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# LEFT VENTRICULAR ROTATIONAL MECHANICS DIFFER BETWEEN LIPEDEMA AND LYMPHEDEMA: INSIGHTS FROM THE THREE-DIMESIONAL SPECKLE TRACKING ECHOCARDIOGRAPHIC MAGYAR-PATH STUDY

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*ABSTRACT*

*The present study aimed to assess LV rotational mechanics by three-dimensional speckle-tracking echocardiography (3DSTE) in lipedema (n=25), lymphedema (n=26) patient groups with age- and gender-matched healthy controls (n=54). 3 lipedema and 4 lymphedema patients were excluded due to insufficient image quality for 3DSTE analysis. LV apical rotation (9.61 ± 4.25 degree vs. 6.40 ± 2.63 degree, p <0.05) and LV twist (13.83 ± 4.89 degree vs. 10.04 ± 3.56 degree, p <0.05) are impaired in lipedema patients as compared to matched controls; similar alterations in lymphedema were not found. Moreover, in some lipedema and lymphedema patients severe LV rotational abnormalities could be detected. Our results suggest that lipedema-associated impaired LV apical rotation and twist assessed by 3DSTE could be a novel differential diagnostic point between lipedema and lymphedema.*

**Keywords:** lipedema, leg lymphedema, left ventricular rotation, twist, three-dimensional, echocardiography

Lymphedema is tissue swelling resulting from excessive accumulation of lymphatic fluid in the interstitial compartment pathophysiologically based on impaired lymphatic conductancy due to mechanical or dynamic causes. Lymphedema is a chronic progressive disease with serious physical and psychosocial implications. If remaining untreated, connective tissue proliferation and enlargement can be observed and the characteristic pitting edema is converted into non-pitting swelling (1).

Lipedema is an often under-diagnosed masquerading disease of obesity or primary lymphedema where the underlying causes are barely understood. Clinically, it is a disproportional, bilateral, and symmetrical fat deposition developing downward from the hips with disease-free feet and occasional affected arms. It predominantly affects women with a high incidence of familial accumulation and usually appears by the third decade of life. Non-pitting edema is a striking hallmark as well as tenderness, spontaneous or minor trauma induced pain, and bruising. Various dietary approaches usually result in poor success rate, however, as lipedema is frequently combined with obesity. The most effective current treatment is liposuction although a pivotal differential diagnostic point needs to be resolved by ruling out primary lymphedema and genetically determined malformation of lymphatic vasculature and/or lymph nodes (2).

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In healthy subjects, the left ventricular (LV) apex rotates in counterclockwise direction while simultaneously the LV base rotates in a clockwise direction resulting in a towel-wringing motion-like LV twist (3,4). This finding is due to complex contraction of two orthogonally oriented muscular bands of the LV helical myocardial structure. In recent studies, adaptive changes in LV rotational mechanics have been detected in selected disorders (5). Theoretically, there could be a cardiovascular adaptation to lipedema/lymphedema-related hemodynamic consequences. However, limited information is available regarding these possible alterations and their clinical significance. Three-dimensional speckle-tracking echocardiography (3DSTE) is a novel, validated, non-invasive imaging method with the ability to assess LV rotational mechanics (6). Therefore, the present study aimed to assess 3DSTE-derived LV rotational mechanics both in lipedema and lymphedema patients and to compare these results to findings in age- and gender-matched healthy controls.

## *PATIENTS AND METHODS*

### *Patient Population*

The present study comprised 25 patients with stage 2 lipedema (mean age: 42.5 ± 12.2 years, BMI: 29.9 ± 2.79 kg/m$^2$, all females) and 26 subjects with stage 2 bilateral leg lymphedema (mean age: 46.5 ± 11.5 years, BMI: 27.64 ± 2.6 kg/m$^2$, 24 females and 2 males). While mean BMI values of the two patient groups differed significantly (P=0.0049), both are in the moderately overweight class (25 kg/m$^2$<BMI<29.9 kg/m$^2$). All lipedema patients were diagnosed based on typical clinical features. The causes of secondary leg lymphedema were malignant melanoma treatment (n=2), gynecological cancer treatment (n=6), bacterial cellulitis (n=2) and venous insufficiency (n=16). Nine lymphedema patients underwent bilateral leg lymphoscintigraphy, and each patient with suspected venous disease had color duplex ultrasound examination in addition to clinical inspection. Each patient was sent from the Phlebolymphology Unit of the Department of Dermatology and Allergology, University of Szeged for routine cardiac examination including two-dimensional Doppler echocardiography extended with 3DSTE. Insufficient image quality for 3DSTE was detected in 3 lipedema and 4 lymphedema patients. None of the patients had known cardiovascular symptoms or disease. Control group consisted of 54 age- and gender-matched healthy individuals (mean age: 40.7 ± 14.0 years, 3 males).

The present study complied with ethical guidelines set by the 1975 Declaration of Helsinki and it was approved by our institution's Human Research Committee. All patients provided informed consent. This study is part of the MAGYAR-Path Study (Motion Analysis of the heart and Great vessels bY three-dimension Al speckle-tRacking echocardiography in Pathological cases), which is aimed to examine the effect of different pathophysiological conditions on myocardial mechanics ('magyar' means 'hungarian' in Hungarian language). Controls were randomly selected from the MAGYAR-Healthy Study population (in this study hundreds of healthy subjects were examined on a voluntary basis to validate 3DSTE-derived parameters and to determine the normal values) (6).

### *2D Echocardiography*

Transthoracic 2D echocardiography and Doppler imaging were performed by experienced operators (PD, AK) using a Toshiba Artida™ imaging system (Toshiba Medical Systems, Tokyo, Japan) and a PST-30SBP (1-5 MHz) phased-array transducer. Complete 2D Doppler study was performed followed by left atrial- (LA) and LV chamber quantification of dimensions, volumes, and ejection fraction. Every measurement complied with the current clinical standards (7). A visually assessed scale was used to assess valvular regurgitations.

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### *3DSTE Measurements*

3DSTE measurements were carried out using the same Toshiba Artida™ echocardiography equipment (Toshiba Medical Systems, Tokyo, Japan) with PST-25SX matrix-array transducer (Toshiba Medical Systems, Tokyo, Japan) with 3DSTE capability. In our study we followed recent practices. Full volume 3D datasets were obtained by recording 6 wedge-shaped subvolumes through 6 heart cycles during a single breath-hold and constant RR intervals from an apical window. To improve spatial resolution and future border delineation, sector width was chosen to be as narrow as possible. 3D Wall Motion Tracking software (version 2.7, Toshiba Medical Systems, Tokyo, Japan) was used for offline image analysis. From the full volume, pyramidal datasets apical 4- and 2-chamber views were automatically selected along with 3 short-axis views (apex, midventricular level, base). Additional "guide planes" were used (provided by the software) to standardize the location of the 3 short-axis views across measurements.

### *LV Rotational and Twist Parameters*

- LV basal (defined as the degree of clockwise rotation of LV basal myocardial segments) and apical (defined as the degree of counter-clockwise rotation of LV apical myocardial segments).
- LV twist (defined as the net difference between LV basal and apical rotation).
- Time-to-peak of LV basal and apical rotation from the start of the heart cycle.
- Time-to-peak of LW twist from the start of the heart cycle.

Proper LV twist data could not be gathered in patients in whom apical and basal LV rotations were in the same direction (called as LV 'rigid body rotation' [LV-RBR]). In these cases LV apico-basal gradient was calculated instead: end-systolic LV apical minus LV basal rotation.

### *Statistical Analysis*

All statistical data are reported as mean ± standard deviation. Confidence interval was chosen to be 95% in every test performed, p values $< 0.05$ were considered statistically significant. Shapiro Wilks test was used to assess normal distribution of the datasets, Levenes's Test for Equality of Variances was used for testing the homogeneity of variances between groups. For datasets following normal distribution, Student's t-test was performed. Data not normally distributed datasets were tested with Mann-Whitney-Wilcoxon test. Fisher's Exact test was performed in case of categorical variables. RStudio was used for statistical analysis [RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA]. For offline data analysis, a commercial software package was used (MATLAB 8.6, The MathWorks Inc., Natick, MA, 2015).

## *RESULTS*

### *Patient Demographic Data*

The basic characteristics of the patients and control probands included in the study are summarized in *Table 1*. The groups of patients and healthy individuals were matched for mean age, gender, and the incidence of concomitant disorders although the size of the control subject group was notably higher than those of lipedema and lymphedema cohorts.

### *2D Echocardiographic Data*

Increased LA and LV dimensions could be demonstrated in lymphedema and lipedema patients without LV hypertrophy as compared to matched healthy controls. Systolic (ejection fraction) and diastolic (E/A) functions proved to be normal in both patient groups. Increased LA and LV volumetric data were more pronounced in lipedema patients as compared to lymphedema cases *(Table 2).* None of the subjects examined showed ≥ grade 2 mitral and tricuspid regurgitations.

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**TABLE 1**
**Baseline Demographic Data on Patients and Controls**

| | Controls (n=54) | Lymphedema patients (n=26) | Lipedema patients (n=25) |
|---|---|---|---|
| Age (years) | 40.7 ± 14.0 | 46.5 ± 11.5 | 42.5 ± 12.2 |
| Male gender (%) | 3 (6) | 2 (8) | 0 (0) |
| Hypertension (%) | 0 (0) | 1(4) | 0 (0) |
| Diabetes mellitus (%) | 0 (0) | 0 (0) | 0 (0) |
| Hyperlipidaemia (%) | 0 (0) | 1 (4) | 0 (0) |

**TABLE 2**
**Two-Dimensional Echocardiographic Data on Patients and Controls**

| | Controls (n=54) | Lymphedema patients (n=26) | Lipedema patients (n=25) |
|---|---|---|---|
| LA diameter (mm) | 35.4 ± 4.1 | 37.7 ± 4.3* | 39.9 ± 4.4*† |
| LV end-diastolic diameter (mm) | 46.9 ± 3.6 | 47.8 ± 4.0 | 50.3 ± 3.3*† |
| LV end-diastolic volume (ml) | 98.4 ± 21.5 | 109.3 ± 20.3* | 121.4 ± 18.3*† |
| LV end-systolic diameter (mm) | 36.0 ± 18.7 | 29.1 ± 3.5* | 31.4 ± 2.7† |
| LV end-systolic volume (ml) | 33.8 ± 8.1 | 33.7 ± 9.6 | 40.0 ± 8.2*† |
| Interventricular septum (mm) | 8.8 ± 1.5 | 8.0 ± 0.9* | 8.6 ± 0.9† |
| LV posterior wall (mm) | 9.0 ± 1.7 | 8.2 ± 1.1* | 8.6 ± 0.9 |
| LV ejection fraction (%) | 65.5 ± 4.2 | 69.7 ± 4.8* | 67.5 ± 3.5 |
| E (cm/s) | 78.3 ± 18.1 | 76.8 ± 15.1 | 87.3 ± 18.6*† |
| A (cm/s) | 65.5 ± 17.6 | 67.2 ± 14.6 | 78.1 ± 17.8*† |
| E/A | 1.29 ± 0.37 | 1.21 ± 0.36 | 1.18 ± 0.40 |

*p<0.05 vs. Controls; †p<0.05 vs. Lymphedema patients;
Abbreviations: LA = left atrial, LV = left ventricular, E and A = transmitral diastolic flow velocities

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*3DSTE-Derived LV Rotation and Twist*

Three lipedema and another three lymphedema patients showed significant LV rotational abnormalities; therefore, their data were managed separately. Among the remaining 19 lipedema patients and negative controls, only LV apical rotation and LV twist differed significantly. Similar differences in LV rotational mechanics between the remaining 19 lymphedema patients and controls could not be detected *(Table 3)*. Moreover, less than 1 degree LV basal rotation could be detected in 2 patients with lipedema (11%), in 2 other

**TABLE 3**
**Three-Dimensional Speckle-Tracking Echocardiography-Derived Parameters on Patients and Controls**

| | Controls (n=54) | Lymphedema patients without significant LV rotational abnormalities (n=19) | Lipedema patients without significant LV rotational abnormalities (n=19) |
|---|---|---|---|
| LV basal rotation deg) | -4.22 ± 2.17 | -3.17 ± 1.50 | -3.75 ± 2.01 |
| LV apical rotation (deg) | 9.61 ± 4.25 | 10.51 ± 4.20 | 6.40 ± 2.63*† |
| LV twist (deg) | 13.83 ±4.89 | 13.68 ± 4.69 | 10.04 ± 3.56*† |
| Time-to-peak LV basal rotation (msec) | 361 ± 105 | 350 ± 134 | 392 ± 167 |
| Time-to-peak LV apical rotation (msec) | 343 ± 105 | 330 ± 56 | 335 ± 86 |
| Time-to-peak LV twist (msec) | 354 ± 98 | 321 ± 70 | 308 ± 60 |

*p<0.05 vs. Controls; †p<0.05 vs. Lymphedema patients without significant LV rotational Abnormalities; Abbreviations: LV = left ventricular

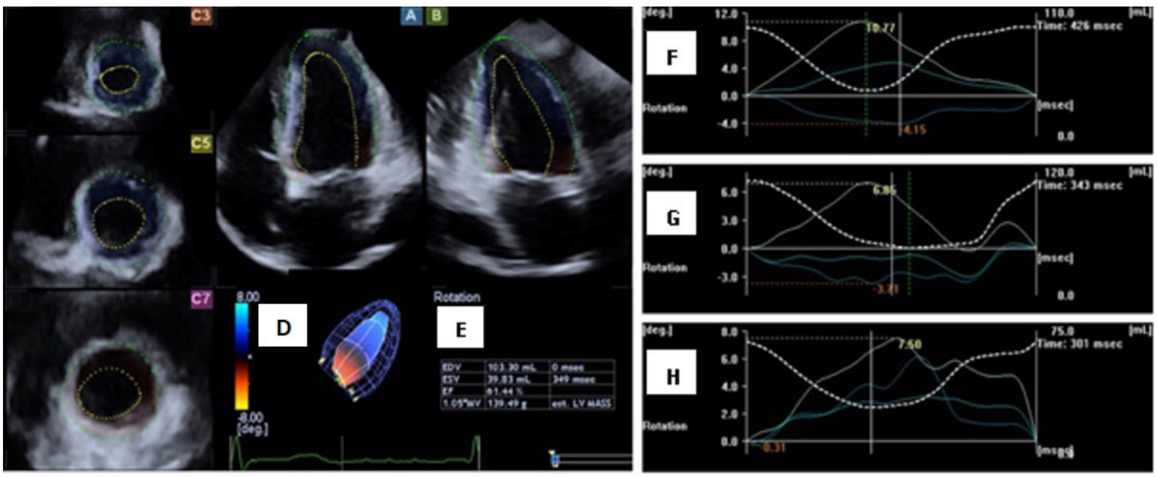


*Fig. 1. (left:) Apical 4-chamber (A) and 2-chamber (B) views and short-axis views (C3, C5, C7) at different levels of the left ventricle (LV) extracted from the three-dimensional (3D) echocardiographic dataset are presented. The 3D mesh model of the LV (D) and calculated LV volumetric data (E) are also shown. (right:) Images with normal LV rotational pattern with counterclockwise apical (white arrow) and clockwise basal rotations (dashed arrow)(F), apical LV hyporotation (G) and the near absence of LV twist called as LV rigid body rotation with LV apical and basal rotations in the same direction (H) are presented.*

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patients with lymphedema (11%), but in none of the controls. See *Fig. 1* for examples of images.

*Lipedema and Lymphedema Patients with Significant LV Rotational Abnormalities*

As aforementioned, 3 out of 22 lipedema patients had significant LV rotational abnormalities. One had minimal (less than 1 degree) clockwise apical (-0.97 degree) and basal (-0.40 degree) LV rotations demonstrating almost absolute absence of LV twist in this case (-0.57 degree). Another lipedema patient had a counter-clockwise apical (14.88 degree) and similarly directed basal (6.68 degree) LV rotations resulting in an 8.20 degree counter-clockwise LV apico-basal gradient. These results suggest the near absence of LV twist with reversed basal LV rotation and compensatory apical LV hyperrotation in this case. In the third lipedema case, reversed LV rotations (6.88 degree clockwise basal and 1.33 degree counterclockwise apical) could be detected.

Three out of 22 lymphedema patients had counter-clockwise apical (9.19 ± 2.69 degree) and basal (3.59 ± 1.24 degree) LV rotations with mean apico-basal LV gradient of 5.59 ± 2.72 degree suggesting normally directed apical but reversed basal LV rotations in these cases (LV-RBR). Extent of apical and basal LV rotations was normal in these cases.

*DISCUSSION*

To the best of the authors' knowledge this is the first study to demonstrate that LV apical rotation and LV twist are impaired in lipedema patients and that similar alterations in lymphedema patients could not be detected. Moreover, in some lipedema and lymphedema patients, severe LV rotational abnormalities could be demonstrated. These alterations were not related to any demographic or echocardiographic features.

There have been no clinical studies in which cardiac alterations could be demonstrated in lipedema/lymphedema patients without overt cardiac symptoms or disease evaluated by conventional echocardiographic methods. 3DSTE is a new non-invasive echocardiographic tool with the capability of assessing objective parameters featuring LV rotational and deformational mechanics (6,8,9).

Both diseases are conditions characterized by bulky lower limbs. Lipedema is associated with subcutaneous fatty edema without relevant intersitial fluid accumulation (10), while lymphedema results from excessive retention of lymphatic fluid in the interstitial compartment. There is no clinical information on the cardiovascular adaptations to these abnormalities. In a recent study, increased aortic stiffness could be detected in lipedema (11), which is known to be associated with LV rotational mechanics (12,13). The basis for our findings is unknown. However, increased fluid accumulation capacity of enlarged and highly vascularized lipedematous fatty tissue and interlobular septae verified by the complicated Streten test (14) might reduce peak torsion and peak apical rotation (15). The gross proportion of mesenchymal cells in lipedematous adipose tissue may be associated with an altered composition of heart tissue including higher number of non-myocytes with mesenchymal cells that could alter LV rotation (16). Moreover, subclinical epicardial fat deposition around the heart and its effect on LV rotational mechanics in lipedema patients could also not be excluded.

It can be hypothesized that subjects with significant LV rotational abnormalities are at the 'end-point' of the disease process. However, this conclusion needs to be reinforced by further research. Additional studies are warranted to confirm our findings and to assess whether LV rotational abnormalities can have a diagnostic role to differentiate between lipedema and lymphedema. However, the present data support 3DSTE-measured lipedema-associated LV rotational abnormalities as a novel differential diagnostic point for lymphedema beyond known parameters (14).

*Limitations of the Study*

This trial aimed to assess only LV rotational parameters although 3DSTE allows simultaneous assessment of LV volumetric data and

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strain parameters at the same time. Moreover, calculation of volumetric and functional features of the left and right atria is also possible by this methodology. However, 3DSTE has some technical limitations and it is important to note the inferior spatial and temporal resolution of this method compared to standard 2D echocardiography.

## *CONCLUSION*

Lipedema is associated with impaired LV apical rotation and twist as assessed by 3DSTE and similar abnormalities in lymphedema could not be detected. In selected cases with lipedema and/or lymphedema, severe LV rotational abnormalities was found.

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## *CONFLICT OF INTEREST AND DISCLOSURE*

All authors declare that no competing financial interests exist.

## *REFERENCES*

1. Lee, BB, PL Antignani, TA Baroncelli, et al: Iua-Isvi consensus for diagnosis guideline of chronic lymphedema of the limbs. Int. Angiol. 34 (2015), 311-332.
2. Lee, BB, M Andrade, PL Antignani, et al: Diagnosis and treatment of primary lymphedema. Consensus document of the International Union of Phlebology (IUP)-2013. International Union of Phlebology. Int. Angiol. 32 (2013), 541-574.
3. Nakatani, S: Left ventricular rotation and twist: why should we learn? J. Cardiovasc. Ultrasound 19 (2011), 1-6.
4. Nemes, A, A Kalapos, P Domsik, et al: Left ventricular rotation and twist of the heart. Clarification of some concepts. Orv. Hetil. 153 (2012), 1547-1551.
5. Phillips, AA, AT Cote, SS Bredin, et al: Heart disease and left ventricular rotation - a systematic review and quantitative summary. BMC Cardiovasc. Disord. 12 (2012), 46.
6. Kormányos, Á, P Domsik, A Kalapos, et al: Left ventricular twist is impaired in acromegaly: Insights from the three-dimensional speckle tracking echocardiographic MAGYAR-Path Study. J. Clin. Ultrasound 46 (2018), 122-128.
7. Lang, RM, LP Badano, V Mor-Avi, et al: Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J. Am. Soc. Echocardiogr. 28 (2015), 1-39. e14.
8. Nemes, A, A Kalapos, P Domsik, et al: Three-dimensional speckle-tracking echocardiography -- a further step in non-invasive three-dimensional cardiac imaging. Orv. Hetil. 153 (2012), 1570-1577.
9. Zhou, Z, M Ashraf, D Hu, et al: Three-dimensional speckle-tracking imaging for left ventricular rotation measurement: An in vitro validation study. J. Ultrasound Med. 29 (2010), 903-909.
10. Szél, E, L Kemény, G Groma, et al: Pathophysiological dilemmas of lipedema. Med. Hypotheses 83 (2014), 599-606.
11. Szolnoky, G, A Nemes, H Gavallér, et al: Lipedema is associated with increased aortic stiffness. Lymphology 45 (2012), 71-79.
12. Nemes, A, A Kalapos, P Domsik, et al: Correlations between echocardiographic aortic elastic properties and left ventricular rotation and twist – insights from the three-dimensional speckle-tracking echocardiographic MAGYAR-Healthy Study. Clin. Physiol. Funct. Imaging 33 (2013), 381-385.
13. Sulemane, S, VF Panoulas, K Konstantinou, et al: Left ventricular twist mechanics and its relation with aortic stiffness in chronic kidney disease patients without overt cardiovascular disease. Cardiovasc. Ultrasound 14 (2016), 10
14. Forner-Cordero, I, G Szolnoky, A Forner-Cordero, et al: Lipedema: An overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome - systematic review. Clin. Obes. 2 (2012), 86-95.
15. Bloechlinger, S, D Berger, J Bryner, et al: Left ventricular torsion abnormalities in septic shock and corrective effect of volume loading: A pilot study. Can. J. Cardiol. 29 (2013), 1665-1671.
16. Varga, I, J Kyselovic, P Galfiova, et al: The non-cardiomyocyte cells of the heart. Their possible roles in exercise-induced cardiac regeneration and remodeling. Adv. Exp. Med. Biol. 999 (2017), 117-136.

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