



Fast track – ISH2022 KYOTO

Pulsatile energy consumption as a surrogate marker for vascular afterload improves with time post transcatheter aortic valve replacement in patients with aortic stenosis

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Abstract

The effect of arterial stiffening on elevated pulsatile left ventricular afterload patients with aortic stenosis (AS) is pronounced beyond systemic hypertension. Circulatory afterload pulsatile efficiency (CAPE) is a marker of vascular function, defined as the ratio of steady state energy consumption (SEC) to maintain systemic circulation and pulsatile energy consumption (PEC). Twenty patients aged 80 ± 7 years were assessed at baseline and a median of 60 days post transcatheter aortic valve replacement (TAVR), with pulsatile vascular load calculated using simultaneous radial applanation tonometry derived aortic pressure and cardiac magnetic resonance phase-contrast imaging derived ascending aortic flow. Eight out of 20 patients had a reduction in PEC post TAVR, and the reduction of PEC correlated strongly with the number of days post TAVR ($R = 0.62$, $P < 0.01$). Patients assessed within the 100 days of TAVR had a rise in their PEC when compared to baseline (0.19 ± 0.09 vs 0.14 ± 0.08 W, $P = 0.04$). Baseline PEC correlated moderately with baseline SEC ($R = 0.49$, $P = 0.03$), and a high baseline PEC was predictive of post TAVR PEC reduction ($R = 0.54$, $P = 0.01$). Overall, no significant differences were found between baseline and post TAVR for systolic aortic pressure (131 ± 20 vs 131 ± 20 mmHg), systemic vascular resistance (1894 ± 493 vs 2015 ± 519 dynes.s/cm⁵), aortic valve ejection time (337 ± 22 vs 324 ± 34 ms) or aortic characteristic impedance (120 ± 48 vs 107 ± 41 dynes.s/cm⁵). Improved flow profiles after TAVR likely unmask the true vascular properties by altering ventriculo-valvulo-arterial coupling, leading to downstream vascular remodelling secondary to flow conditioning, and results in eventual improvement of pulsatile afterload as reflected by our proposed index of CAPE.

Keywords Aortic stiffness · Aortic stenosis · Hemodynamics · Circulatory efficiency

Introduction

Aortic stenosis (AS) is a degenerative process with progressive calcification of the valve causing left ventricular

(LV) outflow obstruction, from which increased LV afterload and subsequent LV hypertrophy, fibrosis and failure ensue if left untreated [1, 2]. As a disease affecting predominantly the elderly with often co-existing hypertension, the histopathological process of AS shares some similarity to that of atherosclerosis [3], with the resulting increased arterial stiffness serving as an independent predictor of mortality [4]. Treatment of AS with transcatheter aortic valve replacement (TAVR) provides an opportunity to study the effect of valvular obstruction relief on vascular loading, without the complicating vascular disruption arising from conventional surgical aortic valve replacement (SAVR).

The traditional view that AS is a fixed, valvular LV outflow obstruction has recently been challenged by the concept that LV afterload is a series circuit involving both

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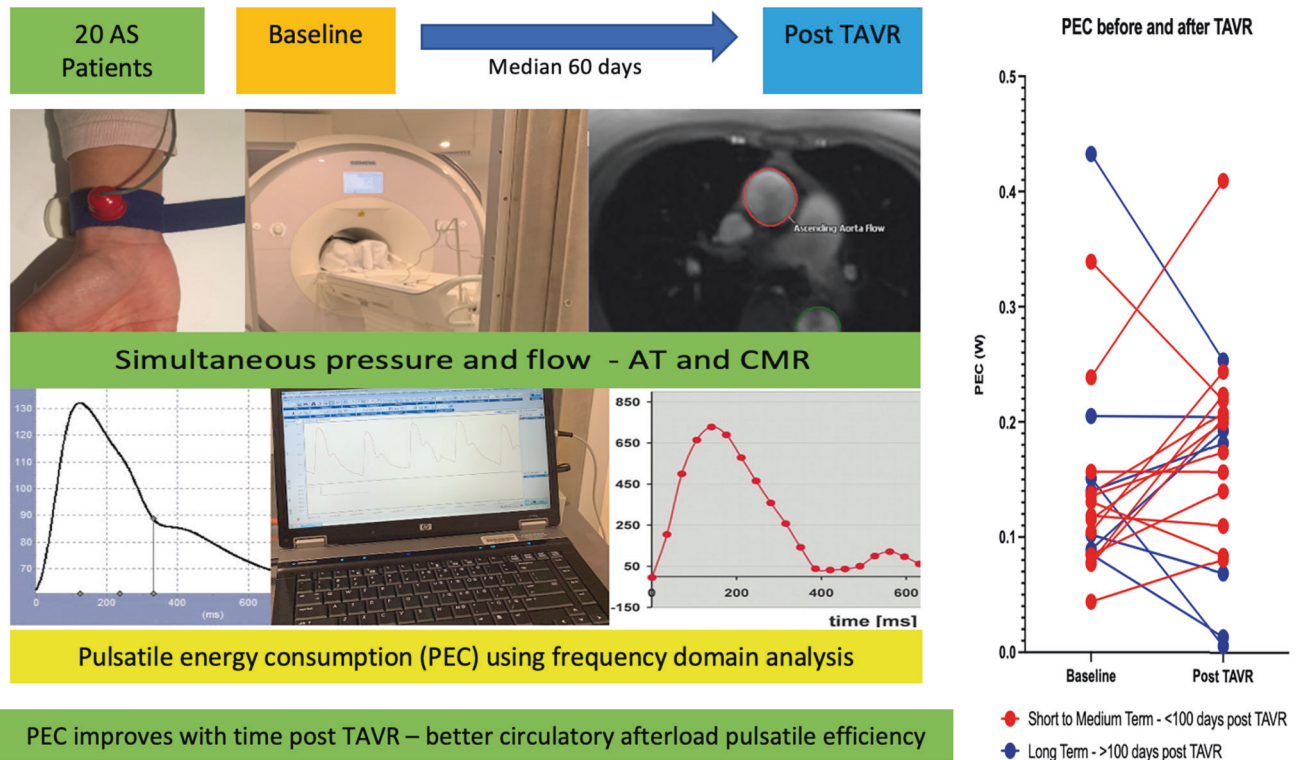
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Graphical Abstract

Pulsatile energy consumption improves with time post TAVR in patients with AS



the valve and the vasculature [5], with an emphasis on ventriculo-valvulo-arterial coupling. Quantification of the vascular load in AS is nebulous, as current methods of afterload assessment typically focus on the LV or the valve itself in isolation, and often underestimate the effect of the vascular load [6]. Separation of pulsatile and steady state arterial load is rarely performed in the assessment of vascular load, especially in the context of AS.

To date, LV afterload indices in AS that incorporate vascular load components such as the valvulo-arterial impedance (Z_{va}) derived using transthoracic echocardiography (TTE) [7], instantaneous impedance from cardiac magnetic resonance (CMR) using time domain analysis (Z_{va-ins}) [8], or energy loss index corrected for ascending aortic cross-sectional area [9], all have varying degrees of valvular contribution. A prior study also demonstrated that an acute transfer of load may occur immediately after TAVR, indicating that vascular parameters may have been modified by upstream valvular obstruction from AS [10], presumably from a reduction in transvalvular flow.

A seemingly forgotten method to assess the vascular component of the afterload is the pulsatile energy loss within the circulation first proposed by O'Rourke et al [11].

Pulsatile load arises from the concept that a proportion of the external work imparted by the LV to systemic circulation is lost to arterial stiffness due to the requirement to maintain the pulsatile nature of circulation, and this energy loss per unit time can be expressed as pulsatile power [11], a hemodynamic parameter that we hypothesise to be theoretically independent of upstream obstruction. The ratio of the pulsatile energy consumption (PEC) to the steady state energy consumption (SEC) by the circulatory system can be represented by the novel index of circulatory afterload pulsatile efficiency (CAPE), which is a surrogate for comparing pulsatile afterload as a measurement of total afterload.

As the valvular obstruction is relieved by TAVR, reverse vascular remodelling may take place independently to myocardial remodelling of the LV, which is likely a time-dependent process. We hypothesise a gradual flow mediated vascular remodelling as the vasculature readapts to improved flow profile post TAVR, with ongoing reduction in PEC and therefore improvement in CAPE when compared to baseline. In this study, we assess the response of pulsatile circulatory efficiency following TAVR and its association with time using non-invasive methods.

Methods

Study population

Twenty patients with moderate to severe symptomatic AS planned for TAVR were studied. Exclusion criteria included the presence of more than moderate concomitant aortic regurgitation, mitral, tricuspid, or pulmonary disease, the presence of un-revascularized severe coronary disease, previous surgery involving the aortic valve or proximal aorta and general contraindications to CMR. All TAVR procedures were discussed at a local hospital multi-disciplinary heart team meeting prior to proceeding.

All patients underwent initial demographic and brachial blood pressure measurements, TTE, and simultaneous radial arterial applanation tonometry (AT) and CMR at baseline and post TAVR (median of 60 days, range 28–812 days). All patients provided informed written consent and the study was approved by the local hospital research ethics committee (HREC 2019/ETH03530).

Study protocol and follow-up

Simultaneous AT and CMR data acquisition method was adapted from our pilot study previously [12]. In brief, a modified high-fidelity arterial tonometer (Millar Instruments, Houston, TX, USA) was applied to the study patients' radial pulse during CMR [13], and real-time aortic pressure waveform was derived from radial AT waveform using a validated transfer function after calibration to brachial blood pressure cuff measurement using the SphygmoCor 8.1 system (AtCor Medical, Sydney, Australia) [14, 15].

CMR studies were performed in a 3T magnet (Siemens Magnetom, Erlangen, Germany) using a previously described protocol [12]. Ascending aortic cross-sectional area, volume and velocity flow profiles were obtained at the level of the main pulmonary artery bifurcation using 2D through plane phase-contrast imaging with velocity encoding (Venc) of 3m/s. Images were acquired at a voxel size of 1.8×1.8 mm at a slice thickness of 6mm. Repetition time was 37.12 ms and echo time was 2.47 ms at a flip angle of 20°. Post processing analyses were performed using CVI 42 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Patients were asked to perform breath hold to minimize the effect of changing intrathoracic pressure to flow profile. Arrhythmia causing high beat-to-beat variability that resulted in gating errors and produced non-physiological flow profiles were rejected and re-acquired after visual assessment.

Transthoracic echocardiographic images were obtained using Affinity ultrasound machine (Phillips Healthcare, Eindhoven, the Netherlands). Quantification of AS was determined using Doppler echocardiography (apical 5-

chamber-view) in accordance with American Society of Echocardiography guidelines [16].

Hemodynamic data analysis

Volume flow impedance parameters and vascular load indices estimation were calculated by frequency domain analysis using simultaneously obtained aortic pressure and flow profile as outlined in a previously published method [12, 14, 15]. In brief, for impedance spectrum estimation, flow velocity and pressure waves were decomposed into their component harmonics using a fast Fourier transform (FFT), and FFT pressure amplitudes were divided by FFT flow velocity amplitudes for frequencies up to 10 Hz. Any harmonics were excluded if the modulus was less than 0.6mmHg for pressure, or less than 1 cm/s for flow velocity when adjusted for cross-sectional area of the ascending aorta, as in Nichols et al. [17]. To account for the difference in heart rate between flow and pressure measurements, pressure and flow harmonics were normalized and interpolated linearly into the nearest integer frequencies, that is 1, 2, 3,..., 10 Hz. The characteristic impedance of the ascending aorta (Z_c) was calculated as the average of impedance moduli between 2–10 Hz. Systemic vascular resistance (SVR) is calculated as the ratio between mean pressure and mean flow at steady state (zero Hz frequency).

Calculation of steady state and pulsatile power

Steady state energy consumption (SEC) was defined as the product of mean pressure and mean flow over the course of the cardiac cycle per time unit. Pulsatile energy consumption (PEC) was defined as the sum of the product of the pressure and flow moduli adjusted by the cosine of the phase angle for first 7 harmonics on frequency domain analysis:

$$SEC = P_{\text{mean}} * Q_{\text{mean}}$$

$$PEC = \sum_{n=1}^7 P_n * Q_n * |\cos \theta_n|$$

Here, P_n and Q_n are the pressure and flow at the n th harmonic respectively, with $\cos \theta_n$ being the cosine of the phase angle at the n^{th} harmonic. The absolute value is taken in the conversion of a vector to a directionless magnitude for the calculation of power as energy expenditure.

Circulatory afterload pulsatile efficiency (CAPE) was defined by the following equation and expressed as a percentage:

$$CAPE = \left(1 - \frac{PEC}{SEC} \right) * 100\%$$

Table 1 Baseline patient characteristics

Baseline characteristics (<i>N</i> = 20)		Mean ± SD or <i>n</i> (%)
Demographics	Age (years)	80.4 ± 6.5
	Males	12 (60%)
	Height (m)	1.68 ± 0.12
	Weight (kg)	78.9 ± 17.1
	BMI (kg/m ²)	28.0 ± 5.2
	BSA (m ²)	1.88 ± 0.24
Co-morbidities	Hypertension	13 (65%)
	Revascularized coronary artery disease	8 (40%)
	Type II diabetes	6 (30%)
	Atrial fibrillation	5 (25%)
	Creatinine (μmol/L)	89.2 ± 28.1
	eGFR (ml/min/1.73 m ²)	66 ± 16.9
	NYHA III-IV	3 (15%)
Medications	ACE-I/ARB	11 (55%)
	Beta blockers	5 (25%)
	Calcium channel blocker or other vasodilator	4 (20%)
	Diuretics	9 (45%)
Aortic valve assessment	AVA TTE (cm ²)	0.92 ± 0.27
	AVA CMR planimetry	0.97 ± 0.21
	Self-expandable TAVR	18 (90%)
	Balloon-expandable TAVR	2 (10%)

ACE-I angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, AVA aortic valve area, BMI body mass index, BSA body surface area, CMR cardiac magnetic resonance imaging, eGFR estimated glomerular filtration rate, NYHA New York Heart Association, TAVR transcatheter aortic valve replacement, TTE transthoracic echocardiogram

A higher CAPE denotes a more efficient pulsatile circulation as less of the total circulatory energy is being dissipated as pulsatile energy loss.

Quality of life measurements

Seventeen of 20 study patients underwent a 6-minute walk test and answered a 12-Item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) for evaluation of functional capacity and quality of life respectively, on the study day at baseline or post TAVR.

Statistical analysis

All data are presented as mean ± SD unless otherwise specified. To test for normality, the Shapiro–Wilk test was used, and a paired two-tailed Student's *t*-test or Wilcoxon Signed-Rank test was performed depending on the normality of the data to assess for differences between baseline

and post TAVR measurements. Pearson or Spearman's Rho test were performed to assess for correlation between ordinal variables where appropriate, accounting for the presence of potential outliers. Significance level was set at $P < 0.05$. Data were analyzed using SPSS (version 27, IBM Inc., Armonk, NY, USA).

Results

Baseline demographic and clinical characteristics of the 20 study patients are summarized in Table 1. Study patients were relatively elderly with a mean age of 80 ± 7 years, mildly overweight (body mass index 28.0 ± 5.2 kg/m²), with 13 out of 20 having pre-existing hypertension requiring pharmacological treatment. Four patients were demonstrated to have evidence of myocardial scarring on late gadolinium enhancement on CMR. There was a significant improvement in KCCQ-12 summary score (and 6-minute walk distance) following TAVR, but the clinical improvement was not predicted by any baseline hemodynamic parameters, including PEC and CAPE (all $P > 0.05$).

Vascular afterload in AS

The study cohort had symptomatic moderate to severe AS with mean aortic valve gradient of 37 ± 12 mmHg, with a calculated aortic valve area by the continuity equation on TTE of 0.92 ± 0.27 cm², which correlated well with the planimetry aortic valve area on CMR at 0.97 ± 0.21 cm² ($R = 0.73$, $P < 0.01$). All patients had procedural success with TAVR and a significant reduction in their aortic valve pressure gradients (Table 2). At baseline, 1 patient had a reduced left ventricular ejection fraction of $<55\%$, and 2 patients had a stroke volume index of <35 ml/m². Three patients had adjustments to their antihypertensive regimen (1 patient required up-titration of antihypertensives, 2 patients reduced their antihypertensives) prior to undergoing repeat study, and 2 patients required pacemaker implantation but were not pacing dependent at the time of the repeat study visit.

The cohort demonstrated a higher-than-expected Zc (120 ± 48 dynes.s/cm⁵) of the proximal aorta when compared to reported values from similar prior studies [14], with a mildly elevated SVR (1894 ± 493 dynes.s/cm⁵). SEC and PEC were calculated to be 0.99 ± 0.24 W and 0.15 ± 0.09 W, respectively, with CAPE calculated to be $85 \pm 8\%$.

Responses following TAVR

Repeat hemodynamic measurements were performed at 149 ± 206 days post TAVR. As expected, there were

Table 2 Comparison of baseline and post-TAVR imaging and hemodynamic indices

Parameters		Days post TAVR (<i>N</i> = 20)		
		149 ± 206, Median = 60 days		
		Baseline	Post TAVR	<i>P</i> Value
TTE	LVOT peak velocity (cm/s)	111.8 ± 20.5	126.8 ± 18.5	0.001
	LVOT VTI (cm)	25.1 ± 6.2	27.3 ± 5.3	0.058
	AV peak velocity (cm/s)	399.9 ± 60.6	175.1 ± 37.6	<0.001
	AV VTI (cm)	87.9 ± 16.6	35.5 ± 7.9	<0.001
	Peak aortic valve gradient (mmHg)	65.5 ± 19.2	12.8 ± 5.8	<0.001
	Mean aortic valve gradient (mmHg)	37.2 ± 12.1	6.3 ± 2.8	<0.001
CMR	Myocardial mass (g)	146.3 ± 43.1	135.7 ± 36.5	0.057
	LVEDV (ml)	130.5 ± 52.7	131.4 ± 45.7	0.912
	LVESV (ml)	48.1 ± 35.8	47.4 ± 33.7	0.866
	Stroke volume (ml)	71 ± 14.8	76 ± 19.7	0.088
	Peak flow rate (ml/s)	330.2 ± 74.3	380.7 ± 104.4	0.005
	Cardiac output (L/min)	4.9 ± 1.3	4.8 ± 1.5	0.660
	LVEF (%)	63 ± 19	66 ± 11	0.427
	Presence of LGE	4 (20%)	-	
Tonometry	Heart rate (beats per minute)	71 ± 9.8	68.1 ± 11.5	0.310
	Brachial systolic pressure (mmHg)	136.3 ± 21.3	142.3 ± 18.7	0.201
	Brachial diastolic pressure (mmHg)	74.7 ± 10.6	72.4 ± 6.7	0.404
	Aortic systolic pressure (mmHg)	131.1 ± 19.8	131.2 ± 19.8	0.983
	Aortic diastolic pressure (mmHg)	77.7 ± 10.7	73.8 ± 6.5	0.172
	Mean aortic pressure (mmHg)	99 ± 12.9	98.4 ± 11.1	0.854
	AV ejection time (ms)	336.7 ± 22.2	324 ± 34.4	0.154
Afterload Indices	SVR (dynes.s/cm ⁵)	1894 ± 493	2015 ± 519	0.217
	Zc (dynes.s/cm ⁵)	120.1 ± 47.6	107.6 ± 40.5	0.229
	SEC (W)	0.97 ± 0.24	0.95 ± 0.36	0.760
	PEC (W)	0.15 ± 0.09	0.17 ± 0.09	0.365
	CAPE (%)	85 ± 8	82 ± 8	0.249
Clinical (<i>N</i> = 17)	KCCQ-12 summary score	70 ± 24.4	88 ± 18.4	0.002
	6-minute walk distance (m)	374.5 ± 61.3	435.8 ± 97.6	0.003

AV aortic valve, CAPE circulatory afterload pulsatile efficiency, KCCQ-12 Kansas City Cardiomyopathy Questionnaire 12-Items, LGE late gadolinium enhancement, LVEDV left ventricular end diastolic volume, LVEF left ventricular ejection fraction, LVESV left ventricular end systolic volume, LVOT left ventricular outflow tract, PEC pulsatile energy consumption, SEC steady state energy consumption, SVR systemic vascular resistance, TAVR transcatheter aortic valve replacement, TTE transthoracic echocardiogram, VTI velocity time integral, Zc characteristic impedance of the aorta

significant improvements in aortic valve-related TTE parameters as summarised in Table 2. On volumetric assessment via CMR, there was significant improvement in peak flow rate, but no differences were observed in stroke volume, cardiac output, or myocardial mass.

With respect to vascular load parameters, there were modest reduction of SVR from 1894 ± 493 dynes.s/cm⁵ to 2015 ± 519 dynes.s/cm⁵, and Zc from 120 ± 48 dynes.s/cm⁵ to 108 ± 41 dynes.s/cm⁵, but neither were statistically significant at *P* = 0.22 and *P* = 0.23 respectively.

When evaluated as a cohort, there were no significant difference between baseline SEC (0.97 ± 0.24 W baseline, 0.95 ± 0.36 W post TAVR) or PEC (0.15 ± 0.09W baseline, 0.17 ± 0.09 W post TAVR).

Predictors for improvement in pulsatile energy loss

The change in PEC and CAPE after TAVR for each patient is demonstrated in Fig. 1. The patients were divided into two sub-groups according to changes in PEC post TAVR for further analysis. Eight out of 20 patients demonstrated a numerical reduction in their PEC following TAVR, with associated improvement in CAPE. The 8 patients who had a reduction in PEC underwent repeat assessment post TAVR after a significantly longer duration than the remaining 12 patients, with a mean duration post TAVR of 284 ± 280 days compared to 59 ± 28 days (Table 3). As a group, there was no overall change in PEC upon comparing baseline with post TAVR. However, when divided into a

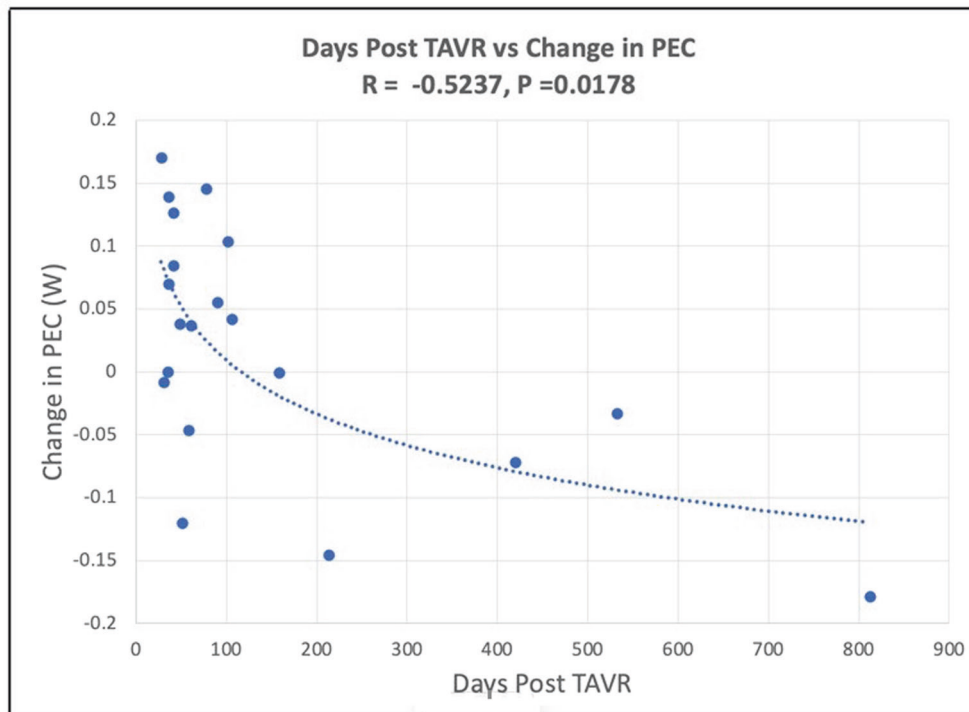
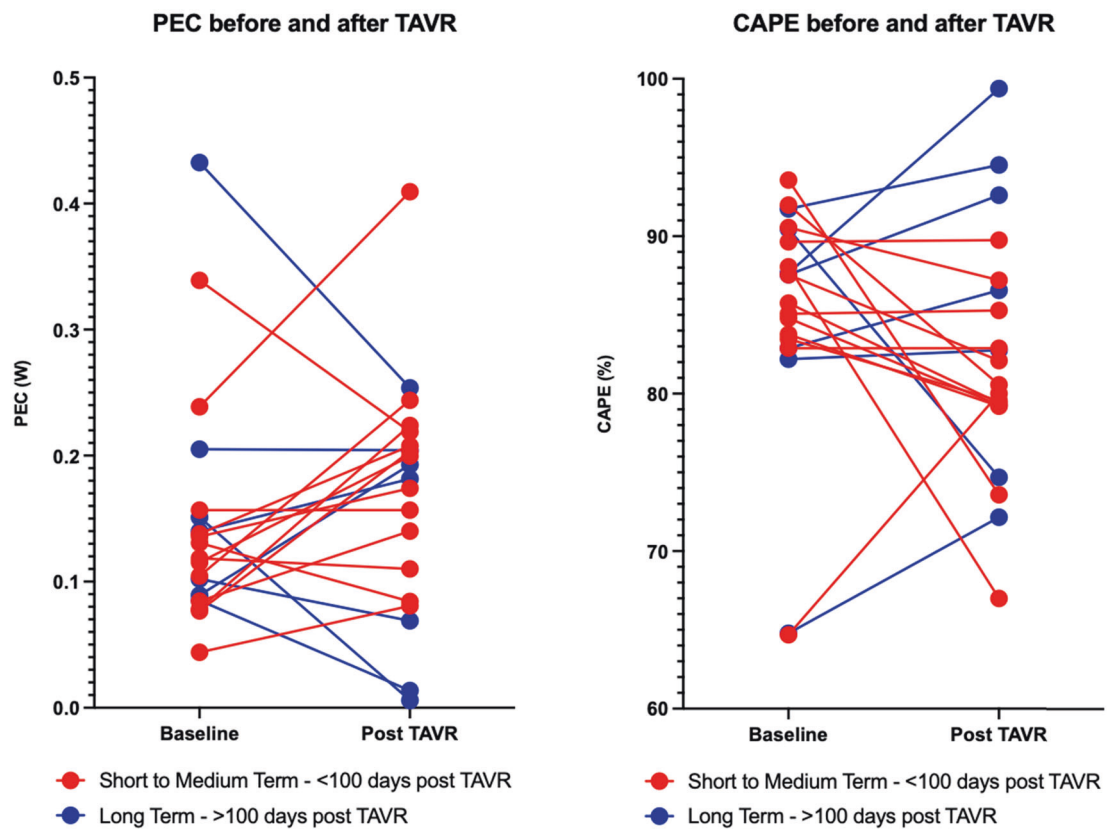


Fig. 1 PEC and CAPE before and after TAVR by duration of follow-up and association between post TAVR and change in PEC

Table 3 Analysis by post TAVR PEC change

Parameters	Baseline		P value	Post TAVR		P Value
	PEC increased (N = 12)	PEC reduced (N = 8)		PEC increased (N = 12)	PEC reduced (N = 8)	
Days post TAVR	N/A		-	58.5 ± 28.2	284.4 ± 280.1	0.041
Heart rate (beats per minute)	70.3 ± 11.7	72.1 ± 6.4	0.651	65.3 ± 11.2	72.3 ± 11.3	0.195
Stroke volume (ml)	69.7 ± 17	73 ± 11.7	0.609	79.4 ± 20.1	70.9 ± 19.4	0.363
Cardiac output (L/min)	4.7 ± 1.5	5.2 ± 0.8	0.372	4.9 ± 1.8	4.7 ± 1	0.756
Myocardial mass (g)	139.3 ± 39.6	156.9 ± 48.6	0.409	135.6 ± 44.5	135.9 ± 22.2	0.985
Aortic systolic pressure (mmHg)	129.2 ± 19.6	134 ± 21.2	0.615	132 ± 21.2	130 ± 18.8	0.827
Aortic diastolic pressure (mmHg)	78.9 ± 12.5	75.9 ± 7.8	0.511	71.8 ± 5.5	76.8 ± 7.1	0.115
Aortic valve ejection time (ms)	334.9 ± 25.9	339.3 ± 16.5	0.653	337.6 ± 30.9	303.5 ± 30.3	0.027
SVR (dynes.s/cm ⁵)	1976 ± 549	1773 ± 396	0.350	2035 ± 614	1983 ± 369	0.815
Zc (dynes.s/cm ⁵)	118.2 ± 44.6	122.9 ± 54.8	0.841	111 ± 46.9	102.6 ± 30.8	0.631
PEC (W)	0.12 ± 0.05	0.20 ± 0.13	0.127	0.20 ± 0.08	0.12 ± 0.09	0.066
SEC (W)	0.91 ± 0.27	1.06 ± 0.16	0.134	0.97 ± 0.36	0.91 ± 0.38	0.739
CAPE (%)	87 ± 4	82 ± 11	0.217	79 ± 5	88 ± 9	0.030

CAPE circulatory afterload pulsatile efficiency, PEC pulsatile energy consumption, SEC steady state energy consumption, SVR systemic vascular resistance, TAVR transcatheter aortic valve replacement, Zc characteristic impedance of the aorta

short-term group (<100 days post TAVR, $N = 13$) and a long-term group (>100 days post TAVR, $N = 7$), there was a significant rise in post TAVR PEC in the short-term group when compared to baseline (0.19 ± 0.09 vs 0.14 ± 0.08 W, $P = 0.04$), which is not observed in the long-term group (0.13 ± 0.10 vs 0.17 ± 0.12 W, $P = 0.33$).

In the cohort of 8 patients, there were no significant baseline predictors for reduction of PEC. In the post TAVR studies, a reduction of PEC was associated with a significant shorter aortic valve ejection time (304 ± 30 ms vs 338 ± 31 ms, $P = 0.03$). The PEC reduction cohort also had a higher CAPE when compared to those whose PEC did not reduce ($79 \pm 5\%$ vs $88 \pm 9\%$, $P = 0.02$).

Correlation between PEC and other variables and its relationship post TAVR

Spearman rho correlations was performed for PEC with other hemodynamic parameters at baseline, as well as the change in PEC post TAVR from baseline with other parameters at baseline to look for predictors (Figs. 2 and 3). At baseline, PEC was positively correlated to SEC ($R = 0.49$, $P = 0.03$) and stroke volume ($R = 0.48$, $P = 0.04$), but not with other hemodynamic parameters including Zc, SVR, aortic mean gradient, aortic valve ejection time, central aortic pressure (all $P > 0.05$). Post TAVR, the change in

PEC (defined as Post TAVR PEC minus baseline PEC) was strongly correlated with the number of days post TAVR ($R = 0.61$, $P < 0.01$), and moderately correlated with baseline PEC ($R = 0.54$, $P = 0.01$). No other baseline parameters predicted the reduction in PEC. The number of days post TAVR also correlated with an improvement in CAPE post TAVR ($R = 0.46$, $P = 0.04$).

Discussion

With a specific focus on the pulsatile elements to the afterload, we evaluated pulsatile energy consumption (PEC) and its relationship with steady-state energy consumption (SEC), and proposed CAPE as a novel surrogate index for pulsatile vascular function. The main finding of our study is that time post TAVR is the most powerful predictor of improvement in circulatory afterload pulsatile efficiency (CAPE). There was a rise in PEC in the short-term (<100 days) post TAVR, but this appears to be a transient process as the PEC and CAPE improves with time, resulting in reduced pulsatile afterload.

We found a significant correlation between baseline PEC and SEC, but PEC was not directly correlated with other traditional afterload parameters including aortic systolic pressure, SVR and Zc of the aorta as we might have

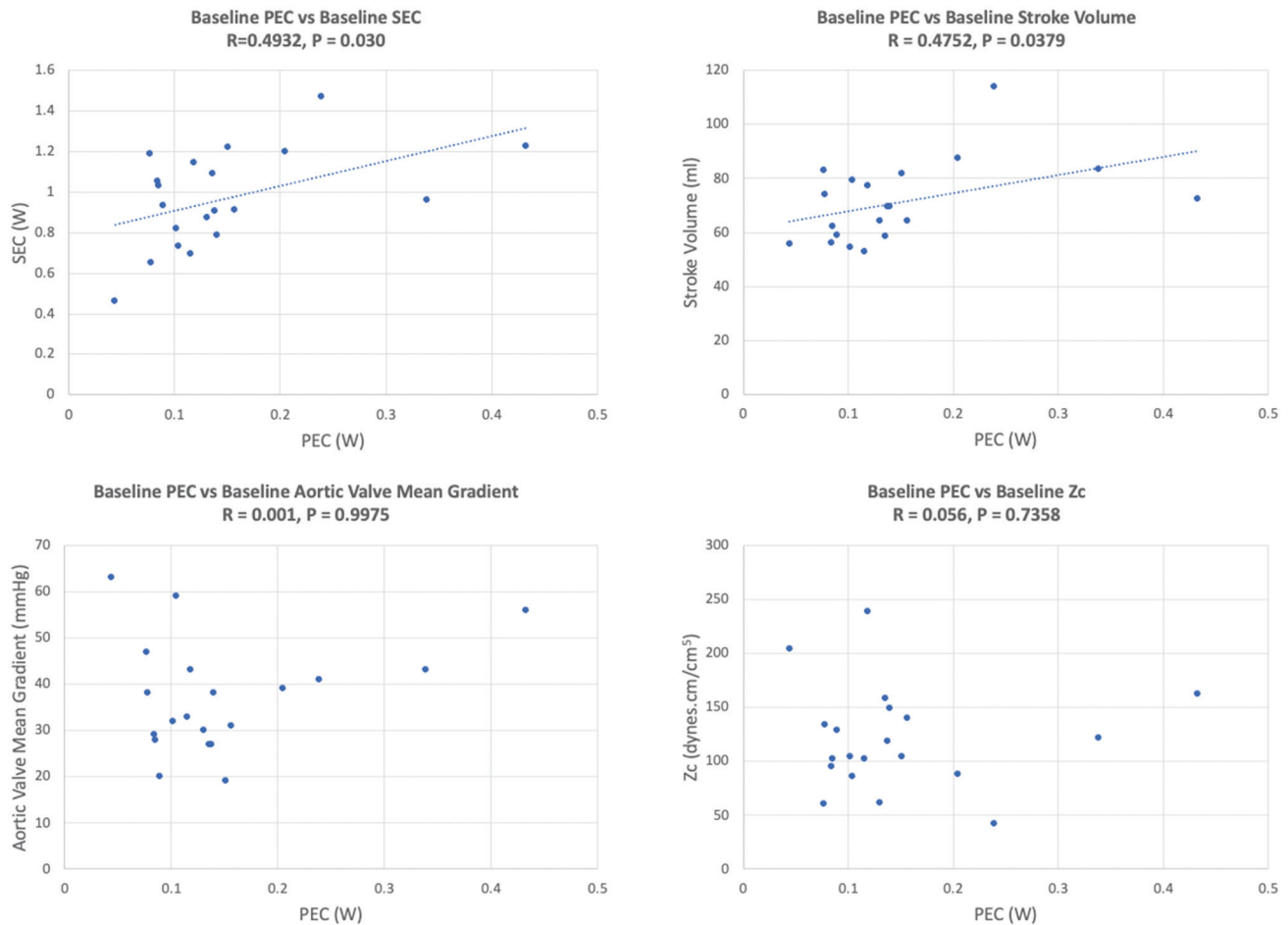


Fig. 2 Predictors for baseline PEC

expected. Whilst the clinical benefit of TAVR in the form of symptomatic relief was readily observed in the short term, measurable improvements in hemodynamic indices requires gradual vascular remodelling with time.

Previous studies have attempted to find a single parameter that encompasses the global left ventricular afterload in AS by incorporating the valvular and vascular components together. The index most widely used is the valvulo-arterial impedance (Z_{va}), termed by Hachicha et al, which had since been demonstrated to be a strong predictor of adverse outcomes in patients with AS [7, 18]. However, Z_{va} had been shown to predominantly focus on the stenotic valve and underestimate the relative contributory values SVR and compliance to overall LV afterload [19], and its derivation process does not adequately consider the pulsatile nature of the circulation [8, 12],

On the other hand, the traditional “gold standard” arterial stiffness parameter of carotid-femoral pulse wave velocity (PWV) does not directly consider the effect of the aortic valve volume flow profiles, and sampling is performed is well downstream of the aortic valve and free of valvular contribution to its assessment, making it less relevant in the

assessment of global LV afterload in AS. This is supported by the prior demonstration that arterial stiffness as measured by PWV is elevated in asymptomatic AS patients but does not correlate with symptoms or severity of AS, despite being an independent predictor of poorer outcomes [20]. Although an initial small scale study suggested improvement in aortic stiffness following SAVR [21], multiple subsequent larger studies have found that SAVR increased arterial stiffness in the longer term [22–24], possibly due to trauma to the vaso-vasorum during transection of the aorta and its associated aortic remodelling upon recovery [25]. The effect of TAVR on arterial stiffness seems less clear, with multiple studies using different assessment modalities demonstrating conflicting findings [10, 26–29].

Our study had found that 8 out of the 20 patients in our study demonstrated a reduction in PEC and an improvement in CAPE. Interestingly, the reduction of PEC is closely associated with the number of days post TAVR, with an initial elevation in PEC. This suggests that there may be an acute rise in pulsatile vascular load in the short-to-medium term, with attenuation over the medium-to-long term. This is consistent with prior studies on arterial stiffness either

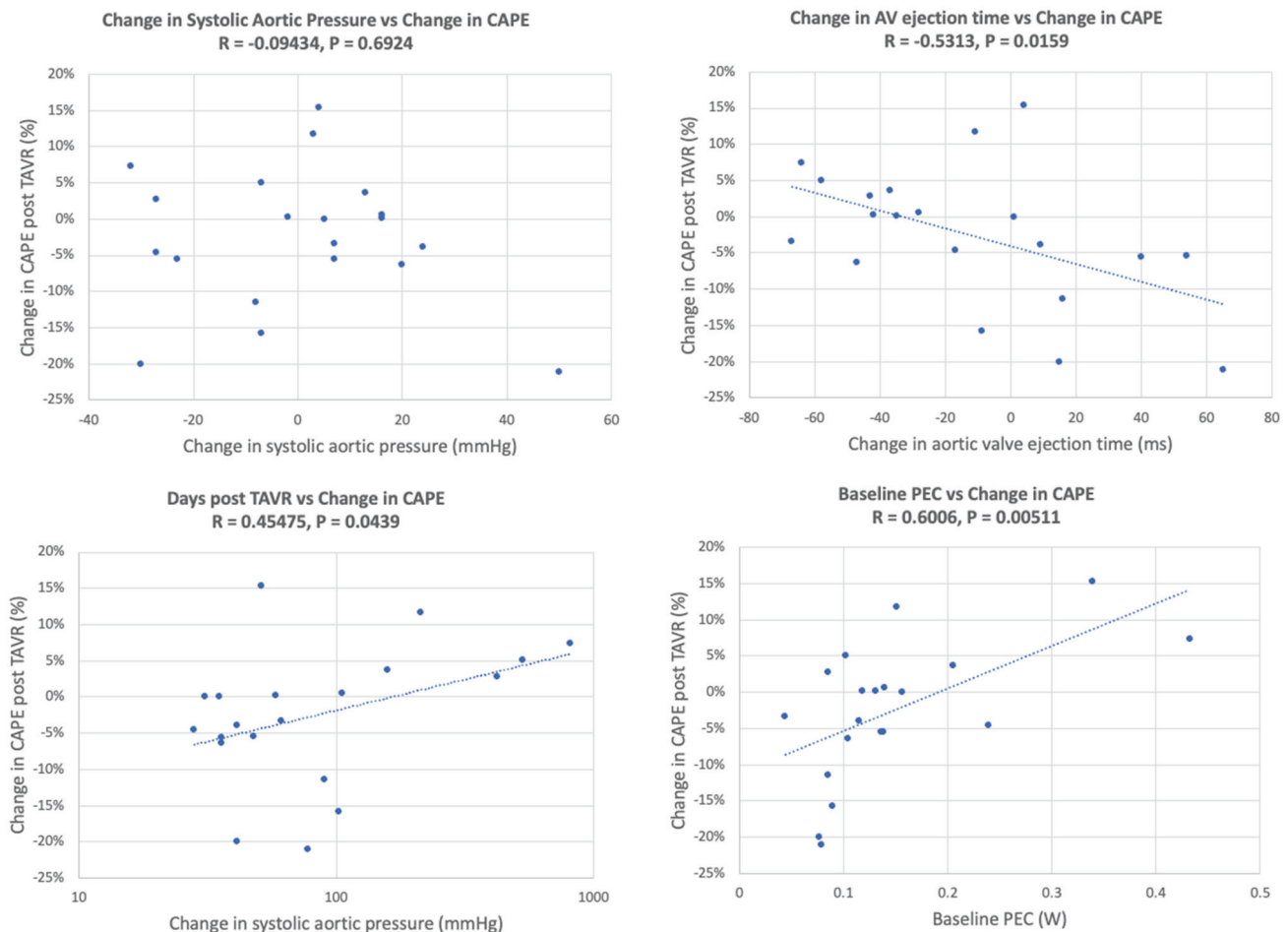


Fig. 3 Predictors of change in CAPE post TAVR

invasively with catheterisation in the short-term [10], or echocardiographic methods [28, 29]. Our finding that higher baseline PEC is predictive of the degree of PEC reduction post TAVR is consistent with prior findings that reduction in PWV following TAVR was largest in those who had the highest PWV at baseline [30].

In our study, there was a trend towards reduction of LV mass post TAVR ($P = 0.06$). Prior larger studies focusing on severe AS demonstrated that LV mass improved at 1 year, with concurrent reduction of extracellular volume [31]. We found that PEC reduction and improvement in CAPE seemed to occur independently to LV mass reduction, which suggests that the vascular remodelling process may be separate to myocardial remodelling and may occur even in patients with symptomatic moderate AS after TAVR treatment.

We hence postulate that true arterial stiffness and pulsatile energy loss will only become apparent after relief of the upstream mechanical obstruction at the level of the aortic valve, and TAVR as a less traumatic treatment modality minimizes the effect of vascular damage subjected by SAVR. This will in turn explain the rise in vascular

loading parameters in the short-to-medium term, as the vasculature conditioned by chronic low flow state is now exposed to unobstructed flow and a much sharper rise to peak velocity with a normalized pulse profile. In support of the concept proposed by Plunde and Bäck [25], the apparent rise of arterial stiffness and associated pulsatile vascular load following TAVR is not reflective of a rapid change of the intrinsic property of the vessel wall, but rather the changes in ventriculo-valvulo-vascular coupling. Nevertheless, the improvement of PEC observed in the medium-to-long suggests that improved valvular flow dynamics likely eventually results in downstream vascular remodelling.

We found that there was a significant 10% reduction in aortic valve ejection time in those patients who had a reduction in PEC post TAVR when compared to their aortic valve ejection time at baseline, but they did not have higher baseline transvalvular gradients or smaller aortic valve area. Ejection time has been associated with the degree of AS [32, 33], and relief of AS mediated LV obstruction by TAVR can result in a reduction in ejection time in the immediate post-op period [34]. Furthermore, a prior study

has demonstrated that a reduction in LV ejection time post SAVR is predictive of elevated arterial stiffness measured by cardio-ankle vascular index [35], suggesting that the effect of wave reflection from the peripheral arterial tree may become more pronounced after relief of valvular obstruction by TAVR. This is likely because ejection time accounts for the changes in pulse contour following TAVR and includes vascular function elements in the peripheral circulation impacted upon by wave reflection indices [25].

Consequently, our finding that PEC reduction is closely associated with aortic valve ejection time reduction also suggests that aortic valve ejection time is a complex marker that incorporates both the valvular properties as well as the vascular properties, and likely serves as a better simple predictor of downstream pulsatile vascular load and arterial stiffness than transvalvular gradients.

Another approach to evaluate global afterload in AS has been to explore the myocardial energy expenditure [36], which had been done using positron emission tomography to measure the myocardial oxygen consumption [37, 38]. More recently, a CMR-based method had also demonstrated the calculation of myocardial energy consumption in AS [39, 40]. However, both methods again fail to account for the pulsatile nature of the circulation, and each study found that TAVR failed to improve the myocardial efficiency of a proportion of patients in the medium term, which was defined as the ratio between steady-state circulatory energy consumption and the apparent myocardial energy consumption [38, 40]. We postulate that the sub-group of patients whose myocardial efficiency fail to improve is likely due to an elevated pulsatile vascular load that is not being accounted for, particularly if their baseline PEC is elevated, and their CAPE has not had adequate time to improve with adequate time since the TAVR.

Hence, the application of a hybrid method as suggested by our study accounting for pulsatile energy consumption with the novel index of CAPE will help to further elucidate the process myocardial and vascular energy efficiency and help to identify individuals who do not have optimal hemodynamic responses post TAVR. Furthermore, the unification of watt as the unit of energy consumption or power loss would help to compare previously separated concepts of myocardial and vascular function due to inconsistent units of measurement.

Study limitations

Our study has several limitations. We studied a group of patients with moderate to severe symptomatic AS with a relatively heterogenous transvalvular gradients and aortic valve area, in line with real-life indications for TAVR rather than a pure severe AS group. Our study patients had a variable follow-up period, which was partially due to

institutional lockdown arising from the COVID-19 pandemic. Hemodynamic loading conditions can also be variable pending on the study patient's fluid status on the day of the study.

Our CMR acquisition time was limited by the tolerance of our elderly study cohort. Sequences for planning and aortic flow lead to prolonged study durations, and patients found it difficult to tolerance prolonged scanning to allow the calculation of pulse wave velocity, and equipment limitation prevented us from performing simultaneous carotid and femoral tonometry for gold standard pulse wave velocity in the confined environment of the CMR with the interference of the magnetic field. Accurate correlation with CMR and/or tonometry-derived pulse wave velocity and other direct measurement of aortic stiffness would have added to the strength of our study. Our study also did not assess the regression of myocardial fibrosis or extracellular volume on CMR due to patient tolerance factors, which would have added to the strength of our analysis.

Frequency domain analysis is sensitive to noise and prone to the introduction of error [10, 41]. However, we have attempted to minimise noise by setting up a stand-alone, operator-independent acquisition system with high-fidelity pressure and flow data output. We have also chosen to sample the ascending aortic flow at the level of the pulmonary artery bifurcation, which allowed adequate distance from the flow artefact produced by the supra-avalvular metal struts of a self-expanding TAVR to dissipate.

Our study cohort was small and sub-group analysis needs to be interpreted with caution. Hard clinical endpoints such as mortality or morbidity were unable to be assessed given the follow-up period and small sample size, and we were unable to demonstrate any association between hemodynamic predictors and clinical outcomes on KCCQ-12 or 6-min walk test. Larger scale longitudinal studies with repeated measurements and correlation with clinical outcomes is required for further elucidation of CAPE post TAVR.

Conclusions

The transient rise in pulsatile vascular load post TAVR in the short-to-medium term appears to attenuate over time and result in medium-to-long-term improvement in CAPE. The improved flow profiles after correction of mechanical obstruction in AS with TAVR likely unmask the true vascular properties by altering the ventriculo-valvulo-arterial coupling and may result in downstream vascular remodeling secondary to improved flow conditioning.

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Compliance with ethical standards

Conflict of interest DWMM has been an advisory board member for Medtronic and Boston Scientific; has been a consultant to Abbott Vascular, Medtronic; has received research grant support from Abbott Vascular and Medtronic; and is a proctor for Medtronic and Abbott Vascular.

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