

Body Positional Effects on Bioimpedance Spectroscopy Measurements for Lymphedema Assessment of the Arm

Louise A. Koelmeyer, BAppSc (OT),¹ Leigh C. Ward, BSc (Hons), FNSA, PhD,²
Catherine Dean, BAppSc (PT), MA, PhD,³ and John Boyages, MBBS, FRANZCR, PhD¹

Abstract

Background: Bioimpedance spectroscopy (BIS) measurements have conventionally been performed using a device that uses gel-backed electrodes with the patient in a supine position. More recently, impedance devices that use stainless steel electrodes with the patient in a standing position have become available. The aim of this study was to assess and compare BIS measurements made in three different body positions using two different impedance devices (lead device and stand-on device) in women with and without arm lymphedema.

Methods: A cross-sectional study design was used to recruit two cohorts of women, healthy controls ($n=47$) and those who had been diagnosed with breast cancer ($n=53$) and were either at risk of ($n=14$) or with unilateral arm lymphedema ($n=39$). BIS measurements were taken three times in each position for each device.

Results: Impedance measurements were reliably made using either a lead or stand-on device with a coefficient of variation being 0.6% or lower. Absolute impedance measurements for the stand-on device were larger than the comparable lead device values due to the difference in electrode position, but were highly correlated ($r=0.92$, $p<0.0001$). Interarm impedance ratios and L-Dex scores were slightly (3.1% equivalence), but significantly different.

Conclusion: The findings support impedance measurements being made reliably using either the lead or stand-on device, representing supine and upright measurement positions, respectively. Data between devices were, however, not directly interchangeable.

Keywords: lymphedema, bioimpedance spectroscopy (BIS), impedance, L-Dex

Introduction

LYMPHEDEMA IS A CHRONIC INFLAMMATORY CONDITION, which is the result of a functional overload of the lymphatic system, whereby the lymph volume exceeds lymphatic transport capacity. As a consequence, abnormal accumulation of protein-rich fluid in the interstitial space of the affected area occurs, causing swelling of limbs and other parts of the body.^{1–3} Lymphedema is a poorly understood and underresearched complication of cancer treatment, which can significantly reduce quality of life.^{4–6}

When lymphedema is present, lymph and other fluids build up in the interstitial spaces of the tissues. This results in an overall increase in the total amount of extracellular fluid (ECF) in the limb, causing swelling. This can be quantified by

measuring the impedance (opposition) to a low-frequency current that has been passed through the limb. Low-frequency current (<10 kHz) travels predominantly through the ECF, where the lymphedema manifests. As lymph accumulates, that is, ECF increases, the impedance to the current proportionally decreases. This decrease in impedance is a quantitative measure of lymphedema.⁷

Bioimpedance spectroscopy (BIS) is a technique used for the measurement of biological impedance at many frequencies, including the ideal frequency of measurement, 0 kHz.⁸ BIS has been reported to be effective for the measurement of ECF and subclinical changes in ECF to predict the onset of lymphedema in the arms.^{7,9,10} It is a noninvasive technique that directly measures the accumulating ECF, which is characteristic of early subclinical lymphedema.^{7,11–13}

¹Australian Lymphoedema Education, Research and Treatment Program, Department of Clinical Medicine, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia.

²School of Chemistry and Molecular Biosciences, The University of Queensland, St. Lucia, Brisbane, Australia.

³Department of Health Professions, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia.

Detection of subclinical lymphedema through surveillance and early intervention has been found to reduce progression to clinical lymphedema.^{11,14}

Conventionally, BIS measurements are performed using an impedance analyzer, which makes its measurements by leads attached to the skin by Ag-AgCl electrocardiography-style electrodes.¹² Measurements are typically performed with the patient supine and electrodes placed on the hands and feet, although measurements may also be performed with the patient sitting. More recently, impedance devices have become available for which the patient remains upright, while standing on stainless steel electrode plates with hands in contact with electrodes located on a bar or handle.^{15,16} These devices are more convenient to use and are able to make measurements of all body segments simultaneously and save time by avoiding the need for the operator to move skin surface electrodes around the body and making repeat measurements. While these stand-on devices have been used extensively for body composition assessment^{17–20} and to a limited extent for lymphedema assessment,²¹ they have not been systematically assessed for comparability with conventional lead-type measurements.²² van Zanten and Ward¹⁵ undertook a small-scale study comparing the two types of devices and found that, while stand-on devices are acceptable, the methods were not directly interchangeable. Thurlow et al. and Esco et al. reported that stand-on devices had several reported practical advantages, including permanently incorporated electrodes standardizing anatomical positioning and reduced total measurement time, all potential critical factors in obtaining accurate and precise measurements.^{17,23}

The aim of this study was to assess and compare BIS measurements made in three different body positions using two different impedance devices (lead device and stand-on device) in healthy women and those at risk of or living with arm lymphedema consequent to breast cancer treatment. Specifically, we plan to evaluate the following:

1. Intrareliability measurement (technical) error across positions and between devices.
2. Repeatability of BIS measurements over time using stand-on device.
3. Differences in impedance measurements for control and lymphedema groups across three body positions and two devices.
4. Impedance ratio differences between devices.
5. Ratio and L-Dex scores comparing current clinical protocol (lying, lead device) with proposed new protocol (standing, stand-on device).

Method

Design

A cross-sectional study design was used to recruit two cohorts of women, healthy controls and those with breast cancer and were either at risk of or living with unilateral arm lymphedema, who were invited to participate in the study from the Australian Lymphoedema Education, Research and Treatment (ALERT) Program's database held at Macquarie University as well as by invitation flyers displayed around the university campus and lymphedema clinics. Ethical approval was obtained from the Macquarie University Human Re-

search Ethics Committee (reference no. 5201700439) and all participants provided written informed consent.

Participants

Eligibility criteria for both groups included women who were between 18 and 90 years of age with self-described health as satisfactory. Participants included both women with clinically ascribed lymphedema as a result of treatment for breast cancer and also those at risk of lymphedema (lymphedema group) and healthy women with no prior incidence of breast cancer (controls). No attempt was made to age match participants between groups as we were exploring the operational equivalence of two impedance devices and different body positions. Participants attended the Macquarie University Lymphedema Clinic on a single occasion for a 45- to 60-minute appointment with all measurements being taken by two trained research assistants. Participants were allocated a case identification number so that all data would be de-identified for analysis.

Participants were excluded from the study if they had implantable devices such as pacemaker or other inbuilt stimulator, or if they were pregnant as these are contraindications for impedance measurement. Participants were also excluded if they reported having a health condition that might affect body fluid status such as renal disease or were taking diuretic medication.

Anthropometric measurements

Demographic information for each participant was obtained along with information regarding cancer, adjuvant treatments, and lymphedema history. Height was measured to the nearest 0.1 cm in a standing position without shoes using a stadiometer (SECA 213, Hamburg, Deutschland). Weight was measured by standing on electronic scales (SECA 813, Hamburg, Deutschland) without shoes and in light clothing to the nearest 0.1 kg. Body mass index (BMI) was calculated from weight in kilograms divided by height in meters squared. Age was calculated from date of birth. Self-ascribed limb dominance was recorded. For those at risk of or living with lymphedema, the at-risk arm was the side of their breast cancer treatment. Stage of lymphedema was determined using the International Society of Lymphology (ISL) classification guidelines.²⁴ For the healthy control group, the dominant limb was considered the "at-risk" limb.⁹

Impedance measurements

Devices. Participants completed BIS measurements of arms using two commercially available impedance devices in a lying (supine), sitting, and standing position for the lead device and in a standing and sitting position for the stand-on device. BIS measurements were taken three times in each position on each device and all data collected were recorded on a Case Report Form and saved in the software for each device securely.

The lead device (L-Dex[®] U400; ImpediMed Limited, Brisbane, Australia) is a BIS device, which uses an "impedance ratio" methodology to assess unilateral lymphedema of the arm and leg.²⁵ The device measures the resistance at 0 kHz (R0) of the unaffected limb and compares this to the resistance at 0 kHz of the affected/at-risk limb expressed as

the following ratio (unaffected: affected/at risk). Alternatively, this ratio may be linearized and expressed as an L-Dex score.²⁵ The lead device is battery powered and portable. It has a tetra-polar set of leads, which were attached to self-adhesive dual-tab pre-gelled Ag-AgCl electrodes (ImpediMed Limited) by means of alligator clips. The electrodes were placed on the hands and feet and the sense electrode aligned with the ulnar styloid and malleolus as per the manufacturer's protocol. The dual-tab electrode automatically locates the current drive electrode 9.5 cm distally. Electrode sites were cleaned with alcohol swabs before electrode attachment.

The newer stand-on device (SOZO®; ImpediMed Limited) is also a BIS device utilizing the same "impedance ratio" methodology as the lead device; however, instead of skin gel electrodes, stainless steel contact electrodes are used. The stainless steel electrodes are inbuilt within the hand and foot plates of the device. The current drive and sense plates are located under the sole of the feet and palm and fingers of the hands. Before measurement, electrode plates were swabbed with alcohol wipes for infection control and to assist in achieving good skin contact with electrodes.

Measurement protocol. Participants were measured in sitting and standing positions for both devices and in supine position only for the lead device. In seated and standing positions, arms were abducted with hands resting on table or hand plate, palms facing down. For the lead device, the table height was adjusted to be the same as the hand unit of the stand-on device. For supine measurements, arms were slightly abducted and palms facing down with the participant lying on a nonconductive examination bed. All jewellery on the wrists and ankles were removed.

The order of measurements was using the lead device in supine, sitting and then standing, followed by standing and sitting measurements with the stand-on device. All measurements were performed on both arms and in triplicate. The stand-on device automatically makes simultaneous measurements on both arms. For the lead device, the operator was required to transfer the leads between electrodes on each arm. All measurements were made according to the principle of equipotentials.^{12,26}

Data analysis

Electrical resistance values at zero current frequency (R0, measured in ohm) for each arm in each measuring condition (device and position) were obtained from the recorded impedances according to Cole theory as described by Ward²⁵ using manufacturer's software (Impsoft V2.2.0.1) for the lead device and in-built software for the stand-on device. ECF, including lymph, is optimally quantified from R0. Unfortunately, a number of technological and safety issues preclude being able to measure R0 directly. Instead, R0 is estimated by modeling the impedance data (measured in ohms) obtained from measurements made within the practical measurement region of 5–1000 kHz.²⁵ R0 data and L-Dex scores for this study were extracted from the software and imported into a spreadsheet for further analysis. Data were expressed as mean ± standard deviation (SD). Data that were manually entered from the case report form into an electronic spreadsheet were checked for accuracy.

Descriptive statistics (mean, SD, and coefficient of variation [CV]) were used to describe the baseline characteristics of the sample by group with group *t*-tests used to investigate significant differences.

Impedance ratios were calculated as R0 unaffected: R0 affected according to dominance as described above. Comparability of the two devices was assessed using generalized linear model (GLM) with paired *t*-tests for *post hoc* multipole comparisons for normally distributed data, concordance correlation,²⁷ limits of agreement analysis,²⁸ and equivalence testing using two one-sided *t*-tests (TOST).²⁹

Statistical analyses were carried out using either NCSS version 10.0.12 (NCSS LLC, East Kaysville) for GLM or MedCalc version 19.0.5 (MedCalc Software bvba, Ostend, Belgium) for other analyses.

Results

Characteristics of participants

One hundred participants were enrolled into the study and were divided into one of two groups. The healthy control group included 47 women who had no history of breast cancer or lymphedema, and the lymphedema group included 53 women who were at risk of ($n = 14$) or had been diagnosed with unilateral arm lymphedema ($n = 39$) following breast cancer treatment. Those with no known history of lymphedema (but at risk) were defined within the lymphedema group as they may have had undiagnosed subclinical lymphedema.³⁰ The demographic characteristics of participants are summarized in Table 1. The lymphedema group was significantly older and heavier, but significantly shorter than the healthy controls. For those participants with lymphedema, the mean time since their breast cancer surgery was 7.2 and 5.7 years since lymphedema diagnosis. The majority (60%) diagnosed with lymphedema were classified as ISL stage 1 or 2 and 26% were classified at risk.

Intrareliability measurement (technical) error across positions and between devices

Both devices were found to have excellent reliability with the CVs being 0.6% or lower (Table 2). Irrespective of body position and whether in the lymphedema group or control group, both devices measured impedance with the similar precision as indicated by the similar low (<1%) CVs. In the lymphedema group, the absolute R0 values were significantly lower (10.5%, $p < 0.0001$) in the affected arm compared to the unaffected arm. These differences were observed irrespective of body position of measurement or impedance device. A similar significant, but smaller difference (1.5%, $p < 0.009$ to $p < 0.012$) in impedance values was also seen in the control group, indicative of the larger ECF volume in the dominant arm (Table 2). Absolute impedance values were significantly greater ($p < 0.001$) when measured by the stand-on device compared to the lead device irrespective of whether the participant was measured in sitting or standing. This reflects the longer interelectrode distance between the palm and the sole of the foot in the stand-on device compared to the wrist to ankle distance for the lead device.

TABLE 1. CHARACTERISTICS OF PARTICIPANTS

Characteristic	Groups		p
	Control n = 47	Lymphedema n = 53	
Age (year), mean \pm SD (range)	37.9 \pm 15.6 (19–74)	60.6 \pm 9.9 (39–80)	<0.0001
Dominance (R:L)	43:4	49:4	
Arm at risk (R:L)		22:31	
Weight (kg), mean \pm SD (range)	66.9 \pm 14.2 (45.8–104.7)	77.0 \pm 15.3 (48.6–132.5)	0.001
Height (cm), mean \pm SD (range)	166.7 \pm 6.4 (152.5–177.8)	163.2 \pm 6.1 (148.5–176.0)	0.006
Body Mass Index (kg/m ²), mean \pm SD (range)	24 \pm 4.7 (15.5–37.0)	28.8 \pm 5.0 (21.4–44.1)	<0.0001
Time since cancer surgery (years), mean \pm SD (range)		7.2 \pm 5.2 (1–28)	
Time since lymphedema diagnosis (years), mean \pm SD (range)		5.7 \pm 4.2 (0.75–16)	
ISL lymphedema stage, n (%)			
At risk		14 (26)	
0		4 (8)	
1		17 (32)	
2		15 (28)	
3		3 (6)	
Adjuvant treatments, n (%)			
Axillary node dissection		44 (83)	
Sentinel node biopsy		9 (17)	
Radiotherapy treatment		43 (81)	
Chemotherapy treatment		42 (79)	
Hormonal treatment		32 (60)	

ISL, International Society of Lymphology ; n, number; SD, standard deviation.

Repeatability of BIS measurements over time using stand-on device

The measurement protocol using the stand-on device provided an opportunity to obtain repeat measurements after a 15-minute interval. Irrespective of sitting or standing positions for both controls and lymphedema participants, there was no significant difference in R0 measurements obtained with the stand-on device over the 15-minute time interval. Data at time zero and 15 minutes were highly correlated [$r_c = 0.993$, $p < 0.0001$; $r_p = 0.994$, $p < 0.0001$; SEE = 5.33 ohm (1.4%)] (Fig. 1).

Differences in impedance measurements for control and lymphedema groups across three body positions and two devices

The effects of dominance/nondominance for the control group and affected/unaffected for the lymphedema group were assessed when comparing devices and across different measurement positions (Fig. 2). R0 of the dominant limbs were lower than the nondominant values in the control group (6.2%, $p < 0.0001$), while in the lymphedema group, R0 of the affected limb was less compared with the unaffected limb (10.6%, $p < 0.0001$) (Fig. 2A, C). Irrespective of device or measurement position, impedance values were lower (9.8%, $p < 0.0001$) (Fig. 2C, D) for the lymphedema-affected arms compared to the contralateral unaffected arm reflecting the greater volume of ECF in these limbs. As expected, impedance measurements for the stand-on device were higher than the comparable lead device values due to the difference in position of electrodes, providing a longer interelectrode length (wrist to palm). These differences were consistently

observed for measurements obtained in lying, sitting, or standing positions (Fig. 2).

Impedance ratios: interdevice comparison

Overall, there were no significant differences in impedance ratios between the two devices, irrespective of position of measurement (sitting or standing) or clinical condition (control or lymphedema) (Fig. 3A–D). However, there was, as expected, a significant effect of clinical condition with mean values for the lymphedema group being significantly larger (9.2%, $p < 0.001$) irrespective of measurement position or device (Fig. 3A, B compared to Fig. 3C, D). However, small, but significant differences were seen between devices for both measurement positions when paired comparisons were tested separately for the control and lymphedema groups. Within the control group, the stand-on device values were 1.7% larger ($p < 0.001$) and 2.0% larger ($p < 0.001$) than the comparative lead device values for the sitting and standing positions, respectively. For the lymphedema group, the converse was found with the stand-on device values being 1.6% smaller ($p < 0.001$) than the comparable values for the lead device for both standing and sitting measurements.

Ratio and L-Dex scores: measurement protocol comparison

Comparisons of the lead device in lying, the current protocol, with the stand-on device in standing, the newly proposed measurement protocol, are presented in Figure 4. The two approaches were highly correlated irrespective of whether data were analyzed as impedance ratios or L-Dex scores ($r_c = 0.921$, $p < 0.0001$; $r_c = 0.925$, $p < 0.0001$; Fig. 4A and B

TABLE 2. INTRAMEASUREMENT ERROR ACROSS POSITIONS AND BETWEEN DEVICES

Group	Lying						Sitting						Standing								
	Unaffected ^a			Affected			Unaffected ^a			Affected			Unaffected ^a			Affected					
	Mean	SD	CV (%)	Mean	SD	CV (%)	p ^b	Mean	SD	CV (%)	Mean	SD	CV (%)	p ^b	Mean	SD	CV (%)	p ^b			
Lead device																					
Control	367.5	0.9	0.2	361.4	1.8	0.5	0.009	377.8	1.5	0.4	371.6	2.1	0.6	0.009	359.3	2.0	0.5	353.4	1.8	0.5	0.012
LE	334.1	1.4	0.4	299.2	1.1	0.4	0.0001	349.3	1.2	0.3	312.8	1.0	0.3	0.0001	331.7	1.3	0.4	295.7	1.1	0.4	0.0001
Stand-on device																					
Control								449.7	2.8	0.6	431.5	2.8	0.6	0.0001	424.8	2.3	0.6	407.0	2.6	0.6	0.0001
LE								401.8	2.0	0.5	364.4	2.0	0.6	0.0001	371.5	1.9	0.5	337.2	1.8	0.5	0.0001
Absolute difference between devices (%)																					
Control								71.9	(19.0)						65.5	(18.2)		53.6	(15.2)		
LE								52.5	(15.0)						39.8	(12.0)		41.5	(14.0)		

Data presented as R0 values (ohm).

^aFor control group, "Unaffected" was assigned as the nondominant arm.^bSignificance of difference Unaffected versus Affected.

CV, coefficient of variation; LE, lymphedema.

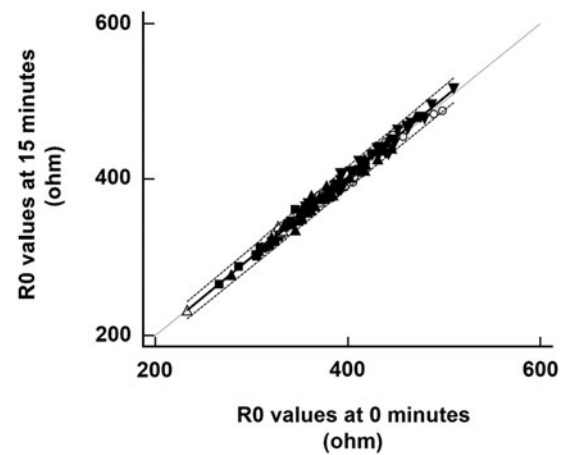


FIG. 1. Repeatability of impedance measurements when standing at 0- and 15-minute intervals for control and lymphedema groups. ○, control dominant; ▼, control non-dominant; △, dominant affected; ▲, dominant unaffected; ■, nondominant affected; ◆, nondominant unaffected; —, 95% confidence interval; ····, line of identity; —, best fit line.

for impedance ratios and L-Dex scores, respectively). Limits of agreement analysis showed no significant ($p = 0.92$, paired t -test) biases in R0 ratio or L-Dex score between lying measurements using the lead device compared to standing measurements obtained using the stand-on device (Fig. 4C, D). The 2 SD limits of agreement were ± 0.10 impedance ratio units ($\pm 9.8\%$) equivalent to a difference of approximately ± 10 L-Dex units. However, it is clear from Figure 4C and D that the spread of individual data for the lymphedema group was wider compared with the control group. Results of separate limits of agreement for the control group were ± 0.07 for impedance ratios compared with ± 0.12 for lymphedema group; the same differences were observed when the data were transformed to L-Dex scores (Fig. 4D).

L-Dex scores for all individuals and group data (as box plots) for the two measurement protocols are presented in Figure 5. The relative positions of individuals within are not identical for two measurement protocols as exemplified by the two highlighted participants. The L-Dex score for participant A was lower (10.1 L-Dex units) when measured with the stand-on device in standing compared to the lead device in lying L-Dex score (20.9 L-Dex units), the reverse being observed for participant B, 4.2 and 16.0 L-Dex units for lying and standing, respectively. Notably, these differences are greater than 10 L-Dex units, the 3 SD threshold indicative of lymphedema, and hence potentially leading to misclassification. While overall there was no difference in mean values, equivalence testing (TOST procedure) indicated that data were equivalent, to within 3.1%, again reflecting differences within individuals. It is noteworthy that this level of equivalence is at least a twofold improvement compared to typical impedance-based prediction of body composition.³¹

Discussion

BIS is an important tool used for the early detection of subclinical lymphedema following breast cancer³² and is recommended in practice guidelines for the detection

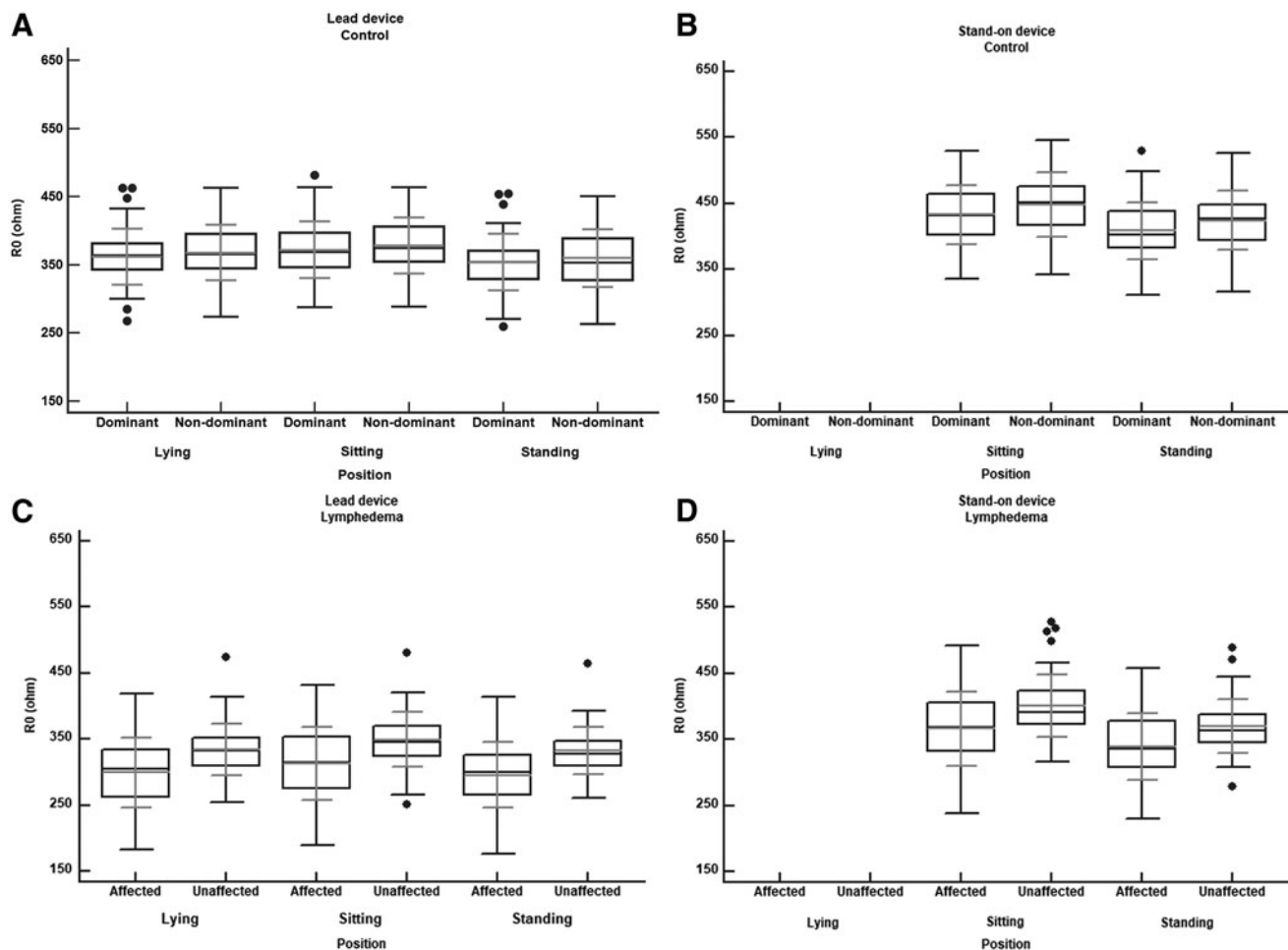


FIG. 2. Effect of limb dominance and presence of lymphedema for control and lymphedema groups across three body positions and two measurement devices. **(A)** Control group dominant versus nondominant limb using lead device in lying, sitting, and standing. **(B)** Control group dominant versus nondominant limb using stand-on device in sitting and standing. **(C)** Lymphedema group affected versus unaffected limb using lead device in lying, sitting, and standing. **(D)** Lymphedema group affected versus unaffected limb using stand-on device in sitting and standing. ●, outside values[†]; T, 1 standard deviation bar; —, mean; —, median; T, range for all data excluding outside values[†]; □, 25th to 75th percentile. [†]Defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (MedCalc Software bvba, Ostend, Belgium).

of breast cancer related lymphedema.³³ The currently accepted BIS measurement protocol for lymphedema assessment is to have the patient in a supine position³³ using a lead device. This study found that, impedance measurements can be reliably made using either the lead device or stand-on device. Irrespective of body position (lying, sitting, or standing), device used, or whether participants had lymphedema or were non-lymphedema controls, both devices measured impedance with similar high precision. Instrumental error (technical measurement error) for each device was small (CV <0.6%), comparable to that found for other BIS devices.³⁴ It was also shown for the stand-on device that there was little variation in impedance measurements over a 15-minute interval, consistent with the results of Thurlow et al.,²³ suggesting that flexibility in the time of measurements during consultations in clinical practice is possible. However, significant differences between the devices in absolute measures resistance were observed, which means, in the clinic or research setting, the devices should not be used interchangeably.

The significant differences between the devices in absolute measures were not surprising for several reasons. First, there are differences in the anatomical position of the sense electrodes, located at the wrist and ankle for the lead device and on the palm of the hand and the sole of the foot for the stand-on device. This effectively increases the interelectrode length and the electrical volume being measured using the stand-on device, leading to an increase in the measured resistance. The magnitude of this effect is also likely to be increased further since the additional tissue volume of hands and feet is of relatively small cross-sectional area compared to the rest of the limb or trunk and impedance is inversely related to cross-sectional area. Second, when moving from upright to supine, fluid that tends to pool in the extremities due to gravity redistributes to the trunk.³⁵ Since, the trunk is of larger cross-sectional area than the limbs, this has the effect of decreasing the measured resistance,^{36,37} observed to be ~2.5% in this study. Thus, changing from a supine, wrist-ankle measurement to an upright, palm-sole measurement will be the sum of

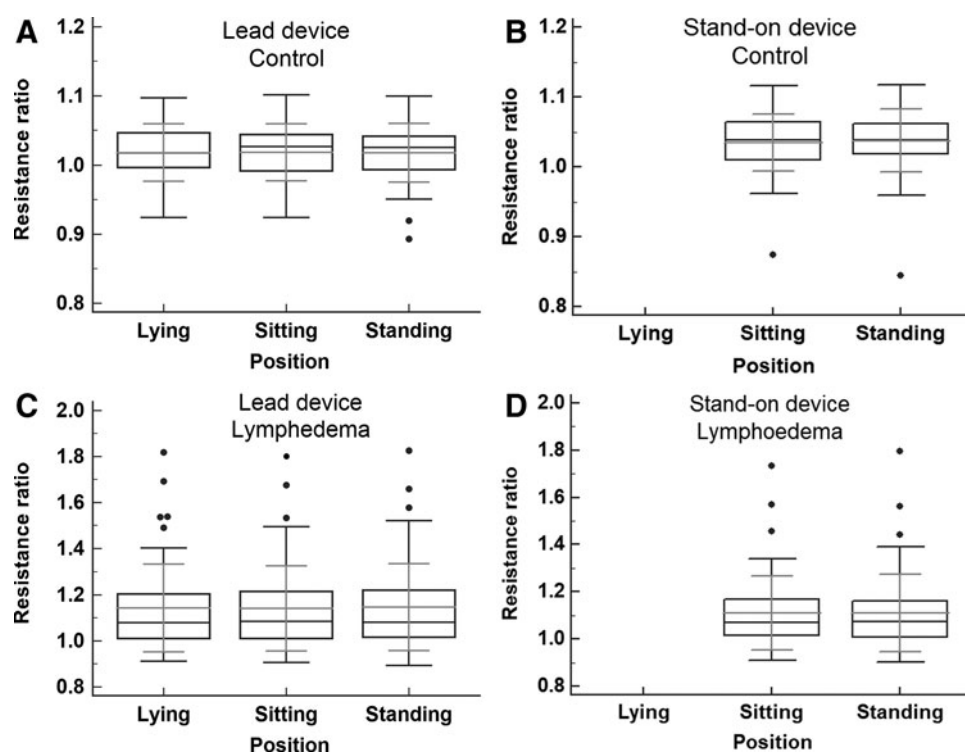


FIG. 3. Impedance ratio interinstrument comparison. (A) Control group using lead device in lying, sitting, and standing; (B) control group using stand-on device in sitting and standing; (C) lymphedema group using lead device in lying, sitting, and standing; (D) Lymphedema group using stand-on device in sitting and standing. ●, Outside values[†]; T, 1 standard deviation bar; —, mean; —, median; T, range for all data excluding outside values[†]; □, 25th to 75th percentile. [†]Defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (MedCalc Software bvba).

these two opposing effects. These data where stand-on device measurements were, on average, 15% larger than supine lead device values, suggest that changing interelectrode distance has a much greater overall effect than fluid redistribution on measurement of impedance.

The anatomical and physiologically based differences in impedance noted above will affect both limbs similarly; consequently, this should minimize differences when expressing arm impedances as interlimb ratios. The results of this study support this view with overall no significant difference in ratios or L-Dex scores between the two devices and measurement protocols. Nevertheless, there were small (<2%) differences observed when the data were analyzed by participant group, control, and lymphedema. Furthermore, the effect was in opposite directions in each group. The reasons for this are unclear. It is possible that, when measured in standing, the inclusion of hand volume magnifies the effect of limb dominance on measured impedance. The dominant hand is ~3% larger than the nondominant hand³⁸ and has an increased ECF volume detectable by impedance.³⁹ In this study, impedance ratios were calculated as unaffected R0: affected (or at risk) R0 in the lymphedema participants and as nondominant: dominant in the controls. For those with lymphedema, superimposed upon any dominance effect on measured impedance would be a decrease in impedance due to the presence of localized hand lymphedema if present. The larger spread of impedance ratios in the lymphedema cohort compared to controls

(Fig. 4) may indicate that, at least in some participants, hand lymphedema may have been present.

The potential clinical significance of these observations deserves consideration. The two measurement approaches were highly correlated with essentially no mean difference between methods (Fig. 4) and both devices may be considered equivalent, (within 3%) at the population level. However, for any individual being measured, the limits of agreement analysis show a 2 SD limit, which is potentially a clinical difference of ± 0.1 ratio units or approximately ± 10 L-Dex units. Since 10 L-Dex units is the conventionally accepted threshold presumptive of lymphedema,²⁵ this raises the possibility of misclassification of patients who are at risk for lymphedema. In this study population, the difference between the standard clinical measuring protocol of the two devices (lead device in lying and stand-on device in standing) could potentially lead to a misclassification of patients with clinically ascribed lymphedema in only 2% (two individuals in this cohort of 100).

There are practical and clinically significant implications arising from this study. Use of the lead device in lying is more time-consuming and cumbersome. A nonconductive measuring bed is required and patients are required to lie down for a period, while separate measurements of limbs are made, necessitating the clinician to move device leads between different combination of electrodes during the measurement procedure. Electrodes are disposable and cost of electrodes may be a significant disincentive to use. The advantage of the stand-on device is that it is self-contained, makes

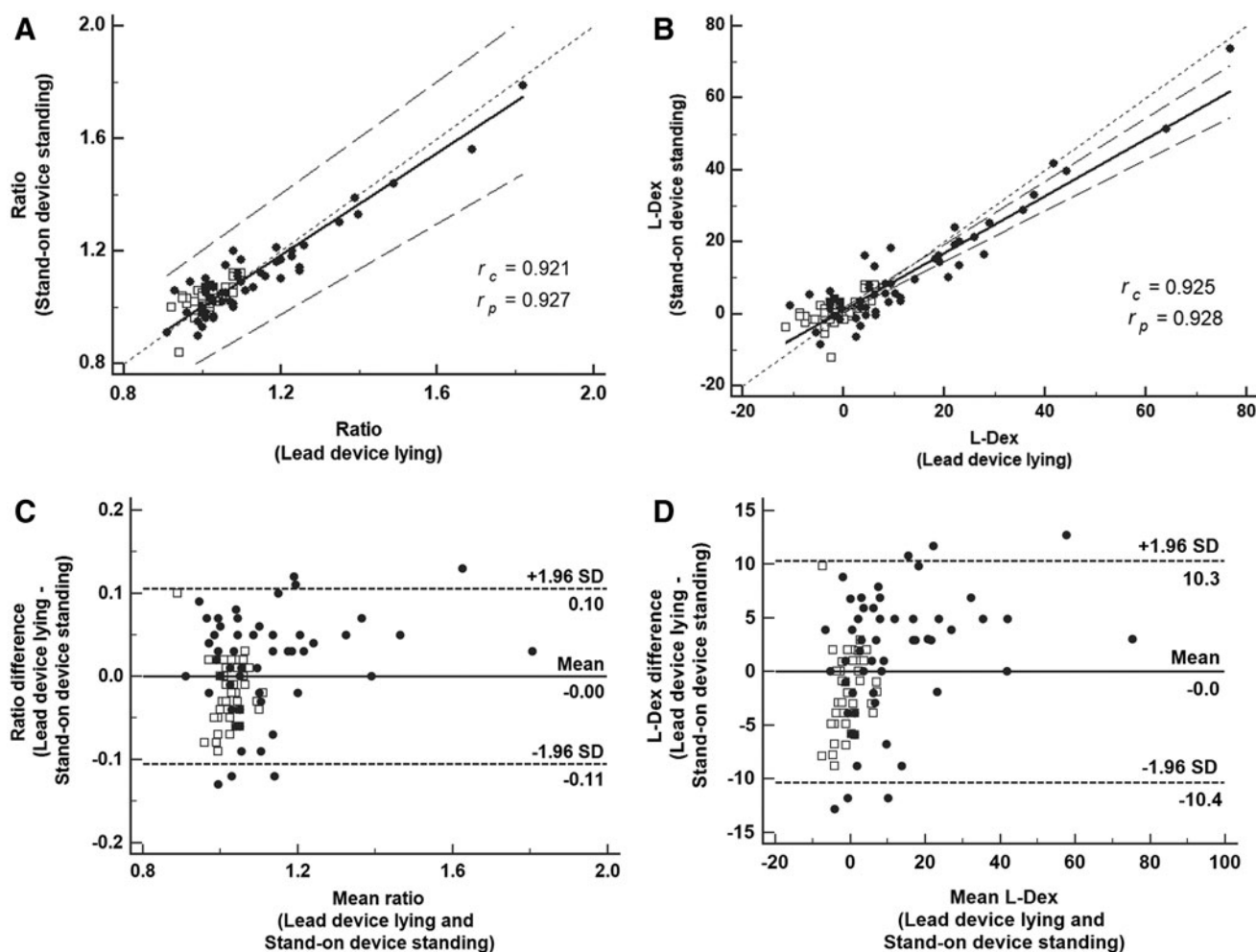


FIG. 4. Comparisons of ratios and L-Dex scores and mean ratios and mean L-Dex scores for lead device in lying with stand-on device in standing. □, Control group; ●, lymphedema group; —, 95% confidence interval; ·····, line of identity; —, best fit line. (A, B) Paired samples *t*-test; Passing and Bablok regression analysis. (C, D) Bland-Altman plots.

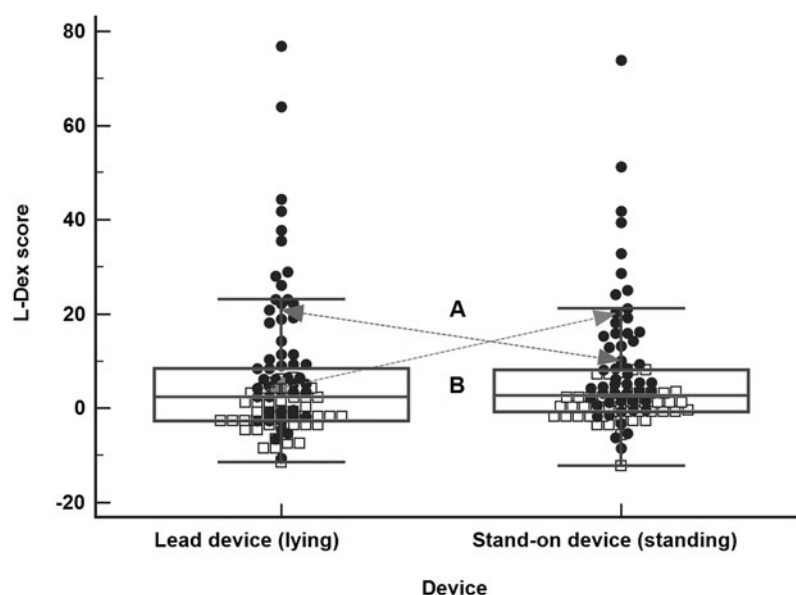


FIG. 5. Comparison of L-Dex scores for individuals using lead device in lying to stand-on device in standing. ●, Lymphedema group; □, control group; T, range for all data excluding outside values[†]; —, median of all data; □, 25th to 75th percentile of all data; ·····, lines connecting paired data for two participants, A and B. [†] Defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (MedCalc Software bvba).

measurement of all body segments automatically, and there is no requirement for ongoing consumable electrodes.

There are strengths and limitations of this study. The main strength is that the two devices were compared to each other at the same time following the same protocol and all aspects of the protocol were completed by two trained research assistants. Participants were also from a broad range of ages and BMIs, although neither age nor BMI matched between groups. Limitations include that this study is limited to comparing two particular impedance devices and the results may not be generalizable to measurements obtained with impedance devices from other manufacturers. Although both devices are capable of measuring impedance of the legs, these results are applicable to arms only.

In conclusion, this study has shown that both measurement approaches reliably measure arm impedance and L-Dex scores. They are, however, not directly interchangeable. The two methods are within 3% equivalence, but nevertheless, this difference has the potential for misclassification of a small number of individuals when transferring between devices. It is recommended to avoid using the two devices interchangeably, particularly for serial monitoring of patients in prospective surveillance and early intervention model of care programs, where 6.5 L-Dex (≈ 2 SD impedance ratio) or 10 L-Dex (3 SD) unit change may be considered clinically significant and trigger early intervention.^{40,41}

Acknowledgment

The authors thank Emma Moloney and Alice Johnson for assistance with data collection.

Authors' Contributions

L.A.K.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, writing—original draft, and writing—review and editing. L.C.W.: data curation and analysis, methodology, supervision, writing—original draft, and writing—review and editing. C.D.: conceptualization, data curation and analysis, methodology, supervision, writing—original draft, and writing—review and editing. J.B.: conceptualization, data curation and analysis, methodology, supervision, writing—original draft, and writing—review and editing.

Author Disclosure Statement

L.A.K. has acted as an Education Consultant to ImpediMed Limited. L.C.W. provides consultancy services to ImpediMed Limited. ImpediMed Limited had no involvement in the conception, design, execution, and data analysis for this study or in the preparation of the article. ImpediMed Limited was sent the final draft version before submission to confirm technical information was accurate. All other authors declare that they have no individual conflicts of interest or financial ties to disclose.

Funding Information

This research was financially supported by a grant from ImpediMed Limited for data collection to the Australian Lymphoedema Education, Research and Treatment (ALERT) Program, Macquarie University.

References

1. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys Ther* 2006; 86:205–214.
2. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphat Res Biol* 2005; 3:208–217.
3. Bernas M. Assessment and risk reduction in lymphedema. *Semin Oncol Nurs* 2013; 29:12–19.
4. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol* 2013; 14:500–515.
5. Hayes S, Di Sipio T, Rye S, et al. Prevalence and prognostic significance of secondary lymphedema following breast cancer. *Lymphat Res Biol* 2011; 9:135–141.
6. Holmes JM, Bryan C, Lytle LA, et al. Impact of lymphedema and arm symptoms on quality of life in breast cancer survivors. *Lymphology* 2010; 43:1–13.
7. Ward LC. Bioelectrical impedance analysis: Proven utility in lymphedema risk assessment and therapeutic monitoring. *Lymphat Res Biol* 2006; 4:51–56.
8. Thomas BJ, Ward LC. Bioelectrical impedance analysis for measurement of body fluid volumes a review. *J Clin Eng* 1992; 17:505–510.
9. Cornish BH, Chapman M, Hirst C, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology* 2001; 34:2–11.
10. Ward L, Winall A, Isenring E, et al. Assessment of bilateral limb lymphedema by bioelectrical impedance spectroscopy. *Int J Gynecol Cancer* 2011; 21:409–418.
11. Soran A, Ozmen T, McGuire KP, et al. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection; a prospective observational study. *Lymphat Res Biol* 2014; 12:289–294.
12. Cornish B. Bioimpedance analysis: Scientific background. *Lymphat Res Biol* 2006; 4:47–50.
13. Ward LC, Bunce IH, Cornish BH, Mirolo BR, Thomas BJ, Jones LC. Multi-frequency bioelectrical impedance augments the diagnosis and management of lymphoedema in post-mastectomy patients. *Eur J Clin Invest* 1992; 22:751–754.
14. Koelmeyer LA, Borotkanics RJ, Alcorso J, et al. Early surveillance is associated with less incidence and severity of breast cancer-related lymphedema compared with a traditional referral model of care. *Cancer* 2019; 125:854–862.
15. van Zanten MPN, Ward L. Inter-changeability of impedance devices for lymphedema assessment. *Lymphat Res Biol* 2015; 1–7.
16. ImpediMed Ltd. 2018–2019. <https://www.hellosozo.com/>. Accessed on January 7, 2019.
17. Esco MR, Freeborn TJ, Moon JR, Wingo JE, Ciccone Z, Holmes CJ, Hornikel B, Welborn B. Agreement between supine and standing bioimpedance spectroscopy devices and dual-energy X-ray absorptiometry for body composition determination. *Clin Physiol Funct Imaging* 2019; 5:355–361.
18. Cheng M-f, Chen Y-Y, Jang T-R, Lin W-L, Chen J, Hsieh K-C. Total body composition estimated by standing-posture 8-electrode bioelectrical impedance analysis in male wrestlers. *Biol Sport* 2016; 33:399–405.
19. Wang JG, Chen HE, Li Y, Cheng XG, Xu L, Guo Z, Zhao XS, Sato T, Cao QY, Chen KM, Li B. Comparison of two bioelectrical impedance analysis devices with dual energy

- X-ray absorptiometry and magnetic resonance imaging in the estimation of body composition. *J Strength Cond Res* 2013; 27:236–243.
20. Peterson JT, Parascand CR. Accuracy of consumer grade bioelectrical impedance analysis devices compared to air displacement plethysmography. *Int J Exerc Sci* 2011; 4: 176–184.
 21. Kim L, Jeon JY, Sung IY, Jeong SY, Do JH, Kim HJ. Prediction of treatment outcome with bioimpedance measurements in breast cancer related lymphedema patients. *Ann Rehabil Med* 2011; 35:687–693.
 22. Perdomo M, Levenhagen K, Davies C, Gilchrist L. Update on bioelectric impedance analysis for upper-quadrant lymphedema: Comments from CPG authors. *Rehabil Oncol* 2018; 36:151.
 23. Thurlow S, Sahota P, Oldroyd B, Hind K. Effects of procedure, upright equilibrium time, sex and BMI on the precision of body fluid measurements using bioelectrical impedance analysis. *Eur J Clin Nutr* 2018; 72:148–153.
 24. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2009 Consensus Document of the International Society of Lymphology. *Lymphology* 2009; 2:51–60.
 25. Ward LC. Bioelectrical impedance spectrometry for the assessment of lymphoedema: Principles and practice. In: Greene AK, Slavin SA, Brorson H, eds. *Lymphedema*. Cham: Springer International Publishing; 2015: 123–132.
 26. Cornish BH, Thomas BJ, Ward LC. Optimizing electrode sites for segmental bioimpedance measurements. *Physiol Meas* 1999; 20:241–250.
 27. Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics* 1989; 45:255–268.
 28. Bland JM. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 327:307–310.
 29. Lakens D. Equivalence tests: A practical primer for t tests, correlations, and meta-analyses. *Soc Psychol Personal Sci* 2017; 8:355–362.
 30. Ward LC. Early diagnosis in latent phase. In: Lee BB, Bergan J, Rockson S, eds. *Lymphedema*. London, United Kingdom: Springer-Verlag London Limited; 2011:105–109.
 31. Ward LC. Bioelectrical impedance analysis for body composition assessment: Reflections on accuracy, clinical utility, and standardisation. *Eur J Clin Nutr* 2019; 73:194–199.
 32. Ward L, Kilbreath SL, Cornish B. Bioelectrical impedance analysis for the early detection of lymphoedema. In: Weissleder H, Schuchhardt C, eds. *Lymphedema Diagnosis and Therapy*. Essen: Viavital Verlag GmbH; 2008:502–518.
 33. Laidley A, Anglin B. The impact of L-Dex((R)) measurements in assessing breast cancer-related lymphedema as part of routine clinical practice. *Front Oncol* 2016; 6:192.
 34. Ward LC. Inter-instrument comparison of bioimpedance spectroscopic analysers. *Open Med Devices J* 2009; 1: 3–10.
 35. Maw GJ, Taylor NA. Redistribution of body fluids during postural manipulations. *Acta Physiol Scand* 1995; 155:157–163.
 36. Scharfetter H, Monif M, László Z, Lambauer T, Hutten H, Hinghofer-Szalkay H. Effect of postural changes on the reliability of volume estimations from bioimpedance spectroscopy data. *Kidney Int* 1997; 51:1078–1087.
 37. Zhu F, Wang E, Levin NW. Dynamics of segmental extracellular volumes during changes in body position by bioimpedance analysis. *J Appl Physiol* 1998; 85:497–504.
 38. van Velze CA, Kluever, I, van der Merwe, CA, Mennen, U. The difference in volume of dominant and nondominant hands. *J Hand Ther* 1991; 4:6–9.
 39. Ward LC, Dylke ES, Kilbreath SL. Measurement of hand volume by bioelectrical impedance spectroscopy. *Lymphat Res Biol* 2012; 10:81–86.
 40. Ridner SH, Dietrich MS, Spotanski K, et al. A prospective study of L-Dex values in breast cancer patients pretreatment and through 12 months postoperatively. *Lymphat Res Biol* 2018; 16:435–441.
 41. Fu MR, Cleland CM, Guth AA, et al. L-dex ratio in detecting breast cancer-related lymphedema: Reliability, sensitivity, and specificity. *Lymphology* 2013; 46:85–96.

Address correspondence to:
 Louise A. Koelmeyer, BAppSc (OT)
 Australian Lymphoedema Education, Research
 and Treatment Program
 Department of Clinical Medicine
 Faculty of Medicine and Health Sciences
 Macquarie University
 Sydney
 Australia

E-mail: louise.koelmeyer@mq.edu.au