LYMPHATIC RESEARCH AND BIOLOGY
Volume 00, Number 00, 2021

DOI: 10.1089/lrb.2019.0070

# The Clinical Usefulness of Lymphedema Measurement Technique Using Ultrasound

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## Abstract

***Background:*** We previously invented a new technique to measure the cross-sectional area of soft tissue of a limb (ΔCSA) with lymphedema using ultrasonography. The measurement correlated strongly with both circumference and volumetry in normal subjects. The purpose of this study was to measure the reliability and accuracy of the method in patients with lymphedema.

***Methods and Results:*** Ultrasonography was performed on both arms of 69 female patients diagnosed with stage ≥1 lymphedema related to advanced breast cancer. At 10 cm above elbow (AE) and below elbow (BE), soft-tissue thicknesses at various locations were measured by two examiners. Subcutaneous tissue stiffness was also obtained by measuring thickness differences of soft tissue when applying minimal and maximal pressure to the skin (compliance) and its ratio to the initial thickness (compliance ratio). ΔCSA showed a strong positive correlation with circumference ($r = 0.758$ to 0.951), and a moderate negative correlation with Z at 5 Hz ($r = -0.326$ to $-0.486$). Intra- and interclass coefficients of all ultrasonography measurements were moderate to excellent (0.623–0.990). Compliance measured at 10 cm BE on the lesion side was significantly higher than on the normal side ($p < 0.001$), and compliance measured at 10 cm AE showed no difference between the two sides ($p = 0.653$). Conversely, compliance ratios measured at 10 cm AE and BE on the lesion side were significantly lower than on the normal side ($p < 0.001$).

***Conclusion:*** Thus, ΔCSA using ultrasonography could be a particularly viable option for determining status in lymphedema patients.

**Keywords:** lymphedema, ultrasonography, cross-sectional area

## Introduction

Lymphedema is a chronic disease of the lymphatic system, including lymph nodes and lymphatic vessels, and is characterized by interstitial accumulation of protein, fluid, and subsequent inflammation and fibrosis.[1] Lymphedema is classified into two types according to its cause. Primary lymphedema is a rare condition and occurs secondary to congenital anatomic abnormalities of the lymphatic system, such as lymphatic dysplasia or valve dysfunction.[2] Secondary lymphedema is a relatively common condition after treatment of malignancy, especially in breast cancer patients treated with axillary lymph node dissection and/or radiation therapy.[3] The incidence of upper limb lymphedema varies from 10% to more than 50%, with a prevalence of 13%–42% in breast cancer patients.[4,5]

Breast cancer-related lymphedema (BCRL) manifests as excess arm volume and distorted shape due to overload of lymphatic fluid. The accumulation of lymphatic fluid in the subcutaneous space leads to various adverse consequences, including distortion in the limb space, increased limb weight and infection risk, and decreased limb function and quality of life.[6–8] As the disease progresses to the chronic state, the subcutaneous tissue undergoes irreversible histologic changes such as thickening and fibrosis.[9]

There are various definitions used to diagnose lymphedema, such as interlimb circumference difference >2 cm, interlimb volume difference >8%–10% or 200 mL, or subjective reports

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of limb heaviness, but no international consensus has been reached.[10,11] As with the definition of lymphedema, many techniques have been applied to examine volume and structural changes of soft tissue, but a gold standard has not yet been established. In the clinical setting, arm circumference measurement is the most popular and widely used method because of its promptness and simplicity. However, it cannot evaluate structural changes in subcutaneous tissues, and technical errors can be made by uncontrolled tape-measurement pressure, inaccurately marked points, or an improper angle relative to the long axis of the limb.[12,13]

Volumetry, using either water or an infrared light, is another volume-measuring method, which can measure the limb volume automatically. However, it also has disadvantages, including that it cannot show structural changes in soft tissue, cannot distinguish the volume of soft tissue from that of deep structures such as muscles and bones, and it might not be suitable for assessing lesions with restricted joint movement.[13–16]

Magnetic resonance imaging and computed tomography can measure the volume and structure of subcutaneous tissues simultaneously. By using these methods, the cross-sectional area of a localized area enables more precise measurement of the amount of lymphedema. However, these methods are not commonly used alone to evaluate lymphedema because of high cost and excessive radiation exposure.[13,17–19]

Bioimpedance analysis (BIA) measurement is a recently developed method that attempts to estimate the amount of body fluid by obtaining parameters after sending low electrical current through a body segment.[20] This method can be used on limbs with lymphedema to determine whether the affected limb consists mainly of fluid or other components.[21–23] However, bioimpedance characteristics might not coincide with the exact mechanical changes of lymphedema. Often, physiologic factors of subjects should be considered to improve the interpretation and reproducibility of lymphedema status.

Ultrasonography is simple, cost-effective, has no radiation exposure, and provides real-time imaging, which enables observation of the changes in subcutaneous tissues.[24,25] However, this method has the limitation that only localized subcutaneous tissue thickness can be obtained.

We previously invented a new measurement technique for lymphedema using ultrasonography.[26] Subcutaneous tissue thickness was measured at a specific point in the arms of 20 healthy female participants, and measured values were assigned to a designed formula to calculate the cross-sectional area of arm soft tissue. Parameters showed high intra- and inter-rater reliabilities, and moderate to strong correlations with other measuring methods, including circumference and volumetry.

On the contrary, Kim et al. tried to evaluate structural changes of the soft tissue by applying minimal and maximal pressure in both healthy populations and lymphedema patients.[12,27] However, this technique has not been widely used in clinics, as it measures only the hardness of lymphedema. Thus, the aim of this study was to determine whether the two ultrasonographic measurement methods are useful in patients with lymphedema by comparing them with other commonly used measuring methods.

## Materials and Methods

### *Subjects*

Sixty-nine patients with unilateral upper extremity lymphedema, secondary to breast cancer surgery and confirmed by clinical examination, were recruited. Lymphedema was confirmed by clinical and lymphoscintigraphic examination. To minimize measurement bias and to facilitate compliance comparisons, we enrolled patients with upper extremity lymphedema stage ≥1 and whose circumference differences between bilateral arms and forearms were >2 cm. Participants with the following criteria were excluded: the presence of certain comorbidities requiring acute treatment (recent metastasis of cancer, active infections such as cellulitis in the affected arm); a history of trauma; primary lymphedema or lymphedema unrelated to breast cancer; or bilateral lymphedema. The study was approved by the Pusan National University Yangsan Hospital Department of Health Institutional Review Board (IRB No. 05-2019-067).

### *Circumference*

Circumferences at 10 cm above the elbow crease (AE) and below the elbow crease (BE) were measured with measuring tape; measurements were performed with care to avoid excessive pressure during evaluation.

### *Ultrasonographic measurements: cross-sectional area and compliance*

Ultrasonography was performed on both arms of each subject. Subjects were asked to lie on a bed in the supine position. The examiner marked the superior (a), medial (b), inferior (c), and lateral (d) areas of patients' arms at 10 cm AE and BE to measure the desired cross section (Fig. 1). The amount of soft tissue was measured using a 7.5 MHz transducer (LOGIQ E9; General Electric, Boston, MA). The probe was placed perpendicularly to the targeted area with minimal pressure and enough lubricant was used to avoid contour

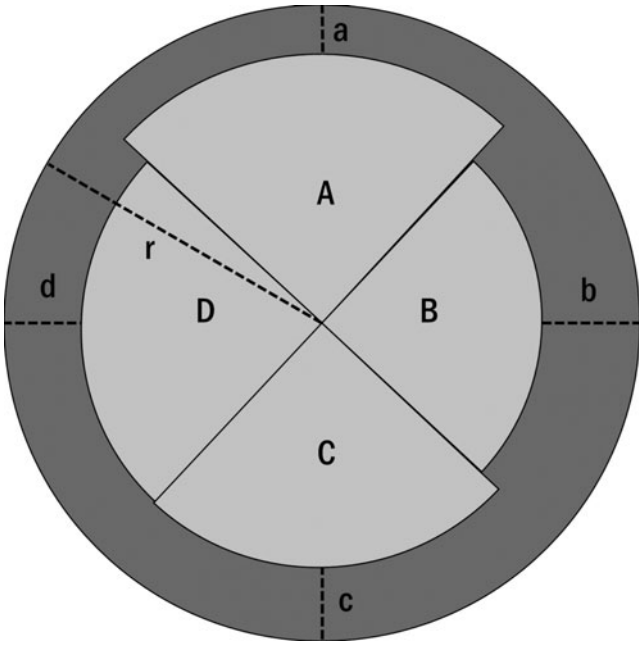


**FIG. 1.** Ultrasonographic measurement at 10 cm above and below elbow crease (a, superior, b, medial, c, inferior, d, lateral direction) is shown. The areas of A, B, C, and D are imaginary inner areas. ΔCSA is calculated by a designed formula described above. ΔCSA, Δ cross-sectional area.

distortion of tissue under the transducer. Soft-tissue thickness was measured as the distance between the skin and fascia of the muscle (Fig. 2). According to the movements of each subject's arm or forearm, the mobile structures were considered to be muscle, and fascia distinct from the muscle layers. After thickness was measured, the examiner applied maximal compression to measure soft-tissue resistance to pressure at the superior aspect (a) of 10 cm AE, and the medial aspect (b) of 10 cm BE, according to the methods of Kim et al.[12, 21, 27] In this study, we defined the difference between initial soft-tissue thickness and thickness after applying maximal pressure, as compliance. In addition, we calculated the ratio of compliance to initial soft-tissue thickness (compliance ratio).

To avoid errors due to variability of the pressure applied via probe, the examiner used the average value of three consecutive measurements. To determine inter-rater reliability, 2 examiners conducted the identical procedure described above in 29 subjects on the same day.

A total of 16 areas from 10 cm AE and BE of bilateral arms were examined in each participant. At each quadrant, soft-tissue thickness was measured (Fig. 1a–d), and circumferences were recorded (Y in Fig. 1). Using measured circumference of the examined area, the total cross-sectional area (whole area in Fig. 1) and radius (r in Fig. 1) were determined. The imaginary inner area, consisting of deep structures, including bones and muscles (light gray area in Fig. 1), was calculated using the formula below. By subtracting inner area from the total cross-sectional area, Δ cross-sectional area (ΔCSA, dark gray area in Fig. 1) was calculated.

*Formula for cross-sectional area of lymphedema*

$$\text{Circumference } (\mathrm{Y}) = 2\pi \mathrm{r}$$

$$\begin{aligned}\Delta\text{CSA of the soft tissue} &= \text{Total CSA of the limb} - (\mathrm{A}+\mathrm{B}+\mathrm{C}+\mathrm{D}) \\ &= \pi \mathrm{r}^2 - 1/4\left\{\pi(\mathrm{r}-\mathrm{a})^2 + \pi(\mathrm{r}-\mathrm{b})^2 + \pi(\mathrm{r}-\mathrm{c})^2 + \pi(\mathrm{r}-\mathrm{d})^2\right\} \\ &= \mathrm{Y}/4(\mathrm{a}+\mathrm{b}+\mathrm{c}+\mathrm{d}) - \pi/4\left(\mathrm{a}^2+\mathrm{b}^2+\mathrm{c}^2+\mathrm{d}^2\right)\end{aligned}$$

*Bioimpedance analysis*

Single-frequency (SF)-BIA (InBody S10; Biospace, Seoul, Republic of Korea) was used. Patients were asked to lie on a nonconductive bed in the supine position, but with arms slightly abducted and palms facing down. All jewelry and conductive metal devices likely to affect electric currents were removed. Electrodes were attached to the bilateral wrists and ankles in a tetrapolar arrangement. To estimate the amount of extracellular fluid in both arms, impedance (Z) at 5 Hz in each arm was obtained.

*Data analysis*

All continuous variables were analyzed using the Kolmogorov–Smirnov test for normality, and all parameters satisfied the test. A paired *t*-test with 95% confidence intervals (CIs) was used to determine statistical differences between measurements on the lesion and normal sides. To evaluate correlations between ΔCSA and other measurements, the Pearson correlation coefficient was used. Intra- and inter-rater reliabilities of ΔCSA were calculated using intraclass correlation coefficients (ICCs) with 95% CIs. All statistical analyses were performed with SPSS/PC+ software version 17.0 (SPSS, Inc., Chicago, IL).

## Results

*Demographic data*

Sixty-nine females with stage 2 BCRL participated in the study. Mean age of the participants was $57.55 \pm 9.64$ years, and mean BMI was $24.79 \pm 2.46\,\mathrm{kg/m^2}$. The lesion side was the right in 39 subjects (56.5%) and the left in 30 subjects (43.5%) (Table 1).

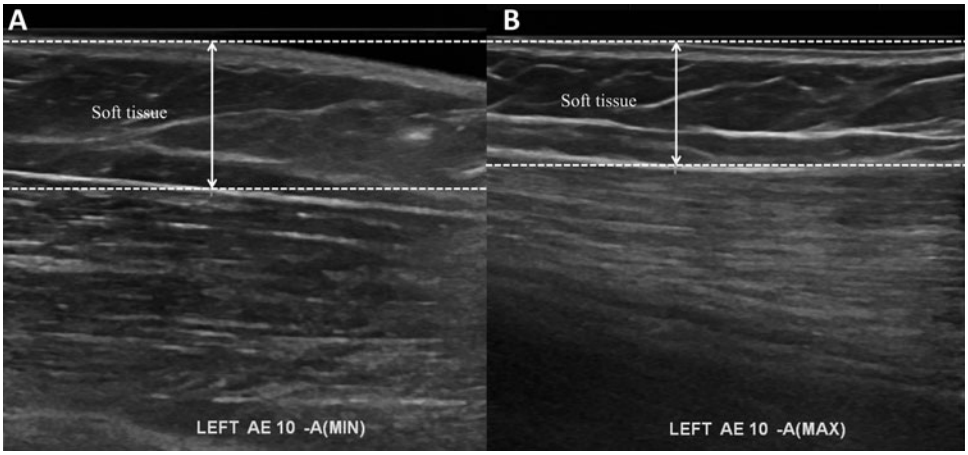


**FIG. 2.** Ultrasonographic images of the arm of a change in thickness between the **(A)** initial soft-tissue thickness and the **(B)** thickness after applying maximal pressure.

Table 1. Demographic Data of the Subjects

| *Variables* | *Values* |
|---|---|
| Age, years | 57.55 ± 9.64 |
| Height, cm | 157.64 ± 5.46 |
| Weight, kg | 61.66 ± 7.32 |
| BMI, kg/m$^2$ | 24.79 ± 2.46 |
| Side of the lesion, right:left | 39 (56.5%):30 (43.5%) |

BMI, body mass index.

### *Ultrasonography*

At both 10 cm AE and BE, ΔCSA for the lesion side was significantly higher than for the normal side ($p < 0.001$). There was no significant difference in compliance measured at 10 cm AE between the lesion and normal side ($p = 0.653$). Compliance measured at 10 cm BE showed a significant difference between the lesion and normal side ($p < 0.001$), but contrary to our expectations, values for the lesion side were lower than for the normal side. Compliance ratios measured at 10 cm AE and BE on the lesion side were significantly lower than on the normal side ($p < 0.001$) (Table 2).

### *Other measurements*

The circumference on the lesion side was significantly larger than on the normal side at both 10 cm AE and BE ($p < 0.001$). The Z at 5 Hz measured on the lesion side showed significantly smaller values than on the normal side ($p < 0.001$) (Table 2).

### *Correlation coefficients for ultrasonographic measurements with other methods*

On the normal side, the correlation coefficients between ΔCSA and circumference, at both 10 cm AE and BE, were strongly positive ($r = 0.909$, $p < 0.001$, and $r = 0.758$, $p < 0.001$, respectively). Conversely, correlation coefficients between ΔCSA and Z at 5 Hz, both at 10 cm AE and BE on the normal side, were moderately negative ($r = -0.326$, $p = 0.006$, and $r = -0.343$, $p < 0.001$, respectively). Similar results were seen on the lesion side: ΔCSA at 10 cm AE and BE showed a strong positive correlation with circumference ($r = 0.951$, $p < 0.001$, and $r = 0.901$, $p < 0.001$, respectively), and showed moderate negative correlations with Z at 5 Hz ($r = -0.360$, $p = 0.002$, and $r = -0.486$, $p < 0.001$, respectively) (Table 3).

### *Intra- and inter-rater reliabilities of ultrasonographic measurements: ΔCSA, compliance, and compliance ratio*

Regardless of the lesion or normal side, soft-tissue thickness measured at 16 sites in both arms showed moderate to excellent inter- and intra-rater reliabilities (ICC 0.623–0.974). ΔCSA values obtained by substituting measured values into the formula also showed significantly high inter- and intra-rater reliabilities (ICC 0.902–0.994). Compliance measured at 10 cm AE and BE, on both the lesion and normal sides, showed moderate to excellent inter- and intra-rater reliabilities (ICC 0.786–0.969). The compliance ratio calculated using compliance and initial thickness with application of minimal pressure showed moderate to excellent inter- and intra-rater reliabilities at 10 cm AE and BE, on both the lesion and normal sides (ICC 0.795–0.980) (Table 4).

## Conclusion

In our previous study, we performed ultrasonography 10 cm AE and BE in both arms of 20 healthy female participants, as in the method described above.[26] ΔCSA measured at 10 cm AE and BE showed excellent intraclass coefficients (0.966 and 0.939, respectively) and interclass coefficients (0.931 and 0.876, respectively). Also, ΔCSA at 10 cm AE and BE revealed a strong positive correlation with volumetry ($r = 0.794$ and 0.756, respectively) and circumference ($r = 0.891$ and 0.801, respectively). However, the limitation was that the study was conducted only in the arms of healthy adults and not in actual lesions in patients with lymphedema.

In the current study, as a follow-up to our previous research, we performed ultrasonography in 69 patients with BCRL. We calculated intra- and interclass coefficients analyzing obtained data and compared data with BIA

Table 2. Lymphedema Measurement Using Ultrasonography, Circumference Measure, and Bioimpedance Analysis

| | *Lesion side* | *Sound side* | *Ratio (lesion:sound)* | p |
|---|---|---|---|---|
| ΔCSA, cm$^2$ | | | | |
| 10 cm AE | 46.14 ± 9.35 | 33.54 ± 7.82 | 1.40 ± 0.22 | <0.001* |
| 10 cm BE | 28.67 ± 8.06 | 14.81 ± 4.32 | 2.01 ± 0.54 | <0.001* |
| RC, cm | | | | |
| 10 cm AE | 0.20 ± 0.09 | 0.19 ± 0.08 | 1.13 ± 0.51 | 0.653 |
| 10 cm BE | 0.38 ± 0.14 | 0.29 ± 0.15 | 1.48 ± 0.75 | <0.001* |
| Compliance | | | | |
| 10 cm AE | 0.19 ± 0.07 | 0.23 ± 0.07 | 0.89 ± 0.35 | <0.001* |
| 10 cm BE | 0.24 ± 0.08 | 0.32 ± 0.09 | 0.78 ± 0.33 | <0.001* |
| Circumference, cm | | | | |
| 10 cm AE | 30.32 ± 4.45 | 27.06 ± 4.35 | 1.12 ± 0.05 | <0.001* |
| 10 cm BE | 25.66 ± 2.21 | 22.25 ± 1.76 | 1.16 ± 0.07 | <0.001* |
| Z at 5 Hz, Ω | 296.82 ± 51.76 | 400.78 ± 47.08 | 0.74 ± 0.10 | <0.001* |

* Means statistically significant ($p < 0.05$).
AE, above elbow; BE, below elbow; BMI, body mass index; ΔCSA, Δ cross-sectional area; Z, impedance.

Table 3. Correlation Between Δ Cross-Sectional Area and Other Parameters

| | | *Lesion side* | | *Sound side* | |
|---|---|---|---|---|---|
| *10 cm AE* | | *Circumference* | *Z at 5 Hz* | *Circumference* | *Z at 5 Hz* |
| ΔCSA | *r* | 0.951 | –0.360 | 0.909 | –0.326 |
| | *p* | <0.001[a] | 0.002[a] | <0.001[a] | 0.006[a] |
| | | *Lesion side* | | *Sound side* | |
| *10 cm BE* | | *Circumference* | *Z at 5 Hz* | *Circumference* | *Z at 5 Hz* |
| ΔCSA | *R* | 0.901 | –0.486 | 0.758 | –0.343 |
| | *p* | <0.001[a] | <0.001[a] | <0.001[a] | <0.001[a] |

[a]Statistically significant.

and circumference measurements. On both lesion and normal sides, ultrasonographic measurements showed excellent intra- and interclass coefficients. Also, a strong positive correlation was identified between ΔCSA and circumference, and a moderate negative correlation was found between ΔCSA and Z at 5 Hz.

Kim et al.[12] performed ultrasonographic evaluation in 13 healthy participants (8 males and 5 females) using a compression method. Skin and subcutaneous tissue thicknesses were measured by two trained examiners on the superior aspect of the upper extremity at 10 cm AE and BE. Thickness differences between when the transducer was placed with maximal compression and minimal contact (i.e., compliance) were calculated. The ''maximal compression'' was defined as compression when additional pressure could not produce a further change of soft-tissue thickness.

The change in thickness was calculated from values obtained by each inspector. Intra- and inter-rater reliability between all values measured by examiners was analyzed. Moderate to excellent intra- and inter-rater correlation coefficients at both the upper arm and forearm were reported, and the examiners concluded that measurement of soft-tissue thickness using ultrasonography may be reliable, and that pressure compliance may reflect tissue softness in the upper extremity.

As a follow-up study, Kim et al.[27] performed the same measurement in 39 females with postmastectomy lymphedema using a compression method. The researchers reported that compliance values in the affected upper extremity were significantly lower than in the contralateral extremity ($p < 0.05$). We also obtained soft-tissue thickness using the same compression method and compliance values showed moderate to excellent inter- and intra-rater reliability.

However, unlike Kim et al., in our study, compliance measured at 10 cm AE showed a tendency (without statistical significance) to be larger in the lesion than the normal side. Compliance measured at 10 cm BE on the lesion side was significantly larger than on the normal side. This was probably due to the soft-tissue characteristics of the participants with lymphedema. We gathered lymphedema patients with stage ≥1 advanced breast cancer, and most of them had accumulation of lymph fluid without soft-tissue stiffness. Due to the nature of the participants, the change in thickness by compression on the lesion side rather than normal side was rather greater, unlike the research of Kim et al.

As a manifestation of chronic lymphedema, the soft tissue became stiff due to histologic changes. Furthermore, in our study, soft-tissue thickness changes with compression itself showed opposite results in patients with early-stage lymphedema.

To correct this limitation, we calculated the compliance ratio, which we defined as the ratio of thickness change to initial thickness. Compliance ratio on the lesion side was expected to be the same or lower than that on the normal side. It was also expected that the closer the compliance ratio on the lesion side to that on the normal side, the less likely were histologic changes of soft tissue. In our study, participants with stage 1 lymphedema had a similar compliance ratio on the lesion and normal sides; nevertheless, there was a significant difference in ΔCSA between the two sides.

This suggests that patients' arms with lymphedema had lymphatic fluid accumulation but had not yet undergone histologic changes. Moreover, the compliance ratio measured at both 10 cm AE and BE was significantly lower on the lesion versus normal side and showed moderate to excellent inter- and intra-rater reliabilities.

In our previous research, we compared ΔCSA to segmental arm volume, from 10 cm AE to BE, using infrared light-based volumetry. However, this method cannot reflect soft-tissue volume only. Therefore, we used BIA, which indirectly measures soft-tissue volume only. BIA is a test that can obtain various parameters by sending a low alternating electric

Table 4. Inter- and Intrarater Reliability of Δ Cross-Sectional Area

| | *Sound side* | | | | *Lesion side* | | | |
|---|---|---|---|---|---|---|---|---|
| | *10 cm AE* | | *10 cm BE* | | *10 cm AE* | | *10 cm BE* | |
| *Parameters* | *Inter-rater* | *Intrarater* | *Inter-rater* | *Intrarater* | *Inter-rater* | *Intrarater* | *Inter-rater* | *Intrarater* |
| a | 0.896 | 0.885 | 0.733 | 0.936 | 0.671 | 0.974 | 0.800 | 0.936 |
| b | 0.834 | 0.920 | 0.774 | 0.959 | 0.857 | 0.949 | 0.864 | 0.933 |
| c | 0.913 | 0.938 | 0.623 | 0.967 | 0.872 | 0.960 | 0.873 | 0.953 |
| d | 0.864 | 0.936 | 0.791 | 0.949 | 0.784 | 0.888 | 0.864 | 0.944 |
| ΔCSA | 0.978 | 0.989 | 0.902 | 0.970 | 0.989 | 0.994 | 0.959 | 0.990 |
| RC | 0.885 | 0.969 | 0.964 | 0.945 | 0.786 | 0.968 | 0.968 | 0.923 |
| Compliance | 0.802 | 0.960 | 0.840 | 0.884 | 0.795 | 0.974 | 0.933 | 0.980 |

All data are statistically significant ($p < 0.005$).
RC, response to compression.

current through the human body and measuring response. The proportion of the electric current penetrating cell membranes is determined by frequency.[28–30]

At zero frequency, the electric current cannot penetrate the cell membrane and takes a detour around cells and through the extracellular fluid. Since lymphedema is an accumulation of lymphatic fluid in subcutaneous tissue, the amount of lymphedema is most accurately estimated by measuring resistance at zero frequency (R0). Due to technical limitations, R0 cannot be obtained directly. Instead, R0 can be calculated by measuring Z at zero frequency using bioimpedance spectroscopy (BIS).

York et al.[31] reported that SF-BIA can be a simple accurate alternative to BIS for the clinical assessment of unilateral lymphedema. They performed both BIS and SF-BIA in a unilateral arm lymphedema group ($n=28$), unilateral leg lymphedema group ($n=16$), and healthy control group ($n=28$). Z ratios were measured with BIS and SF-BIA at low frequency from arms of women with arm lymphedema and controls, and from legs of women with leg lymphedema. BIS-measured ratios were highly concordant with those obtained with SF-BIA ($r=0.99$, $p<0.001$) at any frequency. Based on the research of York et al., we used Z at 5 Hz and SF-BIA in our study. As Z at low frequency is inversely proportional to the amount of fluid, ΔCSA showed a negative moderate correlation with Z at 5 Hz, as we expected.

In our study, we used two ultrasonographic methods to measure lymphedema status. The method for cross-sectional area measurement showed high inter- and intraclass coefficients and moderate to high correlation with other conventionally used methods, such as circumference and BIA. Soft-tissue hardness, which reflects histologic status, could be measured by a compression method and shows different soft-tissue characteristics, even with the same volume of lymphedema. Therefore, a combination of these two ultrasonographic methods seems to reflect not only structural changes but also histologic changes, in soft tissue after lymphedema occurs.

Despite the advantages of these ultrasonographic methods, there are several limitations to our study. First, as ultrasonography is a subjective measurement, output data can vary, depending on the examiners. Although our study showed high inter- and intra-rater reliabilities, examiners should remain fully aware of the detailed anatomic landmarks and techniques. Second, our technique for measurement of cross-sectional area does not assume heterogeneity of soft-tissue thickness in the arm. Specific anatomic regional changes should be considered to make a precise conclusion. Third, there may be a limitation of ultrasonography itself, such that in obese patients it may be hard to distinguish soft tissues from other structures.

In summary, ultrasonographic techniques for measuring the cross-sectional area and compliance appear to be advantageous and identify both structural and hardness changes. Compared with other conventional methods, these techniques are noninvasive, cost-effective, and time-saving, and can be recommended as a particularly viable option for measuring the comprehensive status of lymphedema in clinical settings.

## Author Disclosure Statement

No competing financial interests exist.

## Funding Information

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C2397).

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