Chapter 14
Early Diagnosis in Latent Phase

Leigh C. Ward

Lymphedema is typically characterized by the time of onset (staging) and the severity of the symptoms (grading). Various staging schemes have been proposed, but increasingly most use a four-stage scale: stage 0, a latent or subclinical phase when swelling is not evident, although lymphatic insufficiency is presumed; stage I, accumulation of tissue fluid that generally resolves with elevation of the affected limb with minimal swelling (<20% increase); stage II, when elevation fails to reduce a moderate amount of swelling (20–40% increase) and pitting edema is present; and stage III, irreversible, severe (>40% increase) swelling is present and the tissue is fibrotic.[1] Despite the absence of outward clinical signs of lymphedema in the latent stage, lymphoscintigraphy or lymphangiography shows disrupted lymphatic function.[2] Detection of patients in the latent phase has been recognized as important for identification of those in whom advanced lymphedema may occur.[3] This enables therapeutic intervention at the earliest opportunity, which has been shown to be more effective than intervention after lymphedema has become established,[4] but this approach is predicated on the ability to detect lymphedema in the latent phase.

A wide variety of objective methods, other than clinical examination, are available for the detection of lymphedema.[5] However, many are either technologically complex (e.g., magnetic resonance imaging [MRI] or dual energy X-ray absorptiometry [DEXA]), invasive, and involve a radiation hazard (e.g., isotopic lymphoscintigraphy) or are otherwise not suitable for routine clinical use because of cost, e.g., computed tomography (CT). The most commonly used techniques for lymphedema detection are those based on detecting an increase in volume due to the presence of edema and include water displacement, opto-electrical perometery, bioelectrical impedance and circumferential measurements. Unfortunately, because, by definition, the latent phase of lymphedema is that prior to detectable swelling, the utility of such techniques is questionable. Nevertheless, such methods are currently

L.C. Ward
School of Chemistry and Molecular Biosciences,
The University of Queensland, Queensland, Australia

B.-B. Lee et al. (eds.), *Lymphedema*,
DOI 10.1007/978-0-85729-567-5_14,

Table 14.1 Accuracy and precision of methods for assessment of lymphedema of the limbs

Method	Accuracy	Precision and reproducibility[a]	References
Impedance	<±1%	ICC > 0.94 (15 Ω, ~4%)	[8,9]
Water displacement	±0.5%	ICC > 0.94 (81 mL, ~4%)	[10-13]
Perometry	±2%	ICC > 0.99 (81 mL, ~ 4%)	[8,10,13]
Tape measurement	±1%	ICC > 0.95 (85 mL, ~4%)	[8,12,13]

ICC intra-class correlation coefficient
[a]Absolute values and approximate percentage of measured value

accepted as the best measurement options to detect pre-clinical lymphedema.[6] Stout Gergich and colleagues[4] defined a 3% change in volume from a baseline or pre-operative measurement in the case of secondary lymphedema as a diagnostic criterion for subclinical lymphedema. They further suggested that, in the absence of perometry, (which was used in their study), other tools that assess swelling, such as water displacement, bioimpedance or girth measurements, may be equally useful. Unfortunately, there are no universally recognized diagnostic criteria for each of these methods and equivalence between instruments has not been defined. Furthermore, assessment of lymphedema lags behind many other branches of science where standardization of measurement has long been recognized as the key to quality control and assurance. Preference should be given to methods of assessment that meet accepted standards for accuracy, precision, sensitivity, and specificity of measurement, and that are practical and applicable for routine clinical use.[7]

Accuracy can be difficult to assess because the "true" value, i.e., the smallest change in the measured parameter (volume, impedance, or girth) presumptive of lymphedema, is unknown. It is necessary to resort to using "phantoms" of precisely known characteristics, such as cylinders of known volume or electronic circuits of known impedance. Precision or reproducibility of measurement is more easily determined from repeated measurements, using either phantoms or human subjects. Published data, summarized in Table 14.1, suggests that the various methods used to assess early-stage lymphedema perform similarly with an accuracy of about ±1% and reproducibility of approximately ±4% standard error of measurement.

Of greater importance for the detection of sub-clinical lymphedema than absolute accuracy or precision is the limit of detection; the magnitude of difference for a given measurement parameter that can be reliably detected. This is calculated as the minimal detectable change (MDC) and is given by 1.96 ±2 SEM (standard error of measurement).

The MDC for volume measurements is approximately 140 mL, assuming a typical SEM of 50 mL for volumetric measurement. This can be compared with the generally accepted inter-limb difference of 200 mL used as a detection threshold for breast cancer-related lymphedema (BCRL). Czernieic et al.[8] have shown that a minimum of a 120-mL change is required to account for normal fluctuation in limb volume in the absence of lymphedema to be confident of an effect while Stout Gergich and colleagues[4] have recommended a 3% change in perometrically measured volume from a pre-lymphedema baseline measurement as a threshold for lymphedema treatment intervention. With respect to impedance measurements, similar calculations suggest a detection limit of approximately 40 Ω or an inter-limb

Table 14.2 Comparison of potential technologies for the early detection of lymphedema

	Cost	Portability	Ease of use	Time involved	Patient convenience	Operator skills
Impedance	Low to high	High	High	Low	High	Low
Perometry	Very high	None to medium	High	Low	High	Low
Tape	Very low	High	High	High	Medium to high	Low
Water displacement	Very low	Low	Medium to high	Medium	Low	Low

ratio difference of 0.04 in BCRL.[8] Again, larger change is required (a ratio of 0.08) to account for normal fluctuation of approximately 4.8%.[8] We should, however, question the relevance of this to the detection of pre-clinical lymphedema. By definition, lymphedema in the latent phase is *prior to* a detectable change in volume. On this basis, simple volumetric measurements, irrespective of how small the limit of detection, can never be used for lymphedema assessment at this early stage. Equally, bioimpedance techniques are not suitable either, since the magnitude of changes in impedance equate to changes of comparable magnitude in volume.

A more pragmatic approach is to assess promising technologies on the basis of their practicality in use and sensitivity and specificity for detection at the earliest opportunity. Surprisingly, relatively few studies have been undertaken. Despite detection thresholds such as a 200-mL volume difference being widely promulgated, the evidence base for their validity is sparse and sensitivity and specificity analyses are few in number.[7] Box et al.[14] demonstrated a 100% confirmation of BCRL in women when using a 200 mL detection threshold, but this cannot be classed as latent phase lymphedema. Hayes et al.[15] showed, again in women with BCRL, that compared with bioimpedance, set at 100%, circumferential measurements of the arm had good specificity (88–100%), but much worse sensitivity (35%). The data of Cornish et al.[16] are perhaps most persuasive that bioimpedance, at least, may be capable of detecting changes indicative of impending lymphedema at an early stage. In a prospective study, BCRL was detectable by bioimpedance up to 10 months prior to clinical confirmation. This study has yet to be confirmed and extended to other forms of lymphedema, but provides encouragement that using relatively simple non-invasive technology lymphedema may be detectable in the latent phase or at least prior to observable changes in volume. The sensitivity of impedance assessment over other diagnostic modalities is supported by the theory on which the technology is based. The impedance that is measured is solely that of the extracellular fluid, which includes the lymph.[17] In contrast, simple volume measurement, be it by water displacement, perometry or tape measure, is that of the total tissue and may be confounded by changes in tissue compartments other than lymph, e.g., adipose tissue mass.

Detection of latent phase lymphedema implies screening of at-risk individuals. It is therefore important that the instruments adopted for assessment are fit for this purpose. Ease of use and cost are important considerations in the uptake of technologies into routine clinical practice. All of the methods referred to above have their advantages and disadvantages (Table 14.2). A tape measure is inexpensive to

purchase and is, undoubtedly, easy to use, but its use is time-consuming. Perometry is also easy to use and rapid to perform, but initial equipment costs are high. Water displacement is inexpensive, but may not always be suitable, for example, where there are infections or wounds. Impedance is rapid to perform, with modest cost (dependent upon instrumentation), but its utility for all forms of lymphedema has yet to be established.

In conclusion, detection of lymphedema in the latent phase poses significant challenges. The definition of latent phase or sub-clinical lymphedema that it is prior to appearance of swelling appears to preclude many of the methods currently used to detect lymphedema. Other than technologies that measure lymphatic function, such as lymphoscintigraphy, covered elsewhere in this volume, tools in current use without exception measure volume either directly or indirectly as in the case of impedance. Nonetheless, the routine use of these techniques is of clinical value, particularly where change compared with baseline measures are available, as shown by the work of Stout Gergich.[4] Maximum benefit will be gained by routine surveillance of those at risk of developing lymphedema. At present, the tool most suited for this purpose appears to be impedance in that it is suitable for home use by those at risk of or with incipient lymphedema.[18] It would be remiss, however, not to additionally acknowledge the importance of self-report by those with lymphedema. Objective assessments in current use may simply not be measuring the correct parameters that characterize the subtle early changes in tissue morphology and physiology that occur in the latent phase. These may, however, be apparent to the patient. Much additional research into the biology of the development of early-stage lymphedema is required to allow us to determine the optimal detection strategy.

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