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Diagnostic accuracy of bioimpedance spectroscopy in patients with lymphedema: A retrospective cohort analysis

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Lymphedema;
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Summary *Background:* Bioimpedance spectroscopy (BIS) is used by healthcare specialists to diagnose lymphedema. BIS measures limb fluid content by assessing tissue resistance to the flow of electric current. However, there is debate regarding the validity of BIS in diagnosing early lymphedema. Indocyanine green (ICG) lymphography has been established as the most accurate diagnostic modality to date for lymphedema diagnosis. In this retrospective study, we test the sensitivity, specificity, and diagnostic accuracy of BIS in diagnosing lymphedema by referencing its results with ICG lymphography.
Methods: Patients presented to the University of Iowa Lymphedema Center from 2015 to 2017 were evaluated with a standardized protocol that included history and physical examination, a validated lymphedema-specific quality-of-life assessment (LYMQOL), circumference –measurement-based index, BIS, and ICG lymphography. Diagnostic accuracy of BIS was assessed using ICG lymphography as a reference test.
Results: Fifty-eight patients had positive ICG lymphography results, which confirmed the diagnosis of lymphedema. ICG lymphographic findings consistently correlated with clinical examination, LYMQOL evaluation, and lymphedema indices. By contrast, BIS demonstrated a

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false-negative rate of 36% – 21 out of 58 patients had normal BIS readings, but a positive ICG lymphography result. The 21 false-negative results occurred in patients with early-stage disease. Sensitivity and specificity for BIS were 0.64 and 1, respectively.

Conclusion: BIS carries an excessively high rate of false-negative results to be dependably used as a diagnostic modality for lymphedema. ICG lymphography highly correlates with other tracking modalities, and it remains the most reliable tool for diagnosing lymphedema.

Introduction

Lymphedema is a condition in which lymphatic fluid and fibroadipose tissue atypically accumulate.[1] It presents as swelling of the arm or leg and can cause changes in the skin and tissue as it progresses.[1] It is a common complication following surgical treatments such as lymph node dissections for breast or gynecological cancers[2,3] due to damage of lymphatic vessels and/or lymph nodes. It may also be caused by congenital malformations of the lymphatic system. Later stages of lymphedema are often diagnosed through clinical presentation and history. However, earlier stages of lymphedema may be difficult to distinguish from limb edema caused by systemic conditions such as cardiac failure, chronic venous insufficiency, or myxedema. Currently, various tools including clinical examination, limb measurements (e.g., limb circumference, water displacement, and perometry), bioimpedance spectroscopy (BIS), and advanced imaging such as lymphoscintigraphy and indocyanine green (ICG) lymphography are being used to assess and diagnose lymphedema.

BIS is a simple-to-use, noninvasive tool that has been used for the past few decades to assess lymphedema.[4] BIS determines the quantity of extracellular fluid (ECF) by measuring tissue resistance to the flow of electric current. Current flow through the heterogenous tissues of a limb depends upon the relative conductivities of the different tissues.[5] Bone and adipose tissue are insulators and have a higher impedance, whereas interstitial fluids and muscles are conductive, reducing impedance.[4] The ImpediMed L-Dex U400 was the first BIS device in the U.S. to be cleared by the FDA and it aids in the clinical assessment of unilateral lymphedema,[6] with no disclaimers in its 2013 FDA 510(k) Clearance Summary about not being used to predict or diagnose lymphedema. It has therefore been utilized experimentally and in studies for diagnostic purposes.[4,7–9] Reference thresholds for lymphedema have been derived for BIS and are currently set at three standard deviations (3SD) above the mean impedance ratios of a healthy control population.[10,11] Additionally, the L-Dex U400 produces a linearized Lymphedema Index (L-Dex) value reflecting the impedance ratio of the unaffected and affected limb, with an L-Dex score above 10 indicative of lymphedema.[12]

More recently, two advanced imaging techniques that directly observe the lymphatic system, lymphoscintigraphy and ICG lymphography, are being utilized to diagnose lymphedema. Lymphoscintigraphy is a nuclear medicine imaging test that uses radioactive tracers and a gamma camera to detect lymphatic transport. Lymphoscintigraphy is considered a valid reference standard for diagnosing early lymphedema.[7,13] However, ICG lymphography is a newer technique that has a higher sensitivity and specificity than lymphoscintigraphy.[14] ICG lymphography allows for quick pathological visualization of superficial lymph flow in real-time, without radiation exposure. It precisely and reliably diagnoses, tracks, and stages lymphedema severity, ranging from subclinical or early lymphedema to more advanced cases.[14–17] However, it is not used often unlike basic diagnostic tools because it is less financially sustainable in institutions that do not frequently perform imaging with the machine to offset its initial costs. Therefore, it is primarily used or available in large hospitals and academic institutions.

BIS has been used for both diagnostic and disease management purposes, as it has high specificity (80–99%).[10,18–20] However, its sensitivity remains disputed owing to the wide range of sensitivities observed (30–100%), specifically regarding early lymphedema.[10,18–21] This raises questions on the validity of the reference standards used to test BIS and the ability of BIS to detect the disease early. Advanced imaging with ICG lymphography or lymphoscintigraphy is considered an accurate reference standard for the diagnosis of lymphedema, as dermal backflow patterns are exclusively seen in individuals with lymphedema.[7,16,22] No study has exclusively compared BIS to ICG lymphography to date. In this study, we test the sensitivity, specificity, and diagnostic accuracy of BIS in diagnosing lymphedema by referencing its results with those from ICG lymphography. Our goals were to determine the validity of BIS as a diagnostic tool and identify its ability to diagnose early lymphedema, as more accurate diagnoses and prompt management of lymphedema will result in the prevention of disease sequela and more cost-effective medicine.

Methods

Participants

In this retrospective study, we looked at records of patients who initially presented to the University of Iowa Lymphedema Center with suspected upper extremity (UEL) or lower extremity lymphedema (LEL) between January 1, 2015, and March 9, 2017. This study was approved by the University of Iowa Institutional Review Board and followed the Declaration of Helsinki guidelines. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines were adhered to as well.

Measurements were made at a single session, as part of a pre-lymphatic surgery evaluation. Patient records were excluded if the patient was not assessed using both BIS and