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The impact of lower body compression garment on left ventricular rotational mechanics in patients with lipedema—Insights from the three-dimensional speckle tracking echocardiographic MAGYAR-Path Study

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Summary

Lipedema is a lymphedema-masquerading symmetrical, bilateral and disproportional obesity. Its conservative maintenance treatment comprises the use of flat-knitted compression pantyhoses. Lipedema is known to be associated with left ventricular morphological and functional alterations. The present study aimed to assess the effects of graduated compression stockings on left ventricular (LV) rotational mechanics measured by three-dimensional speckle-tracking echocardiography (3DSTE) in lipedema patients. The present study comprised twenty lipedema patients (mean age: 45.8 ± 11.0 years, all females) undergoing 3DSTE who were also compared to 51 age- and gender-matched healthy controls (mean age: 39.8 ± 14.1 years, all females). 3DSTE analysis was performed at rest, and subsequent to 1 hour application of compression class 2 made-to-measure flat-knitted pantyhose. Six lipedema patients showed significant LV rotational abnormalities. Of the remaining fourteen lipedema patients LV basal rotation rotation showed significant reduction, while LV apical rotation showed significant increase with unchanged LV twist after a 60-minute use of compression garment. Significant changes in LV rotational mechanics could be detected among 14 women with lipedema after the use of compression garment however six probands have special LV rotational abnormalities at baseline and/or after compression.

KEYWORDS

compression, lipedema, left ventricular rotation, three dimensional speckle tracking echocardiography, twist

1 | INTRODUCTION

Lipedema is a poorly diagnosed but common feminine disorder of unknown pathomechanism[1-4] with a usual clinical manifestion consisting of bilateral symmetrical fat deposits developing downward from the hips. It is often mistaken for obesity and primary or secondary bilateral leg lymphedema.[4] Lipedema is characterized by cuffing sign (fat deposition spares feet), non-pitting oedema, easy bruising and pain and often remains refractory to various dietary restrictions.[1] From the cardiological point of view lipedema is known to be associated with higher aortic stiffness[5] and a recent clinical study showed a high incidence of altered left ventricular (LV) standard two-dimensional (2D) echocardiographic parameters (significantly larger dimensions, end-diastolic and end-systolic volumes, transmitral flow velocity) and also LV rotational changes (significantly lower LV apical rotation and twist) detected by three-dimensional speckle-tracking echocardiography (3DSTE).[6] Normally, opposite rotations of the LV apex and base result in LV twisting motion which supports ejection during systole.[7] LV twisting mechanics determine ventricular function, and having a close relationship with preload.[7] The morphological and functional changes in lipedema could be attributed to cardiac remodelling. This structural transformation usually includes LV dilation, hypertrophy and diastolic and systolic dysfunctions.[8,9] Increased preload and high vascular resistance with stiffer arteries result in elevated afterload.[8] In lipedema obesity is not a prerequisite for the development of high aortic stiffness, however, bulky limbs with robust fat deposition may account for arterial resistance.[5]

Lipedematous patients often undergo decongestive lymphatic therapy (DLT) and use compression class (ccl) 2 made-to-measure flat-knitted compression pantyhoses to preserve reduced limb size in the maintenance phase however the most effective treatment is still the liposuction.[1,10] Pantyhose is an ideal compression garment because it covers all affected regions and the flat-knitted material fits best to irregularly shaped legs.[1,11] Based on the prior finding that patients with lipedema tend to have altered LV rotational properties we wondered if the use of medical compression stockings (MCSs) could somehow affect LV rotational mechanics in addition to controlling edema.

To investigate this issue, 3DSTE-derived LV apical and basal rotations were assessed before and 1 hour after the use of MCS in female patients with lipedema.

What is already known about this subject

- Lipedema is a bilateral, symmetrical and disproportional adipose tissue enlargement of the lower and quite frequently the upper extremities
- Lipedema is associated with vascular alterations (decreased capillary resistance, increased aortic stiffness index)
- From the cardiological point of view lipedema is associated with increased left atrial (LA) and ventricular (LV) volumes, mitral annulus enlargement and functional impairment and also with reduced LV apical rotation and twist which might be due to LV remodelling

What this study adds

- Lower body compression strongly influences lipedema-related LV remodelling
- Basal LV rotation decreases while apical LV rotation increases with the use of compression stockings with unchanged LV twist

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-three female patients with stage 2 lipedema were initially enrolled. Three women had to be excluded due to insufficient image quality so that there were a total of 20 patients with lipedema that were evaluated with age (mean ± SD) of 45.8 ± 11.0 years. Typical clinical features (stove pipe legs, non-pitting edema, cuffing sign, spontaneous or minor trauma induced pain perception, easy bruising) were used to define lipedema in all patients at the Phlebolymphology Unit of the Department of Dermatology and Allergology, University of Szeged for routine cardiological examination. Their cardiac parameters were subsequently compared to 51 healthy female controls (39.8 ± 14.1 years). None of the lipedema patients and controls had other known disease or cardiovascular symptoms.

The present study serves as part of the MAGYAR-Path Study (Motion Analysis of the heart and Great vessels bY three-dimensionAl speckle-tRacking echocardiography in Pathological cases), which aimed to evaluate the effect of different pathophysiological conditions on LV myocardial mechanics among others ("magyar" means 'Hungarian' in Hungarian language).[12] All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional research committee (Albert Szent-Györgyi Clinical Centre, University of Szeged, 71/2011) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

2.2 | 2D echocardiography

Routine transthoracic 2D echo-Doppler study was performed by experienced operators (PD, AK) in all lipedema patients before and 1 hour after the use of MCSs with commercially available echocardiography equipment (Toshiba Artida, Toshiba Medical Systems, Tokyo, Japan) using a 1-5 MHz PST-30SBP phased-array transducer. Left atrial (LA) and LV internal dimensions were measured by M-mode echocardiography and LV ejection fraction was calculated in accordance with the guideline instructions.[13] Valvular regurgitations were assessed visually.

2.3 | Three-dimensional speckle-tracking echocardiographic measurements

3DSTE imaging was performed in all patients at the end of the 2D examination with the same Toshiba Artida ultrasound system (Toshiba Medical Systems, Tokyo, Japan) using a PST-25SX matrix-array probe with 3DSTE capability.[14] During 3DSTE ECG-gated full volume 3D dataset was acquired during 6 cardiac cycles. LV images were obtained from the apical 4-chamber (AP4CH) view during a brief expiratory breath hold and constant RR intervals on ECG (Figure 1). LV rotational and twist parameters were measured offline with the commercially

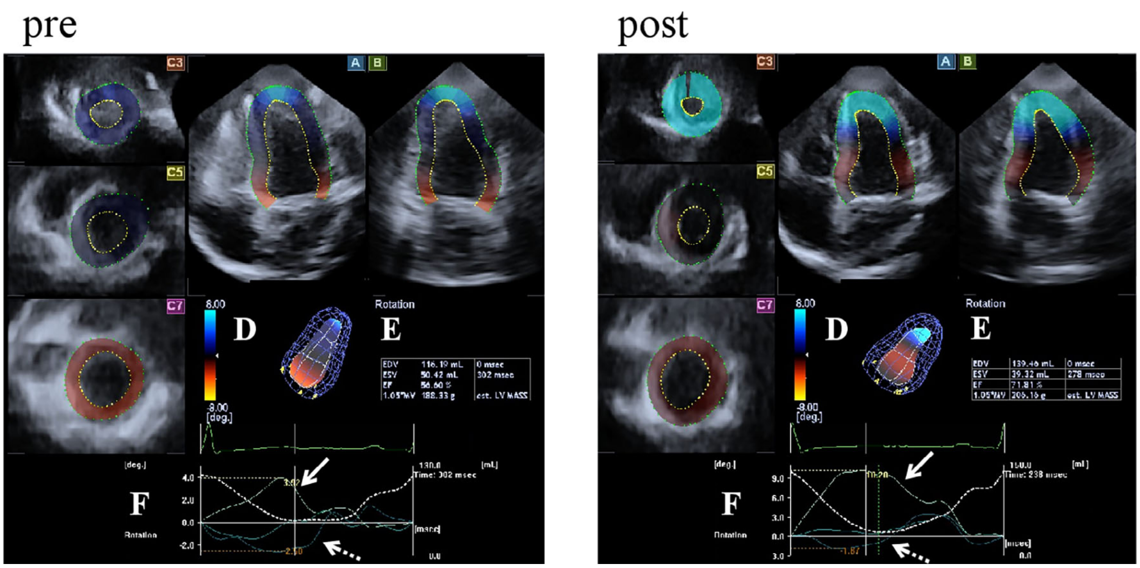

FIGURE 1 Three-dimensional (3D) speckle-tracking echocardiographic images of a patients with lipedema at rest (pre) and following 1 hour use of medical compressions stocking (post). Apical four chamber (A) and two-chamber views (B), short-axis views at different levels of the left ventricle (LV) (C3, C5, C7), 3D cast of the LV (D), LV volumetric data (E) and LV apical (white arrow) and basal (dashed arrow) rotations are presented. LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LV MASS, left ventricular mass

available 3D Wall Motion Tracking software (version 2.7, Toshiba Medical Systems, Tokyo, Japan). From the 3D datasets, apical 2-chamber (AP2CH) and 4-chamber (AP4CH) views were automatically selected by the software together with 3 LV short-axis views at apical, mid-ventricular and basal levels. Following automatic selection of these views at end-diastole by the software, LV endocardial border was traced by setting several reference points at the edges of the mitral valve and at the apex on AP2CH and AP4CH views. LV endocardial surface was then tracked and automatically reconstructed through the heart cycle. Using the virtual 3D LV casts the following LV rotational and twist parameters were calculated over LV volumetric data[14,15]:

- LV basal rotation, defined as the degree of (normally) clockwise rotation of LV basal myocardial segments,
- LV apical rotation, defined as the degree of (normally) counter-clockwise rotation of LV apical myocardial segments,
- LV twist, defined as the net difference between LV basal and apical rotations.

There is a clinical situation when both LV basal and apical rotations are in the same direction called as LV "rigid body rotation" (LV-RBR).[16] In these cases, due to the absence of LV twist data could not be measured, therefore, LV apico-basal rotational gradient was calculated instead of using the following equation: end-systolic LV apical rotation minus end-systolic LV basal rotation.

2.4 | Experimental procedure

Patients were first subjected to 2D echocardiography and consecutively 3DSTE at baseline. After completing echocardiographic measurements they put on their MCSs and wore them for 60 minutes. The repeated echocardiographic procedure was scheduled exactly 1 hour after the beginning of MCS application and this measurement was carried out while patients wore their garments. Patients were not allowed to do any kind of physical exercise nor allowed to consume any meal or liquid until the second echocardiographic procedure had been completed. During the 60-minute stocking application period they could sit with straight legs or stand. Room temperature and relative humidity were stable at 21°C to 22°C and 45% to 50%, respectively. Each garment was used once and our physiotherapist colleagues assisted donning and doffing if needed. Participants were informed precisely about the study protocol right at the onset.

2.5 | Experimental compression garments

Bauerfeind VenoTrain CuraFlow flat-knitted ccl 2 (23-32 mmHg) (Bauerfeind, Zeulenroda, Germany) pantyhose manufactured of 73% polyamid and 27% elasthane and in black colour was used. Measurement (between skin and compression material) using Picopress device (Microlab Elettronica, Nicolò, Italy)[17] at B1 point[18] in standing position revealed a mean pressure of 22.75 ± 3.8 mmHg in the patient cohort.

2.6 | Statistical analysis

Continuous data were expressed as mean ± SD, categorical data were presented in frequencies and percentage. All tests were two-sided and a *P* value below .05 was considered statistically significant. Normally distributed datasets verified by Kolmogorov-Smirnov test were analysed by Student's *t* test, while non-normally distributed datasets were tested with Mann-Whitney-Wilcoxon test. In case of categorical variables, Fisher's exact test was administered. Intraobserver reproducibility of measurements of LV apical and basal rotational parameters was tested in selected lipedema patients with correlation coefficients. RStudio was used for statistical analysis (RStudio Team [2015] RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). MATLAB version 8.6 software package was used for data analysis (The MathWorks Inc., Natick, MA, 2015). GPower 3.1.9 Software (Heinrich-Heine Universität, Düsseldorf, Germany) was applied for power calculation: in the presence of effect size: 0.8, alpha: 0.05, power: 0.8 the minimum group size is n = 12.

3 | RESULTS

3.1 | Demographic data

Lipedema patients did not significantly differ from the healthy controls in age (45.8 ± 11.0 vs 39.8 ± 14.1 years, p = ns) or in the incidence of hypertension, diabetes or hyperlipidemia (there was a total absence of these disorders).

3.2 | Baseline 2D echocardiographic data

Similarly to our earlier elaborated study baseline 2D echocardiographic data showed significantly greater values for LA diameter (40.1 ± 3.6 vs 35.2 ± 4.1 mm, $P < .05$), LV end-diastolic diameter (50.7 ± 3.2 vs 46.6 ± 3.5 mm, $P < .05$) and end-diastolic (122.8 ± 17.1 vs 96.8 ± 20.8 mL, $P < .05$) and end-systolic (40.5 ± 7.7 vs 33.3 ± 8.0 mL, $P < .05$) volumes of lipedema patients compared to those of control probands.[6]

3.3 | Compression garment-induced changes of 3DSTE-derived LV rotation and twist

Six lipedema patients had significant LV rotational abnormalities, therefore, their data were assessed separately. Of the remaining 14 lipedema persons LV basal rotation showed significant reduction, while LV apical rotation represented significant increase with unchanged LV twist 1 hour after the use of MCS (Table 1).

3.4 | Compression garment-induced LV volumetric changes measured with 3DSTE

Fourteen lipedema probands with normally directed LV rotational patterns showed increasing end-diastolic and end-systolic volumes as well as ejection fractions after the use of compression hosiery, however, these changes did not reach the level of significance (Table 2).

TABLE 1 Changes of LV rotational parameters 1 hour after the use of stocking in 14 patients with lipedema with normally directed LV rotations (degrees are measured at end-systole where negative sign means clockwise, positive sign denotes counterclockwise rotation)

	Controls (n = 51)	Lipedema patients at rest (n = 14)	Lipedema patients 1 hour after the use of MCS (n = 14)
basal LV rotation (degree)	−4.18 ± 2.14	−4.45 ± 1.65	−2.79 ± 1.84*
Apical LV rotation (degree)	9.69 ± 4.29	6.68 ± 2.67	9.08 ± 3.14*
LV twist (degree)	13.87 ± 5.03	11.14 ± 3.32	11.87 ± 3.42

Abbreviations: LV, left ventricular; MCS, medical compression stocking.
*$P < .05$ vs Lipedema patients at rest.

3.5 | Lipedema patients with significant LV rotational abnormalities

The following cases showed interesting changes after the use of stockings so they were managed separately (Table 3):

- In one case basal and apical LV rotations were less than 1° at rest demonstrating almost the absence of LV twist. LV rotational mechanics of this patient did not change significantly after 1 hour use of stocking.
- There were two cases with basal LV rotations of less than 1° suggesting the absence of basal LV rotation with preserved apical LV rotation. In the first case both normally directed basal and apical LV rotations increased after the application of MCS. In the other case basal LV rotation did not change, while apical LV rotation decreased.
- There were another two cases where normally directed resting LV rotational mechanics turned into LV-RBR after 60-minutes wear of MCS.
- Finally, there was a single case showing LV-RBR at rest which remained unchanged after the use of MCS.

3.6 | Intra-observer reproducibility

In a separate cohort comprising 10 lipedema patients without rotational abnormalities prior to the application of compression hosiery, intra-observer reproducibility was assessed from two subsequent measurements of the same observer for LV basal and apical rotations: LV basal rotation variability: 0.18 ± 0.09° (correlation coefficient: 0.96; $P < .0001$), LV apical rotation variability: 0.21 ± 0.15° (correlation coefficient: 0.96; $P < .0001$).

4 | DISCUSSION

Lipedema is a massively underdiagnosed, obesity and lymphedema masquerading disease which predominantly affects women usually from the third decade of their lifespan.[1-4] Earlier studies demonstrated that increased aortic stiffness,[5] and common LV rotational abnormalities (increased LA and LV dimensions, higher end-diastolic and end-systolic volumes, lower LV apical rotation and twist) are the hallmarks of the disease.[6]

LV rotational mechanics is a pivotal component of the LV myocardial function.[14,15,19,20] In normal clinical circumstances the LV base rotates clockwise, while the LV apex rotates in the opposite direction. The complex contraction of two orthogonally oriented muscular bands of the LV helical myocardial structure creates this kind of motion. The net difference between these oppositely directed rotations is called LV twist.[19-21] This towel-wringing-like movement is responsible for ~40% of systolic pumping function.[20] LV twist is impaired is several pathologic conditions[22] and its absence (LV-RBR) can be detected in large percent of patients with noncompaction cardiomyopathy[16] or cardiac amyloidosis.[23]

We have recently found altered 2D echocardiography-related LV morphological parameters (significantly higher LA and LV dimensions, end-diastolic and end-systolic volumes, transmitral flow velocities) together with significantly impaired LV apical rotation and LV twist detected by 3DSTE in lipedema patients as compared to matched controls.[6] The suspected culprit accounting for these alterations in lipedema may refer to LV remodelling for which increased aortic stiffness may be, in part, responsible. Myocardial remodelling has been reported to occur in several disorders like dilated cardiomyopathy[9] and obesity.[8] Remodelling usually comprises LV hypertrophy, dilation and diastolic as well as systolic functional changes. Alternatively, the heart of lipedema patients may possess different myocardial structure, function or less likely alternative composition. The true cause(s) of morphological and functional changes in lipedema has remained unknown and autopsy studies regarding cardiac histology focusing especially on myocardial fibres including fibroblasts, extracellular matrix besides cardiomyofibroblasts may presumably also be helpful. In the absence of this insightful knowledge any approach is still a theoretical notion.

Regardless whether lipedema patients undergo DLT or liposuction, the maintenance treatment complies with the wear of MCSs which are known to enhance venous return and lymph flow and are found to aid in orthostatic intolerance cause by various factors.[24,25] Cardiovascular implications of different types of compression garments are poorly investigated however the longest garments, the pantyhoses proved to have measurable cardiovascular effects in head-up tilt tests.[26] Since lipedematous legs often have shape irregularities and contour deformities they require custom-made and flat-knitted pantyhoses in order to fully cover involved regions and to avoid strangulations caused by round-knitted material. The most commonly prescribed range of compression is 20 to 30 mmHg which refers to ccl2.[24,25]

In patients without significant LV rotational abnormalities the application of lower body compression with flat-knitted pantyhose led to a significant decrease in basal LV rotation whereas apical LV rotation rose nearly to the same degree resulting in the persistence of LV twist at the same value. Tendentiously higher end-diastolic and end-systolic LV volumes were detectable along with an augmentation of LV ejection fraction after 60-minutes wearing of compression

TABLE 2 Changes of left ventricular end-diastolic and end-systolic volumes and ejection fractions before and 1 hour after the use of compression garment in 14 lipedema probands with normally directed left ventricular rotations measured by 3DSTE

	Controls	Lipedema patients at rest	Lipedema patients 1 hour after the use of MCS
LV end-diastolic volume (mL)	72.1 ± 12.2	87.0 ± 15.6	91.8 ± 16.9
LV end-systolic volume (mL)	31.0 ± 5.5	33.0 ± 5.8	36.0 ± 7.9
LV ejection fraction (%)	57.2 ± 5.4	60.0 ± 4.7	62.3 ± 4.2

Abbreviations: LV, left ventricular; MCS, medical compression stocking.

TABLE 3 Changes in LV rotational mechanics in lipedema patients with pathologic features

	Basal LV rotation at rest (degree)	Basal LV rotation 1 hour use of stocking (degree)	Apical LV rotation at rest (degree)	Apical LV rotation 1 hour use of stocking (degree)	LV twist at rest (degree)	LV twist 1 hour use of stocking (degree)
Case without basal and apical LV rotation (<1°) at rest						
Case 1	−0.40	1.93	−0.97	0.45	0.57	1.48
Cases without basal LV rotation (<1°) and normal apical LV rotation						
Case 2	0.00	−5.82	6.87	7.83	6.87	13.66
Case 3	−0.24	−0.13	8.99	5.36	9.23	5.49
Cases with normal resting LV rotations but LV-RBR 1 hour after						
Case 4	−1.87	4.48	4.01	8.51	5.88	4.03
Case 5	−3.62	4.39	7.58	10.00	11.20	5.61
Case with LV-RBR at rest which remained unchanged 1 hour after						
Case 6	6.68	6.16	14.88	16.98	8.20	10.82

hosieries. The countercurrent change of LV basal and apical rotations with unchanged LV twist in part gives rise to an adaptational mechanism on this lipedema-related LV volume changes, which may comprise a quasi neutralization of fluid shift caused by lower body compression along stimulating venous return and consequently increasing cardiac preload.[27] As models for fluid load in standard situations normal saline infusion increases end-diastolic and end-systolic volumes with a stable ejection fraction which are consistent with rise in preload.[28,29] Volume load is associated with stronger apical LV rotation leaving basal LV rotation unchanged.[29]

Nevertheless we cannot rule out the additional peripheral arterial resistance modifying effect of external compression. Fujii et al. showed that wearing graduated ccl 2 compression pantyhoses augmented cutaneous vasodilation under distinct circumstances.[30] This intensified vasodilation seems likely a consequence of compression garment-induced modulation of baroreceptor loading status brought about by the enhanced venous flow.[30] Besides the aforementioned phenomenon higher arterial carbone-dioxide pressure associated with the application of compression pantyhose may in part explain skin vasodilation.[30] In other serial of experiments Lee et al. measured hemodynamic responses and large vessel diameters subsequent to the application of below knee and below groin compression stocking of various compression pressures.[31] Probands were subjected to magnetic resonance imaging so as to assess cross sectional areas of muscles, adipose tissue and large vessels besides common cardiovascular examinations. Calf deep arteries and surprisingly deep veins appeared to have significantly higher diameters compared to those of baseline under the application of pressure within the range of ccl 2.[31] This pressure range generating less peripheral resistance eased LV function thus higher stroke volume and cardiac output were detected.[31] The application of compression garment in lipedema could also elicit a reduction in peripheral arterial resistance similarly to these recent clinical experiments among healthy individuals.

The given results demonstrated that LV in lipedema without major rotational abnormalities is capable of the induction of change in myocardial function with good contractility and deformation capacity. The most plausible explanation of these LV rotational changes in lipedema may reside in the plasticity of LV myocardium which enables significant and opposite rotational changes without a major impact on net twist value highlighting sufficient contractility.

4.1 | Limitation section

Only LV rotational parameters were assessed during 3DSTE, although this methodology allows simultaneous assessment of LV volumetric and strain data at the same time from the same dataset.[14] Two- and three dimensional speckle tracking echocardiography enables assessment of LV deformation and geometrical changes. Radial, circumferential and longitudinal strains are the three measurable natural deformations that give essential additional information of true myocardial function.[32] LV volumes in lipedema patients were somewhat different found in other studies, which in part could be explained by low number of patients, significant LV rotational abnormalities, the method used and technical reasons.[6]

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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