Impact of aortic stiffness on left ventricular function and B-type natriuretic peptide release in severe aortic stenosis

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Aims
In aortic stenosis (AS), both reduced systemic arterial compliance and increased valvular load have been shown to contribute to impaired left ventricular (LV) function. However, the relationship between LV function and aortic stiffness has not yet been investigated. We aimed to assess the relationship between aortic stiffness and LV global longitudinal strain (GLS), LV filling pressures (E/E′) and B-type natriuretic peptide (BNP) in AS.

Methods and results
A comprehensive echocardiogram was performed in 48 consecutive patients with severe AS (<0.6 cm²/m²) and preserved LV ejection fraction (≥50%). Aortic stiffness index (beta) was calculated based on aortic diameters measured by echocardiography and blood pressure. Systemic arterial compliance (SAC) and valvulo-arterial impedance (Zva) were also determined. Aortic beta index was significantly correlated with Zva (r = 0.30, P = 0.03) and SAC (r = −0.29, P = 0.04). GLS (r = 0.45, P = 0.001), E/E′ (r = 0.48, P = 0.001) and BNP levels (r = 0.45, P = 0.001) were significantly related to aortic beta index. No significant correlation was found between GLS or E/E′ and SAC or Zva. In multivariate regression analysis, aortic beta index remained correlated with GLS, E/E′, and BNP levels.

Conclusions
In patients with severe AS and preserved LV ejection fraction, independently of the valvular load, an increase in aortic rigidity, as assessed by aortic beta index, is independently correlated with reduced LV longitudinal function, increased LV filling pressures, and BNP levels.

Keywords
Aortic valve disease • Haemodynamics • Cardiac remodelling • Diastolic dysfunction • Strain

Introduction
Aortic stenosis (AS), the most common valvular disease in developed countries, cannot be viewed as an isolated disease of the valve. Indeed, a loss of arterial elasticity is a common finding in these patients who are relatively old and often present traditional cardiovascular risk factors for atherosclerosis. Reduced systemic arterial compliance (SAC) additionally contributes to the increased systolic load caused by the outflow tract obstruction. This double load (valvular and arterial) may have a complementary detrimental effect on left ventricular (LV) function. The non-invasive estimation of systemic arterial mechanical properties, based on a number of assumptions, has important theoretical limitations. Conversely, local arterial stiffness, determined by direct measurements of parameters strongly linked to wall stiffness, has the advantage to require no assumption from models of circulation. Moreover, it is known that the aorta, especially in its proximal segments, stiffens more than the peripheral arteries in this type of population. Thus, assessment of the ascending aorta rigidity could provide a better estimate of the arterial load imposed by the vascular system on the LV. In patients with hypertension or diabetes, aortic stiffness has been closely related to LV diastolic function. Hitherto no study has examined the impact of aortic stiffness on LV function in patients with AS. In AS, LV ejection fraction—the recommended parameter to monitor the LV function—may remain normal for years despite deep structural (i.e. LV remodelling) and functional changes (i.e. 

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revascularization, or coronary artery stenosis of coronary artery disease (history of myocardial infarction, coronary systemic arterial hypertension (blood pressure under lipid lowering therapy), current smoking, diabetes mellitus, systolic hypercholesterolemia (total cholesterol entry, the following clinical data were collected: age, gender, history and optimal quality of speckle-tracking imaging analysis. At study entry, the following clinical data were collected: age, gender, history of hypercholesterolemia (total cholesterol > 190 mg/dl or patients under lipid lowering therapy), current smoking, diabetes mellitus, systemic arterial hypertension (blood pressure ≥ 140/90 mmHg or patients under anti-hypertensive treatment), and previous evidence of coronary artery disease (history of myocardial infarction, coronary revascularization, or coronary artery stenosis > 50% on angiography). Information regarding current medication was also obtained. The protocol was approved by the relevant institutional review boards and all patients gave written informed consent.

Methods

Population
A total of 48 patients (70 ± 10 years, 64% men) with severe AS were prospectively screened from our echocardiographic laboratories for inclusion in this study. All patients met the following criteria: severe AS defined by an aortic valve area < 0.6 cm²/m², normal LV ejection fraction (≥ 50%) as calculated by two-dimensional echocardiography, normal dimension of the ascending aorta (≤ 40 mm), no more than mild associated cardiac valve lesion, sinus rhythm, no renal failure, and optimal quality of speckle-tracking imaging analysis. At study entry, the following clinical data were collected: age, gender, history of hypercholesterolemia (total cholesterol > 190 mg/dl or patients under lipid lowering therapy), current smoking, diabetes mellitus, systemic arterial hypertension (blood pressure ≥ 140/90 mmHg or patients under anti-hypertensive treatment), and previous evidence of coronary artery disease (history of myocardial infarction, coronary revascularization, or coronary artery stenosis > 50% on angiography). Information regarding current medication was also obtained. The protocol was approved by the relevant institutional review boards and all patients gave written informed consent.

Echocardiographic study
A commercially available ultrasound machine (Vivid 7, General Electric Medical Systems, Horten, Norway) equipped with an M4S probe was used for all echocardiographic examinations. Standard echocardiographic views were obtained using second-harmonic imaging with frequency, depth, and sector width adjusted for frame-rate optimization (60–100 fps). LV volumes and ejection fraction were calculated using the biplane Simpson disk method. Continuous wave Doppler was used to measure the aortic transvalvular peak velocities; peak systolic and mean gradients were calculated using the simplified Bernoulli equation.

Aortic valve area was calculated using the continuity equation. Mean gradients were calculated using the simplified Bernoulli equation. Aortic valve area was calculated using the continuity equation. Mean gradients were calculated using the simplified Bernoulli equation. Aortic valve area was calculated using the continuity equation. Mean gradients were calculated using the simplified Bernoulli equation.

The ratio of the stroke volume index to the brachial pulse pressure (the difference between the systolic and the diastolic blood pressure) was used as an indirect measure of the total SAC. To estimate the global LV afterload, the valvulo-arterial impedance (Zva) was calculated as the sum of the systolic arterial pressure and the mean transvalvular pressure gradient divided by the stroke volume index.

Plasma B-type natriuretic peptide
Venous blood samples for BNP were drawn before echocardiography, after 10 min of supine rest. Chilled ethylenedinitrilotetraacetic acid tubes were centrifuged immediately at 4000 rpm (4°C) for 15 min. Separated plasma samples were processed by immuno-fluorescence assay (Beckman-Coulter, Biositew). The inter- and intra-assay variations were 5 and 4%, respectively. The assay detection limit was 1 pg/mL.

Statistical analysis
Data are presented as mean ± SD or percentages unless otherwise specified. Variables were compared using Student’s t-test or Fisher exact test, as appropriate. Relationships between different parameters were assessed by linear correlation analysis. Skewed data such as BNP values were logarithmically transformed and logBNP values were used in correlation and regression analyses. To determine the impact of aortic stiffness on LV function, BNP release and LV filling pressure, stepwise multiple linear regression analyses were performed. Variables with a P value < 0.20 on univariable analysis were incorporated into the logistic regression models. All statistical analyses were performed using SPSS 14.0 software for Windows (SPSS Inc., Chicago, IL). A two-sided P value of 0.05 was considered significant. Inter-observer reproducibility for the measurement of the ascending aortic diameters was assessed on recorded images from 15 randomly selected patients. The agreement between two observers was good for measuring the systolic 95% confidence interval of the difference − 0.61 to 0.34 mm, standard error of estimate (SEE) = 0.22 mm) and diastolic diameters (95% confidence interval of the difference − 0.47 to 0.45 mm, SEE = 0.21 mm), similar to previously reported data.

Results

Characteristics of the patients
Table 1 lists the demographic and echocardiographic characteristics of the study population. Nineteen patients were asymptomatic and 29 patients were symptomatic (dyspnea = 25, angina = 3, syncope = 1). Of the 29 symptomatic patients, 10 patients had peak systolic local strain in each segment was measured with systole manually defined at aortic valve closure.
combined symptoms. Eight patients (16.6%) had evidence of coronary artery disease, 32 patients (66.6%) were hypertensive, 10 patients (20.8%) had diabetes mellitus and 19 patients (39.5%) had hypercholesterolemia.

**Arterial haemodynamics, aortic stenosis severity, and left ventricular function**

Aortic beta index was correlated with age ($r = 0.40, P = 0.005$), SAC ($r = -0.29, P = 0.04$), and $Z_{va}$ ($r = 0.30, P = 0.03$), but not with systolic or diastolic blood pressure, pulse pressure, or body mass index ($P > 0.5$ for all). Aortic beta index was higher in women than in men (17.9 $\pm$ 5.5 vs 7.7 $\pm$ 4.5, $P = 0.001$). Patients with either systemic arterial hypertension or diabetes mellitus had slightly higher values for aortic beta index, without reaching statistical significance ($P > 0.20$ for both) (Table 2). Aortic beta index was not significantly different between patients treated with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, or statins and those who did not receive these drugs. Aortic beta index was significantly correlated with peak $S$ ($P = 0.04$), GLS ($P = 0.001$), $E'$mean ($P = 0.004$), $E/E'$ ratio ($P = 0.001$), and logBNP levels ($P = 0.001$). There was no correlation between aortic beta index and classical parameters of AS severity: aortic jet velocity, mean pressure gradient, or aortic valve area (AVA) index ($P > 0.05$ for both) (Table 2). In multivariate regression analysis, aortic beta index was independently correlated with age and GLS (Table 2).

Nineteen patients had low-gradient (mean gradient $<40$ mmHg) severe AS (AVA $<1.0$ cm$^2$) and preserved LV ejection fraction ($> 50$%). These patients tended to have higher values of aortic beta index than patients with high-gradient AS ($11.3 \pm 5.2$ vs. $8.5 \pm 5.3$, $P = 0.07$). Of note, only eight of these patients had a low flow state (indexed stroke volume $\leq 35$ mL/m$^2$).

**Impact of aortic stiffness on left ventricular systolic function**

GLS was correlated with indexed LV mass ($r = 0.42, P = 0.003$), LV ejection fraction ($r = -0.32, P = 0.02$), $E'$mean ($r = -0.45, P = 0.001$), $E/E'$ ratio ($r = 0.38, P = 0.01$), and aortic beta index ($r = 0.45, P = 0.001$) (Figure 2). Conversely, no significant correlation was found between GLS and age, gender, the severity of AS, SAC, or $Z_{va}$ ($P = NS$ for all). With multiple linear regression analysis, after adjustment for cofactors, aortic beta index ($\beta = 0.43, P = 0.001$) and indexed LV mass ($\beta = 0.41, P = 0.002$) emerged as independently associated with GLS (model $r^2 = 0.37, P < 0.001$). When LV mass was replaced by LV ejection fraction, both LV ejection fraction ($\beta = -0.37, P = 0.006$) and aortic beta index ($\beta = 0.48, P < 0.001$) were independently associated with GLS (model $r^2 = 0.33, P < 0.001$).

**Cofactors associated with B-type natriuretic peptide levels**

LogBNP was correlated with LV ejection fraction ($r = -0.33, P = 0.02$), indexed LV mass ($r = 0.30, P = 0.03$), aortic beta index ($r = 0.45, P = 0.001$) (Figure 3), peak $S$ ($r = -0.34, P = 0.02$), GLS ($r = 0.54, P < 0.001$), $E'$mean ($r = -0.44, P = 0.002$), $E/E'$ ratio ($r = 0.51, P = 0.001$), and indexed AVA ($r = -0.31, P = 0.03$). Conversely, no significant correlation was found between BNP and SAC, or $Z_{va}$. In multivariate regression analysis, aortic beta index ($\beta = 0.36, P = 0.01$), LV ejection fraction ($\beta = -0.40, P = 0.001$), and $E/E'$ ratios were independently associated with logBNP (model $r^2 = 0.33, P < 0.001$).
(β = 0.34, P = 0.01) were independently correlated with logBNP (model r^2 = 0.50, P < 0.001).

Cofactors associated with increased left ventricular filling pressures

Age (r = 0.37, P = 0.01), peak S (r = −0.52, P < 0.001), GLS (r = 0.38, P = 0.01), indexed AVA (r = −0.31, P = 0.03), and aortic beta index (r = 0.48, P = 0.001) were correlated with E/E′ (Figure 4). Conversely, no significant correlation was found between E/E′ and LV ejection fraction (r = 0.02, P = 0.88), SAC (r = −0.11, P = 0.46), or Zva (r = 0.25, P = 0.09). After correction for cofactors, beta index emerged as the only independent parameter associated with E/E′ (β = 0.48, P = 0.001) (model r^2 = 0.23, P = 0.001).

Discussion

The results of the present study provide new insights into the pathogenesis of LV dysfunction and BNP release in patients with AS. We show for the first time that independently of the increased valvular load—outflow tract obstruction—the increase in proximal aortic stiffness—arterial load—has a direct detrimental impact on
LV long-axis function, BNP release, and LV filling pressure in patients with severe AS and preserved LV ejection fraction.

**Aortic stiffness in aortic stenosis patients**

In patients with AS, systemic arterial mechanical properties can be affected by the combination of several factors (ageing, hypertension, diabetes); all being generally related to a systemic atherosclerotic disease expression that often leads to a non-uniform and accelerated stiffening process of the vascular tree. As the proximal part of the aorta usually stiffens more than the peripheral arteries, the assessment of the ascending aortic stiffness could better reflect the load imposed by the vascular system on the LV. Moreover, the local arterial stiffness has the advantage that can be accurately and non-invasively directly measured and not only estimated. Aortic stiffness, calculated from the aortic diameters measured by echocardiography and blood pressure obtained by sphygomanometry, proved to be a reliable measure of aortic mechanical properties. We used beta index for the assessment of aortic stiffness, a parameter adjusted for the logarithmic relationship between stiffness indices and pressure, and thus less affected by arterial pressure changes. This study confirms the previous finding of a direct correlation between age and aortic stiffness. Female gender was associated with higher vascular stiffness, as previously described. As expected, aortic beta index was also correlated with SAC but not with pulse pressure, systolic, and diastolic blood pressure. Paradoxical low-gradient ‘severe’ AS with preserved LV ejection fraction is a clinically challenging scenario that has been recently highlighted. It is associated with higher afterload and reduced survival. In the present study, the prevalence of such entity (39%) was close to that observed by Hachicha et al. Of note, although aortic beta index was slightly higher in these patients, the difference did not reach the statistical significance. This could be partly related to the small number of patients with a low flow state (indexed stroke volume ≤ 35 mL/m²).

**Impact of aortic stiffness on left ventricular function and B-type natriuretic peptide release in aortic stenosis patients**

The increased stiffness of large arteries is regarded as a major contributor to the development of isolated systolic hypertension with reduced diastolic blood pressure and increased pulse pressure. These haemodynamic changes contribute additionally to the increased systolic load caused by the outflow obstruction and to the reduced myocardial oxygen balance. The chronically increased afterload leads to progressive LV remodelling and myocardial hypertrophy in an attempt to reduce LV end-systolic wall stress. Compensatory pathological hypertrophy, involving myocardial fibrosis, results in impaired LV relaxation, reduced LV compliance, and elevated LV filling pressures. Elevated LV diastolic pressure associated with reduced arterial diastolic blood pressure limits the coronary flow reserve and leads to subendocardial ischaemia even in the absence of significant coronary artery disease. Hence, the longitudinal function, governed by the subendocardial fibres, is the first to be altered, while LV ejection fraction, depending more on mid-wall myocardial fibres, is maintained within the normal range until the compensatory mechanisms are exhausted.

In AS, myocardial dysfunction might thus reflect the complementary effects of the increased valvular and arterial load. Reduced SAC has been shown to be associated with increase in diastolic dysfunction degree and reduced LV ejection fraction in moderate to severe AS patients. Moreover, it has recently been demonstrated that LV longitudinal strain is reduced in asymptomatic AS patients with increased global (valvular and vascular) LV afterload. In the present study, we have examined, for the first time, the relationship between aortic stiffness and LV function. An increase in aortic stiffness, independent of the AS severity, the LV ejection fraction, or the degree of LV hypertrophy, was directly associated with a significant decrease in LV longitudinal myocardial function.
deformation (GLS), an increase in LV filling pressure, and a higher BNP release. Of note, these parameters have been shown to be associated with symptomatic status and poor prognosis.\textsuperscript{27–29} However, whether an increase in aortic stiffness may directly affect the clinical outcome of patients with AS needs to be determined in specifically designed longitudinal studies. Moreover, we did not find a significant correlation between SAC and the extent of subendocardial dysfunction, BNP level, and LV filling pressure highlighting that the stiffness of the proximal part of the aorta plays a direct detrimental effect on LV functional parameters in AS. Noteworthy, SAC represents a rough estimation of the systemic arterial stiffness.\textsuperscript{4} Conversely to previous studies,\textsuperscript{30} we found no significant correlation between AVA and the degree of LV dysfunction or the BNP levels. Such a discrepancy may be related to different patient selection. For instance, our study only concerned patients with indexed AVA < 0.6 cm\textsuperscript{2}/m\textsuperscript{2}, whereas other studies have included patients with a wide spectrum of AS severity. Moreover, paradoxical low-gradient ‘severe’ AS, an entity incompletely characterized and difficult to classify, represented an important percentage in our study population. A few retrospective studies suggested that these patients might represent a subgroup with an advanced stage of aortic valve disease and poor prognosis,\textsuperscript{31} although recently published data suggested that they have an outcome similar to that of patients with moderate AS.\textsuperscript{31} However, when these patients were excluded from the statistical analysis, aortic beta index remained independently correlated with LV longitudinal function ($\beta = 0.45$, $P = 0.005$), and BNP release ($\beta = 0.41$, $P = 0.01$).

\textbf{Study limitations}

This study has some limitations. Coronary angiography was not performed in seven patients. However, these asymptomatic patients had a normal exercise stress echocardiography test indicating the absence of active myocardial ischaemia. We used brachial blood pressure for the calibration of carotid diameter changes. Brachial pressure usually overestimates central pressure. However, this is true especially in young subjects, while in older people there is less amplification of pulse pressure from central to peripheral blood vessels.\textsuperscript{4} Moreover, recent data showed a clinically acceptable agreement between non-invasive brachial pressures and directly measured central aortic pressure in patients with aortic stenosis.\textsuperscript{32} Of note, the present study was, by its design, limited to the evaluation of the relationship between aortic stiffness and LV function. No data regarding the clinical impact of aortic stiffness was available. However, the inclusion of both symptomatic and asymptomatic patients made unsuitable the evaluation of the prognostic impact of aortic stiffness in our population.

\textbf{Conclusion}

As impaired LV longitudinal deformation is associated with reduced exercise tolerance and increased risk of cardiac events,\textsuperscript{27} knowing the main predictors of progressive LV myocardial dysfunction is clinically relevant. In patients with severe AS, we show for the first time that increased aortic rigidity, assessed by aortic beta index, is independently correlated with reduced LV longitudinal function and increased LV filling pressures and BNP levels. Our data suggest that independently of the valvular load, the overload induced by the rigidity of the proximal part of the aorta could directly contribute to the decline of LV function in these patients. The potential prognostic implications of increased aortic stiffness in patients with AS and whether these alterations can be modified by treatment remain to be determined in future longitudinal studies.

\textbf{Conflict of interest:} none declared.

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