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COMMENTARY

Arterial Stiffness in Aortic Stenosis and the Impact of Aortic Valve Replacement

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Abstract: The most common cause for interventional valve treatment is aortic stenosis. A cardinal symptom of aortic stenosis is heart failure due to the increased load exerted on the left ventricle. However, the left ventricular load is not solely determined based on the degree of aortic stenosis but is also impacted by arterial stiffness. The combined load can be determined by valvulo-arterial impedance (Zva), which is associated with poor outcome in aortic stenosis. We recently demonstrated low measures of systemic arterial stiffness in patients with aortic stenosis, and that arterial stiffness was increased after surgical aortic valve replacement. The results indicated a masked arterial stiffness in aortic stenosis when using methods incorporating peripheral arterial segments. Available studies using several different methods to assess arterial stiffness in relatively small aortic stenosis cohorts examined before and after either surgical or transcatheter aortic valve replacement/intervention have generated contradictory results. In this commentary, we present a detailed literature review to explore how different methods and measures of arterial stiffness in aortic stenosis capture or not, a masked arterial stiffness in aortic stenosis and possible reasons for the observed results. Future studies validating a non-invasive reproducible method to assess arterial stiffness in aortic stenosis patients could potentially lead to an implementation in pre-interventional risk assessment for aortic stenosis.

Keywords: aortic stenosis, arterial stiffness, pulse wave velocity, cardio ankle vascular index, valvular heart disease, ventricular-arterial coupling

The Importance of Arterial Stiffness in Aortic Valve Stenosis

The importance of increased afterload in aortic stenosis has long been acknowledged and the vascular component of the afterload is receiving emerging attention. A stiffened arterial tree confers risk of damage to organs including the heart and independently predicts all-cause mortality.[1] The combined left ventricular (LV) load may be assessed by transthoracic echocardiography determined valvulo-arterial impedance (Zva), which is independently associated with poor aortic stenosis outcome.[2] However, Zva cannot discriminate the valvular and arterial respective contribution, raising the notion that direct measurement of arterial stiffness would represent additional value in aortic stenosis evaluation. Indeed, increased measures of arterial stiffness have been associated with aortic valve calcium,[3] aortic valve sclerosis,[4] aortic stenosis[5] and poor prognosis after aortic valve replacement.[6] However, the effect of aortic valve replacement on arterial stiffness, although studied, remains to be clinched. We recently reported that arterial stiffness was normal or low in patients with aortic stenosis but increased to pathological measures after aortic valve replacement surgery.[7] Thus, alleviation of the LV outflow obstruction could unmask an increased arterial stiffness. In this commentary, we have made a detailed literature review to explore how methods may capture or not the masked arterial stiffness in aortic stenosis.

Methods to Determine Arterial Stiffness in Aortic Valve Stenosis

In addition to the gold standard method to measure arterial stiffness, carotid femoral pulse wave velocity[8] (cfPWV), several other methods are used with specific advantages and disadvantages. However, few studies of arterial stiffness

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have been performed in valvular heart disease. Studies that assessed arterial stiffness before and after either surgical aortic valve replacement (SAVR) or transcatheter aortic valve intervention (TAVI) are outlined in Table 1.

Aortic Stiffness Index

Early studies used echocardiography to determine aortic stiffness index (ASi) by the relation between blood pressure and change in the ascending aortic diameter. The ASi studies reported contradictory results with a tendency towards decreased stiffness when measured >3 weeks after TAVI but increased stiffness 7 days after SAVR.[9–12] Of importance, ASi only measures the stiffness in a small area of the ascending aorta and limited conclusions may be drawn about the overall arterial stiffness. Furthermore, the results indicate a distinctive response depending on intervention which is supported by studies using cardiac magnetic resonance imaging (cMRI) to calculate PWV.[13] Some have argued that this might be due to the surgical trauma, disrupting vasa vasorum and causing aortic stunning. However, we have demonstrated that arterial stiffness measured by cfPWV, brachial ankle (ba) PWV and cardio-ankle vascular index (CAVI) remain unaltered in patients undergoing surgery for ascending aortic dilatation in the absence of aortic stenosis.[7]

Oscillometric Based Pulse Wave Velocity

The Mobile-O-Graph utilizes an oscillometric brachial cuff to measure blood pressure and pulse wave analysis yielding augmentation index (AIx) and PWV, termed oscillometric PWV (oPWV). Two studies used this method of which one noted decreased oPWV 1 day after TAVI and another unchanged oPWV 90 days after SAVR.[14,15] However, concerns have been raised based on a study showing that 99.1% of the variation in oPWV was explained by age and systolic blood pressure.[16] Also, a considerable discrepancy between oPWV and cfPWV was observed in a Marfan cohort[17] indicating that oPWV may need validation in specific populations.

Augmentation Index

The invasive measurement of arterial stiffness using pressure wires offers a robust assessment of aortic pressure waves that can be used to calculate AIx. However, only two studies have used this technique and despite using similar cohorts, reached conflicting results.[18,19] Although invasive pressure techniques might be feasible in the AVR setting, we argue that a non-invasive method is preferred to assess the arterial stiffness as part of the preoperative risk assessment. Non-invasive AIx measurement has been used in 2 studies, which showed decreased AIx after AVR.[20,21] The reason for this decrease is likely explained by the arguments that Pagolatou et al outlined.[19] First, the timing of the reflective wave changes after the relief of the aortic stenosis implies that the relative contribution of the reflective wave decreases leading to a lowering of AIx. Second, wave separation analysis did not demonstrate a decrease in the reflective pressure wave which would be expected if explained by decreased arterial stiffness.[19]

Pulse Wave Velocity and Cardio Ankle Vascular Index

As opposed to AIx, cfPWV uses the foot of the wave to detect the arrival of the pulse wave. Hence, the method should be less sensitive to the prolonged arterial pressure curve in aortic stenosis. Three previous studies incorporating both TAVI and SAVR subjects demonstrated an increased cfPWV after AVR.[21–23] However, two studies, including ours, did not reach a statistically significant increased cfPWV.[7,24] This might be due to lack of power as the increase is rather small and that the inter-observer variability of the Sphygmocor device is about 9%.[25] Building on the same principle as measuring cfPWV, both baPWV and CAVI determined arterial stiffness including peripheral segments. Two studies reported an increase in baPWV following AVR with our study demonstrating a similar CAVI response.[7,21] It is important to stress that proximal stiffness affects the valve hemodynamics leading to increased Zva and therefore, we argue that it is of value also to include peripheral segments when determining arterial stiffness in aortic stenosis patients.

The reason for an increased peripheral arterial stiffness following AVR is likely to involve the previously mentioned prolonged pulse wave in aortic stenosis. The change in ejection time was one of the strongest predictors of the increase in CAVI in our study where a decreased ejection time was associated with a more pronounced increase in CAVI.[7] When the propagation of the pulse wave is prolonged, arteries may comply better to the volume change causing a prolongation of time to detection of the pulse wave. Pulse wave analysis[18] and decreased upstroke time[7] support

Table 1 Studies of Arterial Stiffness in Aortic Valve Stenosis

Study	Cohort	Change in SBP	Change in Stiffness	Day Post AVR	Method	Comments
Barbetseas et al 2006[9]	31 SAVR, 52% male, mean age 67	⇔	↑	7 and 180	ASi	No change in stiffness after 6 months. ΔASi correlated with AVAi.
Nemes et al 2007[10]	12 SAVR, 58% male, mean age 65	↓SBP	↓	21, 180 and 365	ASi	Gradual decreased ASi with time
Vavuranakis et al 2012[11]	30 TAVI, 47% male, mean age 80	↑ MAP ⇔ SBP	⇔	7–8	ASi	No significant Δstiffness nor aortic distensibility
Vizzardi et al 2014[12]	15 TAVI, 40% male, mean age 83	⇔	↓	180 and 365	ASi	Sustained decreased stiffness after 12 months and increased distensibility
Cantürk et al 2017[14]	38 SAVR, 78% male, mean age 59	⇔	⇔	90	PWV (MOG)	Baseline PWV was associated with MPG and AVA.
Goudzwaard et al 2019[15]	40 TAVI, 58% male, mean age 80	↓	↓	1	PWV and AIx with MOG	ΔPWV was inversely correlated with baseline PWV
Yotti et al 2015[18]	23 TAVI, 63% male, mean age 79	↑ SBP, DBP, MAP	↑	0	Invasive AIx	↑ Vascular load after TAVI
Pagolatou et al 2020[19]	33 TAVI, 49% male, mean age 84	↑ aortic BP	↓ AIx	1	Invasive AIx	
Müller et al 2018[20]	50 TAVI, 45% male, mean age 83	⇔	↓	2–7	AIx (SphygmoCor)	↓ Time to peak after TAVI
Terentes-Printzios et al 2020[21]	90 TAVI, 50% male, mean age 80	⇔	↓AIx	1–365	AIx (SphygmoCor)	↓AIx directly after TAVI but no difference after 1 year.
Al Musa et al 2016[13]	32 TAVI, 63% male, mean age 81	⇔	⇔	90	aPWV-MRI	Also, decreased distensibility ascending/ descending aorta
	40 SAVR, 78% male, mean age 73	⇔	↑	90		
Bruschi et al 2016[24]	15 SAVR, 60% male, mean age 77	↓ SBP	⇔	7	cfPWV (Complior)	cfPWV correlated with Pmax/mean
	15 TAVI, 40% male, mean age 82	⇔	⇔	7		
Chirinos JA et al 2019[22]	38 SAVR, 68% male, mean age 72	⇔	↑cfPWV ↑ cMRI	180	cfPWV (SphygmoCor and MRI)	↓ LV mass, ↑ total peripheral resistance, ↓ total arterial compliance

(*Continued*)

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Table 1 (Continued).

Study	Cohort	Change in SBP	Change in Stiffness	Day Post AVR	Method	Comments
Terentes-Printzios et al 2020[21]	90 TAVI, 50% male, mean age 80	⇔	↑cf/baPWV ↓ AIx@75	6 and 365	cfPWV (Complior), baPWV, AIx	Sustained cf/baPWV after 1 year.
Raimundo et al 2021[23]	150 SAVR, 51% male, mean age 73	?	↑	~60	cfPWV Complior	cfPWV 9.0±2.1 → 9.9±2.2
Plunde et al 2021[7]	32 SAVR, 67% male, mean age 69	⇔	⇔/↑	3	cfPWV (SphygmoCor) CAVI, baPWV	↑ CAVI/baPWV, ⇔ cfPWV

Notes: A summary of studies assessing aortic/arterial stiffness before and after aortic valve replacement (AVR). Importantly, this tables incorporate a variety of methods including indirect measures of stiffness such as augmentation index, which is also dependent on other entities. Mobil-O-Graph (MOG) is a highly questioned method to determine arterial stiffness as it is almost entirely dependent on age and systolic blood pressure.
Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; cfPWV, carotid-femoral pulse wave velocity; AIx, augmentation index; MRI, magnetic resonance imaging; ASi, aortic stiffness index; LV, left ventricle; aPWV, aortic pulse wave velocity.

an altered pulse wave morphology following AVR. When the obstruction is relieved by AVR, a true arterial stiffness can be measured. Hence, the properties of the arterial wall itself are not changed but rather the ventricular-aortic-vascular coupling. Including intrinsic stiffer peripheral arteries may facilitate the detection of a masked increased arterial stiffness.

Arterial Stiffness – in the Long Run

Arterial stiffness has been followed up to 1 year after AVR (Table 1). The heterogeneity of the studies for the timely proximity to AVR precludes a conclusion on the precise time-course for the changes. However, the changes observed postoperatively were sustained at longer follow-up, albeit numerically attenuated, yet significantly different from the first measurement. This has been reported for both decreased ASi and for increased cfPWV and cMRI PWV. The difference could possibly be explained by a ventricular-arterial coupling optimization[26] during an adjusting time after the relief of the LV outflow obstruction. Furthermore, it may be of particular importance to capture long term elevated arterial stiffness as it often take years for the LV to recover after AVR.[27] Future studies should aim at identifying the importance of sustained arterial stiffness after AVR.

Conclusion

In summary, arterial stiffness is an important contributor to the combined LV load in aortic stenosis. The evaluation of arterial stiffness may have prognostic implications in aortic stenosis and could potentially be implemented in pre-interventional risk assessment, in particular for asymptomatic patients. Furthermore, exceptionally low CAVI could be useful in AVS screening. It is important to establish an easy, reliable, and correct measurement of arterial stiffness that may capture the possibly masked arterial stiffness in aortic stenosis. As such, future studies are needed to validate a non-invasive method in aortic stenosis patients and establish the prognostic value of the change in arterial stiffness after aortic valve replacement.

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Disclosure

The authors report no conflicts of interest in this work.

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