.7 ± 1.3	9.2 ± 3.0	$p = 0.13$	< 5.2 cm ²
Global LV load, n				
Global LV load determination (dyne.s.cm ⁻³) Linear	740 ± 522	946 ± 318	$p = 0.02$	
Global LV load determination (dyne.s.cm ⁻⁵) Volume	96 ± 60	106 ± 33	$p = 0.35$	
SVR (dyne.s.cm ⁻³) Linear	14228 ± 5637	19906 ± 7039	$p = 0.02$	
SVR (dyne.s.cm ⁻⁵) Volume	1873 ± 628	2215 ± 616	$p = 0.07$	700-1500 dyne.s.cm ⁻⁵

Abbreviations: AT, arterial tonometry; AV, aortic valve; AVA, aortic valve area; CMR, cardiac magnetic resonance; CO, cardiac output; CSA, cross-sectional area; EF, ejection fraction; LV, left ventricular; MPA, main pulmonary artery; SD, standard deviation; SV, stroke volume; SVR, systemic vascular resistance; VL, vascular load; VAL, valvulo-arterial load.

3.3. Hemodynamic parameters including vascular and valvulo-arterial load estimation

Fig. 2 shows ensemble average VL, VAL and SVR. Vascular load for all healthy elderly patients was 740 ± 522 dyne.s.cm⁻³ by linear flow or 96 ± 60 dyne.s.cm⁻⁵ by volume flow. Valvulo-arterial load averaged for all patients with AS, was 946 ± 318 dyne.s.cm⁻³ by linear flow or 106 ± 33 dyne.s.cm⁻⁵ by volume flow. A significant difference was found between VL and VAL by linear flow ($p = 0.02$) but not by volume flow ($p = 0.35$), owing to dilatation of the aorta in patients with AS (7.7 ± 1.3 cm² versus 9.2 ± 3.0 cm²; $p = 0.13$). Linear regression modelling adjusted for SP also showed a significant difference in VAL by linear ($p < 0.05$) but not by volume flow ($p = 0.07$). Systemic vascular resistance averaged for all healthy elderly patients, was 14228 ± 5637 dyne.s.cm⁻³ by linear flow and 1873 ± 628 dyne.s.cm⁻⁵ by volume flow. Average SVR was 19906 ± 7039 dyne.s.cm⁻³ by linear flow and 2215 ± 616 dyne.s.cm⁻⁵ by volume flow in patients with AS ($p = 0.02$).

3.4. Correlation between vascular load, valvulo-arterial load and other variables

A Spearman's rho analysis was performed to assess correlation between VL, VAL and variables thought to be related to increased global LV load. In elderly patients, increased VL was found to be associated with aortic flow peak ($p = 0.01$; $r = -0.58$) and mean ($p < 0.01$; $r = -0.63$) velocity, SV ($p = 0.01$, $r = -0.54$) and PP (linear flow; $p = 0.03$; $r = 0.49$). In patients with AS, increased VAL was found to be associated with raised SP ($p < 0.01$, $r = 0.83$) and advanced age ($p = 0.04$, $r = 0.51$) as we might have expected.

4. Discussion

In the present study of older patients both with and without AS, we compare for the first time, the difference in total hemodynamic load presented to the LV, through characteristic changes in aortic flow velocity, pressure contour and other indices using a non-invasive CMR/AT technique. We demonstrate the progressive effects of aortic dilatation and valvular stenosis on increased global LV load.

4.1. Evolution of methods to estimate global left ventricular load

Among surviving patients who undergo TAVI, more than 10% of patients experience a worsening of symptoms or re-hospitalization for heart failure at 5-years [6]. Predictors are not well defined, however patients with low-flow and/or low-ejection states have notably poorer survival when flow or ejection fraction fail to improve [20], as do patients with post-operative hypotension [21]. Both are presumed due to unrecognised VA coupling mismatch.

Advances in cardiac imaging have created renewed focus on methods to identify VA coupling mismatch in patients with AS. Valvuloarterial impedance (Z_{VA}) by Doppler echocardiography is the most readily accessible method [22], however this index has several well recognized limitations, not least of which are flow artefacts from turbulent ascending aorta flow that create unreliable values. The superiority of simultaneous CMR/AT includes its ability to consider the pulsatile features of the systemic circulation; it does not require any assumption of aortic geometry, and; provides high-fidelity pressure and flow measurements [9-12]. We have previously shown that CMR flow velocity sampling at the level of the MPA after TAVI (which typically extends from just below the aortic annulus to the Sinotubular junction) is free from stent artefact and captures the multiple disturbed aortic root flow velocity patterns known to occur [12]. This method has previously been validated in healthy populations and other cardiovascular disease states [9-12], can be performed at ease in patients and does not require additional diagnostic time.

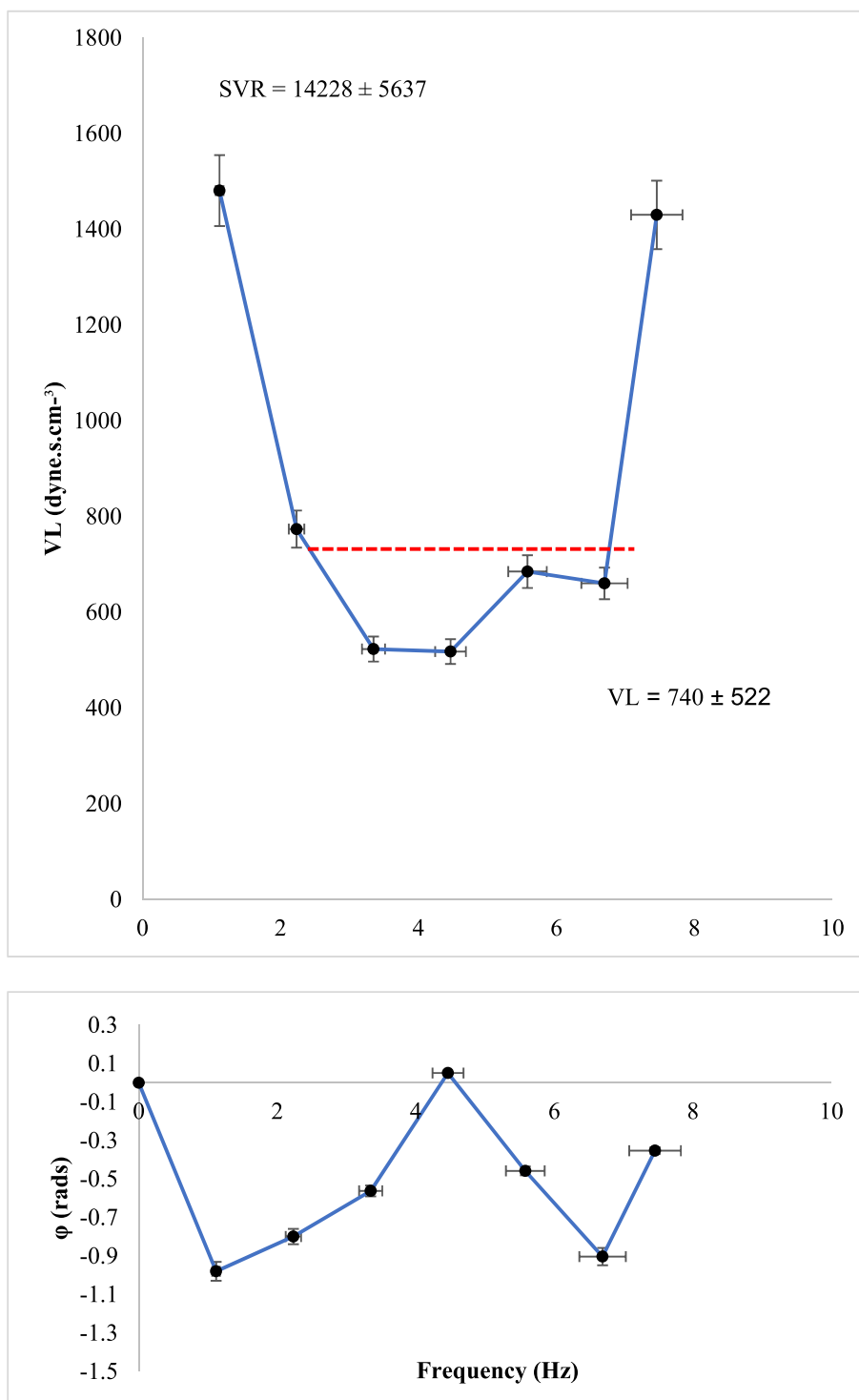


Fig. 2. Ensemble average vascular load in elderly patients (top) and those with AS (bottom).

4.2. Age- and valvular-related changes to aortic flow velocity

Ageing and cardiovascular disease states greatly impact upon aortic material properties and cushion-conduit hemodynamics [23]. Age-related changes in aortic flow are closely associated with alterations of aortic arch geometry (such as dilation and elongation). Aortic unfolding leads to changes in local pressure gradients and rotating blood vortices [24]. Low peak flow velocity in older patients is often observed

and attributable, at least partially, to progressive aortic root dilatation. Phase contrast CMR analysis allows for measurement of forward and backward aortic flow [23]. The CMR-derived aortic flow waveforms in this study are consistent with what has been reported in previous studies (Fig. 1) [18,25–27]. The lower peak flow velocity ($p < 0.01$) observed in patients with AS is attributable to progressive aortic root dilatation and age.

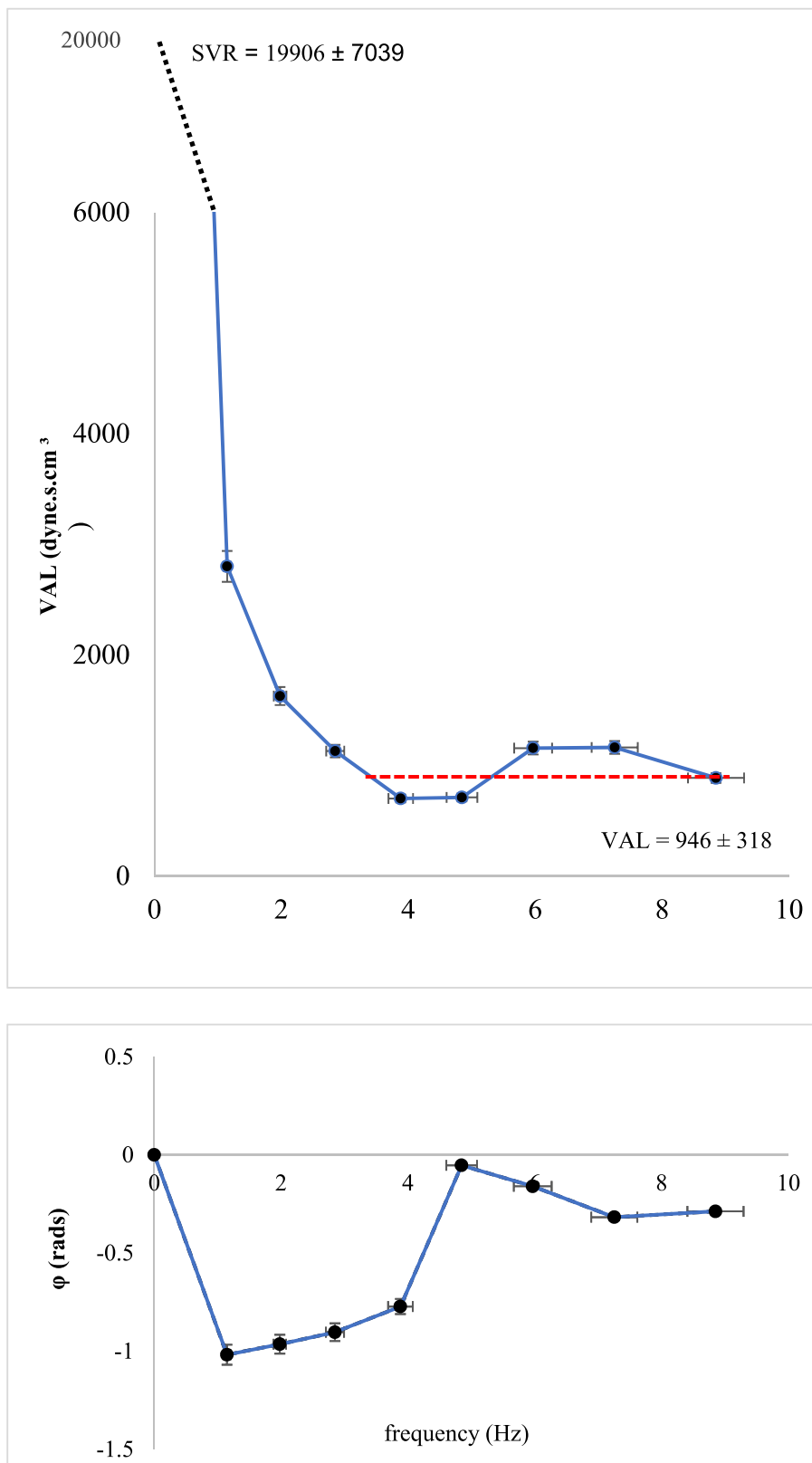


Fig. 2. (continued).

4.3. Age- and valvular-related changes to aortic pressure waveforms

Aortic pressure waves change more than flow waves with ageing [28]. In normal healthy patients, the ascending aortic flow wave is nearly triangular through adult life. However, the effects of wave

reflection in reducing forward flow during mid-systole just after peak flow are apparent in older patients and are even more marked in the presence of impaired contraction. Pulse wave velocity increases in elderly patients owing to wall stiffening. Reflections arrive at the aorta in mid-to-late systole producing systolic pressure augmentation with the

loss of diastolic pressure augmentation and widening of the aortic PP [29]. Whereas reflected pressure adds to forward pressure, reflection subtracts from forward flow out of the contracting left ventricle. The aortic pressure waveform is again altered in the presence of AS. The upstroke becomes slurred, with a small indistinct incisura and/or the loss of the dicrotic notch. The derived central aortic pressure waveforms in our patients with AS have previously been reported to show close correlation with invasive aortic pressure using high-fidelity catheters [12].

4.4. Age- and valvular-related changes to steady state and pulsatile load

Stiffer vessels lead to a faster velocity of pressure pulse and earlier timing of the reflected pulse wave from the periphery, augmenting central aortic SP and yielding a greater LV afterload on the heart [14,30]. Arterial stiffness is the result of a complex interplay of endothelial and smooth muscle cell function, extracellular matrix composition, genetics, hemodynamic factors, vasoactive properties and ageing. Prior studies have utilized either SP, systemic arterial compliance (SAC), PP or the valvulo-arterial impedance (Z_{VA}) index as a surrogate for load [22,31]. None of these indices consider the effects of resistive and pulsatile load separately from BP. By definition, total vascular hydraulic load is comprised of both steady and pulsatile components. Steady load is best represented by SVR, whereas pulsatile load is represented by VL and VAL in this study. Load values reported in this study are similar to those previously reported in invasive studies using cuff type EMF probes [27, 32] – a minimal value of modulus around 3–4 Hz with the impedance phase, initially negative, crossing zero at 3–4 Hz. There was an age-related increase in impedance modulus at zero frequency in both cohorts [9], however VAL was the higher of the two as we might have expected.

4.5. Clinical significance of increased load in patients with aortic valve stenosis

In clinical practice, BP targets in elderly patients and those with AS have remained the source of some confusion due to widespread belief that higher BP is preferred because a lower, more normal BP might increase the risk of adverse cardiac events. There is however, growing recognition that higher BP and increased arterial load increases the LV afterload in patients with AS, which has adverse consequences on LV remodelling, function and survival [22,33–36]. Accumulating evidence emphasizes the benefit of lower SBP targets for clinical outcomes among adults greater than 75 years of age [37,38]. Indices of increased total arterial load (arterial elastance, SAC, PP and Z_{VA}) have been associated with increased all-cause mortality post TAVI [39]. Despite no significant difference between brachial or central aortic pressure, patients with AS in this study had an elevated SVR ($p = 0.02$) and VAL ($p = 0.02$) as expected.

4.6. Limitations

This is a small comparative study. Although all patients recruited were 60 years or older, there was a difference in age ($p < 0.01$) as well as a trend towards higher brachial and central aortic pressures in those with AS. This may partially explain the elevated VAL and SVR values in the AS cohort. Although radial AT is validated to measure central aortic pressure, no such study has previously been conducted in patients with AS. It is possible that calibration of radial pressure waves using standard oscillometric blood pressure underestimated central aortic pressure but overestimated diastolic blood pressure to a degree [40].

5. Conclusions

The present study is the first to directly compare the difference in total hemodynamic load presented to the LV, through characteristic

changes in aortic flow velocity, pressure contour and other indices using a non-invasive CMR/AT technique. Our data demonstrates the progressive effects of aortic stiffening in humans with age and AS. Non-invasive load data have not previously been reliable with Doppler echocardiography in patients with AS since the flow tracings in the aorta or LV outflow tract do not show consistent flow contour change with age. The ability to measure ascending aortic flow, pressure, SVR and global LV load in elderly patients and those with AS opens up new areas of research into ventricular-vascular interactions that have not previously been readily accessible. This technique may help to better identify future patients at risk of VA coupling mismatch after correction of AS.

Credit author statement

SL HUNGERFORD was responsible for all aspects of Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing. AI ADJI was responsible for all aspects of Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing. NK BART was responsible for all aspects of Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing. L LIN was responsible for all aspects of Data curation; Formal analysis. N SONG was responsible for all aspects of Conceptualization; Data curation; Methodology; Project administration; Resources; Software. A JABBOUR was responsible for all aspects of Conceptualization; Methodology; Visualization; Roles/Writing – original draft. MF O’ROURKE was responsible for all aspects of Conceptualization; Methodology; Visualization; Roles/Writing – original draft. CS HAYWARD was responsible for all aspects of Conceptualization; Formal analysis; Funding acquisition; Project administration; Resources; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing. DWM MULLER was responsible for all aspects of Conceptualization; Formal analysis; Funding acquisition; Project administration; Resources; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing.

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Declaration of competing interest

Assoc. Prof. Muller has been an advisory board member for Medtronic and Boston Scientific; has been a consultant to Abbott Vascular, Medtronic, Tendyne Holdings, and Cephea; has received research grant support from Tendyne Holdings, Abbott Vascular, and Medtronic; and is a proctor for Medtronic and Abbott Vascular. Prof. O’Rourke is a founding board member of AortaMate Pty. Ltd., Sydney, a company formed to aid measurement of central aortic pressure, development of software for pulse wave analyses and methods to reduce aortic stiffness. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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