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Regression of left ventricular hypertrophy provides an additive physiological benefit following treatment of aortic stenosis: insights from serial coronary wave-intensity analysis

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Short title: Coronary WIA following aortic valve therapy

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Abstract

Aim: Severe aortic stenosis frequently involves the development of left ventricular hypertrophy (LVH) creating a dichotomous hemodynamic state within the coronary circulation. Whilst the increased force of ventricular contraction enhances its resultant relaxation and thus increases the distal diastolic coronary 'suction' force, the presence of LVH has a potentially opposing effect on ventricular-coronary interplay. The aim of this study was to use non-invasive coronary wave-intensity analysis (WIA) to separate and measure the sequential effects of outflow-tract obstruction

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relief and then left ventricular hypertrophy (LVH) regression following intervention for aortic stenosis.

Methods: 15 patients with unobstructed coronary arteries undergoing aortic valve intervention (11 SAVR, 4 TAVI) were successfully assessed before and after intervention, and at 6- and 12-months post-procedure. Coronary WIA was constructed from simultaneously acquired coronary flow from transthoracic echo and pressure from an oscillometric brachial-cuff system.

Results: Immediately following intervention, a decline in the BDW was noted (9.7±5.7 vs 5.1±3.6 $x10^3$ $Wm^{-2}s^{-1}$, $p<0.01$). Over 12 months, LV mass-index fell from 114±19 to 82±17 kg/m^2. Accompanying this, the BDW fraction increased to 32.8±7.2% ($p=0.01$ vs post-procedure) and to 34.7±6.7% at 12 months ($p<0.001$ vs post-procedure).

Conclusion: In aortic stenosis, both the outflow-tract gradient and the presence of LVH impact significantly on coronary haemodynamics that cannot be appreciated by examining resting coronary flow rates alone. An immediate change in coronary wave-intensity occurs following intervention with further effects appreciable with hypertrophy regression. The improvement in prognosis with treatment is likely to be attributable to both features.

Keywords: Aortic Valve Replacement / Transcatheter Aortic Valve Implantation; Hemodynamics; Hypertrophy; Pathophysiology; Valvular Heart Disease; .

Abbreviations

BDW – Backward Decompression Wave

CFR – Coronary Flow Reserve

LVH – Left Ventricular Hypertrophy

LVM – Left Ventricular Mass

LVMI – Left Ventricular Mass Index

PET – Positron Emission Tomography

SAVR – Surgical Aortic Valve Replacement

TEE – Transesophageal Echo

TAVI – Transcatheter Aortic Valve Implantation

WIA – Wave Intensity Analysis

Introduction

Two dominant structural changes occur in aortic stenosis, that of an increasingly stenotic outflow tract along with the development of left ventricular hypertrophy (LVH). Whilst many investigative modalities have shown the effect of aortic valve intervention on coronary haemodynamics[1–6], the individual effect of LVH regression is yet to be directly demonstrated using serial post-operative measurements despite the positive impact this change has in a non-valvular setting[7]. Whilst some indirect approaches have suggested that such intervention-driven LVH-regression does not markedly influence coronary physiology[2] recent data has shown that these structural changes result in more favourable clinical outcomes[8] implying at least a moderate impact on the coronary axis. Furthermore, ventricular remodelling may even confound some studies where a follow-up measure is performed outside of the immediate peri-operative setting as the most rapid hypertrophy regression occurs largely within the first 6 months[3].

Wave-intensity analysis (WIA) is constructed from simultaneously obtained pressure- and flow-signals and within the coronary system allows quantification of the forces responsible for blood flow velocity changes. It has proven able to document the potentially opposing influences of LVH[9] and aortic stenosis[10] on coronary physiology where abnormalities can be appreciated in the Backward Decompression Wave (BDW). This wave is formed by the elastic re-expansion of intramyocardial vessels at the start of diastole[11] creating a negative distal-to-proximal pressure gradient. When an increased systolic force is required to expel blood through a stenotic aortic valve this translates to a similarly increased force of relaxation which can be quantified as the BDW[10,12]. Furthermore, in patients without significant valvular disease, LVH results in a relative reduction in the BDW reflecting a disruption in ventricular-coronary interaction[9].

Whilst initial work demonstrated that the effect of aortic stenosis on the BDW is reversed immediately after intervention[10], recent data has surprisingly suggested that the BDW actually increases further after TAVI[12] – a finding difficult to rationalise with the above hypothetical and anatomically-substantiated[11] constructs of wave intensity and which therefore warrants further investigation. More importantly, delineation of the impact of LVH reversal on wave intensity clearly would be insightful and could offer a physiological explanation for the improvement in clinical outcomes following such LVH-regression. In order to investigate these features we employed our recently validated technique of non-invasive coronary WIA[13] which enabled measurements to be undertaken conveniently and risk-free in a serial fashion immediately before and then in the 12 months after aortic valve intervention.

Results

Baseline and interventional details

Of the 30 patients recruited adequate pre-operative non-invasive coronary flow and pressure signals were obtained in 23 who compromised our initial study population. Of these, we excluded a further eight from follow-up analysis because of either the development of post-operative persistent atrial fibrillation (n=4), unsatisfactory windows for coronary flow in the peri-surgical period (n=3) or because of the development of a significant paravalvular leak (n=1). The average length of stay was 6.3 days with no patients discharged before day 3 - thus a minimum of 72 hours passed from TAVI /

AVR to post-procedure assessment. Baseline characteristics for the completed patients are shown in Table 1.

Echocardiographic measures

All patients had a tricuspid aortic valve with preserved left ventricular function. LVH was present in 14 (93%) subjects prior to intervention. LVMI declined markedly in the first 6 months by 20.6% (114±19 kg/m^2 pre-procedure vs 86±17 kg/m^2 at 6 months, p=0.01) with only a further 2.9% reduction at 12 months (82±17 kg/m^2); only one patient still fulfilled criteria for LVH at this stage (Figure 2).

Pressure and velocity changes

Immediately following aortic valve intervention there was a decrease in peak coronary flow velocity (44.2±13.5 cm/s pre-procedure vs 35.0±9.3 cm/s post-procedure, p=0.03) with a further decrease by 12 months (29.3±8.7 cm/s, p<0.01 vs post-operative). Mean and minimum flow velocity fell similarly. There was no change in pressure following aortic valve intervention with a moderate increase in systolic (113±14.0 mmHg pre-procedure vs 124±16.0 mmHg at 12 months, p<0.01) and diastolic (65±9.7mmHg pre-procedure vs 72±10mmHg at 12 months, p=0.03) over time. The full echocardiographic dataset is displayed in Table 2.

Wave intensity with aortic valve intervention and LVH regression

Pre-procedure a correlation was noted between the backward-decompression wave (BDW) fraction and peak aortic gradient (r=0.55, p=0.02). A trend was noted with cumulative BDW (r=-0.41, p=0.1) but no other correlates were found with resting aortic gradient. Immediately following aortic valve intervention, a correlation was noted between the BDW fraction and LVM (r=-0.53, p=0.04) and LVMI (r=-0.49, p=0.048). To confirm the dominant influences on the BDW fraction linear regression confirmed significance for aortic gradient only pre-procedure (β=5.8, p=0.04) and LVMI only post-procedure (β=-0.2, p =0.04).

The effect of aortic valve intervention and regression of LVH on the wave intensity profile is demonstrated in Table 1. There was an immediate decline in the BDW following relief of the aortic stenotic burden (cumulative BDW -9.7±5.7 $Wm^{-2}s^{-1}$ pre-procedure vs -5.1±3.6 x10^3 $Wm^{-2}s^{-1}$ post-procedure, p<0.01; BDW fraction 37.3±6.2% pre-procedure vs 27.2±7.0% post-procedure, p<0.01). At 6 months after aortic valve intervention the BDW fraction increased to 32.8±7.2% (p=0.01 vs post) and to 34.7±6.7% at 12 months (p<0.001 vs post) with no significant difference from pre-operative values (Figure 2, Figure 3).

The forward decompression wave was significantly reduced with aortic valve intervention (cumulative 2.4±1.7 $Wm^{-2}s^{-1}$ pre-procedure vs 1.1±0.8 $Wm^{-2}s^{-1}$ post-procedure, p=0.03). No other significant changes were noted within the wave-intensity profile with intervention or over time.

Discussion

Previous work has demonstrated that both LVH[9] and the presence of an outflow tract obstruction[10,12] have individual effects on coronary WIA. In this study we have identified and separated these contrasting effects within individual patients with severe aortic stenosis and as such have shown that three states exist:

1. Pre-operatively the total wave intensity is greatly increased including the main determinant of coronary blood flow, the BDW intensity.
2. Immediately post operatively there is a significant reduction in the total wave intensity but with a relatively larger reduction in the BDW (the BDW fraction) reflecting the negative effect of the residual LVH.
3. After 6 months post-operatively coronary efficiency is improved with LVH-regression evidenced by an isolated increase in the BDW size, appreciable as an increase in the size of the BDW energy fraction.

This study is also the first to determine such detailed haemodynamics effects outside of the peri-operative window avoiding the potential confounding influence of anaesthesia, acute myocardial insults, inotropic support or marked volume changes. We have shown that aortic valve therapy imparts sub-acute changes in coronary physiology over-and-above that produced by relief of the mechanical obstruction.

The effect of severe aortic stenosis and its treatment on coronary haemodynamics

An improvement in Coronary Flow Reserve (CFR) after SAVR is well documented[5] driven by improvements in vasodilatory reserve[6]. The reason for this appears twofold with some studies suggesting it is due to a fall in the resting coronary flow velocity[1,4] and others showing an increase in hyperaemic flow velocity[3,6]. Certainly, relative high coronary flow rates are recognised in severe aortic stenosis[14], particularly when symptomatic[15] and a reduction in resting coronary flow velocity has been seen when measured using intracoronary Doppler wires[1] or transthoracic echocardiography[4] before and after SAVR. Here we have shown a similar high coronary flow velocity with severe aortic stenosis and have demonstrated that this is associated with a large BDW. Following aortic valve intervention, the wave magnitude immediately falls resulting in a reduction in velocity.

The BDW is generated from the diastolic re-expansion of the intramyocardial vessels that are compressed in systole[11] with the force of re-expansion reflecting the force of compression hence the increased BDW in aortic stenosis. This work therefore mimics our previous data obtained peri-procedurally at the time of TAVI[10] but has the advantage of being free from inotropic support, general anaesthesia and the potentially stunning effect of rapid-sequence pacing. It also fits with the accepted hypothetical constructs of WIA and our methodology used a reasonable number of cardiac cycles to avoid ensemble errors. We note recently published data[12] demonstrating differing findings from this and our original work[10]. This data is difficult explain with reference to current wave-intensity theory and we would suggest that these physiological and methodological issues may account at least in part for this discrepancy (most notably that through a non-objective selection of low number of cardiac cycle making this data prone to error amplification).

Interestingly, despite co-existing LVH, in severe aortic stenosis the BDW fraction is preserved compared to post-operative values. This implies that under these extreme conditions a series of physiological changes have occurred in order to preserve coronary efficiency (such as a reduction in basal coronary resistance[6]) and optimise ventricular-coronary coupling. Recent work by Lumley et al. has also demonstrated this feature and insightfully gone on to show that this preservation is affected by exercise as this coupling becomes disrupted[16].

The effect of LVH and its regression on coronary haemodynamics

With the treatment of severe aortic stenosis there is a decrease in both the absolute and relative contributions of the BDW within the coronary wave-intensity profile. With regression of hypertrophy the absolute values of the BDW increase but with no change in the total wave-intensity per cardiac cycle, identifiable as a significant increase in the BDW fraction. This reflects an improvement in the ventricular-coronary coupling and an increased 'efficiency' of the cardiac cycle.

Previous studies using PET[17] and TEE[18] in severe aortic stenosis have suggested that the dominant effects on haemodynamics are due to the imposed haemodynamic load rather than from the LVH. We have confirmed this finding using WIA where the major influence on the BDW fraction pre-intervention is that of the aortic valve gradient with less influence from LV mass index. This ratio is reversed immediately after intervention where the negative influence of LVH dominates coronary haemodynamics, allying with previous wave-intensity work in patients with no structural heart disease[9]. Novel to this manuscript we have found that this effect is reversible with the resultant regression of LVH.

LVH is well recognised as having both a negative clinical and physiological effect distinct from other cardiovascular risk factors. Its regression causes an improvement in coronary physiology in both animal[19,20] and human[7] models. However, animal studies are often confounded as the mechanism used to create an artificial afterload is distal to the coronary arteries (such as aortic banding[20]) and human studies are possibly confounded by the direct effects of the pharmacological agent driving LVH regression[21]. By using patients undergoing treatment for aortic stenosis as our model to study LVH regression we have negated these issues.

Coronary physiological dysfunction and its improvement has been identified in aortic stenosis using a wide variety of investigative modalities over the last 50 years[5]. However, to our knowledge almost the entirety of the evidence base in this field has involved 2 measurements only, performed pre-operatively and at a variable time post-operatively, the latter of which may therefore be influenced by both the reduction in outflow-tract gradient and the regression of LVH. For example, CFR measured through transthoracic echocardiography improves at 6 months compared to pre-operative values but after a significant amount of hypertrophy regression has also been documented[3], a feature already noted to have an influence on CFR[1]. This may account for some of the opposing published data such as that seen with PET scanning that suggests a relatively larger influence on CFR from the change in aortic valve gradient than LVM[2], contrasting with recent invasive data demonstrating an improvement in CFR that continues over the 12 months after intervention[22] and a marked improvement in clinical outcomes with LVH regression[8].

By employing our novel technique of non-invasive coronary WIA we have managed to circumvent these issues with the ability to apply convenient, risk-free serial measurements on this cohort of patients undergoing aortic valve intervention. We have shown that both the outflow tract gradient and the presence of LVH have a significant impact on coronary haemodynamics in patients with severe aortic stenosis. Additionally, even though the clinical benefit in aortic stenosis is evident immediately after valve replacement, further positive haemodynamic effects occur over time with regression of LVH (Figure 4). We note data from myocardial contrast echocardiography showing that this influence is likely to be dominantly exerted at an endocardial rather than epicardial level[23,24].

Finally, we found no increase in coronary flow rate with this hypertrophy regression, and in fact velocity rates actually fell further over time. This highlights the sensitivity of wave-intensity to identify subtle changes in coronary haemodynamics in revealing the delicate pathophysiological changes behind the previously documented effects on CFR.

Applications and future directions

Previous invasive work involving pacing during TAVI has shown an immediate benefit of intervention on coronary wave intensity[10]. Furthermore, other groups have demonstrated the possibility of identifying changes in the wave-intensity profile in awake patients during physiological exercise during invasive catheterisation[16]. It should also now be possible to measure the response of the BDW to increasing heart rate and thus guide the need for intervention in a sensitive but non-invasive fashion. We have suggested that whilst the BDW is able to increase in response to exercise, physiological reserve persists and only when it fails to increase appropriately does replacement become necessary[5]. This may prove additionally useful in the assessment of various subsets of aortic stenosis such as low-flow low-gradient patients where decision can be more complex.

The invasive assessment of coronary stenoses in aortic stenosis is a debated subject. Previous work has demonstrated the effect of afterload on whole-cycle indices[25] but not those from the wave-free window[26]. Our work fits with these findings as we have demonstrating changes in the wave-intensity profile but not wave-free window.

We also note the effect of aortic valve intervention on strain-imaging[27]. We would suggest that the incorporation of strain-mapping in future studies would provide further valuable insight into the coronary-myocardial coupling and its dysfunction in aortic stenosis and would be more sensitive than the conventional measures of diastolic function we have reported here. We also highlight previously reported data demonstrating the impact of diastolic function on the BDW in the context of coronary occlusion[28] and would emphasize the importance of incorporating all these features in futures studies.

The magnitude of the BDW corresponds to the degree of the outflow tract obstruction and as such is a potentially new measure of aortic stenosis severity. Importantly, unlike physiological or anatomical measures that focus only on the aortic valve for stenosis quantification (such as velocity through the valve or valve area), WIA has the advantage of providing a measure of overall cardiac burden which may be advantageous in some settings[29].

In patients with LVH remodelling resulting from correction of hypertension, medical treatment improves coronary flow reserve[7]. An assumption that a similar effect on wave intensity could now be made and future work exploring this area non-invasively would be insightful, particularly to document the BDW fraction and the ultimate use of this value for prognostication.

Disadvantages and limitations

Four patients had an alteration in cardiac-acting drugs (addition of beta-blockade x2, increase in amlodipine x1 and increase in ACE-inhibitor x1) over the course of follow up. As this was only 27% of the study population, and not all impact directly on haemodynamics[30] we would anticipate little effect of these alterations on the overall results. Furthermore, these drugs may have increased the rate of regression of hypertrophy, and therefore it is probably their dominant effect would be synergistic rather than confounding effect on the wave-intensity profile. However, we acknowledge these points as partly speculative.

After TAVI, a degree of paravalvular leak is possible. However, none of our TAVI patient group developed anything other than a mild regurgitant leak. One patient who underwent SAVR developed a moderate-severe paravalvular leak that ultimately necessitated percutaneous closure and this patient was excluded from the study.

Our pre-determined exclusion criteria meant 7 patients were not included after recruitment because of difficulties in mapping the entire coronary flow envelope accurately pre-operatively as the potential for error-amplification with wave-intensity processing is high. Additionally, a further 3 had poor windows post-operatively because of presumed chest wall edema. We also excluded any patients who went into atrial fibrillation (n=3) as flow and pressure ensembling becomes inaccurate in these individuals. However, there is nothing to suggest that these patients otherwise differed from our cohort, so we feel this aggressive exclusion protocol enhanced our mathematical rigour at the expense a reduced cohort size. Furthermore, these patients were excluded before long-term follow-up measures were obtained precluding any potential operator bias. We must acknowledge that this also reflects some of the technical difficulties in the measurement of non-invasive WIA, particular when used post-operatively, but for reasons elaborated on above we anticipate that this tool may find more applicability in the pre-operative state. We also believe that the rate of success will improve with the continuing echocardiographic advances in coronary flow assessment. Finally we would comment that our completed cohort size (n=15) is similar in size to all other published wave-intensity studies (mean 20, range 10-33)[31].

We also note the physiological insult of rapid sequence pacing[32] and that of cardiopulmonary bypass. We endeavoured to avoid this by performing the post-procedure measure of coronary WIA at the point of discharge. The average length of stay was 6.3 days with no patients discharged before day 3 when we anticipate the physiological insult of these effects would have dissipated – however, this statement carries a degree of assumption that should be recognized.

For the purpose of this study we also excluded any patients with prior evidence of coronary disease. At present, the effects of coronary artery lesions on wave-intensity are yet to be fully elucidated. Whilst the BDW is thought to be a direct representation of myocardial function, this needs to be borne out in investigations of patients with both structural heart disease and coronary lesions. As

50% of patients with severe aortic stenosis will have evidence of coronary disease, this warrants clarification before a more widespread application of this technology to this population can be firmly recommended.

We also highlight the fact that our measure of central aortic pressure was obtained non-directly from a brachial cuff system. This system has been well validated against invasive[33,34] and tonometric[35] measures of central pressure. We recognise that even in the presence of severe aortic stenosis resting central aortic and coronary pressure waveforms are near-identical[6,26] and would therefore suggest that our measure of central pressure is likely to be robust even in this setting. However, we acknowledge that this has yet to be directly proven. We provide more detailed support for this aspect of our methodology (including experimental data) in the supporting information.

Finally, we note that previous work validating this approach to measuring coronary wave-intensity analysis has shown that waves other than the backward decompression wave may be underestimated[13]. Whilst this may confound comparisons between invasive and non-invasively obtained values, we have avoided this by using only this non-invasive technique.

Conclusion

Aortic stenosis exerts a marked effect on coronary haemodynamics through two opposing effects – directly through the outflow tract obstruction and indirectly through the presence of left ventricular hypertrophy. As such, with aortic valve intervention there is a reduction in the *absolute* size of the BDW immediately post-operatively followed by a *relative* increase over the following year. Therefore, whilst intervention immediately improves coronary haemodynamics, this improvement continues further with LVH regression and both features may be involved in the prognostic benefit of therapy.

Materials and Methods

Patient Characteristics

30 consecutive patients with severe aortic stenosis who were scheduled to undergo either TAVI or Surgical Aortic Valve Replacement (SAVR) were recruited. All patients underwent pre-operative angiography and standard transthoracic echocardiography. Exclusion criteria included angiographic coronary artery disease within the LAD or stenoses of >50% in other arteries, previous coronary intervention, reduced left ventricular systolic function (<50%), the presence of moderate or severe co-existing valvular lesions, poor coronary flow signals in the pre- or post-operative period or the presence or development of atrial fibrillation.

The study was approved by the Fulham-Local Research Ethics Committee and all subjects gave written informed consent (11/LO/1454).

Non-invasive pressure and flow measurements

Non-invasive wave-intensity was measured according to our previously validated methodology[13] (Figure 1). In brief, echocardiography was performed using either a Phillips ie33 (Amsterdam, Netherlands) or Esaote MyLabTwice (Genova, Italy) with appropriate settings[36]: high wall filters, low pulse Doppler filters, colour PRF typically in the range of 15-25cm/s and a wide Doppler sampling width (7.5-10mm). The LAD was imaged initially in the parasternal long axis view and carefully manipulated laterally until the LAD was clearly in view with an angulation of less than 20^{o} to the probe. Multiple coronary flow signals recorded as high-resolution image files. Simultaneously, a suprasystolic waveform was recorded and calibrated with the brachial blood pressure using a cuff-based device (Pulsecor, Auckland, New Zealand). The unprocessed data was exported as a Matlab file.

Data Processing

The central pressure waveform was estimated from the Pulsecor raw data using a modification of the approach described by Lowe *et al*[34] as previous described[13]. At minimum of two recordings were made with repeat measurements if data quality was not 'good' or more. As before, alignment was according to the peak negative dP/dt prior to ensembling in order to prevent over smoothing of the early diastolic portion. Although this a relatively indirect way of assessing coronary pressure, our previous study has demonstrated a strong cross-correlation coefficient between invasive and non-invasive measures[13]; further validation is shown in our supporting information.

Each flow image file was processed using bespoke Matlab software. In brief, the file was imported and a semi-automated tracking programme used to identify the coronary flow envelope. If inaccurate, the tracking could be manipulated manually. Each flow file was segmented according to the ECG and once the entire recording was processed, assembled to produce a continuous recording of flow. We used a relatively high sweep speed for recording flow data which made this process slightly more laborious but promoted accuracy. Specific computational details are provided in the supporting information.

Non-invasive pressure was aligned with flow using the "foot" of the pressure waveform and the ECG-QRS from echocardiography. The data was then processed using our automated Matlab programme which involved a Savitsky-Golay filter (polynomial order 3, window size 51).

We have previously demonstrated the validity of this approach in establishing non-invasive coronary wave-intensity[13].

Wave-intensity analysis

Wavespeed (c) was calculated using the single-point method[37]. Wave-intensity analysis was calculated as previously described[9] using the product of the first-time derivatives of pressure (dP/dt) and velocity (dU/dt) so the results are independent of sampling frequency . The waves can be separated into proximally (WI_{+}) and distally (WI_{-}) originating waves as well as net wave intensity using:

$$WI_{+} = \frac{1}{4\rho c}\left[\frac{dP}{dt} + \rho c\left(\frac{dU}{dt}\right)\right]^{2}$$

$$WI_{-} = -\frac{1}{4\rho c}\left[\frac{dP}{dt} - \rho c\left(\frac{dU}{dt}\right)\right]^2$$

$$WI_{NET} = WI_{+}WI_{-} = \left(\frac{dP}{dt}\right)\left(\frac{dU}{dt}\right)$$

where ρ is the density of blood (taken as 1050 kg m^{-3})

To separate coincident waves from proximal and distal coincident origins the change in pressure was separated into its wave components: dP_+/dt(proximal) and dP_-/dt(distal).

$$\frac{dP_{+}}{dt} = {}^{1}/_{2}\left(\frac{dP}{dt} + \rho c\left(\frac{dU}{dt}\right)\right)$$

$$\frac{dP_{-}}{dt} = {}^{1}/_{2}\left(\frac{dP}{dt} - \rho c\left(\frac{dU}{dt}\right)\right)$$

Separated wave energy was expressed as peak, cumulative (the area under the peak wave intensity-versus-time curve) values along with wave energy fraction (the cumulative intensity of each individual wave expressed as a proportion of the total cumulative wave intensity).

Study Protocol

In addition to wave-intensity, continuous wave (CW) Doppler was used to derive the peak transvalvular pressure gradient across the aortic valve[38]. Left ventricular mass (LVM) was calculated and hypertrophy ascertained according to standard formulae and definitions[39]. Left ventricular mass index (LVMI) was defined as mass indexed for body surface area.

Non-invasive coronary flow and pressure were recorded 24 hours prior to the procedure, on the day of hospital discharge and at 6- and 12-months following intervention. Care was taken to identify and assess the same part of the proximal LAD in all follow-up measurements and a mean of 11.5 cycles used per assessment. Data were exported and analysed off-line using a custom-built Matlab (Mathworks, Natick, MA) programme. WIA was calculated after completion of all data collection by a researcher blinded to the chronology of data acquisition.

Statistics

Data were analysed by STATA v13.1 for Windows (STATA software, TX, USA). Continuous data is expressed as mean ± SD. Correlation was assessed using Pearson's rank correlation coefficient. Serial measurements were analysed using Kruskal-Wallis tests followed by a Dunn's test for pairwise difference when an overall difference was recorded. Multivariable linear regression was used to ascertain the relative influence of LVM and aortic stenosis on the BDW fraction before and after SAVR/TAVI. A p value of <0.05 was deemed significant.

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Conflict of interest
The authors report no relevant conflict of interests.

Tables

Table 1. Baseline characteristics and operative details
Table 2. Echocardiographic data pre- and immediately post-aortic valve intervention and at 6 and 12 months.
Table 3. Full data-set for cumulative, peak and fractional wave intensity profile measured pre-, post- and at 6 and 12 months after aortic valve intervention.

		No (%)
Male (%)		10 (67)
Age (years)		78±9.0
Body surface area (m^2)		1.95±0.20
Diabetic (%)		5 (33)
Medication	Calcium channel antagonist (%)	6 (40)
	Beta blocker (%)	6 (40)
	ACE-inhibitor (%)	5 (33)
	Angiotensin receptor blocker (%)	3 (20)
	Statin (%)	13 (87)
	Aspirin (%)	8 (53)
	Loop diuretic (%)	7 (46)
	Bendroflumethiazide (%)	2 (13)
Symptoms	Angina (%)	5 (33)
	Syncope (%)	0
	Dyspnoea (%)	15 (100)
Valve Type	Edwards (%)	2 (13)
	CoreValve (%)	2 (13)
	Bioprosthetic (%)	11 (73)

Table 1. Baseline characteristics and operative details

		Pre	Post	6 months	12 months
Aortic Valve	AV max (m/s)	4.5±0.6	2.6±0.9*	2.3±0.5*	2.1±0.6*
LV dimensions	LVEDD (cm)	4.7±0.6	4.6±0.6	4.3±0.6	4.0±0.8
	PWTd (cm)	1.2±0.3	1.1±0.1	1.0±0.14	1.1±0.2
	SWTd (cm)	1.3±0.3	1.2±0.1	1.2±0.3	1.2±0.2
	LVEDS (cm)	3.0±0.5	2.9±0.5	3.0±0.6	3.0±0.4
	LVMI (kg/m^2)	114±19	108±17	86±17*	82±17*
Tissue Doppler	E / A ratio	1.1±0.8	1.6±0.6	1.1±0.2	1.1±0.5
	E / e' ratio	14.1±5.2	13.9±5.1	11.1±8.3	10.8±3.6
Coronary flow (cm/s)	Peak	44.2±13.5	35.0±9.3	36.0±11.0*	29.3±8.7*
	Mean	27.1±6.6	22.5±0.60	22.0±6.5	18.6±5.3*
	Min	15.9±4.0	12.8±3.9	12.7±4.1	10.2±3.6*†
Pressure (mmHg)	Systolic	113±14	106±12	121±17*	124±16*†
	Diastolic	65±9.7	63±9.7	70±11	72±10*
	Mean	81±11	76±10	88±14*	89±12*
Heart rate (bpm)		69±13	78±12	70±13	68±12

Table 2. Echocardiographic data pre- and immediately post-aortic valve intervention and at 6 and 12 months.

* $p < 0.05$ compared to pre-procedure. † $p < 0.05$ compared to post-procedure. All other values are non-significant.

Wave intensity		Time				Kruskal-Wallis	
		Pre	Post	6 months	12 months	χ2(2)	p value
FCW	Cumulative x10^3 ($Wm^{-2}s^{-1}$)	5.9±2.4	5.3±2.5	5.5±2.2	4.8±3.0	2.40	0.49
	Peak x10^4 ($Wm^{-2}s^{-1}$)	9.2±4.1	8.9±5.5	8.2±3.9	6.5±4.0	3.43	0.33
	Fraction (%)	24.8±4.9	29.1±7.16	28.9±6.8	26.3±5.5	6.39	0.09
FDW	Cumulative x10^3 ($Wm^{-2}s^{-1}$)	2.4±1.7	1.1±0.8	1.5±0.9	1.9±1.6	6.16	0.10
	Peak x10^4 ($Wm^{-2}s^{-1}$)	6.2±4.8	3.5±2.9	3.6±1.7	2.2±1.8	11.68	0.009*
	Fraction (%)	9.0±4.5	6.4±3.7	7.9±3.2	10.4±5.3	3.71	0.29
FCW2	Cumulative x10^3 ($Wm^{-2}s^{-1}$)	1.1±1.2	0.9±1.1	0.6±0.6	0.4±0.5	4.73	0.19
	Peak x10^4 ($Wm^{-2}s^{-1}$)	0.4±0.3	0.5±0.6	0.6±1.3	0.6±0.4	7.27	0.06
	Fraction (%)	4.7±4.4	4.2±3.5	2.9±1.7	2.4±2.2	3.26	0.35
BCW early	Cumulative x10^3 ($Wm^{-2}s^{-1}$)	1.4±0.9	1.8±1.6	1.6±1.6	1.2±1.1	1.37	0.71
	Peak x10^4 ($Wm^{-2}s^{-1}$)	5.0±3.2	6.6±5.2	5.6±4.3	3.5±2.1	3.77	0.29
	Fraction (%)	5.7±4.1	10.1±6.5	7.5±6.3	8.1±6.9	4.10	0.25
BCW late	Cumulative x10^3 ($Wm^{-2}s^{-1}$)	4.5±2.8	4.4±3.7	4.0±2.1	2.9±1.7	3.16	0.37
	Peak x10^4 ($Wm^{-2}s^{-1}$)	7.4±4.4	9.1±7.3	8.4±5.0	6.1±4.0	1.64	0.65
	Fraction (%)	18.5±7.7	22.4±8.6	20.1±6.4	18.0±7.4	3.37	0.34
BDW	Cumulative x10^3 ($Wm^{-2}s^{-1}$)	9.7±5.7	5.1± 3.6	6.8±4.2	6.0±3.1	10.4	0.015*
	Peak x10^4 ($Wm^{-2}s^{-1}$)	16.8±10.3	8.5± 5.5	13.6±12.3	12.2±8.6	8.75	0.033*
	Fraction (%)	37.3±6.2	27.2±7.0	32.8±7.2	34.7±6.7	14.88	0.002*
Total WI	($Wm^{-2}s^{-1}$)	25.1±11.5	18.6±10.7	20.0±9.7	17.2±8.7	5.40	0.15

Table 3. Full data-set for cumulative, peak and fractional wave intensity profile measured pre-, post- and at 6 and 12 months after aortic valve intervention.

FCW=Forward Compression Wave, FDW=Forward Decompression Wave, FCW2=second Forward Compression Wave, BCW=Backward Compression Wave, BDW=Backward Decompression Wave, WI=Wave Intensity. *=significant. Backward originating waves are expressed as absolute values. Dunn's test for pairwise difference for those significant values are reported in the Results section.

References

1. Eberli, Ritter M, Schwitter J, Bortone A, Schneider J, Hess OM, Krayenbuehl HP. Coronary reserve in patients with aortic valve disease before and after successful aortic valve replacement. *Eur Heart J* 1991;12:127–138.
2. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional Changes in Coronary Microcirculation After Valve Replacement in Patients With Aortic Stenosis. *Circulation* 2003;107:3170–3175.
3. Hildick-Smith DJR, Shapiro LM. Coronary flow reserve improves after aortic valve replacement for aortic stenosis: an adenosine transthoracic echocardiography study. *J Am Coll Cardiol* 2000;36:1889–1896.
4. Nemes A, Forster T, Kovacs Z, Thury A, Ungi I, Csanady M. The effect of aortic valve replacement on coronary flow reserve in patients with a normal coronary angiogram. *Herz* 2002;27:780–784.
5. Broyd CJ, Sen S, Mikhail GW, Francis DP, Mayet J, Davies JE. Myocardial ischemia in aortic stenosis: insights from arterial pulse-wave dynamics after percutaneous aortic valve replacement. *Trends Cardiovasc Med* 2013;23:185–191.
6. Wiegerinck EMA, Hoef TP van de, Rolandi MC, Yong Z, Kesteren F van, Koch KT, Vis MM, Mol BAJM de, Piek JJ, Baan J. Impact of Aortic Valve Stenosis on Coronary Hemodynamics and the Instantaneous Effect of Transcatheter Aortic Valve Implantation. *Circ Cardiovasc Interv* 2015;8:e002443.
7. Motz W, Strauer BE. Improvement of Coronary Flow Reserve After Long-term Therapy With Enalapril. *Hypertension* 1996;27:1031–1038.
8. Lindman BR, Stewart WJ, Pibarot P, Hahn RT, Otto CM, Xu K, Devereux RB, Weissman NJ, Enriquez-Sarano M, Szeto WY, Makkar R, Miller DC, Lerakis S, Kapadia S, Bowers B, Greason KL, McAndrew TC, Lei Y, Leon MB, Douglas PS. Early Regression of Severe Left Ventricular Hypertrophy After Transcatheter Aortic Valve Replacement Is Associated With Decreased Hospitalizations. *JACC Cardiovasc Interv* 2014;7:662–673.
9. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Evidence of a Dominant Backward-Propagating 'Suction' Wave Responsible for Diastolic Coronary Filling in Humans, Attenuated in Left Ventricular Hypertrophy. *Circulation* 2006;113:1768–1778.
10. Davies JE, Sen S, Broyd C, Hadjiloizou N, Baksi J, Francis DP, Foale RA, Parker KH, Hughes AD, Chukwuemeka A, Casula R, Malik IS, Mikhail GW, Mayet J. Arterial pulse wave dynamics after percutaneous aortic valve replacement: Fall in coronary diastolic suction with increasing heart rate as a basis for angina symptoms in aortic stenosis. *Circulation* 2011;124:1565–1572.
11. Broyd CJ, Hernández-Pérez F, Segovia J, Echavarría-Pinto M, Quirós-Carretero A, Salas C, Gonzalo N, Jiménez-Quevedo P, Nombela-Franco L, Salinas P, Núñez-Gil I, Trigo M Del, Goicolea J, Alonso-Pulpón L, Fernández-Ortiz A, Parker K, Hughes A, Mayet J, Davies J, Escaned J. Identification of capillary rarefaction using intracoronary wave intensity analysis with resultant prognostic implications for cardiac allograft patients. *Eur Heart J* 2017;
12. Rolandi MC, Wiegerinck EMA, Casadonte L, Yong Z-Y, Koch KT, Vis M, Piek JJ, Baan JJ, Spaan

JAE, Siebes M. Transcatheter Replacement of Stenotic Aortic Valve Normalizes Cardiac-Coronary Interaction by Restoration of Systolic Coronary Flow Dynamics as Assessed by Wave Intensity Analysis. *Circ Cardiovasc Interv* United States; 2016;9:e002356.

13. Broyd CJ, Nijjer S, Sen S, Petraco R, Jones S, Al-Lamee R, Foin N, Al_Bustami M, Sethi A, Kaprielian R, Ramrakha P, Khan M, Malik I, Francis D, Parker KH, Hughes AD, Mikhail G, Mayet J, Davies JE. Estimation of coronary wave intensity analysis using non-invasive techniques and its application to exercise physiology. *Am J Physiol - Hear Circ Physiol* 2015;310:H619-27.
14. Meimoun P, Germain AL, Elmkies F, Benali T, Boulanger J, Espanel C, Clerc J, Zemir H, Luycx-Bore A, Tribouilloy C. Factors associated with noninvasive coronary flow reserve in severe aortic stenosis. *J Am Soc Echocardiogr* 2012;25:835–841.
15. Isaaz K, Bruntz JF, Paris D, Ethevenot G, Aliot E. Abnormal coronary flow velocity pattern in patients with left ventricular hypertrophy, angina pectoris, and normal coronary arteries: A transesophageal Doppler echocardiographic study. *Am Heart J* 1994;128:500–510.
16. Lumley M, Williams R, Asrress KN, Arri S, Briceno N, Ellis H, Rajani R, Siebes M, Piek JJ, Clapp B, Redwood SR, Marber MS, Chambers JB, Perera D. Coronary Physiology During Exercise and Vasodilation in the Healthy Heart and in Severe Aortic Stenosis. *J Am Coll Cardiol* 2016;68:688–697.
17. Rajappan K, Rimoldi OE, Dutka DP, Ariff B, Pennell DJ, Sheridan DJ, Camici PG. Mechanisms of Coronary Microcirculatory Dysfunction in Patients With Aortic Stenosis and Angiographically Normal Coronary Arteries. *Circulation* 2002;105:470–476.
18. Omran H, Fehske W, Rabihieh R. Relationship between symptoms and profile of coronary artery blood flow velocities in patients with aortic valve stenosis: a study using transoesophageal echocardiography. *Heart* 2011;75:377–383.
19. Sato F, Isoyama S, Takishima T. Normalization of impaired coronary circulation in hypertrophied rat hearts. *Hypertension* 1990;16:26–34.
20. McGoldrick RB, Kingsbury M, Turner MA, Sheridan DJ, Hughes AD. Left ventricular hypertrophy induced by aortic banding impairs relaxation of isolated coronary arteries. *Clin Sci* 2007;113:473–478.
21. Parodi O, Neglia D, Palombo C, Sambuceti G, Giorgetti A, Marabotti C, Gallopin M, Simonetti I, L'Abbate A. Comparative Effects of Enalapril and Verapamil on Myocardial Blood Flow in Systemic Hypertension. *Circulation* 1997;96:864–873.
22. Camuglia AC, Syed J, Garg P, Kiaii B, Chu MW, Jones PM, Bainbridge D, Teefy PJ. Invasively assessed coronary flow dynamics improve following relief of aortic stenosis with transcatheter aortic valve implantation. *J Am Coll Cardiol* Journal of the American College of Cardiology; 2014;63:1808–1809.
23. Galiuto L, Lotrionte M, Crea F, Anselmi A, Biondi-Zoccai GGL, Giorgio F De, Baldi A, Baldi F, Possati G, Gaudino M, Vetrovec GW, Abbate A. Impaired coronary and myocardial flow in severe aortic stenosis is associated with increased apoptosis: a transthoracic Doppler and myocardial contrast echocardiography study. *Heart* 2006;92:208–212.
24. Miyagawa S, Masai T, Fukuda H, Yamauchi T, Iwakura K, Itoh H, Sawa Y. Coronary Microcirculatory Dysfunction in Aortic Stenosis: Myocardial Contrast Echocardiography Study.

Ann Thorac Surg 2009;87:715–719.

25. Pesarini G, Scarsini R, Zivelonghi C, Piccoli A, Gambaro A, Gottin L, Rossi A, Ferrero V, Vassanelli C, Ribichini F. Functional Assessment of Coronary Artery Disease in Patients Undergoing Transcatheter Aortic Valve Implantation. *Circ Cardiovasc Interv* 2016;9:e004088.
26. Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, Gottin L, Zanetti C, Faggian G, Ribichini F. Physiologic evaluation of coronary lesions using instantaneous wave-free ratio (iFR) in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention* EuroPCR; 2018;13:1512–1519.
27. Garg V, Ho JK, Vorobiof G. Changes in myocardial deformation after transcatheter and surgical aortic valve replacement. *Echocardiography* Wiley/Blackwell (10.1111); 2017;34:603–613.
28. Ladwiniec A, White PA, Nijjer SS, O'Sullivan M, West NEJ, Davies JE, Hoole SP. Diastolic Backward-Traveling Decompression (Suction) Wave Correlates With Simultaneously Acquired Indices of Diastolic Function and Is Reduced in Left Ventricular Stunning. *Circ Cardiovasc Interv* American Heart Association, Inc.; 2016;9:e003779.
29. Briand M, Dumesnil JG, Kadem L, Tongue AG, Rieu R, Garcia D, Pibarot P. Reduced Systemic Arterial Compliance Impacts Significantly on Left Ventricular Afterload and Function in Aortic Stenosis: Implications for Diagnosis and Treatment. *J Am Coll Cardiol* 2005;46:291–298.
30. Kamezaki F, Tasaki H, Yamashita K, Shibata K, Hirakawa N, Tsutsui M, Kouzuma R, Nagatomo T, Adachi T, Otsuji Y. Angiotensin receptor blocker improves coronary flow velocity reserve in hypertensive patients: comparison with calcium channel blocker. *Hypertens Res* 2007;30:699–706.
31. Broyd CJ, Davies JE, Escaned JE, Hughes A, Parker K. Wave intensity analysis and its application to the coronary circulation. *Glob Cardiol Sci Pract* 2015;2015:64.
32. Axell RG, White PA, Giblett JP, Williams L, Rana BS, Klein A, O'Sullivan M, Davies WR, Densem CG, Hoole SP. Rapid Pacing–Induced Right Ventricular Dysfunction Is Evident After Balloon-Expandable Transfemoral Aortic Valve Replacement. *J Am Coll Cardiol* 2017;69:903 LP-904.
33. Lin ACW, Lowe A, Sidhu K, Harrison W, Ruygrok P, Stewart R. Evaluation of a novel sphygmomanometer, which estimates central aortic blood pressure from analysis of brachial artery suprasystolic pressure waves. *J Hypertens* 2012;30:1743–1750.
34. Lowe A, Harrison W, El-Aklouk E, Ruygrok P, Al-Jumaily AM. Non-invasive model-based estimation of aortic pulse pressure using suprasystolic brachial pressure waveforms. *J Biomech* 2009;42:2111–2115.
35. Park CM, Korolkova O, Davies JE, Parker KH, Siggers JH, March K, Tillin T, Chaturvedi N, Hughes AD. Arterial pressure: agreement between a brachial cuff-based device and radial tonometry. *J Hypertens* 2014;32:865–872.
36. Rigo F, Murer B, Ossena G, Favaretto E. Transthoracic echocardiographic imaging of coronary arteries: tips, traps, and pitfalls. *Cardiovasc Ultrasound* 2008;6:7.
37. Davies JE, Whinnett ZI, Francis DP, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Use of simultaneous pressure and velocity measurements to estimate arterial wave speed at a single site in humans. *Am J Physiol - Hear Circ Physiol* 2006;290:H878–H885.

38. Currie PJ, Seward JB, Reeder GS, Vlietstra RE, Bresnahan DR, Bresnahan JF, Smith HC, Hagler DJ, Tajik AJ. Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation* 1985;71:1162–1169.

39. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, St John Sutton M, Stewart WJ. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiograph. *J Am Soc Echocardiogr* Mosby-Year Book; 2005;18:1440–1463.

Figures

Figure 1. Construction of non-invasive wave-intensity (C) using coronary flow (A, D) and central pressure (B, E). Coronary flow is obtained from transthoracic echocardiography (A) and digitalized (D, solid lines) before being ensemble-averaged (D, dashed line). Central pressure is obtained from a suprasystolic blood pressure cuff system (B) and also ensemble-averaged (E, dashed line). Wave intensity is constructed from these waveforms (C). The Backward Decompression Wave (BDW) is labelled. Note: for clarity in this diagram only a limited number of cardiac cycles from the overall data-set for this patient is shown.

Figure 2. Left ventricular mass index (A), peak aortic valve velocity (B), cumulative BDW (C) and BDW fraction (D) pre, post and at 6 and 12 months after aortic valve intervention. With intervention, there is no immediate change in LV mass index (A). There is however an immediate decrease in aortic valve gradient (B) accompanied by a reduction in the cumulative backward decompression wave(C). This decrease is proportionately greater than the other coronary waves resulting in a fall in the backward decompression wave fraction (D). Over the following 12 months, a reduction in left ventricular mass index occurs accompanied by an increase in the backward decompression wave fraction (D). Relevant p values are displayed and significant values marked: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

Figure 3. Serially measured wave intensity profile in severe aortic stenosis and with its treatment; shaded waves are accelerating waves and unshaded decelerating waves. The Backward Decompression Wave (BDW) is large pre-operatively (A). After intervention, it decreases in size (B). Whilst all other coronary waves also decrease the BDW is affected to a relatively greater extent due to the dominating effect of LVH post-operatively. As this hypertrophy regresses, there are subtle changes in the absolute wave-intensity profile with an increase in the backward decompression wave and a decrease in all the other waves within the cardiac cycle. This is recognisable as a significant increase in the relative magnitude of the backward decompression wave (its fractional

energy) (C).

Figure 4. Schematic representation of the effect of aortic stenosis and its treatment of coronary WIA. The width of the LVH line indicates LV mass index and the width of the AV gradient indicates the gradient across the aortic valve. With severe aortic stenosis the total wave-intensity profile is large including a relatively large BDW. Immediately following therapy there is a decline in both the overall wave-intensity and the BDW. At this point the effect of the residual LVH dominates coronary haemodynamics causing the BDW to account for a smaller fraction of the total coronary wave intensity profile. As the LVH regresses the BDW increases with little change in the total coronary wave intensity resulting in a significant increase in the BDW fraction.