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**Author:** Bertini, Matteo  
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CHAPTER 3

Left ventricular rotational mechanics in acute myocardial infarction and in chronic (ischemic and nonischemic) heart failure patients.

Matteo Bertini, Gaetano Nucifora, Nina Ajmone Marsan, Victoria Delgado, Rutger J. van Bommel, Giuseppe Boriani, Mauro Biffi, Eduard R. Holman, Ernst E. Van der Wall, Martin J. Schalij, Jeroen J. Bax.

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Left ventricular (LV) twist and untwisting rate are emerging as global and thorough parameters for the assessment of LV function. This study explored the differences of LV twist and untwisting rate among acute myocardial infarction (AMI) patients and ischemic and non-ischemic chronic heart failure (HF) patients. A total of 50 AMI patients, 49 ischemic HF and 38 non-ischemic HF patients were studied. As a control group, 28 normal subjects were included. Speckle tracking analysis was applied to LV short-axis images at basal and apical level. LV twist was defined as the net difference of apical and basal rotation at isochronal time points. The first time derivative of LV untwist was defined as LV untwisting rate. As compared to normal subjects, peak LV twist was reduced in AMI patients and extremely reduced in HF patients (ANOVA p value <0.001). A strong correlation (r=0.87, p<0.001) was found between peak LV twist and LV ejection fraction in the overall study population. LV untwisting rate was progressively reduced in AMI and HF patients as compared to normal subjects (ANOVA p value <0.001). A moderate correlation (r=0.56, p<0.001) was noted between peak LV untwisting rate and the grade of diastolic dysfunction in the overall study population. In conclusions LV twist and untwisting rate are strongly related with LV systolic and diastolic function, respectively. The impairment of LV function observed in AMI and HF patients is associated with a reduction of LV twist and untwisting rate.
**INTRODUCTION**

Recently, novel speckle tracking analysis has become available as a simple echocardiographic modality to assess LV twist and the untwisting rate. This technique has been validated against sonomicrometry and tagged magnetic resonance imaging, which are currently considered the gold standards for the assessment of rotational parameters.\(^1,2\) Initial studies evaluated LV twist and the untwisting rate in patients with myocardial infarction and heart failure (HF),\(^3-5\) but thus far, the impact of these different diseases on rotational mechanics has never been systematically evaluated. The present study assesses the differences of LV twist and the untwisting rate between patients with acute myocardial infarction (AMI) and chronic HF.

**METHODS**

A total of 137 consecutive patients were enrolled: 50 AMI patients, 49 patients with chronic ischemic HF and 38 with non-ischemic HF. The diagnosis of AMI was based on the presence of symptoms consistent with myocardial ischemia lasting \(\geq 30\) minutes and \(\geq 2\) mm ST-segment elevation in \(\geq 2\) contiguous electrocardiographic (ECG) leads.\(^6\) All AMI patients underwent urgent coronary angiography, followed by primary percutaneous coronary intervention, and the echocardiographic examination was performed within 48 hours after AMI. Etiology of HF was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in \(\geq 1\) major epicardial coronary artery) on coronary angiography and/or the history of AMI or previous revascularization.

In addition, 28 subjects without evidence of structural heart disease, matched for age and gender were included as a normal control group. The clinical echocardiographic analysis included standard 2-dimensional echocardiography to assess LV systolic and diastolic function. Furthermore, speckle tracking analysis was applied to assess LV rotational parameters (the twist and untwisting rate).

All patients were imaged in the left lateral decubitus position with a commercially available system (Vingmed Vivid 7, General Electric-Medical Systems, Milwaukee, Wisconsin, USA) equipped with a 3.5-MHz transducer. Standard 2-dimensional images and Doppler and color-Doppler data acquired from the parasternal and apical views (2-, 3-, and 4-chamber) were digitally stored in cine-loop format; analyses were subsequently performed offline using EchoPAC version 7.0.0 (General Electric-Medical Systems).
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Left ventricular (LV) end-diastolic (EDV) and end-systolic (ESV) volumes were measured according to the Simpson’s biplane method and LV ejection fraction (EF) was calculated as [(EDV-ESV)/EDV] x100.7

Transmitral and pulmonary vein pulsed-wave Doppler tracings, obtained in accordance to the recommendations of the American Society of Echocardiography,8 were used to classify diastolic function as follows: 1) normal, when the E/A ratio = 0.9-1.5, deceleration time = 160-240 ms and pulmonary vein systolic velocity (PVs) ≥ pulmonary vein diastolic velocity (PVd); 2) diastolic dysfunction grade 1 (mild), when the E/A ratio was <0.9, deceleration time >240 ms and PVs >> PVd; 3) diastolic dysfunction grade 2 (moderate), when the E/A ratio = 0.9-1.5, deceleration time = 160-240 ms and PVs < PVd; 4) diastolic dysfunction grade 3 (severe), when the E/A ratio >2.0, deceleration time <160 ms and PVs << PVd; 5) diastolic dysfunction grade 4 (severe), when the E/A ratio >2.5, deceleration time <130 ms and PVs << PVd.9

Speckle tracking analysis is based on tracking of natural acoustic markers, or speckles, on standard gray scale images. This novel technique is angle independent and permits evaluation of myocardial contraction/relaxation along the circumferential, longitudinal and radial direction.10, 11

In the present evaluation, speckle tracking analysis was applied to determine the LV twist and LV untwisting rate. Parasternal short-axis images were acquired at 2 distinct levels: 1) basal level, identified by the mitral valve; 2) apical level, defined as the smallest cavity achievable distally to the papillary muscles (moving the probe down and slightly laterally, if needed). The frame rate ranged from 45 to 100 frame/s and 3 cardiac cycles for each parasternal short-axis level were stored in cine-loop format for the offline analysis. The endocardial border was traced at an end-systolic frame and the region of interest (ROI) was chosen to fit the entire myocardium. The software allows the operator to check and validate the tracking quality and to adjust the endocardial border or modify the width of the ROI, if needed. Furthermore, each short-axis image was automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior.

Subsequently, the speckle-tracking software calculates LV rotation from the apical and basal short-axis images as the average angular displacement of the 6 standard segments referring to the ventricular centroid, frame by frame. Counter-clockwise rotation was marked as positive value and clockwise rotation as negative value when viewed from the LV apex. The software automatically calculates LV twist, defined as the net difference (in degrees) of apical and basal rotation at isochronal time points. The opposite rotation following LV twist was defined as LV untwist and the time derivative of LV untwist was defined as LV untwisting rate (in °/s) (Figure 1).

The following measurements were obtained:
1) peak apical and basal rotation,  
2) peak LV twist and peak LV untwisting rate,  
3) time to peak apical and basal rotation,  
4) time to peak LV twist and untwisting rate.

A pulsed-wave Doppler tracing obtained from the LV outflow tract was used to identify the timing of aortic valve opening and closure. All the timings were expressed as percentage of systolic phase.

Figure 1 Left ventricular twist and untwisting rate in a normal control (Panel A), AMI patient (Panel B), ischemic HF patient (Panel C) and non-ischemic HF patient (Panel D).
The green line represents apical rotation (upper) and apical rotation rate (lower); the purple line represents basal rotation (upper) and basal rotation rate (lower); the white line represents left ventricular twist/untwist (upper) and left ventricular twisting/untwisting rate (lower).
To assess the reproducibility of peak LV twist and peak LV untwisting rate measurements, 20 patients were randomly selected. Bland-Altman analysis was performed to evaluate the intra- and inter-observer agreement repeating the analysis 1 week later by the same observer and by a second independent observer. Bland-Altman analysis demonstrated good intra-observer and inter-observer agreement, with small bias not significantly different from zero. Mean differences ± 2 standard deviation (SD) for peak LV twist and peak LV untwisting rate were 0.05±0.43° and -1.93±15.97°/s, for intra-observer agreement and 0.17±1.51° and -3.97±35.63°/s for inter-observer agreement.

Continuous variables are expressed as mean ±SD. Categorical data are presented as absolute numbers and percentages. One-way ANOVA test was used to assess differences in continuous variables between the different groups of patients; if the result of the analysis was significant, Bonferroni’s post-hoc test was applied. The differences in categorical variables were analyzed using Chi-square tests or Fischer’s exact tests, as appropriate. Linear regression analysis was used to determine the relations between peak LV twist and LVEF, between peak LV untwisting rate and the grade of diastolic dysfunction, and , between peak LV untwisting rate and LVESV. In order to identify independent determinants of peak LV untwisting rate, a multivariable linear regression analysis was performed including LVESV and the grade of diastolic dysfunction as covariates. All statistical tests were 2-sided, and a p value <0.05 was considered significant. Statistical analysis was performed using the SPSS software package (SPSS 14.0, Chicago, Illinois).

RESULTS

Table 1 summarizes clinical and echocardiographic characteristics of the different patient groups and the normal controls.

As compared to normal controls, AMI patients had significantly lower values of LV apical rotation (9.8±3.0° vs. 7.6±3.8°, p = 0.007), LV basal rotation (-6.3±2.4° vs. -4.9±2.1°, p = 0.04), and LV twist (15.7±3.1° vs. 11.6±3.8°, p <0.001).

LV rotational parameters were not significantly different between ischemic HF and non-ischemic HF patients, but were significantly impaired as compared to AMI patients; peak apical rotation was 2.5±1.9° and 2.4±1.8°, respectively (p <0.001 as compared to AMI patients) and peak basal rotation was -3.4±2.0° and -2.8±2.2°, respectively (p = 0.003 and p <0.001, respectively, as compared to AMI patients). Consequently, the peak LV twist was 5.2±2.2° and 4.0±2.9°, respectively (p <0.001 as compared to AMI patients) (Table 1).
Figure 2 shows the progressive reduction of peak LV twist and LVEF among the 4 different groups. In particular, a strong correlation ($r = 0.87$, $p < 0.001$) was found between peak LV twist and LVEF (Figure 3) and between peak LV apical rotation and LVEF ($r = 0.79$, $p < 0.001$) in the overall study population; conversely, only a modest relation was found between peak LV basal rotation and LVEF ($r = -0.48$, $p < 0.001$). Furthermore, time to peak LV twist occurred earlier in AMI, ischemic HF and non-ischemic HF patients as compared to normal controls (ANOVA $p$ value $< 0.001$, Table 1).

As compared to normal controls, AMI patients had significantly lower values of peak LV untwisting rate (-107±29°/s vs. -78±35°/s, $p = 0.002$).

Table 1. Clinical, echocardiographic and rotational parameters of the different groups: normal controls, AMI patients, ischemic HF patients and non-ischemic HF patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Controls (n = 28)</th>
<th>AMI patients (n = 50)</th>
<th>Ischemic HF patients (n = 49)</th>
<th>Non-ischemic HF patients (n = 38)</th>
<th>ANOVA p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60±11</td>
<td>60±11</td>
<td>64±11</td>
<td>65±13</td>
<td>0.084</td>
</tr>
<tr>
<td>Men</td>
<td>21 (75%)</td>
<td>38 (76%)</td>
<td>43 (88%)</td>
<td>28 (74%)</td>
<td>0.16</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>87±26*</td>
<td>103±28b</td>
<td>179±67¶</td>
<td>214±74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>34±12c</td>
<td>55±21h</td>
<td>130±52c</td>
<td>164±61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>62±6†</td>
<td>47±10a</td>
<td>28±5b</td>
<td>24±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>28 (100%)</td>
<td>7 (14%)</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>19 (38%)</td>
<td>12 (24%)</td>
<td>8 (21%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>14 (28%)</td>
<td>13 (26%)</td>
<td>6 (16%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0</td>
<td>10 (20%)</td>
<td>24 (49%)</td>
<td>24 (63%)</td>
<td></td>
</tr>
<tr>
<td>Peak LV twist (°)</td>
<td>15.7±3.1†</td>
<td>11.6±3.3*</td>
<td>5.2±2.2</td>
<td>4.0±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak LV untwisting rate (°/s)</td>
<td>-107±29c‡</td>
<td>-78±35¶</td>
<td>-58±34</td>
<td>-59±32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time peak LV twist (% systole)</td>
<td>98±8§</td>
<td>83±14</td>
<td>83±19</td>
<td>75±27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time peak LV untwisting (% systole)</td>
<td>114±9</td>
<td>118±17</td>
<td>116±17</td>
<td>116±23</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*= p <0.001 vs. ischemic and non-ischemic heart failure
†= p <0.001 vs. acute myocardial infarction, ischemic and non-ischemic heart failure
¶= p <0.05 vs. non-ischemic heart failure
‡= p <0.01 vs. acute myocardial infarction
§= p <0.01 vs. ischemic and non-ischemic heart failure
||= p <0.05 vs. ischemic heart failure
AMI: acute myocardial infarction, HF: heart failure, LV: left ventricular.
Peak LV untwisting rate was not significantly different between ischemic HF and non-ischemic HF patients with lower values as compared to AMI patients: $-58\pm34^\circ/s$ in ischemic HF patients ($p = 0.018$) and $-59\pm32^\circ/s$ in non-ischemic HF patients ($p = 0.036$) (Table 1).

Peak LV untwisting rate and the grade of diastolic dysfunction among the 4 groups are shown in Figure 4. A moderate correlation ($r = 0.56$, $p < 0.001$) was noted between peak LV untwisting rate and the grade of diastolic dysfunction in the overall study population (Figure 5). Furthermore, peak LV untwisting rate was significantly.
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Figure 4: Left panel: A reduced peak LV untwisting rate is observed in AMI patients, IHF and NIHF patients as compared to normal controls. Right panel: The distribution of the different grades of diastolic dysfunction in normal controls, AMI patients, ischemic HF and non-ischemic HF patients is shown. AMI: acute myocardial infarction, EF: ejection fraction, HF: heart failure, LV: left ventricular.

Figure 5: Correlation between the grades of diastolic dysfunction (see definition in the text) and peak LV untwisting rate in the entire study population: normal controls (white triangle), AMI patients (black triangle), ischemic HF patients (white circles) and non-ischemic HF patients (black circles). AMI: acute myocardial infarction, EF: ejection fraction, HF: heart failure, LV: left ventricular.
related to LVESV ($r = 0.42$, $p < 0.001$). At multivariable linear regression analysis both LVESV ($\beta = 0.16$, $p = 0.047$) and the grade of diastolic dysfunction ($\beta = 0.47$, $p < 0.001$) were independently related to peak LV untwisting rate.

No significant differences were found among the different groups for time to peak LV untwisting rate (Table 1).


discussion

The current study comprehensively evaluated the differences in LV twist and untwisting rate among AMI, ischemic and non-ischemic HF patients, providing new insight in the relationship between LV rotational mechanics and LV function. The main findings can be summarized as follows: 1) LV twist is strongly related to LV systolic function and LV untwisting rate is modestly, but significantly related to diastolic function; 2) impairment of LV function is associated not only with a reduction of LV twist and untwisting rate, but also with an earlier peak of LV twist during systole.

As previously demonstrated in a mathematical model, LV twist distributes equally LV fiber stress and shortening across the LV wall. Accordingly, LV twist increases the efficiency of sarcomere shortening, and improves myocardial deformation during LV ejection. In the current study, a significant impairment of LV twist was observed in AMI and HF patients, compared to normal controls. Moreover, a strong relationship between the degree of impairment of LV twist and the observed impairment of LVEF was noted, confirming the previous findings demonstrating a relation between LV twist and LVEF. The strong correlation found between LV apical rotation and LVEF is not surprising, since LV apical rotation contributes more to LV twist than LV basal rotation.

The different impact of acute myocardial infarction and chronic LV remodeling (in HF) on LV twist was also explored. LV twist was more reduced in chronic HF as compared to AMI patients. These findings may be explained by different mechanisms underlying a reduction in LV twist. In HF patients, LV twist impairment is probably the result of a long-lasting process, with a rearrangement of LV myofibers with a consequent loss of the specific LV architecture responsible for the wringing motion. Conversely, in AMI patients the reduction of LV twist may result from an acute impairment in rotation of the LV region involved in the infarction. The severity of this impairment appears related to the transmurality of the infarction and to the extent of dysfunctional myocardial segments.

Intriguingly, the time to peak LV twist occurred earlier in both AMI and HF patients as compared to normal controls. The impaired LV rotational mechanics observed in AMI and HF most likely explains this finding; less time is needed to reach peak
LV twist because of the reduced contraction and rotation of the LV myofibers. In addition, the diseased LV myofibers are not able to fully counteract the systolic ventricular pressure, preventing further myocardial shortening and, consequently, leading to earlier peak LV twist.\(^{18}\)

LV systolic twist comprehends a deformation of the interstitial matrix resulting in storage of potential energy; the rapid release of the potential energy stored during systole in the isovolumic relaxation time leads to LV untwisting.\(^{19}\) In turn, LV untwisting generates an intraventricular pressure gradient facilitating diastolic LV filling.\(^{19}\) Indeed, the LV untwisting rate is emerging as an index of diastolic function.\(^{20\text{-}22}\) Particularly, LV untwisting rate was related to the time constant of LV pressure decay (Tau) and the intraventricular pressure gradient.\(^{21}\) In the present study, a good relation between the LV untwisting rate and global diastolic function was observed. The relation was not perfect, probably since the LV untwisting rate is a marker of diastolic suction rather than global diastolic function. LV untwisting rate was also independently related with LVESV; however, on multivariable linear regression analysis, the grade of diastolic dysfunction was the strongest determinant of LV untwisting rate.

A significant impairment of LV untwisting rate was observed in AMI and HF patients as compared to control subjects. In AMI patients, the impairment in LV untwisting rate may be related to the increased ventricular stiffness and consequent diastolic dysfunction due to recent acute ischemia and infarction.\(^{23}\) In HF patients, the LV untwisting rate was even more reduced as compared to AMI patients. This observation may be explained by the presence of extensive, diffuse LV fibrosis as encountered in HF patients, which is not (yet) present early after AMI.\(^{24}\)

Finally, although groups of patients with different grades of diastolic dysfunction were studied, no significant differences in time to peak LV untwisting rate were noted. This finding is in line with previous experimental and clinical studies in which only the peak of untwisting rate but not the time to peak untwisting rate was affected by the grade of diastolic dysfunction.\(^{25\text{-}27}\)

As limitations, the acquisition of the LV apical short-axis images (highly dependent on the acoustic window) and through-plane motion, particularly at the basal level, could have affected the accuracy of the measurement of LV rotational parameters.
REFERENCES


(7) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pibarot P, Roman MJ, Seward J, Shaheen WS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.


Ross J, Jr. Is there a true increase in myocardial stiffness with acute ischemia? *Am J Cardiol* 1989; 63:87E-91E.

