Arterial stiffness in aortic stenosis – complex clinical and prognostic implications

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Arterial stiffness and degenerative aortic stenosis (AoS) are frequently associated leading to a combined valvular and vascular load imposed on the left ventricle (LV). Vascular load consists of a pulsatile load represented by arterial stiffness and a steady load corresponding to vascular resistance. Increased vascular load in AoS has been associated with LV dysfunction and poor prognosis in pre-intervention state, as well as after aortic valve replacement (AVR), suggesting that the evaluation of arterial load in AoS may have clinical benefits. Nevertheless, studies that investigated arterial stiffness in AoS either before or after AVR used various methods of measurement and their results are conflicting. The aim of the present review was to summarize the main pathophysiological mechanisms which may explain the complex valvulo-arterial interplay in AoS and their consequences on LV structure and function on the patients' outcome. Future larger studies are needed to clarify the complex hemodynamic modifications produced by increased vascular load in AoS and its changes after AVR. Prospective evaluation is needed to confirm the prognostic value of arterial stiffness in patients with AoS. Simple, non-invasive, reliable methods which must be validated in AoS still remain to be established before implementing arterial stiffness measurement in patients with AoS in clinical practice.

Key words: aortic stenosis, arterial stiffness, total left ventricle pressure load, ventriculo-arterial coupling

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INTRODUCTION

Aortic stenosis (AoS) is the most frequent valvular disease in elderly people, reaching a prevalence of 3% in those older than 65 years[1]. The main pathological modifications include inflammation, lipid deposition and tissue calcification. Besides aging, hypertension, dyslipidemia and diabetes are important risk factors[1].

Arterial stiffness is a characteristic of vascular aging and is aggravated by the presence of other classical cardiovascular risk factors, particularly arterial hypertension. Similar risk factors are associated with the development of AoS (ref.[2,3]).

The gold standard measure of arterial stiffness is aortic pulse wave velocity (PWV) which has independent predictive value for cardiovascular events and cardiovascular and all-cause mortality[4,5]. Arterial stiffness can also be measured using other indices, including markers of local central arterial stiffness (i.e. carotid or aortic stiffness indexes), parameters of both central and peripheral stiffness (cardio-ankle vascular index-CAVI, brachial-ankle PWV) or systemic arterial compliance (SAC) (ref.[5,6]).

Degenerative AoS and arterial stiffness share common risk factors and pathogenic mechanisms[1,4,6] which may explain why valvular and vascular alterations frequently coexist[7-10]. Decreased arterial distensibility in patients with AoS may alter LV-arterial coupling, increasing the risk of left ventricle (LV) function deterioration, cardiac events and poor prognosis[7,11,12]. Moreover, postintervention amelioration of LV function varies considerably between patients and may be negatively influenced by increased arterial stiffness[12,13]. It has been suggested that AoS should not be viewed as an isolated valve disease but rather as a complex systemic disease which also integrates vascular alterations and LV adaptive processes[7,12,13].

The aim of the present literature review was to highlight the pathogenetic mechanisms that may link arterial stiffness to AoS and the clinical and prognostic implications of increased arterial stiffness in patients with AS.

Pathophysiological consequences of increased arterial stiffness in AoS

AoS produces chronic pressure overload and subsequently, LV remodeling and concentric hypertrophy as a compensatory mechanism which limits end-systolic wall stress. Cardiac output and LV filling pressures are preserved if adaptive responses are efficient and transvalvular gradient increases with the degree of valvular stenosis. However, in hypertrophic myocardium oxygen supply to the endocardium is reduced. The association of subendocardial ischemia and fibrosis may deteriorate longitudinal LV function which depends on subendothelial layers. LV ejection fraction is conserved, as it particularly depends on mid-wall myocardial fibres[14-17]. In asymptomatic patients with AoS, depressed LV longitudinal function was associated with the development of symptoms in short

time follow-up, impaired exercise tolerance and higher risk of developing cardiac events[15-19].

Subendocardial LV function may also be depressed in patients with central arteries' stiffness[20]. Once arterial walls become stiff, the speed of forward aortic pulse wave increases. The reflected arterial wave generated at arterial bifurcations returns faster to the LV and contributes to systolic aortic pressure augmentation and increased LV afterload. At the same time, increased central artery stiffness reduces aortic diastolic pressure and subsequently myocardial vascularization during diastole, even in the absence of significant coronary atherosclerosis[21]. Increased arterial stiffness is a risk factor for LV diastolic dysfunction[22,23].

In AoS, LV is exposed mainly to the pressure load represented by the valvular aria narrowing, but the association of reduced arterial distensibility adds a second arterial load. Moreover, hypertension, which has a prevalence of more than 75% among elderly patients with AoS, is another contributor to increased arterial load[24,25]. The real arterial load in AoS consists of a pulsatile component which is represented by arterial stiffness and/or a steady one expressed by vascular resistance. LV diastolic dysfunction can develop earlier in patients with associated increased arterial load than in those without arterial stiffness or hypertension. It has been suggested that vascular stiffness may cause LV systolic and diastolic dysfunction in patients with moderate degrees of AoS (ref.[11]). LV diastolic dysfunction has been associated with an increased risk of cardiovascular death and aortic valve replacement in AoS (ref.[17]). Thus, increased vascular stiffness could explain the increased mortality in patients in whom AoS severity indices failed to predict outcomes[26].

Assessment of arterial stiffness in AoS patients

Various indices of local, regional or systemic arterial stiffness have been evaluated in AoS patients and compared to controls with similar classical cardiovascular risk factors.

Using transesophageal echocardiography, Nemes et al. investigated aortic elastic modulus and Young's circumferential static elastic modulus in AoS patients with normal epicardial coronary arteries compared to subjects with left anterior descending coronary artery stenosis but without AoS. The authors reported increased aortic stiffness in AoS patients and in those with coronary atherosclerosis compared to controls, suggesting early development of aortic wall alterations in AoS, reaching a similar degree to those found in patients with coronary atherosclerosis[9]. In another study, baseline aortic β stiffness index measured using transthoracic echocardiography was increased in 12 patients with AoS who underwent AVR compared to controls[27].

Laskey et al. evaluated 18 patients with symptomatic degenerative calcific AoS reporting a pressure-independent increase in the steady and pulsatile components of arterial load (higher vascular resistance and aortic characteristic impedance and reduced arterial compliance) compared to controls. These differences persisted or even increased after exercise. It has been speculated that the increase LV vascular load may be an important contributor to the diminished stroke output response to exercise in patients with severe AoS (ref.[8]).

Aortic PWV measured invasively during catheterization was increased in patients with severe AoS compared to controls. Increased serum matrix metalloproteinases (MMP-3, MMP-9) and tissue inhibitor of metalloproteinases-1 were found in patients with AoS and correlated with aortic PWV, suggesting their implication in both valvular and vascular diseases[28].

Nevertheless, El-Chiali et al. who measured aortic PWV during cardiac catheterization in 40 elderly patients (>70 years) with severe AoS and 20 matched controls found similar values which were within the reference value for age in both groups. The authors suggested that advanced age of their study subjects may have influence their results masking the effects of AoS on arterial stiffness parameters[29].

No difference has been found for the majority of carotid parameters measured using echo-tracking (β index, pressure-strain elastic modulus, arterial compliance, augmentation index, and local pulse-wave velocity) as well as SAC between patients with moderate to severe AoS and controls having similar age, sex, and cardiovascular risk factors, except for carotid augmentation index[10]. As was previously shown, the augmentation index is influenced not only by the vascular distensibility but also by other factors including age, height, heart rate and LV contractility, and therefore, it cannot be considered a pure measure of arterial stiffness[30]. Because the augmentation index was significantly correlated with both ventricular ejection pattern and arterial properties, in patients with AoS, the authors speculated that it may be particularly useful for the assessment of ventriculo-valvulo-arterial interaction[10].

Arterial stiffness has also been investigated in relation with aortic valve sclerosis defined echocardiographically as thickness and calcification of the aortic wall without obstruction. In a meta-analysis which investigated the relationship between aortic valve sclerosis and markers of preclinical atherosclerosis, the authors concluded that carotid-femoral PWV was significantly increased in patients with aortic valve sclerosis. Similar associations were found for other markers of preclinical vascular disease including intima-media thickness, carotid plaques and flow-mediated dilation, supporting the hypothesis that degenerative aortic valve disease and atherosclerosis share common etiopathological mechanism and/or risk factors[31]. Korkmaz et al. measured arterial stiffness as CAVI, an index which takes into consideration both central and peripheral stiffness reporting increased values in patients with aortic valve sclerosis compared to controls[32].

Arterial stiffness and AoS severity

Severe AoS is classically defined as aortic valve area < 1.0 cm^2 and aortic valve mean pressure gradient ≥ 40 mmHg (ref.[33,34]). The relationship between various arterial stiffness parameters and AoS severity has been evaluated and the reported results have been contradictory, indicating direct, inverse or no correlation between parameters of AoS severity and arterial stiffness (Table 1).

Table 1. Relationship between arterial stiffness parameters and aortic stenosis severity.

Study, year	Patients with AoS	Mean or median age (years)	Arterial stiffness measures	AoS severity parameters	Relationship between arterial stiffness and AoS severity	Ref.
Bruschi et al., 2016	30 patients with severe AoS	79.3 ± 6.3	Carotid-femoral PWV (piezoelectric sensors Complior® Analyse)	MPG, PPG (echocardiography)	High vs low PWV subjects (according to median PWV value =10.4 cm/s) present higher MPG and PPG at baseline (mean: 56.5 ± 15.1 vs 45.4 ± 9.5, peak: 93.3 ± 26.4 vs 73.3 ± 14.9, *P*=0.02 for both comparisons	35
Cantürk et al., 2017	38 patients with severe AoS	59.0 ± 16.1	Aortic PWV (oscillometric device – Mobil-O-Graph)	MPG, AVA AVA index (echocardiography)	PWV values (9.07 ± 1.28) correlated positively with the MPG (r=0.350, *P*=0.031) and negatively with AVA (r=–0.475, *P*=0.003) and AVA index (r=–0.512, *P*=0.001)	36
Liu et al., 2004	30 patients with AoS/30 controls	61.3 ± 8.2	Aortic PWV (invasive measurement)	Invasively measured aortic transvalvular gradient	Positive correlation (univariate analysis) between increased PWV and severe AoS (transvalvular gradient ≥50 mmHg) Multivariate analysis: PWV, diabetes and hypertension independent predictors for severe AoS	28
El-Chilali et al., 2016	40 patients with symptomatic severe AoS/20 controls	81 (78,86)	Aortic PWV (invasive measurement)	MPG, AVA	Inverse correlation (univariate analysis) between aortic PWV and MPG: r=–0.40, *P*=0.011 No correlation with AVA (r=0.10, *P*=0.55)	29
Raimundo et al., 2021	150 patients with severe AS who underwent surgical AVR	72 ± 8	Carotid-femoral PWV (piezoelectric sensors – Complior® Analyse)	MPG, PPG, AVA	Inverse correlation (bivariate analysis) between baseline PWV and MPG (r=–0.28, *P*<0.01), PPG (r=–0.31, *P*<0.01) (multivariate regression analysis): MPG (β=–0.029, *P*=0.007)	37
Weisz et al., 2014	53 patients with moderate to severe AS	75 ± 10	Carotid β-stiffness index Aortic β-stiffness index (echo-tracking technique)	PAV, PPG, MPG, AVA, AVA index	Carotid and aortic β-stiffness index - not correlated with AVA, AVA index, PAV, MPG (*P*=NS)	38
Antonini-Canterin et al., 2009	19 patients with isolated moderate (AVA ≤1.5 and >1 cm^2) or severe AS (AVA ≤1 cm^2)	73 ± 9	Carotid β index, AC, AIx, local carotid PWV, Ep (echo-tracking system) -SAC, Zva (echocardiography)	PPG, MPG, ELI, SWL	Carotid AC positively correlated with SWL (r=0.51, *P*=0.02), No other correlations between vascular parameters and indices of AS severity	10
Saeed et al., 2020	103 asymptomatic patients with moderate (n=50) and severe (n=53) AoS	66.6 ± 13.2	Carotid-femoral PWV (applanation tonometry-SphygmoCor device)	MPG, AVA, SVI, FR (echocardiography)	Patients with moderate (AVA 1.0–1.5 cm^2) vs. severe (AVA<1.0 cm^2) AoS had similar degree of aortic PWV (10.7±3.3 vs. 10.5±3.0 m/s) PWV ≥10 m/s did not correlate with markers of aortic flow (bivariate analysis): stroke volume (r=–0.11, *P*=0.332), trans-aortic FR (r=–0.03, *P*=0.783) and severity of AoS (univariate linear regression): AVA (r=–0.05, *P*=0.635)	39
Kidher et al., 2014	56 patients with severe AoS	71 ± 8.4	Carotid-femoral PWV (applanation tonometry-SphygmoCor device)	Aortic PPG, MPG, AVA	PWV-high group (values above the reference for patients' age) had not increased PPG, MPG, AVA compared to normal PWV group (*P*=NS for all comparisons)	40

AoS, aortic stenosis; PAV, peak aortic velocity; PPG, peak pressure gradient; MPG, mean pressure gradient; AVA, aortic valve aria; PWV, pulse wave velocity; AC, arterial compliance; Aix, augmentation index; Ep, pressure-strain elastic modulus; SAC, systemic arterial compliance; ELI, energy loss index; SWL, stroke work loss; Zva, valvulo-arterial impedance; FR, flow rate.

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Bruschi et al. reported positive correlation between increased aortic PWV and mean and peak transvalvular pressure gradient in patients with symptomatic severe AoS undergoing surgical AVR or transcatheter aortic valve implantation (TAVI) (ref.[35]). Cantürk et al. reported that aortic PWV values, measured with an oscillometric device, correlated positively with mean aortic gradient and negatively with the aortic valve aria index in severe stenosis[36]. Invasively measured aortic PWV positively correlated with aortic transvalvular pressure gradient and the degree of aortic valve calcification in another study, suggesting the role of calcium deposits may play in both degenerative AoS and arterial stiffness[28].

Inverse correlation between increased arterial stiffness and AoS severity has also been reported. El-Chaili et al. reported that invasively measured increased aortic PWV correlated with low mean pressure gradient in elderly patients with severe AoS. The authors emphasized the fact that their results suggested a trend towards increased prevalence of low gradient severe AoS in patients with abnormal aortic PWV (ref.[29]). Raimundo et al. found that increased aortic transvalvular gradients correlated with low carotid-femoral PWV in a retrospective study, including 150 patients with severe AS who underwent AVR. This inverse association has been explained by a possible reduction of arterial stiffness measure due to upstream obstruction. This hypothesis was supported by the augmentation of PWV after AVR (ref. [37]).

Other studies found no relationship between arterial stiffness and the degree of AoS. Increased carotid β stiffness index was not correlated with AoS severity assessed by peak aortic jet velocity, transvalvular pressure gradient, or aortic valve aria in patients with moderate to severe AoS (ref.[38]). Antonini-Canterin et al. also reported the absence of any correlation between carotid stiffness parameters and AoS severity except for carotid compliance, which was correlated with stroke work loss, a valid measure of aortic stenosis severity[10]. Saeed et al. reported similar degree of arterial stiffness measured as carotid-femoral PWV in patients with moderate to severe AoS. Increased arterial stiffness did not correlate with the severity of AoS or with symptoms developed during exercise[39]. In patients undergoing AVR for severe AoS, increased aortic PWV did not correlate with AoS severity even though it was associated with functional NYHA class before and after surgery[40]. Increased SAC associated with NYHA class in a retrospective study of 157 patients with moderate to severe AoS irrespective of stenosis severity or LV systolic function[41]. These results suggested that increased arterial stiffness may be a marker of clinical status alteration in patients with AoS.

Contradictory findings regarding the relationship between arterial stiffness and AoS severity may have several explanations. Even though AoS and arterial stiffness share similar risk factors and pathophysiological mechanisms, other different processes may be involved in the development of valvular and vascular alterations which may define different diseases. The great majority of studies assessed the relationship between arterial stiffness and classical markers of AoS severity, such as the transvalvular gradients and aortic valve aria. However, establishing AoS severity may be challenging as it imposes in most cases a more extensive evaluation which might include the assessment of vascular load as well as LV remodelling and function[13]. It has been shown that increased arterial load caused by arterial hypertension or increased arterial stiffness may mask the severity of AoS. Increased arterial afterload may reduce the transvalvular flow rate and subsequently the transvalvular gradient. According to the physics principles of Gorlin formula, for the pressure gradient to decrease, the transvalvular flow rate needs to decrease, the effective valve area must increase, or both. Arterial hypertension, frequently associated in AoS, may reduce mean pressure gradient and peak aortic velocity[42,43].

In an experimentally induced severe AoS, Coté et al. have shown that reduced arterial compliance produces marked decrease in mean pressure gradient and aortic peak velocity for any AoS severity and even in the presence of a stable flow and in the absence of hypertension. It has been speculated that increased velocity of forward pulse wave and early return of backward wave from the periphery to the heart may blunt the transvalvular gradients and velocities, independently of flow conditions leading to underestimation of AoS severity. From a clinical point of view, a correct estimation of AoS severity might be done after normalization of arterial pressure and stiffness values. However, because optimal values of these parameters are difficult to obtain, the authors suggested the use of computed tomography for the quantification of aortic valve calcification in order to assess AoS severity in these situations[44].

Conversely, a possible influence of valvular obstruction induced by AoS on aortic stiffness measures has been considered. It has been shown that aortic expansion and compression waves are much lower in AoS than in normal subjects producing low systolic and pulse arterial pressures. The removal of aortic obstruction, immediately after TAVI, increased wave speed velocity, forward and backward compression waves and, subsequently, mean, systolic and pulse pressure, augmenting arterial stiffness[45]. Nevertheless, this hypothesis was not confirmed by Ranjan et al. who found that patients with increased aortic PWV had higher LV systolic volume index and mean pressure gradient. They suggested that a higher systolic volume index induced a faster arterial pulse wave which maintains a higher transvalvular gradient[46]. Moreover, an associated severe atherosclerosis may also explain both increased arterial stiffness and severe AoS with higher transvalvular gradients[35,28,46].

Relationship between arterial stiffness and LV remodeling and function

The relationship between arterial stiffness parameters and markers of LV systolic and diastolic function, as well as the predictive value of vascular parameters in AoS patients have been also investigated.

Rosca et al., evaluated by transthoracic ultrasonography proximal aortic stiffness in relation with LV function in patients with severe AoS (valve aria < 0.6 cm^2/m^2) and

preserved LV ejection fraction. The authors reported that increased aortic β stiffness index correlated with reduced LV longitudinal function, increased LV filling pressures, and plasma brain natriuretic peptide levels, independently of the valvular load and highlighted the importance of proximal aortic stiffness which directly opposes to LV ejection, in the development of LV dysfunction[47].

In a series of patients with moderate to severe AoS (aortic valve area < 1.2 cm^2) with preserved LV ejection fraction, both increased carotid and ascending aorta β stiffness index were independently associated with LV filling pressures, plasma brain natriuretic peptide levels (BNP) and symptoms, all of them markers of poor prognosis in AoS (ref.[38]).

Increased carotid stiffness, independent of AoS severity, LV ejection fraction, or the degree of LV hypertrophy, was directly associated with a significant decrease in LV diastolic performance and increased LV filling pressures. Carotid stiffness also corelated with BNP values and with the presence of symptoms, indicating more severe disease in patients with increased arterial stiffness[10].

Briand et al. studied SAC, measured as the ratio between stroke volume and brachial pulse pressure and reported that up to 40% of patients with at least moderate AoS had reduced SAC. The association of decreased SAC with AoS was shown to have additive effects on the development of LV diastolic dysfunction and reduced LV ejection fraction. To assess the combined valvular and arterial load in AoS, the authors proposed the valvulo-arterial impedance (Zva), calculated by dividing LV systolic pressure (systolic arterial pressure + mean transvalvular gradient) by the stroke volume. According to their results, a value of Zva ≥ 5.0 mmHg/mL/m^2 might represent a level of afterload that exceeds the limit of LV compensatory response leading to LV systolic dysfunction. This parameter was found to be superior to standard indexes of AoS severity in predicting LV dysfunction[7].

Cramariuc et al. extended these results, showing that Zva in asymptomatic AoS patients significantly alters LV systolic function measured as low stress-corrected midwall shortening, which is a more sensitive marker of myocardial systolic function than LV ejection fraction. LV global load was an independent predictor of low stress-corrected midwall shortening, after adjusting for the main confounders of LV systolic function, including LV hypertrophy, concentric LV geometry and concomitant hypertension or aortic regurgitation. This study pointed out that, besides male sex and left ventricular hypertrophy, LV global load may be an important contributor to LV systolic function alteration[18].

An extensive review of studies regarding the impact of Zva measured using transthoracic echocardiography 2-D (with or without speckle tracking) on LV remodeling, symptoms and outcome) had been previously published by Tiwari and Madan. They emphasized the fact that increased Zva was associated with impaired preclinical markers of LV function, aggravation of symptoms, unfavourable outcome and increased mortality[48].

The global valvulo-arterial load has been recently estimated using simultaneous cardiac magnetic resonance (CMR)/arterial tonometry in patients with AoS (ref.[49,50]). This method quantifies LV pressure–volume relationships and aortic pressure-flow-impedance parameters noninvasively from a single diagnostic encounter and can determine load independent LV myocardial contractility, arterial elastance, systemic vascular resistance, and aortic characteristic impedance, leading to a more accurate estimation of global LV afterload in AoS than previously reported by echocardiographic measurements[51].

Using carotid tonometry, central pressure and LV outflow tract magnetic resonance flow curves, Soulat et al. determined Zva in 40 patients with severe AoS (aortic valve area < 1 cm^2, mean pressure gradient > 40 mmHg, or aortic peak velocity > 4 m/s) and investigated its associations with symptoms, LV diastolic function and aortic stiffness. Their results indicated that Zva, measured using this new method, was more strongly associated with diastolic dysfunction than classical parameters used to assess AoS severity. Zva was higher in symptomatic patients and seemed to further improve LV afterload estimation in patients with AoS (ref.[49]).

Arterial stiffness and paradoxical low flow-low gradient AoS

Even though the great majority of patients with severe AoS have increased transvalvular gradient, in nearly one third of patients with aortic valve aria < 1.0 cm^2, a low transvalvular gradient (< 40 mmHg) has been found. An important part of these patients with low transvalvular gradients have also low transvalvular flow. According to current guidelines low flow state is defined by a stroke volume index < 35 mL/m^2. However, a transvalvular flow rate (calculated by dividing stroke volume by the LV ejection time) < 200 mmL/s) is considered physiologically more appropriate[52]. Low flow-low gradient (LFLG) AoS may be caused by a reduced LV ejection fraction, but it may appear even in cases of preserved LV ejection fraction, a situation which defines paradoxical LFLG AoS (ref.[26]).

The pathophysiology of paradoxical LFLG AoS in not completely understood but two important mechanisms have been emphasized: on the one side, an alteration of LV function caused by a smaller end-diastolic volume associated with an impairment of systolic contractility and, on the other side, an increased LV afterload produced by the abnormal vascular and aortic valve function[53].

LFLG AoS has been found in 5 to 15% of AoS patients, more frequently in elderly women with severe LV hypertrophy, and it was explained by the association of small LV cavity due to concentric remodelling with intrinsic myocardial dysfunction and subsequently low systolic volume index, even if LV ejection fraction remains normal[46,52-54].

Increased arterial stiffness is frequently found in these patients adding an abnormal LV pulsatile load which may independently alter myocardial function, increase LV filling leading to LV diastolic dysfunction with preserved ejection fraction[11,54-56]. It has been shown that most patients with paradoxical LFLG AoS develop concentric LV hypertrophy and low stroke volume even if they do not have severe AoS (ref.[57]). The increased arterial afterload

may partly explain the marked LV remodeling despite a less severe AoS. Lowering blood pressure with vasodilator therapy in patients with low gradient AoS with preserved ejection fraction resulted in a reduction of the total LV afterload, with a decrease in LV filling pressures[58,59]. Establishing severity of AoS in these patients may be challenging. Careful measurements of echocardiographic parameters and corroboration with clinical status and assessment of the degree of aortic valve calcification by echocardiography and/or multi-detector computer tomography have been proposed for an accurate diagnosis[52,53]. Whether identification and treatment of the increased arterial afterload in patients with paradoxical LFLG AoS will be reflected in a more efficient assessment and better prognosis of these patients remains to be established.

Arterial stiffness changes after aortic valve replacement

According to the latest ESC/EACTS Guidelines for the management of valvular disease, TAVI is recommended in older patients (≥ 75 years), or in those who are high risk (class IA) whereas surgical AVR is recommended in younger patients (< 75 years) who are at low risk for surgery (class IB) (ref.[60]). Even though interventions to correct valvular stenosis are expected to be followed by regression of LV dysfunction, it has been shown that the postintervention improvement of LV function vary among patients[48]. From a pathophysiological point of view, persistent elevated vascular load may impair LV function recovery.

Several studies, the great majority with small number of patients, investigated vascular hemodynamic changes following intervention to remove valvular obstruction in severe AoS. Short term and/or long-term vascular responses have been evaluated[61].

Various methodologies, including echocardiography, applanation tonometry, MRI techniques and cardiac catheterization have been used to measure local (carotid, ascending and descending aorta) or regional (central or central and peripheral arteries) arterial stiffness parameters after both surgical AVR and TAVI in patients with severe AoS.

After surgical AVR, early and transient alteration of aortic distensibility has been found. However, aortic properties restored 6 months after the intervention. The initial alteration of aortic distensibility was explained by aortic wall damage during surgery (aortic root "stunning") leading to local edema and destruction of vasa vasorum with media necrosis and fragmentation of elastic and collagen fibers[62]. This hypothesis is supported by the findings of an experimental porcine model that have shown abnormal straightening of elastin and collagen fibers leading to wall stiffness in avascular aorta caused by surgical manipulation[63].

In another study, aortic β stiffness index that was increased in patients with AoS before AVR compared to controls, progressively improved after surgery. At 1 year after AVR, aortic β stiffness index reached the values of controls. This favorable evolution has been explained by the recovery of the damaged aortic root endothelium and the changes in aortic pressures[27].

Increased carotid-femoral PWV measured using applanation tonometry has been reported on average 2.2±1.4 months after AVR in one study. The increased arterial stiffness post intervention has been explained by a possible increase in blood pressure level caused by the relief of valvular obstruction[37].

In 36 patients with severe AoS, CAVI, carotid-femoral PWV and brachial-ankle PWV were measured before and early after surgical AVR. The authors reported increased values of CAVI and brachial-ankle PWV suggesting that low arterial stiffness measured before intervention may be explained by the fact that AoS may mask the real values of arterial stiffness parameters. The authors emphasized the possible role of LV ejection time normalization after AVR which may lead to an appropriately measurement of arterial stiffness resulting in an increased CAVI. No modification in carotid-femoral PWV was found. The fact the CAVI and brachial-ankle PWV measure both central and peripheral stiffness, while carotid-femoral PWV reflects aortic stiffness, may be a possible explanation for these discrepant results[64].

Musa et al. measured aortic distensibility and aortic PWV using cardiovascular magnetic resonance examination, before and six months after aortic valve replacement and compared the effects of TAVI and surgical AVR on arterial stiffness. Surgical AVR but not TAVI was associated with an increase in aortic stiffness at 6 months. This study indicates that aortic stiffness post-surgical AVR may persist for at least 6 months, with possible prognostic implications[65].

Nevertheless, arterial stiffness may also increase after TAVI. Acute increase in systolic, mean and pulse pressure and augmentation index, measured invasively, using high-fidelity sensors, including frequency domain and wave intensity analyses, has been reported in 23 patients with severe symptomatic calcific degenerative AoS undergoing TAVI. These modifications were explained by the improved transmission of blood momentum to the arterial system. It has been suggested that because of the non-linear viscoelastic strain of large arteries and changes in the pressure-mediated deformation of the aorta stiffness may increase after AVR. Moreover, most of these patients had persistent hypertension during follow-up, which was particularly attributed to an increase of vascular stiffness rather than to the augmentation of systolic volume, suggesting a persistent increase in vascular load after intervention[45]. In accordance with this study, Chirinos et al. reported significant increase in aortic PWV measured with aortic MRI phase-contrast imaging, concordant increase of tonometry-based carotid–femoral PWV and a parallel reduction in total arterial compliance. Aortic characteristic impedance did not change significantly after AVR, which was explained by the fact that it reflects predominantly aortic geometry rather than stiffness. This study demonstrated, for the first time, the positive correlation between magnitude of the reflected waves and LV interstitial expansion whereas aortic characteristic impedance was correlated with low interstitial volume. It has been suggested that wave reflections which are responsible for the augmentation of mid to late systolic pulsatile

load are more important contributors to LV fibrosis and maladaptive response after AVR than aortic characteristic impedance which is a measure of early systolic pulsatile arterial load[66].

Both carotid-femoral PWV and brachial-ankle PWV increased immediately after TAVI and remained unchanged at 1 year follow-up, in a study which included 90 patients (mean age 80.2 years) with symptomatic severe aortic stenosis[67].

In contrast with the previously mentioned studies, a decrease in aortic stiffness has been reported in several other studies. Acute reduction in SAC and Zva measured by echocardiography have been reported after TAVI (ref.[68]). Decreased aortic PWV and augmentation index measured using an oscillometric method have been found at shot term after TAVI (ref.[69]) while a sustained decrease in echocardiographic aortic stiffness index has been measured after 12 months of follow-up[70].

Decreased augmentation index immediately after TAVI has been reported in three other studies but it could not be linked with a concomitant decrease in arterial stiffness[67,71-73]. Measuring invasively aortic pressures early after TAVI, Pagoulatou et al. found a steeper earlier increase in the amplitude of the forward systolic wave and subsequently of the reflected wave without modification of the reflection coefficient. The authors explained the reduced augmentation index by the timing/slope of the enhanced forward wave emphasizing that augmentation index might not be a suitable parameter of arterial stiffness in patients with AoS. The increase in systolic, diastolic in central pulse pressure was explained by the improve in LV function without any change in aortic characteristic impedance, arterial compliance and total vascular resistance[72].

No change in arterial stiffness (aortic stiffness index, SAC or aortic PWV) has been found in several studies after both surgical AVR (ref.[35,36,64]) or TAVI (ref.[35,65,69,74]).

These contradictory results are difficult to interpret and a clear conclusion regarding vascular hemodynamics after aortic valvular obstruction removal cannot be formulated. The various methodologies used to determine arterial stiffness measured different parameters of local, regional or systemic arterial distensibility and the results cannot be appropriately compared. It has been suggested that the acute increase in arterial stiffness after TAVI may be a consequence of the phenomenon of complementarity and competitiveness[45], described previously in AoS after percutaneous balloon angioplasty[75]. Complementarity means that both vascular and valvular components contribute additively to LV afterload, while competitiveness indicates that one compartment cannot be lowered without raising the other one. In accordance with this principle, the increase in vascular stiffness follows the reduction of valvular load[76,77]. Moreover, AoS may mask the real value of arterial stiffness indices explaining the increase in arterial stiffness after valvular interventions. However, the mechanisms that underlie the acute response of vascular tree after AVR and its adaptation at long term to the new hemodynamic status are not completely elucidated.

Arterial stiffness as a predictor of prognosis in AoS

The prognostic value of both total global load and arterial stiffness has been investigated in patients with AoS before as well as after AVR.

In a prospective study including 163 patients with asymptomatic moderate to severe AoS, Lancelotti et al., found four Doppler-echocardiographic parameters that strongly predicted cardiac events: aortic jet velocity, Zva, left atrial area index (marker of LV diastolic dysfunction) and LV longitudinal deformation (indicator of subclinical LV systolic dysfunction), emphasizing the important predictive value of total LV load in asymptomatic patients with moderate to severe AoS (ref.[12]).

In patients with severe AoS, many of them symptomatic at baseline, a value of Zva > 5.5 mmHg/mL/m^2, was associated with a 2.5 fold increase in the risk of overall mortality, regardless of the type of therapeutic intervention, AVR or medical[26]. Moreover, Zva has been shown to predict adverse outcome in asymptomatic patients with at least moderate AoS. A value of Zva > 3.5 mmHg/mL/m^2 has been shown to identify patients with poor prognosis (Zva > 3.5 and < 4.5 mmHg/mL/m^2 being associated with 2.30- and 3.11- fold increase in the risk of overall and cardiovascular morality, respectively) (ref.[11]).

High baseline total ventricular load, measured as Zva, was associated with increased mortality after TAVI in several studies[48,74,78].

In a prospective study which included data from 1641 patients with asymptomatic mild to severe AoS, enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis study, low SAC was associated with higher cardiovascular and all-cause mortality independent of diabetes and known cardiovascular and renal disease, after a median follow-up of 4.3 years[79].

Carotid-femoral PWV, the gold standard method for the evaluation of arterial stiffness, has been investigated in relation to symptoms and clinical outcome in patients with moderate to severe AoS. Nearly 50% of patients have been found to have increased carotid-femoral PWV (≥ 10 m/s). Lower event free survival has been found in patients with PWV ≥ 10 m/s compared to those with carotid-femoral PWV < 10 m/s (ref.[39]). Moreover, Broyd et al., have shown that an optimum cut-off of PWV at 11 m/s invasively measured during TAVI was a strong predictor of mortality in patients followed 1 year after intervention[80]. Increased pre-procedural brachial-ankle PWV, in 161 consecutive patients who underwent TAVI, was an independent predictor of one-year composite outcome comprising all-cause mortality and rehospitalization related to heart failure. Patients with high brachial-ankle PWV had a delayed reverse LV remodelling[81].

After removal of valvular obstruction, the patients' outcome may be influenced by persistent increased vascular load.

Although surprisingly, several studies have shown that patients with higher arterial pressure have better prognosis compared to those with normal blood pressure[82-84]. The acute increase in post procedural blood pressure accompanied by an increase in cardiac output[68,72,85,86] and

improvement of subendocardial viability ratio have been proposed as potential mechanisms of improved prognosis[86]. Sustained systemic hypertension following TAVI has been reported in 51% of the patients included in a prospective study. The increase in arterial pressure was associated with an increase in cardiac output and predicted better prognosis with fewer adverse cardiovascular events at one year follow-up[82]. In contrast, Yotti et al. found acute increase in steady and pulsatile load after TAVI which persisted at 6 month and was associated with increased vascular load rather than improved LV systolic function. Post-procedural reduction in LV systolic volume was related to absence of NYHA class improvement[45]. In another study, uncontrolled hypertension (≥ 140/90 mmHg) after TAVI was associated with persistence of symptoms, impaired reverse of LV remodeling, increased all-cause and cardiovascular mortality compared to patients with controlled blood pressure[87].

Nevertheless, in a large study which included 1794 patients with TAVI and 1103 surgical AVR, Lindman et al. reported that low systolic blood pressure (< 120 mmHg) and low diastolic blood pressure (< 60 mmHg) were associated with increased mortality and repeated hospitalization[83]. The investigation of the prognostic value of total arterial load and pulsatile load (SAC and pulse pressure) after TAVI in 2141 patients with symptomatic AoS revealed that higher total and pulsatile load but not resistive load were associated with increased all-cause mortality. Moreover, low systolic blood pressure was associated with increased mortality 30 days after TAVI while the worst prognosis was found in patients with low systolic blood pressure and increased pulsatile arterial load. Patients with low 30-day SBP and high pulsatile load had a 3-fold higher mortality than those with high 30-day SBP and low pulsatile load. The underling mechanisms that explain the association of postintervention high blood pressure with better outcome are not clarified but it has been suggested that a low blood pressure may reduce myocardial perfusion. An associated increased pulsatile load may contribute to a supplementary decrease in diastolic blood pressure and LV subendocardial perfusion[88].

CONCLUSIONS

The relationship between AoS and vascular function is not completely elucidated, nor are the mechanisms that determine vascular function modifications after removal of AoS obstruction. Increased arterial stiffness associated to valvular stenosis augments LV afterload and aggravates ventricular-vascular mismatch and patient outcome. After removal of valvular obstacle, LV remodelling regression as well as the patients' symptoms and outcome may be influenced by a persistent increase in arterial load. Prospective studies are needed to assess the effect of long-term increased post-procedural arterial stiffness and pulsatile load on left ventricle remodelling and function in patients with AoS.

The assessment of arterial stiffness which reflects LV pulsatile load in AoS may contribute to improve evaluation and treatment of these patients. Nevertheless, future studies are needed in order to validate a non-invasive, simple, reliable and reproducible method for implementing arterial stiffness measurement in the clinical evaluation of patients with AoS.

Search strategy and selection criteria

We performed a search on PubMed/Medline, Web of Science, and Google Scholar using the key words: "arterial stiffness and aortic stenosis", "pulse wave velocity and aortic stenosis", "arterial stiffness and surgical aortic valve replacement in aortic stenosis", and "arterial stiffness and transcatheter aortic valve implantation in aortic stenosis", between 2000 and 2022. Only articles written in English were included.

Author contributions: AA, IP, CB: study design, data analyse, supervision; AA: manuscript writing/preparation; All authors have read and agreed to the published version of the manuscript.

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