

Bioelectrical Impedance Analysis of Water Reduction in Lower-Limb Lymphedema by Lymphaticovenular Anastomosis

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Abstract

Background Although lymphedema is fundamentally abnormal accumulation of excess water in the extracellular space, previous studies have evaluated the efficacy of physiological bypass surgery (lymphaticovenular anastomosis [LVA]) for lymphedema without measuring water volume. This study clarified the water reductive effect of LVA using bioelectrical impedance analysis (BIA).

Methods The efficacy of LVA for unilateral lower-limb lymphedema was evaluated using BIA in a retrospective cohort. The water volume of affected and unaffected legs was measured using multifrequency BIA before and after LVA. Preoperative measurements were undertaken after compression therapy for at least 3 months. The follow-up period after LVA was a minimum of 6 months.

Results Thirty consecutive patients with unilateral lower-limb lymphedema were enrolled. The mean water volume reduction of the affected leg by LVA (Δ LBW) was 0.86 L (standard deviation [SD]: 0.86, median: 0.65) with a mean number of 3.3 anastomoses (SD: 1.7). The mean reduction rate of edema was 45.1% (SD: 36.3). Multiple linear regression analysis revealed water volume difference between the affected and unaffected legs before LVA (excess LBW) as the strongest predictor of Δ LBW ($R^2 = 0.759$, $p < 0.01$; $\beta = 0.500$, $p < 0.01$).

Conclusion The LVA reduces the volume of accumulated body water in lower-limb lymphedema. As excess LBW most strongly predicted the amount of water volume reduction by LVA, body water volume measurement by BIA before LVA might identify patients with low excess LBW not expected to benefit from LVA, regardless of apparent differences in limb circumference.

Keywords

- ▶ lymphedema
- ▶ lymphaticovenular anastomosis
- ▶ bioelectrical impedance analysis

The fundamental cause of lymphedema is the abnormal accumulation of excess water, filtered or diffused plasma proteins, extravascular blood cells, and parenchymal or stromal cell products in the extracellular space.¹ Lymphaticovenular anastomosis (LVA) is a physiological bypass surgery that redirects excessive lymph fluid from the

lymphedematous limb into the venous system by anastomosing lymphatic vessels to subdermal venules.^{2,3} Numerous investigations including two systematic meta-analyses have evaluated the efficacy of LVA for the treatment of compression-refractory lymphedema and demonstrated promising overall results.^{4–28} The majority of those studies,

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however, used limb circumference or outer volume of the limb as an indicator of the efficacy of LVA despite water accumulation being the origin of lymphedema. Limb circumference and outer volume techniques are influenced not only by body water volume but also by bone, muscle, and adipose tissues, which can confound assessment of the net water reductive effect of LVA. Evaluation of body water mobilization using bioelectrical impedance analysis (BIA) has already been reported in complex decongestive physiotherapy for lower-limb lymphedema,²⁹ but little is known on the water changes induced by LVA using BIA. This study aimed to clarify the water reductive effect of LVA on unilateral lower-limb lymphedema by means of BIA.

Patients and Methods

Patients

The efficacy of LVA for unilateral lower-limb lymphedema was evaluated objectively using BIA in the present retrospective study. Patient data were collected from a medical chart database. The inclusion criteria were unilateral lower-limb lymphedema, compression therapy for at least 3 months, LVA at our hospital at least once between April 2013 and May 2017, and a minimum of 6 months of follow-up. Subjects with symptoms of lower-limb edema after cancer treatment or trauma were diagnosed as having secondary lymphedema, while those with other causes of edema were judged as having primary lymphedema using lymphoscintigraphy or indocyanine green (ICG) lymphography according to previous reports.^{24,30} Lymphedema was graded according to International Society of Lymphology (ISL) lymphedema staging.¹ Patients in whom both legs were classified as ISL stage I or more were considered as cases of bilateral lower-limb lymphedema and excluded. Indications for LVA included compression-refractory edema, an episode of cellulitis, or patient desire to halt compression regardless of the cause of lymphedema. For subjects undergoing multiple LVA procedures, the follow-up period was defined as the time from the most recent LVA. Patient characteristics, limb circumference measurements, and body water analysis by BIA were recorded prior to LVA subsequent to compression therapy for at least 3 months. Limb circumference measurements were taken at the foot dorsum, ankle, 10 cm below the inferior margin of the patella, superior margin of the patella, and 10 cm above the superior margin of the patella, the sum of which being defined as Σ Circumference. Lower extremity lymphedema (LEL) index values were calculated from the circumferences according to a published formula.³¹ Limb circumference values and body water analysis were later recorded at least 6 months following LVA. This study was conducted in accordance with the declaration of Helsinki, and the protocol was approved by the ethics committee of School of Medicine, Shinshu University (approval number: 3965).

Bioelectrical Impedance Analysis Assessment

To evaluate the severity of lymphedema and the water volume reductive effect of LVA, body water composition

was assessed by BIA using the InBody S10 (InBody Co., Ltd., Seoul, Korea), multifrequency bioelectrical impedance analyzer. Electrodes were placed at eight precise tactile points on the body and a total of 30 impedance measurements were obtained for six different frequencies (1, 5, 50, 250, 500, and 1,000 kHz) at the following five segments of the body: right and left arms, trunk, and right and left legs. The measurements included intracellular water (ICW), extracellular water (ECW), total body water (TBW; the sum of ICW and ECW), and ratio of ECW to TBW (%ECW) at each of the five segments of the body without empirical estimations using age, gender, weight, or body type. The TBW of one leg was defined as leg body water (LBW). The preoperative water volume difference between affected and unaffected legs was defined as excess LBW and the water volume reduction of the affected leg by LVA was defined as Δ LBW.

Lymphaticovenular Anastomosis Procedure

Surgery for LVA was performed under general anesthesia except for one patient with heart disease. ICG lymphography and vein visualization using an infrared vein finding technology device (Veinsite; VueTek Scientific, LLC, Gray) were undertaken to identify lymphatic vessels and veins prior to incisions. When an intersecting lymphatic vessel and vein were found, the crossing point was cut after subdermal injection of 5% patent blue dye 10 cm distal to the incision site. LVAs were performed through 2 to 5 cm skin incisions in the lymphedematous leg using a surgical microscope (Leica M525 OH4). The outside diameter of the lymphatic vessels was measured using a crack scale (Shinwa Rules Co., Ltd., Niigata, Japan) and recorded before anastomosis. The lymphatic vessel and the vein were anastomosed using 11–0 microsutures in either a side-to-end or an end-to-end fashion, with preference to the former. Patency of the newly formed anastomosis was confirmed intraoperatively by ICG lymphography under a microscope. Patients were given an intravenous prophylactic antibiotic intraoperatively and once postoperatively.

Postoperative Management

A foot compression device was used except when walking until discharge within 7 days of LVA. Walking around was not restricted during hospitalization. Patients resumed wearing elastic stockings from day 1 after the operation. Although most subjects wore the same stockings as they did preoperatively, some were able to decrease compression pressure or stop altogether due to edema improvement.

Patients with insufficient LVA results, such as edema progression, an episode of cellulitis, or limited reduction of water volume or limb circumference, or who requested additional reduction, underwent another LVA procedure. The need for additional LVA was judged at least 6 months after the previous one.

Statistical Analysis

Descriptive statistics for continuous variables are presented as the mean (standard deviation [SD], range). Paired *t*-tests were used to analyze differences between preoperative and

postoperative quantitative measurements. Pearson's correlation analysis was employed to calculate the correlation between Δ LBW and preoperative and intraoperative variables. Paired *t*-test and Pearson's correlation analysis were two tailed. Kolmogorov–Smirnov's test was used for statistical testing of normality before paired *t*-test and Pearson's correlation analysis. Stepwise multiple linear regression analysis was adopted to predict Δ LBW. A *p*-value of < 0.05 was considered significant. All statistical analyses were conducted using SPSS PASW Statistics version 23.0 software (IBM Inc., Armonk).

Results

Patient Characteristics

The cohort's details are summarized in ▶Table 1. Thirty consecutive patients (26 females and 4 males) with unilat-

Table 1 Patient characteristics

Variable	N (%)
Patient number	30
Sex	
Female	26/30 (86.7%)
Male	4/30 (13.3%)
Age (y, mean [SD, range])	60.1 (9.1, 43–74)
Height (cm, mean [SD, range])	155.9 (7.1, 137.6–171.2)
Body weight (kg, mean [SD, range])	56.0 (8.5, 39.9–81.0)
BMI (kg/m ² , mean [SD, range])	23.1 (3.5, 17.5–32.4)
Etiology	
Primary	2/30 (6.7%)
Secondary	28/30 (93.3%)
Laterality	
Left	16/30 (53.3%)
Right	14/30 (46.7%)
ISL stage	
I	3/30 (10.0%)
Early II	16/30 (53.3%)
Late II	11/30 (36.7%)
III	0
Number of operations (mean [SD, range])	1.6 (0.7, 1–3)
Number of anastomoses (mean [SD, range])	3.3 (1.7, 1–7)
Diameter of largest lymphatic vessel (mm, mean [SD, range])	0.79 (0.24, 0.4–1.4)
Follow-up period (mo, mean [SD, range])	12.2 (6.5, 6–31)

Abbreviations: BMI, body mass index; ISL, International Society of Lymphology; SD, standard deviation.

Note: BMI = weight (kg)/(height [m])².

eral lower-limb lymphedema were eligible for inclusion. No patient received other surgical treatments for lymphedema within 6 months after LVA. Mean age was 60.1 years at the first LVA operation. Mean height was 155.9 cm, mean body weight was 56.0 kg, and mean body mass index was 23.1 kg/m² before LVA. There were 2 cases of primary lymphedema and 28 cases of secondary lymphedema, of which 27 were caused by cancer treatment and 1 was due to a catheter-related scar in the inguinal region. Sixteen patients had lymphedema in their left leg and 14 in their right leg. Three cases were classified as ISL stage I, 16 cases as early stage II, and 11 cases as late stage II. There were no cases of ISL stage III. No patients were diagnosed as having varicose veins or deep venous thrombosis in their legs before LVA.

The mean number of operations performed was 1.6. Sixteen patients received one LVA operation, 10 patients received two LVA operations, and 4 patients received three LVA operations. The mean number of anastomoses created per patient was 3.3. The mean diameter of the largest lymphatic vessel anastomosed in each case was 0.79 mm. The mean follow-up period was 12.2 months.

Mean body weight decreased from 56.0 kg (SD: 8.5) before LVA to 55.4 kg (SD: 8.3) afterward, although the difference was not significant (*p* = 0.20). After the operation, most patients wore stocking as they did preoperatively, with two patients (6.7% [2/30]) able to halt compression afterward.

Body Water Volume Measurements

Mean Σ Circumference of the affected leg was 171.3 cm (SD: 17.3) before LVA and 166.3 cm (SD: 16.1) afterward (*p* < 0.01, 95% confidence interval [CI]: 1.9–7.9). Mean LEL index of the affected leg was 276.8 (SD: 37.2) before LVA and 264.2 (SD: 30.7) afterward (*p* < 0.05, 95% CI: 2.2–23.0) (▶Fig. 1A). Mean LBW of the affected leg was 5.89 L (SD: 1.25) before LVA and 5.03 L (SD: 0.84) afterward (*p* < 0.01, 95% CI: 0.54–1.18) (▶Fig. 1B). All three of these values had decreased significantly after LVA. Mean Δ LBW was 0.86 L (SD: 0.86, median: 0.65) as a cumulative value after one to three LVA operations (▶Fig. 1C). The LBW of the affected leg increased in two patients (6.7% [2/30]).

Δ LBW and the reduction of Σ Circumference by LVA ($\Delta\Sigma$ Circumference) were significantly correlated (*r* = 0.61, *p* < 0.01). Simple linear regression to predict Δ LBW based on $\Delta\Sigma$ Circumference revealed a significant regression equation: predicted Δ LBW (L) = 0.544 + 0.0647 × $\Delta\Sigma$ Circumference (cm) (F [1, 28] = 16.372, *p* < 0.01, *R*² = 0.369) (▶Table 2, ▶Fig. 1D). This predictive formula showed that LBW decreased by 867 mL when Σ Circumference decreased by 5 cm, for example, a 1-cm reduction at each of the five measurement sites.

Mean excess LBW was 1.28 L (SD: 0.85) before LVA and 0.60 L (SD: 0.42) afterward, and the difference between them was significant (*p* < 0.01, 95% CI: 0.39–0.96) (▶Fig. 1B). The mean reduction rate of edema, calculated as (1 – [excess LBW_{after LVA}/excess LBW_{before LVA}]) × 100 was 45.1% (SD: 36.3). When the LBW of the affected leg was less than the LBW of the unaffected leg after LVA, a 100% reduction rate was assigned.

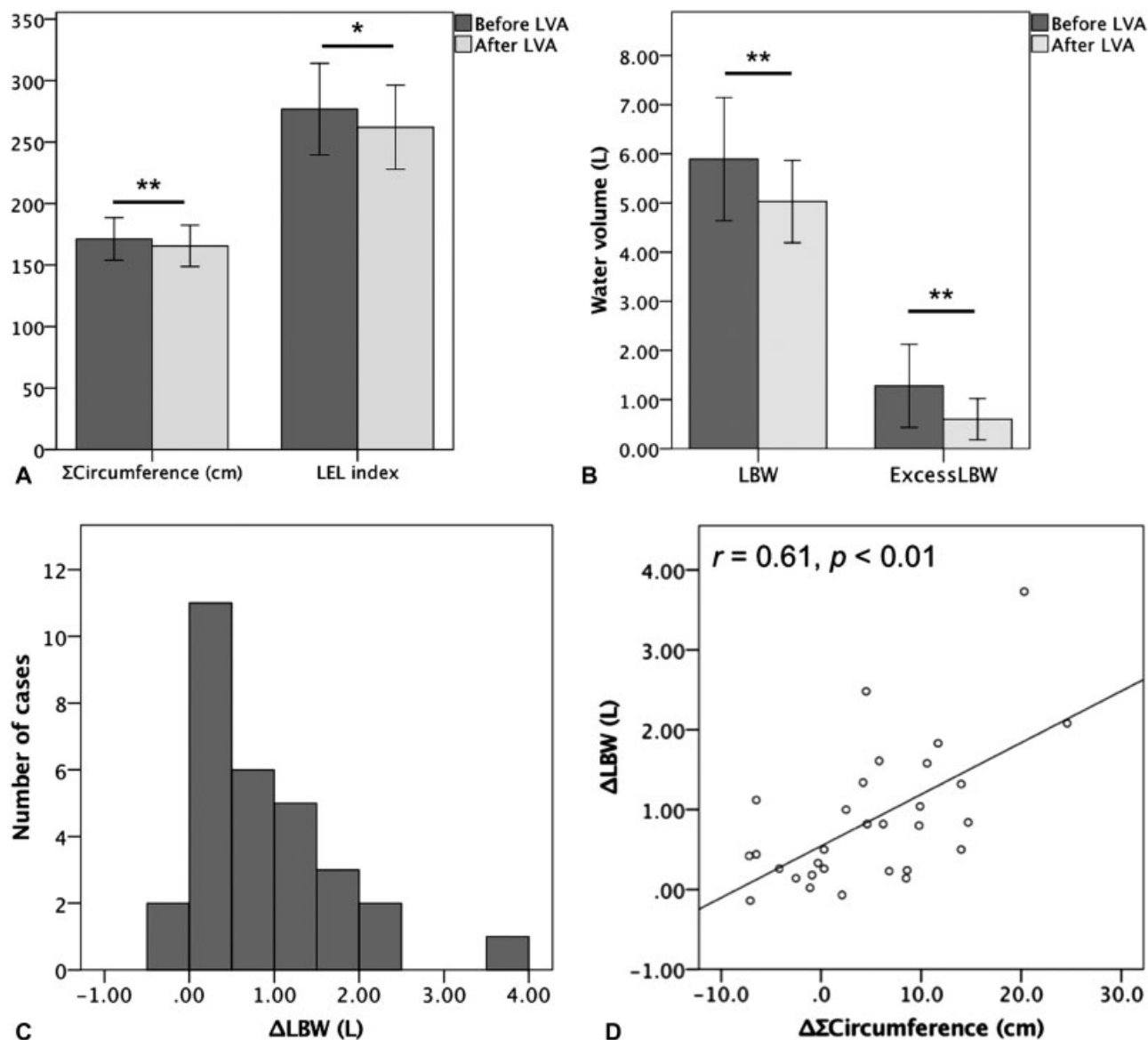


Fig. 1 Changes in limb circumference, LEL index, and LBW in affected legs after LVA. (A) Mean Σ Circumference of the affected leg was 171.3 cm (SD: 17.3) before LVA and 166.3 cm (SD: 16.1) afterward. Mean LEL index of the affected leg was 276.8 (SD: 37.2) before LVA and 264.2 (SD: 30.7) afterward. (B) Mean LBW of the affected leg was 5.89 L (SD: 1.25) before LVA and 5.03 L (SD: 0.84) afterward. Mean Δ LBW was 0.86 L (SD: 0.86). Mean excess LBW was 1.28 L (SD: 0.85) before LVA and 0.60 L (SD: 0.42) afterward. The mean reduction rate of edema was 45.1% (SD: 36.3). (C) Histogram of Δ LBW. Median Δ LBW was 0.65 L. (D) Δ LBW correlated strongly with $\Delta\Sigma$ Circumference ($r = 0.61$, $p < 0.01$). Predicted Δ LBW (L) = $0.544 + 0.0647 \times \Delta\Sigma$ Circumference (cm). Error bars: mean \pm 1 SD, *: $p < 0.05$, **: $p < 0.01$. LBW, leg body water; LEL, lower extremity lymphedema; LVA, lymphaticovenular anastomosis; SD, standard deviation.

Significant correlations were found between Δ LBW and the variables of age ($r = 0.37$, $p < 0.05$), LBW before LVA ($r = 0.75$, $p < 0.01$), excess LBW ($r = 0.83$, $p < 0.01$), and % ECW ($r = 0.81$, $p < 0.01$). There were no significant associations between Δ LBW and the variables of ISL stage ($r = 0.24$, $p = 0.19$), number of operations ($r = 0.19$, $p = 0.53$), number of anastomoses ($r = 0.13$, $p = 0.49$), or diameter of the largest lymphatic vessel ($r = 0.36$, $p = 0.058$) (\rightarrow Figs. 2, 3).

Stepwise multiple linear regression was performed to predict Δ LBW based on the preoperative and intraoperative variables and revealed a significant regression equation of predicted Δ LBW (L) = $-8.554 + 0.507 \times$ excess LBW (L) + $21.109 \times$ %ECW (F [2, 27] = 42.519, $p < 0.01$,

$R^2 = 0.759$) (\rightarrow Table 3, \rightarrow Fig. 4). This predictive formula showed that Δ LBW increased by 507 mL when excess LBW increased by 1 L. Both excess LBW and %ECW were significant predictors of Δ LBW. The former variable had a larger standardized partial regression coefficient ($\beta = 0.500$ vs. 0.421), indicating a stronger prognostic ability.

Discussion

This is the first report to assess the water reductive effect of LVA using BIA and analyze the relationship between LVA outcome and preoperative and intraoperative variables by multivariate analysis. Only patients with unilateral lower-

Table 2 Summary of simple linear regression analysis for predicting Δ LBW based on $\Delta\Sigma$ Circumference

Coefficients							
	Unstandardized coefficients		Standardized coefficients	t-Value	p-Value	95% CI for B	
	B	SE	β			Lower	Upper
Constant	0.544	0.149	0.544	3.641	0.001	0.238	0.849
$\Delta\Sigma$ Circumference	0.0647	0.0160	0.607	4.046	0.000	0.0319	0.0974
ANOVA							
	SS	df	MS	F-Value	p-Value		
Regression	7.904	1	7.904	16.372	0.000		
Residual	13.517	28	0.482				
Total	21.421	29					
Regression statistics							
R	0.607						
R ²	0.369						
Adjusted R ²	0.346						
SE	0.695						
N	30						

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; *df*, degrees of freedom; LBW, leg body water; MS, mean square; SE, standard error; SS, sum of squares.

limb lymphedema were included, which allowed the unaffected leg to be used as an inpatient control. We witnessed an overall mean reduction of 45.1% of excess body water in the affected leg by LVA after a minimum 6-month follow-up. The preoperative water volume difference between a patient's legs (excess LBW) proved to be the most powerful predictor of decrease in water volume in the affected leg (Δ LBW) by LVA, which could have implications on the decision for LVA.

The BIA is a noninvasive measurement method of body water volume obtained using body impedance values that is not subject to the influence of bone, muscle, or adipose tissue.³² The technique is based on the principle that the electrical impedance of human body changes according to the amount of water in it.³³ The accuracy of the multi-frequency BIA used in this study has been validated as having a high correlation with deuterium oxide dilution, the current gold standard method, for TBW ($r = 0.974$ and adjusted $R^2 = 0.83\text{--}0.87$).^{32,34,35} Another advantage of multifrequency BIA for assessing lymphedema is its ability to measure segmental water volume in the body. In the field of lymphedema, the BIA method has already been reported as having strong correlations with outer volume limb measurement.³⁶

One of the biggest obstacles in managing and monitoring lymphedema is consistent volume measurement, with no established standard for diagnosing and monitoring lymphedema progression.³⁷ To quantify the severity of lymphedema or effect of lymphedema treatment, some authors have adopted outer volume measurements such as water displacement¹⁴ or perometry with an infrared optoelectronic limb volumeter,^{38,39} while others have employed a modified cone

equation⁴⁰ or LEL index calculated from segmental circumferential measurements. However, those assessments are considered indirect for measuring water reduction as they are affected by the presence of bone, muscle, and adipose tissue.

Few studies have described the effect of LVA on lower-limb lymphedema by volume in an absolute value. Huang et al reported a mean reduction of 703 mL (SD: 850) using the water displacement method,⁷ while Maegawa et al observed a mean improvement of 600 mL (SD: 969) for the patency-confirmed cases using a modified cone equation.²³ Although both of their results were lower than ours of 860 mL (SD: 860) with BIA, we presumed this discrepancy to stem from differences in measurement methods rather than surgical technique. The earlier studies and ours indicate that the water volume change assessed by BIA is larger than that of outer volume change of the limb by water displacement or a modified cone equation. As it is associated with the cytoskeleton, the outer volume change of the limb is possibly underestimated compared with water volume change; for example, the limb's outer volume will not drop to zero if the water in the limb completely disappears. Indeed, the change rate of LBW (14.6%) was larger than those of Σ Circumference and LEL index (2.9 and 4.6%, respectively) in our cohort (**Fig. 1A, B**).

Ancukiewicz et al pointed out that the lack of a standardized and reliable method of quantifying lymphedema has impeded comparisons of different studies and contributed to the ongoing uncertainty regarding treatment response.³⁸ Garza et al also insisted in their review that centers focusing on lymphedema treatment should have standardized methods of

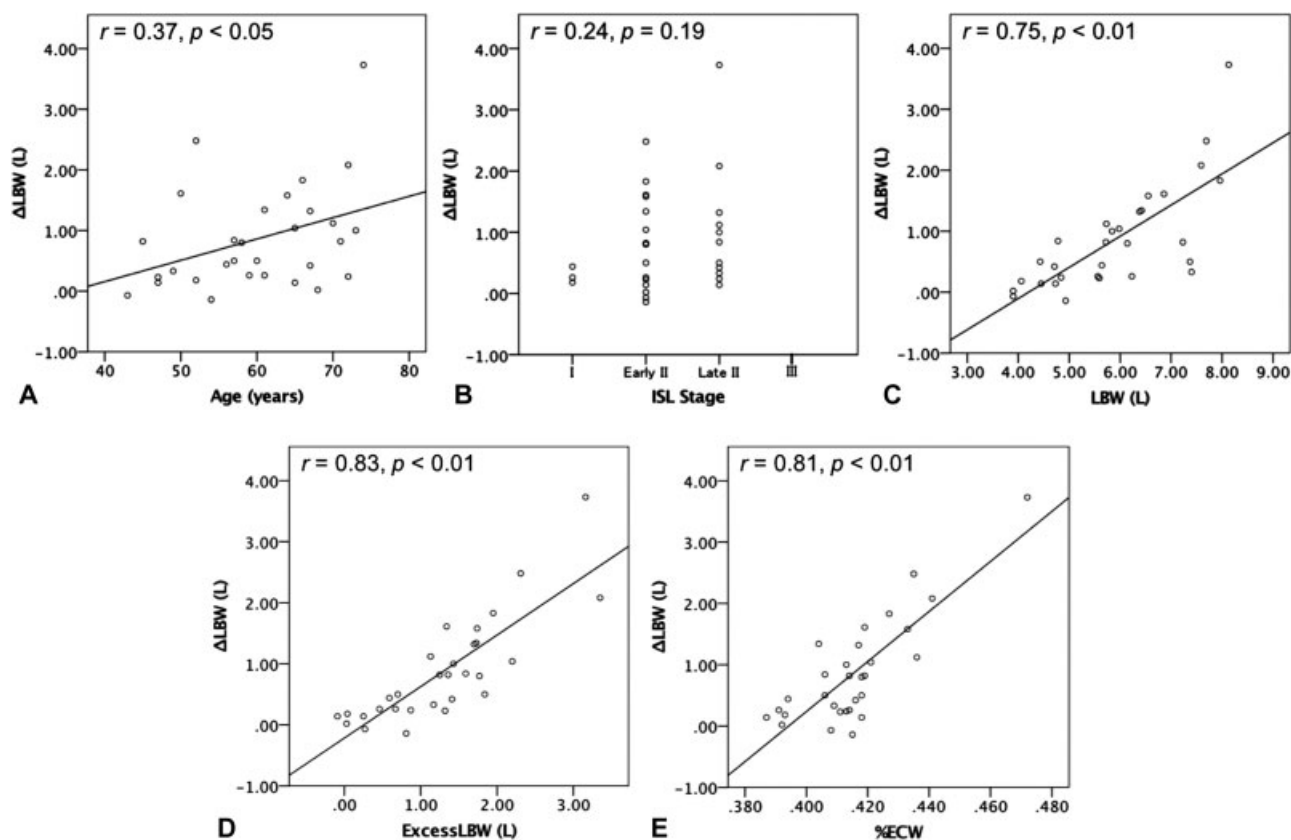


Fig. 2 Correlations between Δ LBW and five preoperative variables: linear regression lines are drawn for significant correlations. (A) Age correlated moderately with Δ LBW ($r = 0.37, p < 0.05$). (B) There was no significant correlation between ISL stage and Δ LBW. (C) LBW before LVA correlated strongly with Δ LBW ($r = 0.75, p < 0.01$). (D) Excess LBW correlated very strongly with Δ LBW ($r = 0.83, p < 0.01$). (E) %ECW correlated very strongly with Δ LBW ($r = 0.81, p < 0.01$). ECW, extracellular water; ISL, International Society of Lymphology; LBW, leg body water; LVA, lymphaticovenular anastomosis; SD, standard deviation.

evaluating and monitoring patients.³⁷ To overcome this unfavorable situation and establish more objective LVA evaluation, we consider the BIA method as appropriate to assess the severity of lymphedema and water reductive effect of LVA because it can noninvasively determine the water volume of the affected limb and its difference from the unaffected side without influences by bone, muscle, or adipose tissue.

Our results showed a positive correlation between Δ LBW and excess LBW using multivariate analysis, which indicated that the effects of LVA could be predicted by measurement of the preoperative water volume difference between the affected and unaffected legs. Accordingly, unilateral lower-limb lymphedema patients without a remarkable water volume difference between legs may not fully benefit from

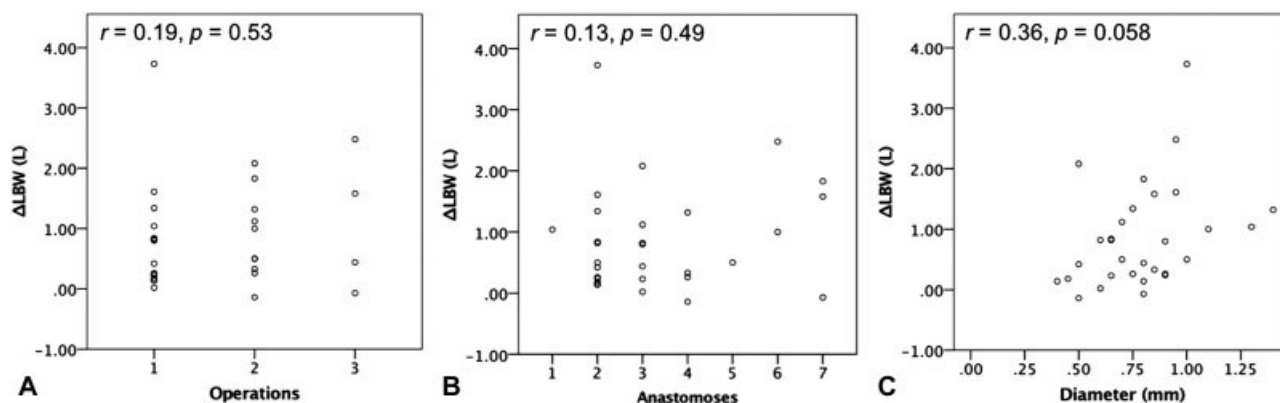


Fig. 3 Correlations between Δ LBW and three intraoperative variables: No significant correlations were seen for (A) number of operations performed, (B) number of anastomoses created, or (C) diameter of the largest lymphatic vessel anastomosed. LBW, leg body water.

Table 3 Summary of stepwise multiple linear regression analysis for variables predicting Δ LBW

Coefficients									
	Unstandardized coefficients		Standardized coefficients	t-Value	p-Value	95% CI for B		Collinearity statistics	
	B	SE	β			Lower	Upper	Tolerance	VIF
Constant	-8.554	3.026		-2.826	0.009	-14.763	-2.344		
Excess LBW	0.507	0.155	0.500	3.273	0.003	0.189	0.826	0.382	2.616
%ECW	21.109	7.653	0.421	2.758	0.010	5.406	36.812	0.382	2.616
ANOVA									
	SS	df	MS	F-Value	p-Value				
Regression	16.259	2	8.129	42.519	0.000				
Residual	5.162	27	0.191						
Total	21.421	29							
Regression statistics									
R	0.871								
R ²	0.759								
Adjusted R ²	0.741								
SE	0.437								
N	30								

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; LBW, leg body water; df, degrees of freedom; MS, mean square; SE, standard error; SS, sum of squares; VIF, variance inflationary factor.

LVA, regardless of apparent differences in limb circumference caused by the accumulation of fat. Although this does not marginalize the improvement of lymph flow by LVA in such patients, in advanced cases where fat deposition and fibrosis are progressed and excess water is relatively little, LVA should be conducted while considering the possibility that

water volume and limb circumference may not decrease as expected. Thus, preoperative prediction represents another possible benefit of BIA adoption for preoperative water volume measurement.

Our cohort exhibited no significant correlation between Δ LBW and the number of anastomoses. Narushima et al described in their retrospective study that the average percentage reduction in cross-sectional area increased exponentially with increasing number of LVA anastomoses per limb using nonlinear regression analysis.¹⁴ Mihara et al retrospectively showed that the amount of volume reduction became more significant as the number of LVA sites was increased, but a 1.9% mean increase in limb volume was observed in the four limbs on which LVA was performed over a total of nine sites.⁴¹ Those reports indicated a positive correlation between the effect of LVA and the number of anastomoses as a result of univariate analysis that was absent in our study. However, it is difficult to deny the possibility that more anastomoses were created for severe cases as a limitation of their retrospective design. Our results from multivariate analysis indicated a positive correlation between the severity of lymphedema (excess LBW) and the volume reductive effect of LVA (Δ LBW). Thus, when surgeons create more anastomoses for severe cases, it follows logically that a larger volume reduction will be observed as the number of anastomoses increases. We consider the strength of our study to be the use of multivariate analysis to demonstrate the correlations between Δ LBW and variables including the number of anastomoses. Based on our results, we recommend emphasizing secure anastomoses over number of anastomoses. After obtaining the results of this study,

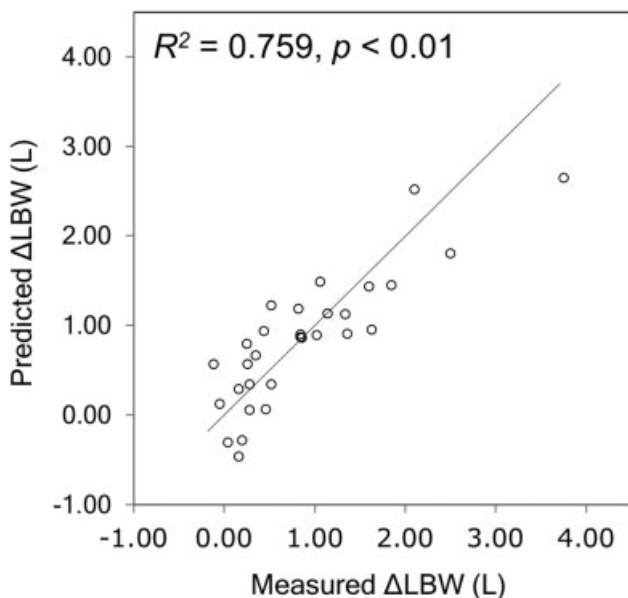


Fig. 4 Correlation between predicted Δ LBW and measured Δ LBW: Measured Δ LBW correlated very strongly with predicted Δ LBW ($R^2 = 0.759$, $p < 0.01$). Predicted Δ LBW (L) = $-8.554 + 0.507 \times$ excess LBW (L) + $21.109 \times$ %ECW. ECW, extracellular water; LBW, leg body water.

we have opted for two secure anastomoses for each LVA operation, not only one in consideration of early obstruction as reported by Maegawa et al.²³ Well-controlled prospective studies are required to elucidate the precise correlation between the volume reductive effect of LVA and number of anastomoses.

There are several limitations to this study. To evaluate the efficacy of LVA as a whole, we included two patient characteristics: compression-refractory edema and the desire to halt compression. The effect of LVA was evaluated only quantitatively using BIA and limb circumference measurements, and qualitative assessments, such as subjective symptoms and the frequency of cellulitis, were not considered. No quality of life scores, such as the Lymphedema Quality of Life Questionnaire,⁴² were collected in this study. The postoperative patency of LVA was not confirmed by ICG lymphography. Due to the small sample size of the primary and male subgroups, respective LVA effect differences between etiologies and sexes were uncertain. Moreover, because ISL stage III cases were not included in this study, the impact of LVA on fibrotic, thick-skinned, and fat-deposited lymphedema was not clarified. We consider BIA assessment of lymphedema to be limited to ISL late stage II where excess water, and not fat or fibrosis is the main component of lymphedema, as in the indication for LVA. Although our results implied that LVA became more effective as lymphedema progressed, they could not specify the optimal timing for LVA as they only addressed water volume changes. Finally, our investigation was retrospective, but all data were collected according to a standardized protocol and main parameters (limb circumference, LBW, %ECW, excess LBW, and Δ LBW) were available for each patient at predetermined times during follow-up.

Conclusion

LVA has a volume-reducing effect on accumulated body water in unilateral lower-limb lymphedema. The amount of water volume reduction by LVA appears to be predicted by the preoperative excess body water in the affected leg. Body water volume measurement using BIA could have implications on the decision for LVA and may spare patients without remarkable excess water in their legs from unnecessary surgery, regardless of apparent differences in limb circumference resulting from fat deposition and connective tissue fibrosis.

Financial Disclosure

None of the authors have nothing to disclose.

Note

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References

- International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. *Lymphology* 2013;46(01):1–11
- Lee KT, Park JW, Mun GH. Serial two-year follow-up after lymphaticovenular anastomosis for the treatment of lymphedema. *Microsurgery* 2017;37(07):763–770
- Sosin M, Yin C, Poysophon P, Patel KM. Understanding the concepts and physiologic principles of lymphatic microsurgery. *J Reconstr Microsurg* 2016;32(08):571–579
- Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. *Plast Reconstr Surg* 2014;133(04):905–913
- Carl HM, Walia G, Bello R, et al. Systematic review of the surgical treatment of extremity lymphedema. *J Reconstr Microsurg* 2017;33(06):412–425
- Felmerer G, Sattler T, Lohrmann C, Tobbia D. Treatment of various secondary lymphedemas by microsurgical lymph vessel transplantation. *Microsurgery* 2012;32(03):171–177
- Huang GK, Hu RQ, Liu ZZ, Shen YL, Lan TD, Pan GP. Microlymphaticovenous anastomosis in the treatment of lower limb obstructive lymphedema: analysis of 91 cases. *Plast Reconstr Surg* 1985;76(05):671–685
- Matsubara S, Sakuda H, Nakaema M, Kuniyoshi Y. Long-term results of microscopic lymphatic vessel-isolated vein anastomosis for secondary lymphedema of the lower extremities. *Surg Today* 2006;36(10):859–864
- Yamamoto Y, Horiuchi K, Sasaki S, et al. Follow-up study of upper limb lymphedema patients treated by microsurgical lymphaticovenous implantation (MLVI) combined with compression therapy. *Microsurgery* 2003;23(01):21–26
- Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S. Long-term follow-up after lymphaticovenular anastomosis for lymphedema in the leg. *J Reconstr Microsurg* 2003;19(04):209–215
- Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J Reconstr Microsurg* 2000;16(06):437–442
- Furukawa H, Osawa M, Saito A, et al. Microsurgical lymphaticovenous implantation targeting dermal lymphatic backflow using indocyanine green fluorescence lymphography in the treatment of postmastectomy lymphedema. *Plast Reconstr Surg* 2011;127(05):1804–1811
- Yamamoto T, Narushima M, Kikuchi K, et al. Lambda-shaped anastomosis with intravascular stenting method for safe and effective lymphaticovenular anastomosis. *Plast Reconstr Surg* 2011;127(05):1987–1992
- Narushima M, Mihara M, Yamamoto Y, Iida T, Koshima I, Munding GS. The intravascular stenting method for treatment of extremity lymphedema with multiconfiguration lymphaticovenous anastomoses. *Plast Reconstr Surg* 2010;125(03):935–943
- Auba C, Marre D, Rodríguez-Losada G, Hontanilla B. Lymphaticovenular anastomoses for lymphedema treatment: 18 months postoperative outcomes. *Microsurgery* 2012;32(04):261–268
- Ipsen T, Pless J, Frederiksen PB. Experience with microlymphaticovenous anastomoses for congenital and acquired lymphoedema. *Scand J Plast Reconstr Surg Hand Surg* 1988;22(03):233–236
- Demirtas Y, Ozturk N, Yapici O, Topalan M. Comparison of primary and secondary lower-extremity lymphedema treated with supermicrosurgical lymphaticovenous anastomosis and lymphaticovenous implantation. *J Reconstr Microsurg* 2010;26(02):137–143
- O'Brien BM, Mellow CG, Khazanchi RK, Dvir E, Kumar V, Pederson WC. Long-term results after microlymphaticovenous anastomoses for the treatment of obstructive lymphedema. *Plast Reconstr Surg* 1990;85(04):562–572
- Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. *Plast Reconstr Surg* 2010;126(03):752–758
- Baumeister RG, Siuda S. Treatment of lymphedemas by microsurgical lymphatic grafting: what is proved? *Plast Reconstr Surg* 1990;85(01):64–74, discussion 75–76

- 21 Weiss M, Baumeister RG, Hahn K. Post-therapeutic lymphedema: scintigraphy before and after autologous lymph vessel transplantation: 8 years of long-term follow-up. *Clin Nucl Med* 2002;27(11):788–792
- 22 Olszewski WL. Lymphovenous microsurgical shunts in treatment of lymphedema of lower limbs: a 45-year experience of one surgeon/one center. *Eur J Vasc Endovasc Surg* 2013;45(03):282–290
- 23 Maegawa J, Yabuki Y, Tomoeda H, Hosono M, Yasumura K. Outcomes of lymphaticovenous side-to-end anastomosis in peripheral lymphedema. *J Vasc Surg* 2012;55(03):753–760
- 24 Maegawa J, Miikami T, Yamamoto Y, Satake T, Kobayashi S. Types of lymphoscintigraphy and indications for lymphaticovenous anastomosis. *Microsurgery* 2010;30(06):437–442
- 25 Mukenge SM, Catena M, Negrini D, et al. Assessment and follow-up of patency after lymphovenous microsurgery for treatment of secondary lymphedema in external male genital organs. *Eur Urol* 2011;60(05):1114–1119
- 26 Yamamoto Y, Sugihara T. Microsurgical lymphaticovenous implantation for the treatment of chronic lymphedema. *Plast Reconstr Surg* 1998;101(01):157–161
- 27 Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. *Breast Cancer Res Treat* 2009;113(02):199–206
- 28 Pereira N, Lee YH, Suh Y, et al. Cumulative experience in lymphovenous anastomosis for lymphedema treatment: the learning curve effect on the overall outcome. *J Reconstr Microsurg* 2018. Doi: 10.1055/s-0038-1648220
- 29 Pereira De Godoy JM, Franco Brigidio PA, Salles Cunha SX, Batigália F, De Fatima Guerreiro Godoy M. Mobilization of fluids in large volumetric reductions during intensive treatment of leg lymphedema. *Int Angiol* 2013;32(05):479–482
- 30 Yamamoto T, Narushima M, Doi K, et al. Characteristic indocyanine green lymphography findings in lower extremity lymphedema: the generation of a novel lymphedema severity staging system using dermal backflow patterns. *Plast Reconstr Surg* 2011;127(05):1979–1986
- 31 Yamamoto T, Matsuda N, Todokoro T, et al. Lower extremity lymphedema index: a simple method for severity evaluation of lower extremity lymphedema. *Ann Plast Surg* 2011;67(06):637–640
- 32 Cha K, Chertow GM, Gonzalez J, Lazarus JM, Wilmore DW. Multi-frequency bioelectrical impedance estimates the distribution of body water. *J Appl Physiol* (1985) 1995;79(04):1316–1319
- 33 Hoffer EC, Meador CK, Simpson DC. Correlation of whole-body impedance with total body water volume. *J Appl Physiol* 1969;27(04):531–534
- 34 Sartorio A, Malavolti M, Agosti F, et al. Body water distribution in severe obesity and its assessment from eight-polar bioelectrical impedance analysis. *Eur J Clin Nutr* 2005;59(02):155–160
- 35 Bedogni G, Malavolti M, Severi S, et al. Accuracy of an eight-point tactile-electrode impedance method in the assessment of total body water. *Eur J Clin Nutr* 2002;56(11):1143–1148
- 36 Moseley A, Piller N, Carati C. Combined opto-electronic perometry and bioimpedance to measure objectively the effectiveness of a new treatment intervention for chronic secondary leg lymphedema. *Lymphology* 2002;35(04):136–143
- 37 Garza R III, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. *BMC Cancer* 2017;17(01):468
- 38 Ancukiewicz M, Russell TA, Otoole J, et al. Standardized method for quantification of developing lymphedema in patients treated for breast cancer. *Int J Radiat Oncol Biol Phys* 2011;79(05):1436–1443
- 39 Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg* 2013;132(05):1305–1314
- 40 Casley-Smith JR. Measuring and representing peripheral oedema and its alterations. *Lymphology* 1994;27(02):56–70
- 41 Mihara M, Hara H, Tange S, et al. Multisite lymphaticovenular bypass using supermicrosurgery technique for lymphedema management in lower lymphedema cases. *Plast Reconstr Surg* 2016;138(01):262–272
- 42 Salgarello M, Mangialardi ML, Pino V, Gentileschi S, Visconti G. A prospective evaluation of health-related quality of life following lymphaticovenular anastomosis for upper and lower extremities lymphedema. *J Reconstr Microsurg* 2018. Doi: 10.1055/s-0038-1642623