Left ventricular torsional dynamics in aortic stenosis: relationship between left ventricular untwisting and filling pressures. A two-dimensional speckle tracking study†

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Aims
The contribution of left ventricular (LV) untwisting to LV suction and early-diastolic filling was previously demonstrated, but this was not yet tested in patients with aortic stenosis (AS). We sought to assess the relationship between LV untwisting and LV filling pressures in patients with severe AS and normal left ventricular ejection fraction (LVEF) using speckle tracking echocardiography.

Methods and results
Sixty-one consecutive patients (66 ± 9 years) with severe AS, preserved LVEF (63 ± 6%), and 40 normal subjects (47 ± 12 years) were prospectively enrolled. A comprehensive echocardiographic examination was performed in all. LV rotation and twisting were assessed using speckle tracking echocardiography. Peak apical back rotation rate, peak LV untwisting rate, and time intervals from QRS onset (ECG) to each of them were measured. Brain natriuretic peptide (BNP) levels were determined in 30 patients. Patients with AS were older than normal subjects (P < 0.001). LV mass, LA volume, LV filling pressures as well as peak apical back rotation rate and time to peak apical back rotation rate were increased in patients (P < 0.05 for all). In patients with AS, both time to peak LV untwisting rate and time to peak apical back rotation rate were significantly related to E/E’ ratio and to BNP levels (P < 0.04 for all).

Conclusion
In patients with severe AS and preserved LVEF, there is a significant relationship between LV untwisting and LV filling pressures, suggesting a role for impaired LV untwisting in the pathophysiology of diastolic dysfunction in this setting.

Keywords
Aortic stenosis • Left ventricular torsion • Untwisting • Filling pressures • Speckle tracking echocardiography

Introduction
Aortic stenosis (AS) represents the most common form of valvular heart disease.1 Once severe and symptomatic, surgical valve replacement is warranted.2,3 Apart from stenosis severity, left ventricular (LV) dysfunction plays a critical role in symptom occurrence and clinical decision.2,3 Understanding the pathways of progression towards heart failure may bring important information for better decision-making. Left ventricular ejection fraction, the currently recommended parameter for assessing LV function in severe AS,2,3 represents a rather crude measure of LV function in this setting.4 More than half of patients with severe AS and congestive heart failure have normal ejection fraction.5 Decline in tissue Doppler-derived myocardial velocities6 and strain/strain rate6,7 have been reported in patients with AS and normal LV ejection fraction, allowing an earlier identification of LV dysfunction. Left
ventricular torsion, twisting, and untwisting have been shown to be integral components of ventricular contractility, diastolic suction, and filling both in normal subjects and in different cardiac diseases.

In previous tagged magnetic resonance imaging studies, changes in LV rotation parameters have been described in AS patients. However, these studies were particularly limited by the very small number of patients examined. The effect of AS on LV torsion mechanics has thus not been entirely evaluated. We hypothesized that in patients with severe AS there will be significant changes in both systolic twist and diastolic untwist, which may be involved in the development/progression of LV dysfunction: (i) increased LV systolic twisting; (ii) delayed LV diastolic untwisting; and (iii) increased LV filling pressures, in proportion to LV untwist delay.

Two-dimensional (2D) speckle tracking echocardiography (STE) is a new non-invasive imaging modality allowing assessment of LV torsional dynamics. We therefore sought to examine the impact of AS on LV rotation parameters by using 2D-STE and to determine how changes in LV torsion mechanics may affect LV systolic and diastolic function.

**Methods**

We prospectively screened 167 consecutive patients with severe AS, who were referred for the assessment of valve disease severity. Severe AS was defined as an indexed aortic valve area (AVAi, measured by the continuity equation) <0.6 cm²/m². We excluded 32 patients with more than mild aortic or mitral regurgitation, seven patients with mitral stenosis/prosthesis, 12 patients with LV ejection fraction <50%, and 24 patients with coronary artery disease (by history, echocardiography, and/or coronary angiography). After also excluding 25 patients with poor acoustic window or technically unsuitable for speckle tracking analysis and six patients with rhythm and conduction disturbances, the remaining 61 patients with severe AS constituted the final study group. A normal coronary angiography was available in 35 of these 61 patients, as this was performed based on routine clinical grounds, at the discretion of the referring physician.

Forty healthy volunteers served as a control group. They had no evidence of heart disease by physical examination, 12-lead electrocardiogram, and echocardiography, and were taking no medication. All subjects gave their informed consent to participate in the study, the protocol of which was approved by the Ethics Committee of Prof. Dr. C. C. Iliescu’s Institute of Cardiovascular Diseases, Bucharest, Romania.

**Echocardiography**

All subjects underwent 2D, conventional Doppler echocardiography and STE. Images were obtained using a commercially available cardiac ultrasound machine (Vivid 7 Dimension, GE Healthcare, Horten, Norway) equipped with a 4S probe. Gray scale images were obtained using second-harmonic imaging. Standard views and techniques were used according to the American Society of Echocardiography/European Association of Echocardiography guidelines. Left ventricular volumes and LV ejection fraction were measured using the modified Simpson’s rule from apical four- and two-chamber views and were normalized to body surface area (BSA). LV mass was calculated by the equation of Devereux. Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated using the simplified Bernoulli equation. Aortic valve area was calculated using the continuity equation. For systolic and diastolic function, peak systolic (S) and peak early diastolic (E) mitral annular velocities were obtained by pulse-wave tissue Doppler imaging from the apical four-chamber view using both the septal and the lateral sides. The average E’ was used to calculate the ratio of peak early-diastolic transmural flow velocity E to E’, in order to estimate LV filling pressures.

**Left ventricular rotation parameters**

Gray scale digital cine loops triggered to QRS complexes were acquired from two LV short-axis planes at the basal and apical levels for rotation and torsion analysis. Care was taken to ensure that the basal short-axis plane contained the mitral valve. The apical plane was acquired distally to the papillary muscles and transducer position was optimized to ensure a proper, circular short-axis cut, as previously described. At each plane, three consecutive cardiac cycles were acquired during breath-hold at a frame rate of 70–100 frames/s, without using dual focus, and stored in hard disk for off-line analysis using commercially available software (EchoPAC PC 08, GE Healthcare). The off-line analysis was performed by a single observer, blinded to clinical data. The region of interest (ROI) of the LV was set at the endocardial margin to the epicardial margin, thus delineating the entire circumference. The ROI width was adjusted as needed to fit the wall thickness, as previously described. The tracking quality of each segment was indicated by the software, and segments with insufficient tracking quality were excluded. Averaged apical and basal rotation data were used for calculation of LV twist and torsion. LV twist was calculated as the net difference of LV rotation at isochronal time points between the apical and basal short-axis planes. Whenever possible, cycles with identical or very similar heart rates were selected for measuring rotation at the apical and at the basal levels. This was the case for the majority of patients, as all were in sinus rhythm and the short-axis views at the apical and at the basal levels were recorded immediately one after another. Moreover, the software used does not allow calculation of LV twist by this method if the difference in heart rate between cardiac cycles used to measure apical and basal rotation is significant. The mean heart rate of the recordings at both basal and apical level in our study was 67 ± 10 beats per minute. LV torsion was defined as LV twist divided by end-diastolic LV longitudinal length measured in the apical four-chamber view. The following measurements were performed: peak basal and apical rotation, peak LV twist, peak LV twist rate, peak apical rotation rate, peak basal rotation rate, peak apical back rotation rate and time to it, peak LV untwisting rate, and time to it (Figure 1). Time intervals were normalized to the percentage duration of systole and diastole separately as previously described (i.e. at end systole, t was 100%, at end diastole, t was 200%). For diastole, the time of each frame was expressed as a percentage of the duration of diastole and added to 100, such that the diastolic period was defined from 100 to 200%. The end of systole was defined by the aortic valve closure signal on Doppler interrogation of the LV outflow tract and diastole was defined as the remainder of the cardiac cycle.

**Plasma BNP**

Brain natriuretic peptide (BNP) levels were determined at the discretion of the referring physician using commercially available kits based on microparticle enzyme immunoassay (AxSYM System, Abbott Laboratories). Venous blood samples were taken from an antecubital vein at the time of the echocardiogram into appropriate vacutainer test tubes, according to the manufacturer’s instructions.
Statistical analysis
Measurements are presented as mean ± SD. Variables were compared using Student’s t-test, ANOVA, or χ² test when appropriate. Relationships between different parameters were assessed by correlation analysis (Pearson’s method). Skewed data such as BNP values were logarithmically transformed [ln(BNP)] and ln(BNP) values were used in correlation and regression analyses. All statistical analyses were performed using SPSS 14.0 software for Windows (SPSS, Inc., Chicago, Illinois). A two-sided P-value of 0.05 was considered significant.

Measurement variability was assessed for peak apical and peak basal rotation as well as for time intervals, in a randomly selected group of 15 patients with AS. For interobserver variability, measurements were carried out by a second operator on previously acquired images, but not necessarily the same heart beats. For intraobserver variability, two sets of measurements were carried out by the same operator, one month apart. Variability was calculated as the absolute differences between two measurements divided by the mean of the two measurements.
Table 1  Echocardiographic variables in control subjects and patients with aortic stenosis

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 40)</th>
<th>AS (n = 61)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm/m²)</td>
<td>27 ± 3</td>
<td>27 ± 3</td>
<td>0.7</td>
</tr>
<tr>
<td>LVESE (mm/m²)</td>
<td>16 ± 2</td>
<td>16 ± 3</td>
<td>0.9</td>
</tr>
<tr>
<td>LVEDV (mL/m²)</td>
<td>51 ± 8</td>
<td>46 ± 17</td>
<td>0.07</td>
</tr>
<tr>
<td>LVESV (mL/m²)</td>
<td>19 ± 4</td>
<td>21 ± 8</td>
<td>0.1</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>89 ± 14</td>
<td>139 ± 32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAVi (mL/m²)</td>
<td>33 ± 8</td>
<td>41 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVFS (cm/s)</td>
<td>36 ± 13</td>
<td>40 ± 9</td>
<td>0.09</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62 ± 3</td>
<td>63 ± 6</td>
<td>0.2</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>76 ± 15</td>
<td>75 ± 25</td>
<td>0.8</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>184 ± 50</td>
<td>236 ± 64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S lateral (cm/s)</td>
<td>9.6 ± 2.5</td>
<td>8.6 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E’ average (cm/s)</td>
<td>11.9 ± 2.5</td>
<td>5.6 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/E’ average</td>
<td>6.6 ± 1.4</td>
<td>3.6 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AVAi (cm²/m²)</td>
<td>—</td>
<td>0.39 ± 0.11</td>
<td>—</td>
</tr>
</tbody>
</table>

Left ventricular end-diastolic diameter indexed to body surface area (BSA); LVESE, left ventricular end-systolic diameter indexed to BSA; LVEDV, left ventricular end-diastolic volume indexed to BSA; LVESV, left ventricular end-systolic volume indexed to BSA; LAVi, left atrial volume indexed to BSA; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; E, E-wave deceleration time; IVRT, isovolumic relaxation time; AVAi, aortic valve area indexed to BSA.

Results

Study participants

Thirteen AS patients were in NYHA class I, six of them presenting for angina or syncope, the rest being asymptomatic. Thirty-seven patients were in NYHA class II, and 11 in class III. BNP levels were available in 30 patients with AS and ranged from 36 to 878 pg/mL (median: 202.7 pg/mL; interquartile range 99–326 pg/mL). When compared with controls, AS patients were older (66 ± 9 vs 47 ± 12 years, P < 0.001) and more often of male gender (67 vs 33%, P < 0.001). Body surface area (1.83 ± 0.21 vs 1.81 ± 0.18 m²) and resting heart rate (66 ± 12 vs 68 ± 9 b.p.m.) were similar in both groups (P > 0.3 for both).

Left ventricular systolic and diastolic function

In Table 1, the echocardiographic characteristics of the study population are depicted. Left atrial volume and LV mass were increased in AS patients when compared with controls. Although LV ejection fraction was similar in both groups, peak systolic velocity—a parameter of LV longitudinal myocardial function—was reduced in AS (P < 0.001). Parameters of LV diastolic function were often impaired in AS patients. The E-wave velocity deceleration time and the E/E’ ratio were increased whereas the E’ was significantly reduced in AS patients (P < 0.001, respectively for all).

Left ventricular rotation parameters

Left ventricular apical rotation, torsion, and twist parameters were increased in AS patients (Table 2). LV untwisting rate and time to peak LV untwisting rate were similar in both groups. There were no significant differences in LV rotation parameters between asymptomatic and symptomatic patients with AS. In AS patients, LV apical back rotation rate was increased, while time to peak apical back rotation rate was delayed when compared with controls.

Intraobserver variability for measuring LV twist was 6.8 ± 4.9%, for time to peak apical back rotation rate was 2.6 ± 2.9%, and for time to peak LV untwisting rate was 3.9 ± 5.5%. Interobserver variability for the same parameters was 8.5 ± 7.8, 2.1 ± 3.4, and 3.0 ± 5.4%, respectively.

Relations of left ventricular rotation parameters to conventional echocardiographic parameters of left ventricular function in patients with aortic stenosis

Left ventricular torsion correlated to LV volumes (r = −0.38, P = 0.003 for indexed LV end-diastolic volume and r = −0.31, P = 0.019 for indexed LV end-systolic volume), while there was no significant relationship between LV rotation parameters and LV ejection fraction. Peak LV twist rate had a direct correlation with peak systolic myocardial velocities (r = 0.34, P = 0.009 for peak septal S and r = 0.29, P = 0.04 for peak lateral S).

Among diastolic function parameters, E/E’ ratio was significantly correlated to time to peak apical back rotation rate and time to peak LV untwisting rate (Figure 2). Both time to peak apical back
rotation rate and time to peak LV untwisting rate were also corre-
lated to indexed LA volume ($r = 0.39$, $P = 0.002$ and $r = 0.38$, $P = 0.004$, respectively) and to BNP levels (Figure 3).

We entered the correlates of time to peak apical back rotation rate and time to peak LV untwisting rate, respectively, in multi-
virate linear regression analysis (found by univariate analysis at a
significance level of $P < 0.05$): LAVi, ln(BNP), $E/E' \text{ ratio}$. We found that only $E/E' \text{ ratio}$ was independently related to each
time interval ($P < 0.01$).

**Discussion**

In the present study, we found that the chronically increased after
load resulting from AS leads to progressive alterations in LV systo-
lic and diastolic torsional mechanics. To the best of our knowledge,
this is the first study to report a significant relationship between LV
untwisting and LV filling pressures in patients with severe AS and
preserved LV ejection fraction.

**Left ventricular rotation parameters in aortic stenosis**

In AS, the increased pressure overload results in several structural,
haemodynamic, and functional changes. In our study, all patients
had severe AS and, despite preserved LV ejection fraction, they
presented an enlarged left atrium, decreased peak systolic myocard-
dial velocities, and increased $E/E' \text{ ratio}$ when compared with con-
trols. In addition, we found that LV rotation parameters were
altered in AS patients. LV apical rotation and torsion were
increased, while peak apical back rotation rate was increased and delayed, compared with controls.

**Systolic left ventricular torsional mechanics in aortic stenosis**

Left ventricular twist is caused by the dynamic interaction between oppositely oriented subepicardial and subendocardial myocardial fibre helices and has an important role in LV ejection.\(^9,10\) Subendocardial ischaemia has long been recognized as an early sign of myocardial damage from pressure overload caused by AS.\(^21\) As the direction of LV twist is governed by the subepicardial fibres,\(^22\) subendocardial ischaemia may diminish the counteraction of subendocardial myofibres and alter the systolic LV rotation. In the present study, we found that LV apical systolic rotation and global LV twist were increased in AS patients. A possible explanation for the lack of increased basal rotation in the current study may be the greater increase in wall stress in the basal walls which might prevent basal rotation to increase. Increased LV twist and rotation in AS patients has recently been shown in tagged MRI studies.\(^9,10\) However, MRI has limited clinical availability, low temporal resolution, and long acquisition time. Two-dimensional STE is relatively a novel technique that provides accurate information regarding myocardial deformation and LV torsional mechanics\(^16,22\) and overcomes these limitations.

**Diastolic left ventricular torsional mechanics in aortic stenosis**

In the present study, peak apical back rotation was increased and delayed in AS patients, while the basal back rotation was relatively conserved. A significant prolongation of apical back rotation into the filling phase of the LV has also been observed in MRI studies concerning a limited number of patients with various degrees of AS.\(^24\) In normal subjects, over 40% of LV untwisting is completed in the first part of diastole.\(^25\) The untwisting process generates a negative intraventricular pressure gradient and contributes to LV suction and enhanced early-diastolic filling.\(^25\) This early, rapid LV untwisting process is supported by active (potential energy stored from the active systolic twist) and passive (potential energy transformed into kinetic energy) mechanisms. In AS, the subendocardial ischaemia may alter the active part of diastolic untwisting, and the resulting relaxation abnormality, which is frequent in AS, may in turn further compromise the LV untwisting and filling. This vicious circle may ultimately lead to significant LV dysfunction and symptoms development.

**Relation between left ventricular untwisting and filling pressures**

In the present study, we showed, for the first time, a direct, significant relationship between LV untwisting and filling pressures, as assessed by the E/E’ ratio and BNP levels in patients with severe AS. Apical back rotation, but not LV untwisting, was significantly delayed in AS patients. However, a direct relationship was found between both time to peak LV untwisting rate and time to peak apical back rotation rate and LV filling pressures: the longer the time to peak untwisting rate, the higher the filling pressures.

In normal subjects, a rapid diastolic apical back rotation causes a fast decline in LV pressure playing an important role in the suction of blood into the ventricle, promoting its filling at low pressures.\(^25\) Therefore, the finding of a direct relationship between delayed apical back rotation and increased LV filling pressures in patients with AS is not surprising and clinically meaningful.

In patients with AS, exertional dyspnoea is closely associated with elevated LV filling pressures,\(^26,27\) and abnormal LV filling has been reported in at least half of the patients with normal systolic ejection performance and in all patients with depressed systolic function.\(^26\) Increased LV filling pressure represents the common feature for advanced heart failure regardless of underlying aetiology, and has well-known clinical and prognostic implications.\(^28,29\) The extent of diastolic dysfunction in patients with AS independently predicts late mortality after aortic valve replacement.\(^30\)

The E/E’ ratio provides an accurate estimate of LV filling pressures at rest\(^24,31\) and during exercise\(^22\) in several cardiac conditions with both preserved and reduced LV ejection fraction. An elevated E/E’ ratio indicates a poor prognosis in various cardiac conditions\(^33−37\) and was found to be a predictor of mortality and need for aortic valve replacement in a small cohort of patients with different degrees of AS severity.\(^38\) The usefulness of the E/E’ ratio as an estimate of LV filling pressures in patients with moderate to severe AS was validated against invasive measurements derived from cardiac catheterization.\(^4,39\) In these patients, an E/E’ septal ratio ≥13 identified an LV end-diastolic pressure >15 mmHg, with a sensitivity of 93% and a specificity of 88%.\(^4\)

Similarly, plasma levels of natriuretic peptides are related to disease severity\(^40,41\) and symptomatic status\(^42\) in patients with AS, and it was suggested that they could be used to monitor disease progression. Moreover, they provide additional prognostic information beyond clinical and echocardiographic data.\(^43\)

**Clinical implications**

As delayed LV untwisting may partially explain the occurrence of diastolic dysfunction in patients with AS and it is related to parameters with confirmed prognostic value (E/E’ ratio and BNP levels), it would be interesting to test whether changes in LV torsional dynamics have a prognostic role and whether interventions such as aortic valve replacement would lead to an improvement in LV untwisting. It would also be interesting to assess the effect of exercise on LV torsion and untwisting in asymptomatic patients with AS. This has been examined in healthy individuals where enhanced untwisting contributes to the augmentation of LV filling during exertion.\(^25\) In patients with hypertrophic cardiomyopathy, however, this exercise response is blunted,\(^25\) suggesting that the effect of exercise on untwisting may be of relevance to the development of cardiac dysfunction in different clinical settings. Proof of prognostic role or ability to identify incipient LV dysfunction or lack of functional reserve may help clinical decisions, turning these parameters into useful clinical tools.

**Study limitations**

Lack of an age-matched control group is a main limitation of our study. However, this relates only to the comparison between patients with AS and normal subjects, while the main finding of the study (the correlations between LV untwisting parameters
and filling pressures in AS patients) is unrelated to the age difference between groups. Another limitation of our study is the lack of a sizeable subgroup of asymptomatic patients with AS to test differences between symptomatic and asymptomatic patients. This reflects the population of AS patients usually seen in a tertiary referral centre, including mainly symptomatic patients referred for aortic valve replacement.

Left ventricular filling pressures were non-invasively estimated and not directly measured. However, we used two parameters already validated in this setting, reaching concordant results, while crossing the stenotic aortic valve to measure LV pressure overload due to aortic stenosis. Circulation 1999;100:361–8.

Conclusions

In patients with severe AS and preserved LV ejection fraction, there is a significant relationship between LV untwisting and LV filling pressures: the longer the time to peak untwisting rate, the higher the filling pressures. These results suggest a potential role for impaired LV untwisting in the development and progression of diastolic dysfunction in patients with AS.

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