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Echocardiography

Rotational Mechanics of the Left Ventricle in AL Amyloidosis

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Aims: The aim of this study was to investigate whether alterations in left ventricular (LV) twisting and untwisting motion could be induced by cardiac involvement in patients with immunoglobulin light-chain (AL) systemic amyloidosis. Methods and Results: Forty-five patients with AL amyloidosis and 26 control subjects were evaluated. After standard echocardiographic measurement and two-dimensional (2D) speckle tracking echocardiography, LV rotation at both basal and apical planes, twisting, twisting rate, and longitudinal strain were measured. Tissue Doppler imaging (TDI) derived early diastolic peak velocity at septal mitral annulus (E′) was also evaluated. Twenty-six of 45 patients with systemic amyloidosis were classified as having cardiac amyloidosis (CA) if the mean value of the LV wall thickness was $\geq$ 12 mm or not (NCA) if this value was not reached. In NCA patients, both LV twist and untwisting rate were increased while they were decreased in CA patients making them similar to the control group. Longitudinal strain was reduced only in CA patients. Impaired relaxation as indicated by E′ values was progressively reduced in the course of the disease. Conclusions: Both twisting and untwisting motions are increased in patients with AL systemic amyloidosis with no evidence of cardiac involvement while they are reduced in patients with evident amyloidosis cardiac involvement. This finding suggests that impaired LV relaxation induces a compensatory mechanism in the early phase of the disease, which fails in more advanced stage when both twisting and untwisting rates are reduced. The increase in LV rotational mechanics could be a marker of subclinical cardiac involvement. (Echocardiography 2010;27:1061-1068)

Key words: amyloidosis, cardiac involvement, LV rotational mechanics, 2D speckle tracking

Amyloidosis is a rare systemic disease characterized by extracellular deposition of protein-derived fibrils, in various tissues and organs, including the heart; they are characterized by a b-sheet structure with typical apple-green birefringence when viewed after Congo Red staining and under polarized light.[1] Different types of amyloidosis are differentiated through immunohistochemical and genetic testing.

The presence of cardiac involvement or cardiac amyloidosis (CA) has been defined as an infiltrative disorder primarily caused by extracellular tissue deposition of amyloid fibrils in the myocardial interstitium; its relative predominance varies according to the type of amyloidosis, with prognosis and therapeutic strategies different from one another.

CA is common in immunoglobulin light-chain (AL) amyloidosis where it strongly affects both prognosis and treatment options.[2,3] In AL, early diagnosis is critical because chemotherapy with high doses of melphalan, and autologous stem-cell transplantation, may arrest and even reverse the disease, with resultant stabilization or improvement of symptoms.[4,5]

In CA, attention has long been focused on diastolic dysfunction and it was generally thought that systolic function was relatively preserved until the late stage of disease. However in the last few years, by means of more advanced echocardiographic techniques such as tissue Doppler imaging (TDI), various alterations of longitudinal contraction have been described in early stage of CA when traditional parameters of systolic function were still normal.[6–8] Furthermore two recent studies, using TDI, reported reduced LV longitudinal strain even in patients with systemic amyloidosis but without evidence of cardiac involvement when standard echocardiography was used.[9,10]

Recently, two-dimensional (2D) speckle tracking echocardiography has enabled the assessment of a particular mechanical behavior of

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left ventricular (LV) motion defined as twisting/untwisting.[11–13] It consists of an LV torsional deformation around its longitudinal axis, originating from the dynamic interaction between a systolic clockwise rotation of the base and a counterclockwise rotation of the apex followed by untwisting during diastole.

We hypothesized that, in amyloidosis, the twisting/untwisting motion, which involves both myocardial systolic and diastolic function, could be altered and provide insights into the pathophysiologic mechanisms of CA involvement. To test this hypothesis we studied LV rotational mechanics in a group of patients with systemic AL amyloidosis both with and without evidence of cardiac involvement.

Material and Methods:

Forty-five patients with systemic AL amyloidosis entered the study. Patients were referred to our echo laboratory in the setting up of a multidisciplinary evaluation by the Tuscan Regional Amyloid Center, AOU Careggi. The diagnosis of amyloidosis was made either by subcutaneous fat aspiration or biopsy of the organ involved, which demonstrated a typical apple-green birefringence under polarized light after Congo red staining. AL amyloidosis was confirmed by the finding of a monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow when evaluated by immunohistochemistry. Exclusion criteria were the presence of hypertension, atrial fibrillation, coronary artery disease, valvular disease, or diabetes.

Patients were classified as having CA if the mean value of LV wall thickness (half of the sum of ventricular septum and posterior wall (PW) thickness) was $\geq$12 mm or not CA (NCA) if this criterion was not satisfied. A total of 26 asymptomatic healthy, age-matched subjects, were analyzed as the control group. None of them had history of previous or current heart disease, systemic hypertension, diabetes, or were on medication. Of them all had a normal physical examination and a normal electrocardiogram (ECG) and echocardiographic findings. All participants gave informed written consent, and the study was approved by the local ethics committee. In all patients and healthy subjects a complete M-mode, 2D, conventional Doppler, Tissue Doppler and speckle-tracking imaging was performed.

Standard Echocardiography:

Images were obtained using a cardiac ultrasound machine (Vivid 7 System, Vingmed, General Electric, Horten, Norway) equipped with a 3S probe. The following echo M-mode, bidimensional, and pulsed Doppler parameters were evaluated: end-diastolic thickness of the interventricular septum (IVS) and of LV PW, LV end-diastolic and end-systolic diameter indexed by BSA, (EDD_{ind}, ESD_{ind}, respectively), $LVmass_{ind}$, LV fractional shortening (FS), left atrial anteroposterior diameter (LAD), left atrial area (LAA_{ind}), evaluated from the apical chamber view at the end of systole, LV end-diastolic and end-systolic volumes (EDV, ESV, respectively), ejection fraction (EF) with biplane Simpson method, mitral peak flow velocity in early and in late diastole, during atrial contraction (E, A, respectively), E/A ratio, myocardial performance index (MPI) as the sum of isovolumetric contraction and relaxation times divided by ejection time, as previously described,[14] right ventricular free wall thickness (RVFW), RV end-diastolic diameter (RVDD), and the systolic displacement of the lateral portion of the tricuspid annular plane (TAPSE). Pulsed TDI derived early diastolic peak velocity at septal mitral annulus (E′) as index of LV relaxation and E/E′ ratio as index of LV filling pressure were also evaluated.[15,16]

Speckle Tracking Echocardiography:

After completion of the standard echocardiographic examination, 2D gray scale LV short-axis images were acquired at the basal and apical levels at high frame rates (80–100 frame/sec) to assess rotation, rotational velocities, circumferential and radial strain in either the basal or apical planes and LV twist/untwisting. Care was taken to ensure that the basal plane contained the mitral valve, and that the apical plane was acquired distally to the papillary muscles. At each plane, three consecutive cardiac cycles were acquired during a breath hold, and stored for off-line analysis. In order to time cardiac events, LV inflow and outflow velocities were recorded using pulsed-Doppler echocardiography. Apical four-chamber, two-chamber, and long-axis views, were also stored in cineloop format at the same high frame to assess speckle tracking derived LV longitudinal strain.

The time interval between the peak of the R-wave on the electrocardiogram and the aortic valve opening and closure, as well as the time interval between the R-wave and the mitral valve opening and closure were measured using pulsed-Doppler acquired from the LV outflow and inflow, respectively.

From the basal and apical short-axis data sets, one cardiac cycle was selected for subsequent analysis. Using commercially available 2D strain software (Echopac PC, version 6.0.1, GE Healthcare, Milwaukee, WI, USA), the endocardial border of the end-systolic frame was manually traced. The width of the region of interest was adjusted to fit the entire myocardium. From these recordings, Echopac selected the speckles and tracked

them during the cardiac cycle. The accuracy of the tracking was verified with the option of subsequently retracing endocardial border and adjusting the size of the region of interest as needed. The software algorithm first automatically segmented the LV short-axis into six equidistant segments and then performed speckled tracking on a frame by frame basis using the sum of absolute difference algorithm. This resulted in the calculation of the time domain radial, circumferential strain, rotation and rotational velocity profiles for each of the segments in the both short-axis planes. The average LV rotation and rotational velocity profiles from the basal and apical planes were used in calculating LV twist and twist velocity. LV twist and twist velocity were defined as apical LV rotation and rotational velocity relative to the basal plane.

Counterclockwise rotation as viewed from the LV apex was expressed as a positive value, clockwise rotation as a negative value. Data points describing the basal and apical LV rotation and rotational velocities were exported into MATLAB (MathWorks, Natick, MA, USA) and the differences between apical and basal rotations at each corresponding time point were calculated, including the time derivative of LV twisting and untwisting. For temporal analysis, the time sequence was normalized to the percentage of systolic and diastolic duration assuming that the former was 100% time percentage at aortic valve closure and the latter was 100% time percentage at mitral valve closure.

The following parameters were evaluated: LV longitudinal strain (LongSt) expressed as the average of the three-apical view derived longitudinal strain values, circumferential and radial strain both at basal and apical level ($CircSt_{base}$, $RadSt_{base}$, $CircSt_{apex}$ and $RadSt_{apex}$, respectively), basal and apical rotation degree (Rot_{base} and $Rot_{apex)}$ all as the average of the six LV segments derived values. Finally, LV Twist, LV Twist rate, LV Untwisting rate, the systolic time at which LV twist reached its maximal value (LV $twist_{systtime\%}$), and the diastolic time at which LV untwisting rate was maximal (LV $untwist_{diasttime\%}$), as percentage of systolic and diastolic duration, respectively, were analyzed.

Statistical Analysis:

Data are expressed as mean $\pm$ standard deviation (SD). Differences between Control, NCA, and CA groups were analyzed with one-way analysis of variance (ANOVA), and post hoc analyses were performed using Scheffe's method. A backward stepwise linear regression analysis was performed in order to correlate twist and untwisting rate with those variables resulting significantly different at ANOVA between NCA and CA groups. Pearson's correlation coefficients (R) were reported. Interobserver variability was assessed for twist and untwisting measurements in seven randomly selected patients and calculated as the SD of the differences between the measurements of two independent observers who were unaware of the other patient data; this variability was expressed as a percent of the average value. Intraobserver variability was calculated as the SD of the differences between a first and a second determination of a single observer and expressed as percentage of the average value. All statistical analyses were performed using SPSS 13.0 statistical software for Windows (SPSS Inc., Chicago, IL, USA). Values of $P < 0.05$ were considered statistically significant.

Results:

The study population consisted of 26 healthy subjects (control group) and 45 patients with systemic AL amyloidosis. Twenty-six patients of this last group had CA (CA group) defined as half of the sum of ventricular septum and PW thickness $\geq$12 mm and 19 had no evidence of cardiac involvement (NCA). All subjects of the control group and NCA patients were asymptomatic (New York Heart Association [NYHA] class I) while among the CA group, four patients were in NYHA class IV, nine patients in NYHA class III, and 11 patients in NYHA II. EF was normal in all patients except for four CA patients where it was slightly reduced. Pro-BNP plasma level was 718 $\pm$ 1240 pg/mL in NCA and 12140 $\pm$ 17850 pg/mL in CA patients.

Traditional Echo/Doppler Data Analysis:

As reported in Table I, in patients with NCA, BSA-indexed atrial area was significantly larger compared with the control group ($P < 0.001$), and significantly smaller compared with the CA group ($P < 0.0001$), E′ value was significantly lower than in the control group ($P < 0.05$) and higher than in the CA patients ($P < 0.05$). Patients with CA had a significantly higher E/E′ ratio than in the NCA patients ($P < 0.0001$) and than the control group ($P < 0.0001$), however in NCA, E/E′ ratio was significantly higher than in the control group ($P < 0.05$). MPI was significantly higher in CA than in NCA patients ($P < 0.001$) and control group ($P < 0.001$), no difference was observed in this index between the control and the NCA patients. TAPSE was lower in the CA than in the NCA patients ($P < 0.001$) and control groups ($P < 0.0001$) but similar in control and NCA groups.

All other traditional echo/Doppler parameters were similar in the three groups with the exception of LV wall thicknesses that obviously were

TABLE I

Demographic, Two-Dimensional, and Doppler Echocardiographic Parameters

	Control Group	NCA Group	CA Group	P <
Age	65.7 ± 8.5	71.2 ± 9.8	66.9 ± 10.9	NS
LAD (mm)	37.3 ± 3.7	39.7 ± 5.6	44.6 ± 6.3*	0.0001
LAA_{ind} (cm^2/m^2)	8.9 ± 1.6	11.1 ± 1.8#	13.4 ± 2.1&	0.0001
$LVDD_{ind}$ (mm/ m^2)	25.4 ± 2.5	26.2 ± 3.1	24.8 ± 3.3	NS
$LVSD_{ind}$ (mm/ m^2)	15.7 ± 2.4	15.5 ± 2.9	16.2 ± 4.3	NS
FS (%)	38.4 ± 6.6	41 ± 7	35.3 ± 12	NS
IVS (mm)	9.9 ± 1.1	10.5 ± 0.9	15.8 ± 2.6&	0.0001
PW (mm)	9.9 ± 0.8	10.3 ± 0.9	15.9 ± 2.3&	0.0001
LV $mass_{ind}$ (g/m^2)	89.2 ± 21.8	96.3 ± 22	162.9 ± 36.2&	0.0001
RVDD (mm)	26.5 ± 4.1	25.4 ± 5.9	27.4 ± 5.5	NS
RVFW (mm)	5.3 ± 1	6.6 ± 1.2£	7.4 ± 1.2	0.01
LVEDV (mL)	92.5 ± 27.5	78.4 ± 21.7	75.7 ± 24.3**	0.05
LVESV (mL)	34.9 ± 12	32.4 ± 13.7	33.5 ± 17.7	NS
EF (%)	62.3 ± 5.5	59.2 ± 10.5	57.1 ± 11.1	NS
E (cm/sec)	61.6 ± 11	77.1 ± 15.6#	80.4 ± 17.7*	0.0001
A (cm/sec)	67.5 ± 18.1	89 ± 17.9#	58.4 ± 28.1*	0.0001
E/A	0.95 ± 0.23	0.89 ± 0.2	1.72 ± 09&	0.0001
E′ (cm/sec)	9.1 ± 2.2	7.6 ± 2.1£	4.6 ± 1.1&	0.0001
E/E′	7.2 ± 2.4	10.8 ± 3.9$	18.2 ± 5.7&	0.0001
MPISX	0.4 ± 0.1	0.34 ± 0.1	0.55 ± 0.26***	0.0001
TAPSE (mm)	23.5 ± 4	22.1 ± 3.8	17.5 ± 4.6*§	0.0001

*P < 0.0001 CA vs. control, §P < 0.001 CA vs. NCA, &P < 0.0001 CA vs. others, #P < 0.001 NCA vs. control, £P < 0.05 NCA vs. others, $P < 0.05 NCA vs. control, **P < 0.05 CA vs. control, ***P < 0.001 CA vs. others.
LAD = left atrium diameter; LAA_{ind} = Left Atrium Area BSA indexed; $LVEDD_{ind}$ = left ventricular end-diastolic diameter BSA indexed; $LVESD_{ind}$ = left ventricular end-systolic diameter BSA indexed; FS = fraction shortening; IVS = interventricular septum; PW = posterior wall; $LVMass_{ind}$ = left ventricular mass BSA indexed; RVEDD = right ventricular end-diastolic diameter; RVFW = right ventricular free-wall thickness; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; EF = left ventricular ejection fraction); E = early peak transmitral diastolic flow; A = late peak transmitral diastolic flow; E′ = early diastolic mitral annular velocity; MPISX = left ventricular myocardial performance index; TAPSE = tricuspid annulus systolic plane excursion.

higher in CA as compared with both control and NCA groups as well as RVFW, which was higher in NCA than in control group (P < 0.05), but lower than in CA group (P < 0.05).

2D Speckle-Tracking Data Analysis:
LV longitudinal strain in control subjects and NCA patients was similar and significantly higher than in CA patients.

As reported in Table II, at basal plane the degree of clockwise rotation appeared to be significantly lower in CA patients than in NCA patients (P < 0.0001) or in healthy subjects (P < 0.0001). In NCA and in control group this parameter was similar.

Circumferential strain at basal plane was significantly lower in CA than in NCA patients (P < 0.0001) and control group (P < 0.05). Moreover NCA showed higher values if compared with controls (P < 0.05).

Radial strain at basal plane in CA was significantly lower than in NCA (P < 0.0001) and control group (P < 0.0001), no significant difference was observed between NCA and control group for this parameter. The degree of counterclockwise apical rotation was similar in the three groups although in the NCA there was a trend toward increasing without any significant statistical difference that was present in basal rotation. Significant differences between the three groups were observed regarding circumferential strain at apical plane, which was significantly lower in CA than in NCA and control groups (P < 0.01 for both); no significant difference was found for this parameter between NCA and control groups. Similarly radial strain at the apical plane was lower in CA patients than in NCA and control groups (P < 0.01 for both) while this parameter was similar in NCA and control groups.

The degree of LV twist was higher in NCA than in CA and control groups (P < 0.01 and P < 0.05, respectively) but it was similar in control and CA groups. Likewise twist rate was higher in NCA than in CA and control groups (P < 0.05 for both), and similar in NCA and control groups. No significant difference was observed between the three groups in the percentage of systolic time at which LV twist reached the maximum degree. Untwisting rate was higher in NCA than in CA group (P < 0.0001) and control group (P < 0.05)

TABLE II

Two-Dimensional Speckle Strain Derived Parameters

	Control Group	NCA Group	CA Group	P <
LongSt (%)	-19.1 ± 2.5	-18.3 ± 4.8	$-11.1 \pm 5.1^{\&}$	0.0001
$CircSt_{base}$ (%)	$-15.3 \pm 4.7^{£}$	$-20.4 \pm 9.7^{*}$	-10.9 ± 4.3	0.0001
$RadSt_{base}$ (%)	43.5 ± 15.8	38.1 ± 16.3	$18.1 \pm 18.2^{\&}$	0.0001
Rot_{base} (°)	-6.7 ± 2.9	$-8.5 \pm 3.2^{*}$	-4 ± 4.4	0.0001
$CircSt_{apex}$ (%)	-20.6 ± 5.3	-21.8 ± 6.2	$-15.6 \pm 6.4^{**}$	0.01
$RadSt_{apex}$ (%)	33.8 ± 12.1	32.1 ± 14.6	$19.4 \pm 16.7^{**}$	0.001
Rot_{apex} (°)	5.2 ± 3.7	6.9 ± 4.1	5 ± 2.4	NS
LV Twist (°)	10 ± 4	$13.3 \pm 5.7^{****}$	$8.1 \pm 3.9^{\$}$	0.001
LV $twist_{Systtime}$ (%)	96.1 ± 12.9	94.2 ± 31.6	92.8 ± 14.8	NS
LV Twist rate (°/sec)	73.9 ± 25.2	$94.2 \pm 31.6^{***}$	68.3 ± 27.9	0.01
Untwist rate (°/sec)	$-81.5 \pm 34.1^{£}$	$-102.8 \pm 25.1^{*}$	-60.7 ± 27.5	0.0001
$LVuntwist_{diasttime}$ (%)	$20.3 \pm 11.4^{£}$	30.1 ± 15.7	32.4 ± 17.8	0.05

$^{\&}P < 0.0001$ CA vs others, $^{*}P < 0.0001$ NCA VS CA, $^{£}P < 0.05$ control vs others, §P < 0.05 CA vs control, $^{**}P < 0.01$ CA vs others, $^{\$}P < 0.01$ CA vs NCA, $^{***}P < 0.05$ NCA vs others, $^{****}P < 0.05$ NCA vs control.
LongSt = LV longitudinal strain; $CircSt_{base}$ = left ventricular basal circumferential peak systolic strain; $RadSt_{base}$ = left ventricular basal radial peak systolic strain; Rot_{base} = left ventricular basal peak systolic rotation; $CircSt_{apex}$ = left ventricular apical circumferential peak systolic strain; $RadSt_{apex}$ = left ventricular apical radial peak systolic strain; Rot_{apex} = left ventricular apical peak systolic rotation; LV Twist = left ventricular peak systolic twist; LV $twist_{Systtime}$ = % systolic time LV twist peak; LV Twist rate = left ventricular peak systolic twist velocity; Untwist rate = left ventricular peak diastolic untwist velocity; $LVuntwist_{diasttime}$ = % diastolic time LV untwist peak.

in CA patients it was lower than in control group ($P < 0.05$). The diastolic time at which the untwisting rate reached the maximum value was more anticipated in control groups than in CA and NCA groups ($P < 0.05$ for both) however no difference was found in this parameter between NCA and CA groups.

Backward stepwise linear regression analysis shows that longitudinal strain and E′ were the only variables significantly correlated with twist ($R = 0.515$; $P < 0.0001$ and $R = 0.47$; $P < 0.01$, respectively) (Fig. 1).

Moreover, twist and E′ were the only variables significantly correlated with untwisting rate ($R = 0.52$; $P < 0.001$ and $R = 0.476$; $P < 0.01$) (Fig. 2).

Reproducibility:

The interobserver variability was 5.8% for twist, 6.5% for twisting rate, and 6.6% for untwisting rate.

The intraobserver variability was 3.8% for twist, 5.1% for twisting rate, and 4.9% for untwisting rate.

Discussion:

Our study demonstrates that patients with CA have a combination of systolic and diastolic abnormalities of the left ventricle that include longitudinal, radial, circumferential strain, with impaired rotational mechanics and reduced twist and untwisting rate.

Moreover our study shows that in patients with systemic amyloidosis, but no evidence of cardiac involvement, both LV twist and untwisting rate are enhanced.

CA could mirror a model of heart failure with preserved systolic function, that is, diastolic heart failure, where subclinical systolic abnormalities in early stage of the disease are emerging as well.[17–19]

Since twisting/untwisting provides a unique vision of systolic and diastolic motion, we thought that its investigation in amyloidosis patients might provide new insights into the underlying mechanisms of CA involvement. Indeed we observed that the extent of LV twist depends on the stage of the disease: it increases in the early stage and diminishes in more advanced stage becoming similar to the LV twist of the control group. Our results are concordant with a previous study by Park et al.[20] in which the authors analyzing the behavior of twisting and untwisting in patients with different degree of diastolic dysfunction found that systolic twist and diastolic untwisting were significantly increased in those with mild diastolic dysfunction; while they were normalized or reduced in those with more advanced diastolic dysfunction. It appears that our patients with systemic amyloidosis without cardiac involvement had a mild diastolic dysfunction. The larger atrial dimension associated with lower E′ values and a more delayed untwisting rate observed in NCA patients, when compared with healthy subjects, supports this concept. It reflects the existence of a subclinical diastolic dysfunction in NCA patients that becomes more pronounced in CA patients. The increased twisting noted in NCA, might be a

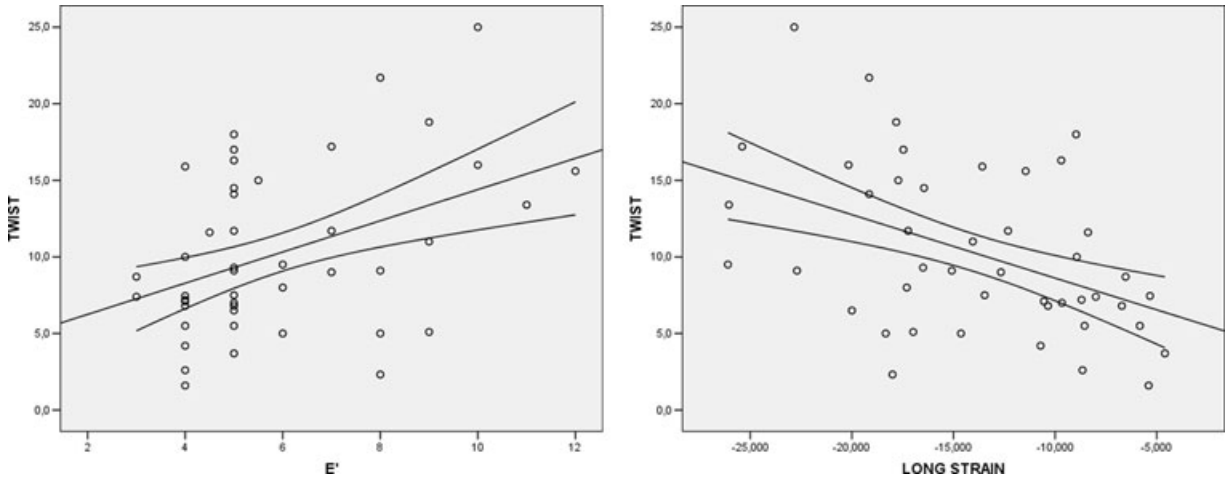

Figure 1. Linear correlation with 95% confidence interval between twist and E′ ($R = 0.47$ $P < 0.01$) and twist and longitudinal strain ($R = 0.515$ $P < 0.0001$).

compensatory mechanism to the impaired myocardial relaxation, operated by the LV in order to store additional potential energy. Subsequently, through the increased untwisting, this energy will be released to enhance diastolic suction. This compensatory mechanism seems to fail in the more advanced stage of the disease where twisting and untwisting rate are worsened. Wang et al.[21] showed that patients with diastolic dysfunction and normal EF have significantly higher untwisting rate than patients with depressed systolic function. Similarly in the present study, twisting and untwisting rate values remain high until the longitudinal and radial strain values (i.e., contractility indexes) are preserved but significantly decrease when they worsen. It is likely that the impaired ventricular relaxation initially triggers the increase of LV twisting and untwisting rate, whereas the subsequent progressive worsening of contractile function in parallel with left atrial pressure increasing might cause reduced restoring forces and hence, progressively less untwisting magnitude.

Altogether from these observations it emerges that the impaired relaxation is not the only determinant of the twist and untwisting rate changes that we observed. Indeed, as stepwise linear regression shows, longitudinal strain and E′ were the variables independently correlated with twist, whereas twist and E′ were independently correlated with untwisting rate. Another interesting finding of the present study was that the untwisting rate was delayed both in CA and NCA patients irrespective of LV mass. Conversely in a previous study of patients with hypertension, Takeuchi et al. found that untwisting was significantly reduced and delayed in parallel with the severity of LV hypertrophy.[22] Therefore whereas

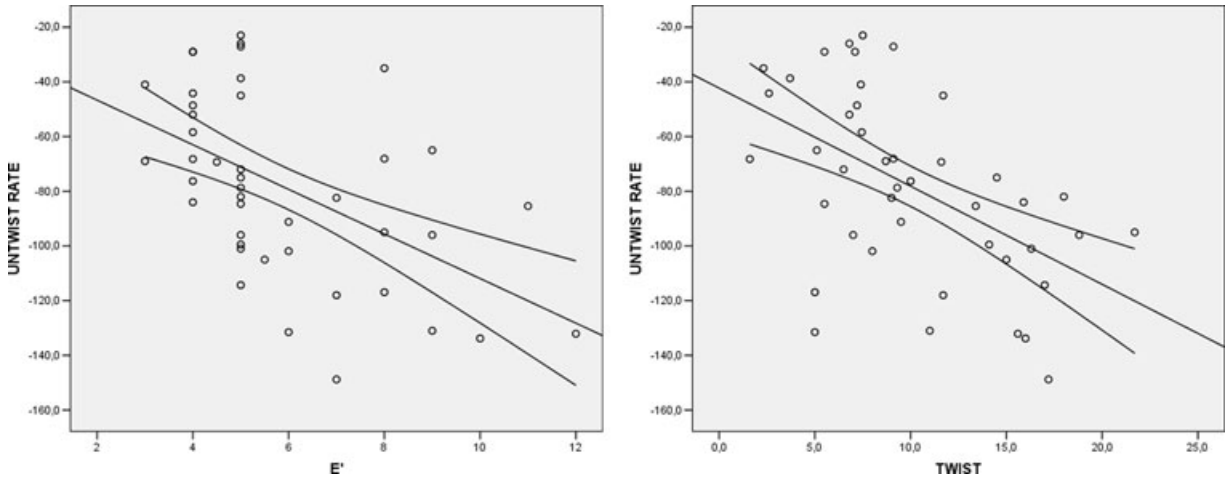

Figure 2. Linear correlation with 95% confidence interval between untwisting rate and E′ ($R = 0.476$ $P < 0.01$) and untwisting rate and twist ($R = 0.52$ $P < 0.001$).

a delayed but increased untwisting rate seems to be a sign of early amyloidosis cardiac involvement when mild diastolic dysfunction is present, a reduced and delayed untwisting rate reflects a more advanced stage of the disease when diastolic and systolic dysfunction are combined. In fact myocardial performance index that combines both systolic and diastolic function is altered in patients with CA but is similar to healthy subjects in NCA patients. Alteration of this index had already been described in a study including 45 patients with biopsy-proved amyloidosis.[23]

The peculiar behavior in LV twist/untwisting rate observed in the course of the disease evolving might be explained by the anatomical arrangement of myocardial fibers.

The LV twisting motion is a consequence of the helical orientation of subendocardial and subepicardial fibers, arranged as a right-handed helix at subendocardial level and as a left-handed helix at subepicardial level, constituting two oppositely directed spirals.

Because of larger radii, the torque of subepicardial fibers dominates and accounts for the normal systolic counterclockwise LV twist.[24]

Thus pathological processes affecting subepicardial or endocardial fibers may affect the balance between counterclockwise or clockwise forces and result in LV twist/untwisting changes. Of note an unusual MRI pattern of late gadolinium enhancement distributed over the entire subendocardial circumference, extending in various degrees into the neighboring myocardium has been described in CA.[25,26]

It is likely that amyloid infiltration at subendocardium level in the early stage reduces the endocardial clockwise rotation so that the unopposed epicardial torque will increase the counterclockwise twist, whereas later more widespread amyloid infiltration will affect global function and will lead to reduced twist and untwisting rate. The increase in LV twisting/untwisting that we observed in patients without evidence of cardiac involvement suggests that the amyloid myocardial infiltration process had already begun even if it could not be evidenced by using traditional echocardiography. Moreover, unexpectedly we found that this myocardial infiltration process in the right ventricle begins earlier than in the left ventricle. In fact in NCA patients RV free wall was more thickened than in healthy subjects in whom LV thickness was similar to NCA. However, similar to LV longitudinal strain, reduction of TAPSE occurs only in CA patients.

This is concordant with a previous study by Ghio et al. in which among a group of patients with AL amyloidosis, those with reduced TAPSE had thicker LV walls.[27]

Conclusions:

Both twisting and untwisting motions are increased in patients with AL systemic amyloidosis and no evidence of cardiac involvement and decreased in patients with evident amyloidosis cardiac involvement. This finding suggests that early in the disease, the impaired LV relaxation induces a compensatory mechanism that fails in more advanced stage of the disease when both twisting and untwisting rate are reduced. The increase in LV rotational mechanics could be a marker of subclinical cardiac involvement. Moreover our data provide interesting insights into the underlying mechanisms of CA disease progression.

Study Limitation:

We have no heart biopsy to prove the evidence of amyloid heart disease. However amyloidosis is a systemic disease and in the diagnosis of amyloid heart disease peripheral biopsies are advocated and regarded as reliable suggestors of possible heart amyloidosis. We have no data regarding NT-proBNP values in the control group. Such data could improve the neurohormonals results. ECG data were available only for few patients, so that statistical analysis was impossible.

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