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Echocardiography

ORIGINAL INVESTIGATION

Aortic Valve Disease and Vascular Mechanics: Two-Dimensional Speckle Tracking Echocardiographic Analysis

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Purpose: Degenerative aortic valve disease (AVD) is a complex disorder that goes beyond valve itself, also undermining aortic wall. We aimed to assess the ascending aortic mechanics with two-dimensional speckle tracking echocardiography (2DSTE) in patients with aortic regurgitation (AR) and hypothesized a relationship with degree of AR. Aortic mechanics were then compared with those of similarly studied healthy controls and patients with aortic stenosis (AS); finally, we aimed to assess the prognostic significance of vascular mechanics in AVD. Methods: Overall, 73 patients with moderate-to-severe AR and 22 healthy subjects were enrolled, alongside a previously examined cohort (N = 45) with moderate-to-severe AS. Global circumferential ascending aortic strain (CAAS) and strain rate (CAASR) served as indices of aortic deformation; corrected CAAS was calculated as CAAS/pulse pressure (PP). Median clinical follow-up was 438 days. Results: In patients with severe (vs. moderate) AR, CAASR (1.53 ± 0.29/sec vs. 1.90 ± 0.62/sec, $P < 0.05$) and corrected CAAS (0.14 ± 0.06%/mmHg vs. 0.19 ± 0.08%/mmHg, $P < 0.05$) were significantly lower, whereas CAAS did not differ significantly. Measurers of aortic mechanics (CAAS, corrected CAAS, CAASR) differed significantly (all $P < 0.01$) in patients with AS and AR and in healthy subjects, with lower values seen in patients with AS. In follow-up, survival rate of AVD patients with baseline CAASR >0.88/sec was significantly higher (log rank, 97.4% vs. 73.0%; $P = 0.03$). Conclusions: Quantitative measures of aortic mechanics were lower for AS patients, suggesting a more significant derangement of aortic elastic properties. In the context of AVD, vascular mechanics assessment proved useful in gauging clinical prognosis. (Echocardiography 2016;00:1–10)

Key words: two-dimensional speckle tracking echocardiography, aortic mechanics, strain, strain rate, aortic regurgitation, aortic stenosis

Introduction:

Degenerative aortic valve disease (AVD) is highly prevalent in developed countries[1,2] and it is increasing given the aging of the population.[3] Transthoracic echocardiography is a widely available noninvasive exam, and it is the most commonly used imaging modality for detecting and evaluating valvular heart disease.

Speckle tracking echocardiography uses standard B-mode images to track blocks of speckles frame-to-frame, measuring dimensional lengthening/shortening relative to baseline.[4] This method enables angle-independent calculations of motion and deformation variables, such as velocity, displacement, strain and strain rate, that can be assessed in the longitudinal, radial and circumferential directions. Initially, the study was confined to left ventricle (LV), but with further validation, scope was expanded to include other cardiac chambers. Since 2008, use of two-dimensional speckle tracking echocardiography (2DSTE) has been demonstrated for examining vascular walls,[5,6] first at abdominal aorta and then along ascending[7] and descending aorta,[8] aortic arch,[9] and carotid arteries.[10] Vascular mechanics similarly have been validated in vivo[11] and in vitro,[12] using sonomicrometry. Moreover, an association of the collagen content of the vessels and vascular mechanics has also been proved, promoting aortic mechanics as a new imaging surrogate of vascular stiffening.[13]

Degenerative AVD is currently viewed as a systemic disease evoking changes in arterial wall

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rigidity and compliance, a concept borne out mainly in aortic stenosis (AS).[14,15] Although a gold standard method of determining local vascular stiffness has yet to be approved, our group has recently shown[7,16] the utility of 2DSTE for this purpose in patients with degenerative AS. The association of vascular mechanics and aortic regurgitation (AR) is less established, but previous studies[17] do indicate that a reduction in aortic distensibility hastens the need for aortic valve replacement in patients with chronic AR.

The purposes of this 2DSTE study were to: (1) assess circumferential ascending aorta strain (CAAS) and strain rate (CAASR) in patients with moderate-to-severe AR; (2) explore a potential association between CAAS and CAASR, and the severity of AR; (3) compare aortic mechanics in patients with AR or AS, relative to healthy controls; and (4) examine the prognostic significance of CAAS and CAASR in the setting of degenerative AVD.

Materials and Methods:

Study Population:

A total of 73 consecutive patients with isolated AR with vena contracta (VC) >3 mm from a single laboratory were prospectively enrolled in a 3-month study, conducted between December 2013 and February 2014. Isolated AR was defined as mean transvalvular pressure gradient <20 mm Hg. AR in patients was considered severe if VC >6 mm, plus one of the following quantitative criteria:[18,19] effective regurgitant orifice area (EROA) $\geq$30 mm^2, regurgitant volume (R Vol) $\geq$60 mL, diastolic flow reversal in descending aorta with end-diastolic velocity >20 cm/sec, or time-velocity integral (TVI) of reverse flow >15 cm.

A cohort of 45 consecutive patients with an indexed aortic valvular area (iAVA) $\leq$0.85 cm^2/m^2, as previously detailed by our group,[7] was also included in this data analysis.

Additionally, we included 22 apparently healthy subjects referred for echocardiography due to suspected cardiac structural disease. These subjects had a normal echocardiography and electrocardiogram.

The study protocol was approved by *Comissão Nacional de Protecção de Dados* (authorization 3611/2015) and by *Faculdade de Medicina da Universidade de Coimbra* ethics committee (protocol reference CE—005/2014).

Clinical Data:

Data recorded for each patient at admission included age, weight, height, and cardiovascular risk factors (such as hypertension, diabetes, dyslipidemia, and smoking habits). Histories of acute myocardial infarction, stroke, chronic kidney disease, and congestive heart failure (HF) were documented. Body surface area (BSA)[20] and body mass index (BMI)[21] were estimated according to applicable formula. Clinical status was assessed in accord with the New York Heart Association (NYHA) classification.[22] Current medications were recorded.

Systemic Arterial Hemodynamics:

Systemic arterial pressure was measured using an arm cuff sphygmomanometer simultaneously with Doppler measurement of left ventricular outflow tract (LVOT) stroke volume. Indexed systemic arterial compliance (SAC) was calculated as follows: SAC = SVI/PP, where SVI is stroke volume index and PP is brachial pulse pressure.[14] Total vascular resistance (TVR) was estimated as follows: TVR = 80 $\times$ MAP/CO, where MAP is mean arterial pressure (i.e. diastolic pressure plus one-third brachial pulse pressure) and CO is cardiac output.[23]

Echocardiography:

Transthoracic echocardiography was performed using a Vivid 7 (GE Healthcare, Horton, Norway) cardiovascular ultrasound device, with a 1.7/3.4 MHz tissue harmonic transducer. Complete echocardiographic studies called for standard views and techniques stipulated by established guidelines.[24] In addition, short-axis views of ascending aorta, distal to sino-tubular junction, 2–3 cm above aortic valve, were obtained at a frame rate >50 frames per second. Machine settings were manually adjusted to optimize 2D aortic wall tracings and 2DSTE grayscale definition. All images were acquired at end-expiratory apnea. Loops of three cardiac cycles were stored digitally and analyzed off line using a customized software package (EchoPAC 9.0, GE Healthcare, Horton, Norway).

Aortic regurgitation assessment: The etiology and mechanism of AR, either from aortic leaflets disease or from aortic root dilatation, were analyzed. Assessment of AR severity was based on the recommended integration of qualitative and quantitative parameters,[18,19] including VC width, proximal isovelocity surface area (PISA) method, diastolic flow reversal in the descending aorta (end-diastolic velocity, TVI of the reverse flow, ratio of reverse to forward TVI), and pressure half-time (PTH) of continuous-wave (CW) Doppler.

Left ventricular assessment: Left ventricular dimensions were acquired through a 2D long-axis parasternal window, in accord with current guidelines.[25] The LV mass was calculated via American Society of Echocardiography corrected

formula and indexed for BSA. LV end-systolic and end-diastolic volumes and LV ejection fraction (LVEF) were assessed using the modified Simpson's rule.[25] LV cardiac index was calculated as the product of heart rate and indexed stroke volume for BSA. Stroke volume was obtained by LV outflow Doppler method as the product of LVOT area and time-velocity integral.[26] The calculation of E/e' ratio (e' being an average of septal and lateral walls in tissue Doppler imaging) was used to estimate LV filling pressures.[27]

Global LV afterload and elastic properties of aorta: Valvulo-arterial impedance (Z_{VA}), as a measure of global LV afterload, was calculated as follows: $Z_{VA} = SAP + MG/SVI$, where SAP is systolic arterial pressure and MG is mean transvalvular pressure gradient.[14]

The aortic stiffness index ($\beta 1$) was calculated as: $\beta 1 = \ln(P_s/P_d)/(A_s - A_d)/A_d$,[28] where P_s and P_d are systolic and diastolic arterial pressures, and A_s and A_d are M-mode-guided systolic and diastolic ascending aortic diameters, 2–3 cm above aortic valve. A_d was obtained as R wave peaked in simultaneously recorded electrocardiograms, and A_s was measured at maximal anterior aortic wall motion. Aortic stiffness index ($\beta 2$) was also assessed using 2DSTE peak systolic circumferential strain according to the equation: $\beta 2 = \ln(P_s/P_d)$/global CAAS.[5]

Two-dimensional speckle tracking strain echocardiography: The 2DSTE technique was used to calculate regional and global thoracic ascending aorta mechanics. With a line manually drawn along inner aspect of aortic wall in short axis, additional lines were automatically generated digitally at the outer aspect of vessel wall. Due to the thinness of vascular walls, relative to cardiac walls, region of interest width was reduced to the minimal value allowable by software, as previously suggested.[29] The initial systolic frame generally served as the frame of interest, to include maximal aortic wall expansion and recoil. As suggested previously,[8,30] aortic wall was divided into six equidistant regions, all similar in size. In each region, numeric expressions of each 2DSTE variable represented mean values calculated from all points in the segment. These were color coded and shown as a function of time throughout the cardiac cycle. The tracking process and conversion to Lagrangian strains were performed off line, using dedicated software (EchoPAQ 9.0). CAAS and CAASR were then determined. The CAAS curve peak value was usually appeared in proximity to (late peak) aortic valvular closure; global CAAS represented the mean of the six segmental peak values. Corrected CAAS was calculated as global CAAS/PP.[30] CAASR curves, as in previously published data,[5,10] included a positive early systolic peak, with global CAASR representing the mean of the six segmental peak values. Quantitative curves reflecting all regions could be expressed for each 2DST variable (Fig. 1).

The intra-observer and inter-observer variability of CAAS and CAASR were assessed in 10% randomly selected subjects from both AR and control groups. These measurements were repeated one month later by the same echocardiographer (LL) to assess intra-observer reproducibility. Inter-observer reproducibility was assessed by a second echocardiographer (MOS), and all values were compared with those of the first study.

Follow-up:
Clinical follow-up was performed targeting the following outcomes: all-cause mortality, cardiovascular (CV) mortality, aortic valve replacement (AVR), and HF hospitalization. We also assessed a combined endpoint of CV mortality, AVR, or HF hospitalization.

Statistical Analysis:
Normality of continuous variables was tested by histogram observation and Kolmogorov–Smirnov test. Continuous variables were expressed as mean $\pm$ standard deviation and categorical variables as percentage. Student's *t*-test or ANOVA was applied for group comparisons. Individual variables were checked for homogeneity of variance via Levene's test. For categorical variables, chi-square or Fisher's exact tests were used as appropriate.

Pearson's correlation was used to analyze relationships between CAAS or CAASR and continuous variables. Linear regression analysis was performed thereafter to identify variables independently associated with CAAS and CAASR. A final multivariate model was subsequently elaborated, assessing all clinically relevant significant ($P < 0.25$) variables identified in univariate analysis.

To control effects of age and gender on vascular mechanics, we also performed one-to-one matching in comparing aortic mechanics in AR and AS patients with healthy control subjects.

Based on stored images of 10% randomly selected patients, intra- and inter-observer reproducibility of CAAS and CAASR values were assessed by intra-class correlation coefficient (ICC) and by coefficient of variation (CoV).[31]

A receiver operating characteristic (ROC) curve analysis was used to compute the discriminatory power of CAASR to predict survival in AVD patients. Cumulative survival curves were constructed using Kaplan–Meier method, and group comparisons relied on log-rank test.

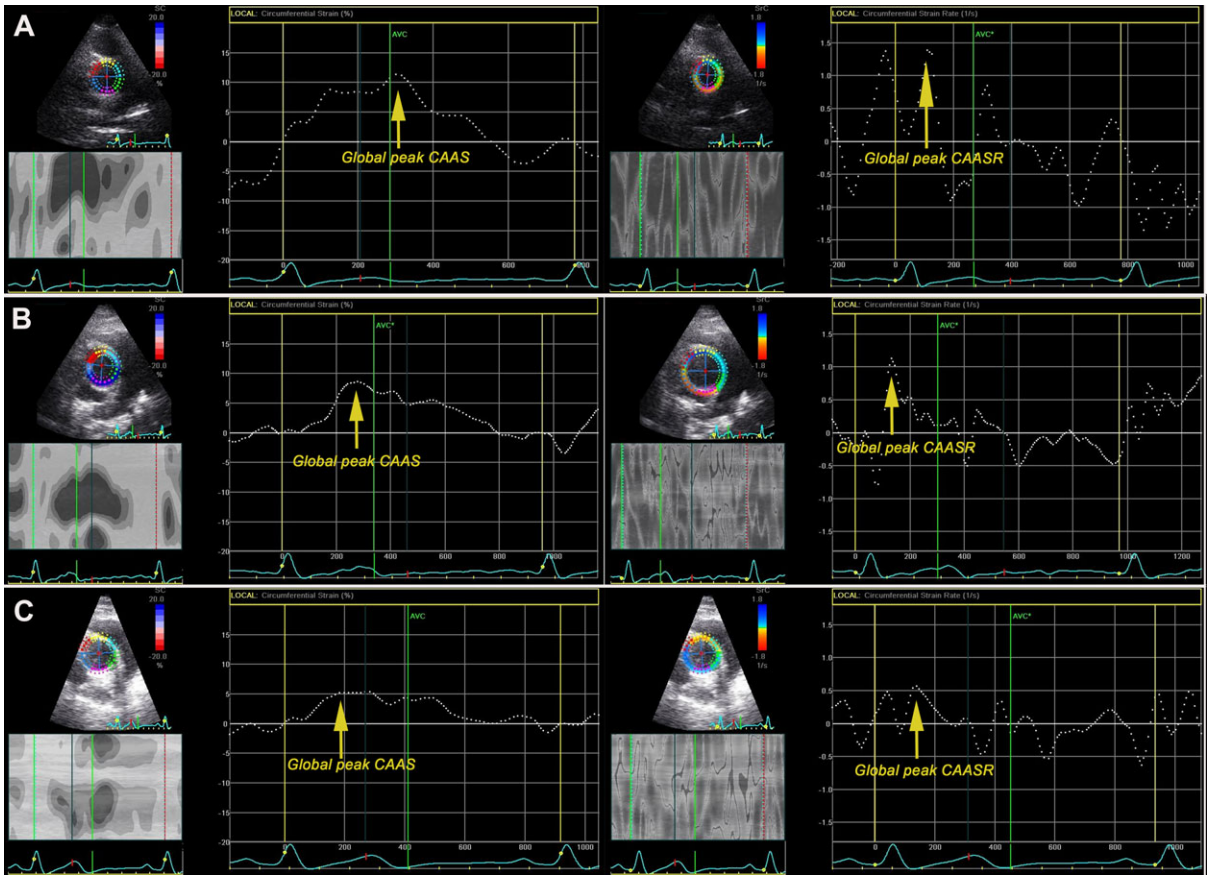

Figure 1. Assessment of ascending aorta mechanics via 2DST echocardiography generated from short-axis view of aorta, 2–3 cm above aortic valve: quantitative curves representing all regions in a control subject (A), in a patient with isolated AR (B) or isolated AS (C). Peaks of CAAS (in proximity to aortic valvular closure) and CAASR (first peak after ventricular systole) both assume positive values due to expansion of vessel wall.

A P-value <0.05 in two-tailed tests was considered statistically significant. Statistical analysis relied on standard software, specifically SPSS v20.0 (SPSS Inc, Chicago, IL, USA), MedCalc 12.2.1 (freeware), and GraphPad Prism 5.00 (GraphPad Software, In, La Jolla, CA, USA).

Results:

Ascending Aortic Mechanics in AR:

Mean age of patients with AR was 72 $\pm$ 10 years, with gender balance. In most patients, the etiology of AR was either degenerative or unclear/mixed. Mean values of global CAAS, corrected global CAAS, and global CAASR were 10.81 $\pm$ 3.95%, 0.17 $\pm$ 0.08%/mm Hg, and 1.81 $\pm$ 0.58/sec, respectively.

Patient stratification by degree of AR (moderate vs. severe): Baseline demographic data, previous cardiovascular histories, and medication use were relatively balanced between groups (Table I). Patients were also homogenous in terms of SAC, although severe AR patients had a higher PP and a lower TVR. Both groups also displayed similar etiologies, aortic diameters, and elastic proprieties (Table II). LV diastolic dimension and volume were significantly higher in patients with severe AR, as were indexed LV mass and SVI. However, values of LVEF, cardiac index, and E/E' ratio were similar for both groups.

In analysis of ascending aortic mechanics, global CAAS was similar in both groups, whereas corrected global CAAS (0.14 $\pm$ 0.06%/mmHg vs. 0.19 $\pm$ 0.08%/mmHg, $P < 0.05$) and global CAASR (1.53 $\pm$ 0.29/sec vs. 1.90 $\pm$ 0.62/sec, $P < 0.05$) were significantly lower in patients with severe AR (Table III).

Variability of vascular mechanics in AR: Global CAASR correlated significantly with VC width ($r = -0.35$, $P < 0.01$) and with TVI of reverse flow ($r = -0.44$, $P < 0.01$) (Table IV). Multiple linear regression analysis revealed an indepen-

TABLE I

Baseline Information, Risk Factors, Medication, and Systemic Arterial Hemodynamics of AR Patients

	Total AR patients (n = 73)	Moderate AR (n = 55)	Severe AR (n = 18)	P
Age (years)	71.5 ± 9.5	71.9 ± 9.7	70.2 ± 9.0	0.48
Male gender (%)	42 (57.5)	30 (54.5)	12 (66.7)	0.37
BMI (kg/m^2)	26.3 ± 3.4	26.4 ± 3.4	25.8 ± 3.4	0.47
Cardiovascular risk factors and medical conditions				
Hypertension (%)	57 (78.1)	13 (76.4)	15 (83.3)	0.75
Diabetes (%)	13 (17.8)	11 (20.0)	2 (11.1)	0.50
Dyslipidemia (%)	47 (64.4)	38 (69.1)	9 (50.0)	0.14
Smoker (%)	2 (2.7)	2 (3.6)	0 (0.0)	0.56
Ex-smoker (%)	5 (6.8)	3 (5.5)	2 (11.1)	0.59
Chronic kidney disease (%)	13 (17.8)	9 (16.4)	4 (22.2)	0.72
Previous MI (%)	9 (4.1)	8 (14.5)	1 (5.6)	0.44
Previous stroke (%)	3 (4.1)	2 (3.6)	1 (5.6)	0.58
Current CHF admission (%)	7 (9.6)	3 (5.5)	4 (22.2)	0.06
NYHA class				
Class I (%)	44 (60.3)	36 (65.5)	8 (44.4)	0.08
Class II (%)	22 (30.1)	16 (29.1)	6 (33.3)	
Class III (%)	7 (9.6)	3 (5.5)	4 (22.2)	
Class IV (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Current medication:				
ACE inhibitor (%)	33 (45.2)	26 (47.3)	7 (38.9)	0.54
ARB (%)	26 (35.6)	17 (30.9)	9 (50.0)	0.14
MRA (%)	5 (6.8)	4 (7.3)	1 (5.6)	0.64
CCB (%)	14 (19.2)	11 (20.0)	3 (16.7)	0.53
β-blockers (%)	30 (41.1)	21 (38.2)	9 (50.0)	0.38
Diuretics (%)	43 (58.9)	29 (52.7)	14 (77.8)	0.10
Statin (%)	35 (47.9)	27 (49.1)	8 (44.4)	0.73
Systemic arterial hemodynamics:				
Systolic arterial pressure (mmHg)	138.1 ± 16.9	137.6 ± 16.2	139.4 ± 18.2	0.72
Diastolic arterial pressure (mmHg)	72.6 ± 14.2	76.0 ± 12.3	62.1 ± 15.1	**<0.01**
Pulse pressure (mmHg)	65.5 ± 18.8	61.7 ± 15.1	77.3 ± 24.0	**<0.01**
Heart rate (bpm)	67.8 ± 13.7	68.9 ± 14.8	64.2 ± 8.9	0.21
Systemic arterial compliance (mL/mmHg/m^2)	0.68 ± 0.30	0.67 ± 0.30	0.71 ± 0.29	0.66
Total vascular resistance (mmHg min/L)	1748.2 ± 640.3	1868.9 ± 651.5	1351.7 ± 413.0	**<0.01**

Bold values represent statistically significant differences. AR = aortic regurgitation; BSA = body surface area; BMI = body mass index; MI = myocardial infarction; CHF = congestive heart failure; NYHA = New York Heart Association; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; MRA = mineralocorticoid receptor antagonists; CCB = calcium channel blockers.

dent association between E/E' ratio and global CAAS ($\beta = 0.28$, $P = 0.04$), when adjusted for end-diastolic velocity of reverse flow and cardiac index (Table V). After adjustment for SAC, only TVI of reverse flow ($\beta = -0.05$, $P < 0.01$) remained significantly predictive of CAASR (Table VI).

Ascending Aortic Mechanics in AR versus AS versus Healthy Controls:

Aortic mechanics (CAAS, corrected CAAS, and CAASR) differed significantly in AS and AR and in healthy control subjects (all $P < 0.01$) (Fig. 2). Because mean age also differed significantly among groups (AS, 77 ± 10 years; AR, 72 ± 10 years; controls, 53 ± 17 years; $P < 0.01$), age- and gender-matched analysis was conducted, with no change in outcome ($P < 0.01$) (Table S1).

The β1 (AS, 7.25 ± 4.42; AR, 4.05 ± 2.90; controls, 3.25 ± 2.99) and β2 stiffness index (AS, 12.44 ± 5.92; AR, 7.16 ± 4.64; controls, 5.08 ± 2.75) also differed significantly by group ($P < 0.01$). Unlike vascular mechanics, SAC ($P = 0.99$) and TVR ($P = 0.43$) in all groups were similar.

Agreement and Reproducibility:

Waveforms adequate for measuring CAAS and CAASR were present in 778 (92.6%) of the 840 arterial segments evaluated. Results of intra-observer variability assessment were as follows:

TABLE II

Aortic Regurgitation Etiology and Severity, LV Geometry and Function, Aortic Diameters and Elastic Properties

	Total AR patients (n = 73)	Moderate AR (n = 55)	Severe AR (n = 18)	P
AR etiology				
Degenerative (%)	14 (19.2)	10 (18.2)	4 (22.2)	0.15
Bicuspid aortic valve (%)	2 (2.7)	1 (1.8)	1 (5.6)	
Cusp rupture (%)	1 (1.4)	0 (0.0)	1 (5.6)	
Aortic root pathology (%)	13 (17.8)	8 (14.5)	5 (27.8)	
Unclear mechanism (%)	43 (58.9)	36 (65.5)	7 (38.9)	
AR severity				
Vena contracta width (mm)	5.0 ± 1.6	4.3 ± 0.7	7.3 ± 1.3	<**0.01**
EROA (mm^2)	28.2 ± 15.5	20.3 ± 7.1	39.9 ± 17.5	<**0.01**
R Vol (mL)	61.5 ± 38.8	39.8 ± 15.0	92.4 ± 41.7	<**0.01**
End-diastolic velocity of the reversal flow (cm/sec)	11.0 ± 7.3	9.4 ± 7.2	14.9 ± 6.0	<**0.01**
TVI of the reversal flow (cm)	13.8 ± 5.6	12.3 ± 4.5	17.4 ± 6.4	<**0.01**
Ratio of reversal to forward TVI	1.2 ± 0.6	1.1 ± 0.6	1.4 ± 0.7	0.16
PTH of CW Doppler AR jet (ms)	435.6 ± 141.3	471.0 ± 129.8	285.1 ± 73.6	<**0.01**
LV assessment				
LV diastolic dimension (mm)	57.8 ± 7.9	56.3 ± 7.5	62.4 ± 7.7	<**0.01**
LV systolic dimension (mm)	39.7 ± 9.1	38.6 ± 9.0	42.9 ± 8.8	0.09
LV EDV indexed (mL/m^2)	76.8 ± 28.0	72.1 ± 35.5	91.0 ± 31.3	**0.01**
LV ESV indexed (mL/m^2)	35.0 ± 21.9	32.6 ± 21.5	42.1 ± 22.4	0.11
LVEF biplane (%)	56.2 ± 11.6	56.3 ± 12.1	55.8 ± 10.3	0.87
LV mass indexed (g/m^2)	72.7 ± 20.2	68.7 ± 18.7	83.7 ± 20.8	**0.01**
Stroke volume index (mL/m^2)	42.0 ± 14.9	39.2 ± 14.1	51.1 ± 14.2	<**0.01**
Cardiac index ($L/min/m^2$)	2.8 ± 1.1	2.7 ± 1.2	3.2 ± 1.0	0.11
E/E′ ratio	11.9 ± 5.3	12.2 ± 5.5	10.5 ± 4.5	0.30
LA volume indexed (mL/m^2)	39.0 ± 17.1	38.1 ± 17.0	41.8 ± 17.6	0.44
Valvulo-arterial impedance ($mmHg/mL/m^2$)	3.9 ± 1.4	4.1 ± 1.5	3.1 ± 1.0	<**0.01**
Aortic diameters				
Valve annulus (mm)	34.9 ± 4.9	34.8 ± 4.5	35.5 ± 6.1	0.62
Aortic sinus (mm)	36.8 ± 5.6	36.4 ± 5.3	38.3 ± 6.3	0.25
Sinotubular junction (mm)	34.8 ± 5.7	34.5 ± 5.7	36.0 ± 6.0	0.33
Proximal ascending aorta (mm)	39.4 ± 5.9	39.0 ± 5.6	40.5 ± 6.7	0.40
Aortic elastic properties				
Stiffness index β1	4.1 ± 7.3	3.9 ± 7.7	4.6 ± 5.9	0.66
Stiffness index β2	7.2 ± 4.6	6.8 ± 4.6	8.3 ± 4.8	0.24

Bold values represent statistically significant differences. AR = aortic regurgitation; EROA = effective regurgitant orifice area; R Vol = regurgitant volume; TVI = tissue velocity index; PTH = pressure half-time; CW = continuous wave; LV = left ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; LVEF = left ventricular ejection fraction; LA = left atrium.

TABLE III

Circumferential Ascending Aortic Strain and Strain Rate

	Total AR patients (n = 73)	Moderate AR (n = 55)	Severe AR (n = 18)	P
Global CAAS (%)	10.81 ± 3.95	10.91 ± 4.22	10.50 ± 3.10	0.72
Corrected global CAAS (%/mmHg)	0.17 ± 0.08	0.19 ± 0.08	0.14 ± 0.06	<**0.05**
Global CAASR (/sec)	1.81 ± 0.58	1.90 ± 0.62	1.53 ± 0.29	<**0.05**

Bold values represent statistically significant differences. AR = aortic regurgitation; CAAS = circumferential ascending aorta strain; CAASR = circumferential ascending aorta strain rate.

global CAAS, ICC = 0.96 (95% CI, 0.84–0.99), and CoV = 6.9%; global CAASR, ICC = 0.96 (95% CI, 0.85–0.99), and CoV = 7.4%. In assessing inter-observer variability, results were as follows: global CAAS, ICC = 0.89 (95% CI, 0.60–0.98), and CoV = 10.4%; global CAASR, ICC = 0.90 (95% CI 0.64–0.98), and CoV = 10.5%.

TABLE IV

Correlations with Global CAAS and Global CAASR

	Global CAAS		Global CAASR	
Variables	r	P value	r	P-Value
Age (years)	0.79	0.54	0.11	0.42
Systemic arterial hemodynamics				
Systolic arterial pressure (mmHg)	−0.01	0.93	0.03	0.83
Systemic arterial compliance (mL/mmHg/m^2)	−0.10	0.49	−0.17	0.25
Total vascular resistance (mmHg min/L)	−0.02	0.92	0.11	0.45
AR severity				
Vena contracta width (mm)	−0.15	0.26	−0.35	<**0.01**
End-diastolic velocity of the reversal flow (cm/sec)	−0.18	0.20	−0.24	0.10
TVI of the reversal flow (cm)	0.03	0.81	−0.44	<**0.01**
LV assessment				
LVEF biplane (%)	0.12	0.34	−0.04	0.79
Cardiac index (L/min/m^2)	0.23	0.10	−0.07	0.64
E/E′ ratio	0.16	0.25	−0.03	0.86
Aortic elastic properties				
Stiffness index β1	0.01	0.99	−0.08	0.56

Bold values represent statistically significant differences.

TABLE V

Linear Regression Model to Predict Global CAAS in AR

Variables	β	T value	P-Value
E/E′ ratio	0.28	2.01	**0.04**
End-diastolic velocity of the reversal flow (cm/sec)	−0.11	−1.56	0.13
Cardiac index (L/min/m^2)	0.80	1.75	0.09

Bold values represent statistically significant differences. $B_0 = 7.3$ ($P < 0.01$); F 3.0 ($P < 0.05$); $R^2 = 0.23$.

TABLE VI

Linear Regression Model to Predict Global CAASR in AR

Variables	β	T value	P-Value
TVI of the reversal flow (mm)	−0.05	−2.29	<**0.01**
Systemic arterial compliance (mL/mmHg/m^2)	−0.43	−1.86	0.07

Bold values represent statistically significant differences. $B_0 = 2.7$ ($P < 0.01$); F 5.7 ($P < 0.01$); $R^2 = 0.26$.

Follow-Up Analysis:

Data were available for all 118 patients with AVD, who were followed for a median period of 438 (IQR 386–539) days. During this time, global mortality was 16.1% and CV mortality was 10.2%. Global CAAS, corrected global CAAS, and global CAASR were significantly lower in all-cause or CV mortality subsets (Table VII).

A CAASR cutpoint of 0.88/sec showed 83.3% sensitivity and 73.5% specificity for estimating global mortality in patients with degenerative AVD during follow-up (AU = 0.79, 95% CI: 0.66–0.93, $P < 0.01$). Patients with a baseline global CAASR > 0.88/sec had a significant higher survival rate (97.4% vs. 73.0%, log-rank $P = 0.03$) (Fig. 3).

Discussion:

Based on 2DSTE study, the following were demonstrated: (1) high feasibility and reproducibility of global CAAS and CAASR determinations in patients with moderate-to-severe AR; (2) significantly lower global CAASR, albeit not global CAAS, in patients with severe (vs. moderate) AR; (3) independent associations between global CAAS and E/E′ ratio and between global CAASR and TVI of reverse flow in patients with AR; (4) significant differences in aortic mechanics (CAAS, corrected CAAS, and CAASR) in AS and AR and in the control subjects; and (5) the clinical prognostic significance of aortic mechanics in degenerative AVD.

Moderate-to-Severe AR:

To the best of our knowledge, this is the first effort to examine the utility of quantifying ascending aortic mechanics by 2DSTE in patients with AR. In our prior report on patients with AS, SVI emerged as the most important determinant of CAAS,[7] whereas stiffness index β1 was strongly associated with CAASR,[16] suggesting that the rate of circumferential vascular deformation depends more on local arterial wall properties and is less influenced by systolic flow.

The concept that degenerative AVD alters arterial wall rigidity and compliance is also valid in the setting of AR. In patients with severe AR, higher vascular load and lower global CAASR were evident, likely reflecting more advanced arteriosclerosis. Wilson et al[17] demonstrated that a decrease in distensibility of aorta imposes a higher afterload and may contribute to deterioration of chronic heart failure over time.

In instances of severe AR, higher SVI (due to increased regurgitant volume) is balanced by significant impairment of vascular elastic properties, perhaps explaining why global CAAS does not differ substantially by grade (moderate vs. severe) of AR. The corrected CAAS, which includes also

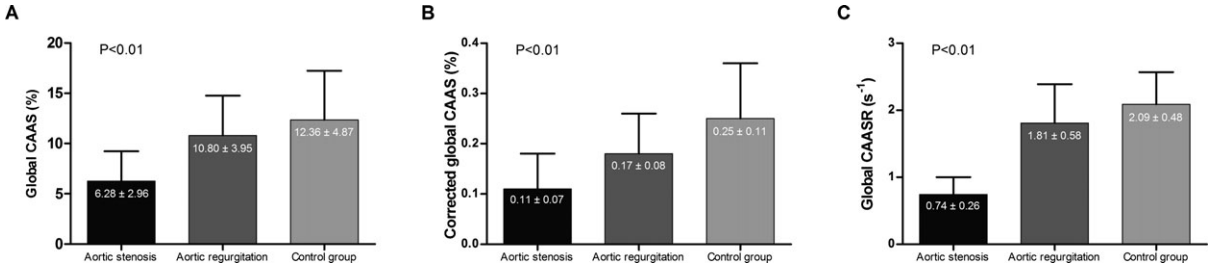

Figure 2. Ascending aorta mechanics in patients with AS and AR and in control subjects: comparisons by global CAAS (A), corrected global CAAS (B), and global CAASR (C).

TABLE VII

Follow-up Data Regarding Ascending Aortic Mechanics

	Global CAAS (%)	Corrected global CAAS (%/mmHg)	Global CAASR (/sec)
Global mortality			
Yes (n = 19)	6.99 ± 4.05	0.11 ± 0.06	0.86 ± 0.50
No (n = 99)	9.30 ± 4.15	0.16 ± 0.08	1.45 ± 0.70
P value	**0.03**	**0.04**	**<0.01**
Cardiovascular mortality			
Yes (n = 12)	6.45 ± 3.38	0.09 ± 0.04	0.77 ± 0.44
No (n = 106)	9.23 ± 4.21	0.15 ± 0.08	1.42 ± 0.70
P value	**0.03**	**0.02**	**<0.01**
Aortic valve replacement			
Yes (n = 17)	7.70 ± 3.55	0.14 ± 0.08	0.99 ± 0.45
No (n = 101)	9.13 ± 4.29	0.15 ± 0.08	1.41 ± 0.73
P value	0.21	0.52	**0.03**
Heart failure hospitalization			
Yes (n = 19)	6.93 ± 3.72	0.13 ± 0.09	1.08 ± 0.72
No (n = 99)	9.34 ± 4.20	0.15 ± 0.08	1.40 ± 0.69
P value	**0.02**	0.33	0.06
Combined end point			
Yes (n = 29)	7.21 ± 3.87	0.12 ± 0.08	1.08 ± 0.66
No (n = 89)	9.52 ± 4.17	0.16 ± 0.08	1.44 ± 0.70
P value	**0.01**	0.08	**0.02**

CAAS = circumferential ascending aorta strain; CAASR = circumferential ascending aorta strain rate.

the PP, was significantly different in moderate versus severe AR patients.

Comparing to the other aortic elastic proprieties analyzed (β1 and β2 stiffness index) which did not significantly differ by AR severity, CAASR and corrected CAAS seemed to be more sensitive parameters.

AR versus AS versus Healthy Controls:
Aortic mechanics (CAAS, corrected CAAS and CAASR) derived from 2DSTE images differed

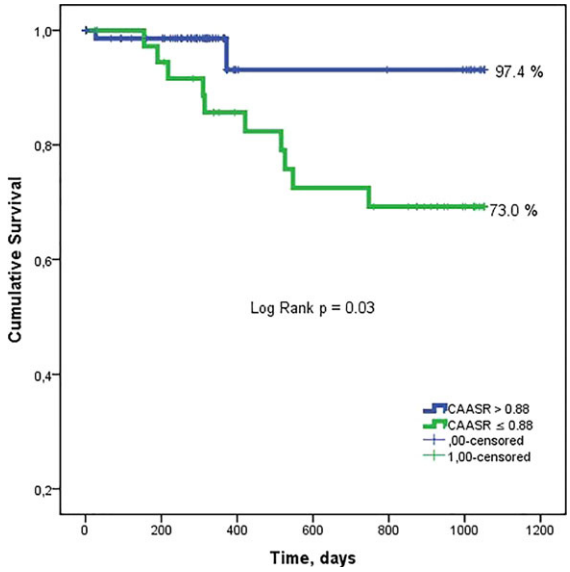

Figure 3. Patient survival in follow-up, stratified by global CAASR cut point (0.88/sec).

significantly in AS, AR, and healthy subjects, even after age and gender matching. These parameters were lower in patients with AS, so in this context, elastic properties of aorta are seemingly altered to a significantly greater extent. The groups also differed significantly in β1 and β2 stiffness index, although not in terms of SAC and TVR, supporting the hypothesis that vascular differences are mainly localized.

In an investigation by Petrini et al,[32] transesophageal echocardiography was performed in patients with isolated severe AS or AR, all prior to surgery in the operating room. Images of descending aorta were analyzed using software developed expressly for speckle tracking imaging (VVI; Siemens Healthcare, Erlangen, Germany), thus enabling automatic frame-by-frame recording of area change, with VVI strain corresponding to maximal systolic circumferential strain. Strain was considerably higher in patients with AR than in those with AS, which corroborates our findings.

Clinical Prognostic Significance of Aortic Mechanics:

In degenerative AS, it is acknowledged that LV afterload increases due not only to valvular obstruction but also to increased vascular load.[33] Reduction in arterial compliance as a consequence increased vascular stiffness then contributed to LV burden, culminating in adverse clinical events.[14] This relationship with vascular load has also been reported in the setting of AR, linking decreased distensibility with faster progression to surgery.[17]

According to our exploratory analysis, aortic mechanics seems to have a prognostic impact in patients with degenerative AVD. Lower values of global CAAS, corrected global CAAS, and global CAASR showed significant associations with higher global mortality and CV death, with lesser differences found for AVR and HF hospitalization endpoints. In long-term follow-up, a significant relationship between CAASR >0.88/sec and global mortality was also demonstrable.

Limitations:

This was a single-center study, based on a relatively small patient sampling (N = 140). Rather than monitoring central blood pressure, brachial pressures were recorded, which typically are overestimated. Furthermore, no invasive data on cardiac output, total systemic resistance, or systemic vascular compliance were available. Although age disparity among groups was potentially problematic, outcomes of age- and gender-matched subgroup analysis upheld our initial findings. The incremental value of 2DSTE aortic mechanics in AVD evaluation, in addition to conventional methods, was not assessed. Further studies should be designed to explore it.

Conclusions:

In patients with AVD, use of 2DSTE to assess ascending aortic mechanics was feasible and proved highly reproducible. Global CAASR was significantly lower in patients with severe (vs. moderate) AR, and measured parameters indicated significantly greater impairment of aortic elastic properties in patients with AS. The prognostic influence of ascending aortic mechanics in AVD was also demonstrable, underscoring the value of studying the vascular component with 2DSTE.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Age and gender match analysis of ascending aorta mechanics in patients with AS, AR and in healthy subjects.