Quantifying Lymphedema with Non-Invasive Methodology
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Quantifying Lymphedema with Noninvasive Methodology

- Physical Principles
- Practical Aspects
- Potential Limitations

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Why Measure/Quantify?

• Track at-risk patients
• Early detection → Early Tx
• Severity stratification
• Treatment outcomes
• Documentation aspects
• Research related
Early Detection of Lymphedema

Pre-Surgical Baseline → Periodic Follow-ups

Threshold Change Detection

Measures and Criteria
- Limb Volumes and Metrics
- Limb Bioimpedance
- Local Tissue Water

Therapy Initiation

Goal: Earlier Detection and Intervention
A Rationale and Sensible Approach
Dr. HN Mayrovitz

Early Detection of Lymphedema
Methods Applicable to **LIMBS**

**Limb Girth (Circumference)**
- Girth $\rightarrow$ Limb Volume or Sum of Girths

**Limb Volume**
- Water Displacement $\rightarrow$ Limb Volume

**Limb fluid content and its change**
- Bioimpedance $\rightarrow$ BIA & BIS $\rightarrow$ Whole Limb
- Tissue Dielectric Constant (TDC) $\rightarrow$ Local

**Physical and Structural Properties**
- Tonometry / Indentometry $\rightarrow$ Various
- Imaging: Ultrasound - MRI - Other
Methods Applicable to MOST Sites

Fluid Content (TDC)
Tissue Dielectric Constant

- Head
- Face
- Neck
- Breast
- Trunk
- Foot
- Toe
- etc

Axilla
Thorax
Methods Applicable to MOST Sites

**Physical Properties**

**Tonometry/Identometry**

![Indentation](image)

**Tissue “Hardness”**

Healthy legs measured 10 cm proximal to the medial malleolus

- Formula: \( F = 108 \delta - 135 \text{ g} \)
- Correlation: \( r = 0.996, p < 0.001 \)
- Sample Size: \( N = 24 \text{ legs} \)

Hardness Changes with LLLT

Data from:
Mayrovitz HN & Davey S. Lymphology 2011;44:168-177
Hardness Changes with LLLT

Data from: Mayrovitz HN & Davey S. Lymphology 2011;44:168-177
Commercial Tonometers

Force Applied

Displacement Determined

Pallota O. J Lymphoedema 2011;6:34-41
Methods Applicable to MOST Sites

Imaging ➔ Ultrasound ➔ MRI ➔ Other

Ventral Forearm US-20 MHz

Gel

Entry Echo

Dermis

Subcutis

Normal

Lymphedematous

0.93 ± 0.13

1.83 ± 1.28

Metric Measures for LIMBS
Metric Measures for LIMBS

Tape Measure Girth at multiple points

• Measure both limbs
  → Inter-limb differentials and sequential changes

• Measure one limb
  → Sequential data but miss systemic changes

Mark then Measure
Segment Length
Limb Girth → Volume

Geometric Model or Algorithm

Circumferences @ 4 – 12 cm intervals

Manual

Volume Tracking

Affected Limb
Contralateral Limb
Edema Volume

V = L/3 (A₁ + A₂ + (A₁A₂)¹/²

General Frustum Calculation Model

Circular to elliptical volume ratio

\[ \frac{V_C}{V_E} = \frac{1}{4} \left( 1 + \alpha \right)^3 / \alpha (1 + \alpha) \]
Perometer: Girth → Volume

Mayrovitz HN et al. Advances in Wound Care 2000;113:272-276
Frame

IR Diode Array

IR Diode Array

D₁

D₂

Area = KD₁D₂
**Limb Girth & Volume LE Thresholds**

**GIRTH**
If unilateral then lymphedema if

- inter-side differential  $> C_1$ cm or

if unilateral or bilateral then

- change from pre-surgery  $> C_2$ cm

**VOLUME**
If unilateral then lymphedema if

- inter-side differential  $> V_1$ ml or

- inter-side ratio  $> \gamma$

if unilateral or bilateral then

- change from pre-surgery  $> V_2$ ml
Arm Lymphedema Metric Criteria

LE rate dependent on criteria used

Differences
• Between sides
• or vs. baseline

Data from: Armer et al. J. Lymphoedema 2009;4:14-18
Practical Aspects of Limb Girth
For Reproducibility: Mark along flat

Mark in Relation To FLAT Surface

NOT along limb

Source of large Follow-up error

Dr HN Mayrovitz
What Segment Length to Use?
What Segment Length to Use?

<table>
<thead>
<tr>
<th>Segment Length</th>
<th>Pre-Treatment Volumes (ml)</th>
<th>Post-Treatment Volumes (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 cm</td>
<td>6649 ± 2482*</td>
<td>5465 ± 1969*</td>
</tr>
<tr>
<td>8 cm</td>
<td>6676 ± 2497</td>
<td>5496 ± 1990</td>
</tr>
<tr>
<td>12 cm</td>
<td>6756 ± 2510</td>
<td>5554 ± 2001</td>
</tr>
</tbody>
</table>

Bilateral lower extremity lymphedema

Mayrovitz et al. Physical Therapy 2007; 87: 1362-1368
Limb Shape as a Factor
If you calculate on the basis of THIS and its really more like THIS then you obtain a volume greater than the true value.
Limb Shape as a Factor

Ve = 0.938 Vc

@ b/a → 0.68
6.2% volume deviation

C1 = 31.4 cm
C2 = 28.3 cm
L = 10 cm

Data from: Mayrovitz HN, Lymphology 2003;31:140-143
Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis

LE if change in edema volume $\geq 5\%$ from pre-surgery

Volumes via $H_2O$ Displacement

Mostly used as a so-called gold standard when comparing other methods and in research studies

Photo from: K. Johansson & E Branje Acta Oncologica 2010;49:166-173

Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis

LE if change in edema volume $\geq 5\%$ from pre-surgery
Normal Arm Volume Differentials

Normal Arm Volume Differentials

At-risk Arm Is:
- Dominant
- Non-Dominant

If dominant = at-risk
Then Greater Threshold

Girths via Perometer $\rightarrow$ Volumes via frustum calculation

Data from: Dylke ES et al Lymphatic Res Biology 2012;10:182-188
Hand Volume
Hand Volume: H$_2$O Displacement

\[ \text{Seg Vol} = kZ \left[ A_i + A_{i+1} + \left( A_i - A_{i+1} \right)^{1/2} \right] \]

From: Mayrovitz HN et al. Lymphology 2006;39:95-103
Algorithm vs. Water Displacement

\[ V_M = 1.02 \, V_W - 12.0 \, \text{ml} \]

\[ r = 0.985, \, p < 0.001 \]

N = 60 Hands

LOA \pm 9.8%
Hand Volume: $\text{H}_2\text{O}$ vs. Perometer

Perometer values $\sim 7.5\%$ greater than $\text{H}_2\text{O}$ values

$r \sim 0.88$

Hand Volume: H₂O vs. Perometer

Perometer values ~ 7.5% greater than H₂O values

Figure-of-Eight: Hand volume Surrogate

Pellecchia GL J Hand Therapy 2003;16:300-304
Maihafer GC J Hand Therapy 2003;16:305-310

cm (fig-8) vs. H₂O displacement (ml)

R = 0.94-0.95 but only normal hands
Tracking ability unproven
Foot Volume: $\text{H}_2\text{O}$ Displacement

Foot Volume: $H_2O$ Displacement

Water Displacement Compared to Metric Measures

Algorithm vs. Water Displacement

\[ V_M = 1.00 V_W + 1.67 \text{ ml} \]

\[ R^2 = 0.931; \ p < 0.001 \]

\[ N = 60 \text{ feet} \]

\[ \text{LOA} = \pm 9.3\% \]

<table>
<thead>
<tr>
<th>Water Displacement</th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Direct – Accurate Limb/Hand/Foot volumes</td>
<td>• Impractical for whole limbs</td>
</tr>
<tr>
<td></td>
<td>• Especially for irregularly shaped limbs</td>
<td>• Bulky equipment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• sterilization procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient mobility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient flexibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Open wounds</td>
</tr>
<tr>
<td>Manual Girth</td>
<td>• Low cost</td>
<td>• Multiple measurements</td>
</tr>
<tr>
<td></td>
<td>• Portable</td>
<td>• Time factor</td>
</tr>
<tr>
<td></td>
<td>• Easy to use</td>
<td>• Volumes from calculations</td>
</tr>
<tr>
<td></td>
<td>• Whole legs measurable</td>
<td>• Site repeatability</td>
</tr>
<tr>
<td></td>
<td>• Hand &amp; Foot algorithms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Limited ROM no issue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Wounds are not an issue</td>
<td></td>
</tr>
<tr>
<td>Optoelectronic</td>
<td>• Quick – Easy</td>
<td>• Accuracy depends on proper positioning</td>
</tr>
<tr>
<td>(Perometer)</td>
<td>• Small segment lengths</td>
<td>• Patient mobility</td>
</tr>
<tr>
<td></td>
<td>• Stored Measurements</td>
<td>• Patient flexibility</td>
</tr>
<tr>
<td></td>
<td>• Automatic processing</td>
<td>• Not portable</td>
</tr>
<tr>
<td></td>
<td>• Selective processing</td>
<td>• Space requirements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• $$$</td>
</tr>
</tbody>
</table>
Bioimpedance Analysis

- Electrical Impedance of a limb depends on the limb’s volume and constituents
- Lymphedema $\rightarrow$ increase in low resistance fluid content of the limb

- Bioimpedance (BIOZ)
- Bioimpedance Spectroscopy (BIS)
- Bioimpedance Analysis (BIA)
- Single Frequency BIA = SFBIA
- Multi-Frequency BIA = MFBIA
Muscle
Bone
Skin
Fat
5-10% H_2O
70-75% H_2O
15-20% H_2O

Limb Conducting Structures

Conductivity @ 5KHz Relative to Bone

1 Bone
20 Muscle
2 Fat
Basic Operating Principle

No cells
Just saline

R = E/I
Basic Operating Principle

\[ R = \frac{E}{I} \]

- Polarized
- Charge Separation
- Electrical Capacitance

No cells
Just saline

Cell Membrane
Basic Operating Principle

Sinusoidal Voltage Excitation

No cells
Just saline

Low Frequency

High Frequency

$Z = \frac{E}{I}$

Current increases with frequency
Frequency Analysis Basis

Z = E / I

Cell Membrane

Cell Interior ICW

Cell Exterior ECW
Cole-Cole Plot: estimate parameters

\[ MFBIA = BIS \]

Increasing frequency

High \( f \)

Low \( f \)

\[ R_\infty \]

\[ R_0 \]

\[ R_i R_e / (R_i + R_e) \rightarrow ECW + ICW \]

ECW \[ \leftarrow R_e \]
Basic Operating Principle

Current Injecting Electrodes

Voltage Measuring Electrodes

\[ Z = \frac{E}{I} \]
Leg Volumes: Supine $\rightarrow$ Stand

Blood volume shift to lower extremities

Girth-Volume Measurements

Supine | Standing | Supine

Leg Volume (ml)

Time (minutes)
Z Depends on Frequency & Volume

|Z| (Ω) | Time (minutes) |
|---|---|
|Supine| Standing| Supine|
|500 KHz| 5 KHz|
Assessing Arm Lymphedema
Assessing Arm Lymphedema

\[
Z = \frac{V}{I}
\]
## Multi-Frequency BIA

<table>
<thead>
<tr>
<th></th>
<th>Nondomnant</th>
<th>Dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0$</td>
<td>360.1 ± 45.8</td>
<td>354.8 ± 45.9</td>
</tr>
<tr>
<td>$R_\infty$</td>
<td>266.5 ± 39.2</td>
<td>257.8 ± 39.4</td>
</tr>
<tr>
<td>$R_i$</td>
<td>1052.3 ± 276.2</td>
<td>966.7 ± 264.9</td>
</tr>
<tr>
<td>$R_i$</td>
<td>2.988 ± 0.653</td>
<td>2.781 ± 0.595</td>
</tr>
<tr>
<td>$R_0^{\text{DOM}}$</td>
<td>0.986 ± 0.040</td>
<td></td>
</tr>
<tr>
<td>$R_0^{\text{NONDOM}}$</td>
<td></td>
<td>172 paired arms</td>
</tr>
</tbody>
</table>

**3SD lymphedema thresholds**

- nondom/dom = at-risk
  - dom = 1.134
  - nondom = 1.106

*Data from: Ward LC et al. Lymphatic Research Biology 2011;9:47-51*
SFBIA = MFBIA for estimating ECW

So .... Why use MFBIA (BIS)?

Proposed Concept

• If $\text{ICW}$ relatively unchanged even with LE then may not have to depend on inter-arm ratios

• May be approximately true if muscle mass does not significantly change since the largest fraction of $\text{ICW}$ is associated with muscle

\[
\frac{\text{ECW}}{\text{ICW}}
\]
ECW / ICW Ratios

Data from: Cornish BH et al. Angiology 2002;53:41-47
Tissue Dielectric Constant (TDC)  
Relative Permittivity ($\varepsilon_r$)  

PRINCIPLE
What is Dielectric Constant?

H$_2$O Molecule

Charge Separation

Dipole
What is Dielectric Constant?

Hydrogen bonding between water molecules

2 molecules

“Hook-up”
What is Dielectric Constant?

Time varying electric field of force - $E$

Dipole movement Displacement - $D$

$D = \varepsilon_0 E = \varepsilon_r \varepsilon_0 E$

$\varepsilon_r = \text{ratio } \varepsilon/\varepsilon_0 = \text{TDC}$

H$_2$O @ 32°C $\implies \varepsilon_r = 76$
Measurement Devices

- Multi-Probe
- Single Probe (compact)
Effective Measurement Depths

0.5 mm                1.5 mm                         2.5 mm

Outer Diameters

10 mm                       15 mm                            22 mm

MoistureMeter-D
• Low power 300 MHz incident wave
• Reflected wave depends on the tissue’s dielectric constant
• Dielectric constant depends on total tissue water (free + bound)
• Pure water has a dielectric constant of about 78
• Calibrated for each probe from 1 - 80

Penetration Depth (0.5 – 5 mm)

0.5  1.5 2.5  5.0 mm
Display has pressure bar indicator during measurement.

Effective measurement depth is between 1.5 & 2.5 mm.

Multi-Probe 20 mm

Artery
Nerve
Capillary
Duct
Epidermis
Dermis
Arteriole
Hair
Pore
Fat
Hypo-Dermis

20 mm

Single Probe (Compact)
**Effective Measurement Depth**

![Diagram showing skin, center conductor, outer conductors, and electric field lines. The diagram includes a graph illustrating the effective measurement depth with a 2.5 mm depth probe.](image-url)
Effective Measurement Depth

Modified from Mellor et al. The Breast J. 2004;10:496-503
Calibration Example
(2.5 mm probe)

\[ Y = 0.632 \, X - 22.1 \]
\[ r^2 = 0.998, \, p < 0.001 \]
Skin Water Distribution

Data: Nakagawi N et al. SRT, 2010:16:137-141; Confocal Raman Spectroscopy


Skin Water Content (%)

Skin Depth (μm)

Epidermis

Dermis

N = 60

60-68 yrs

20-24 yrs

Dermis 70-75% H₂O

70-90% Bound

a

b
Free and Bound Water

Protein (1 g)

Bound H₂O (0.2 – 0.5 g)

Limited Mobility H₂O ~ 20 g

Free Mobile
Fluid Protein Blood Vessel
Lymphatic Dysfunction

Interstitium

Bound and immobile water not readily measurable with Standard BIA

Blood Vessel

Lymph Vessel
Dermal Water in Lymphedema

Mobile water shows intense

Contralateral Leg

Lymphedema calf

40% increase in Calf Dermal Water in Lymphedema

11 primary LE
10 secondary LE

TDC Features and Applications
TDC Site Variability

32 females
19 - 77 years
1.5 mm Depth

Data From: Mayrovitz HN et al. Skin Research and Technology 2013;19:47–54
TDC Site Variability

Data from: Mayrovitz HN et al. Skin Research and Technology 2012;18:504–510

N = 30 young adult males (25.0 ± 2.5 years) @ 1.5 mm depth
Correlation with Total Body Water

N = 130 (50 females)
Age 26.1 ± 3.0 (19-39)
BMI 24.5 ± 4.0 (16-40)

Y = 0.929 X – 22.3
r = 0.740, p < 0.001
TDC Depth Dependence: Forearm

TDC = 32.44 $\delta^{-0.185}$

$r^2 = 0.997$, $p<0.001$

N = 80 females

Pattern of Depth Dependence May Vary by Site
Cuff inflated to 50 mmHg to increase vascular volume and change skin blood flow.
TDC Vascular Component

Large vascular blood volume & flow changes

Minor changes in TDC values

TDC Lymphedema Discriminations

Patients
Affected/Control
1.64 ± 0.30
N=18

Premenopausal
1.04 ± 0.04
N=15

Postmenopausal
1.04 ± 0.04
N=15

Mayrovitz HN Lymphology 2007;40:87-94
Pre-Surgery Reference TDC Ratios

<table>
<thead>
<tr>
<th>- Cancer Side</th>
<th>Healthy Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axilla</td>
<td>Axilla</td>
</tr>
<tr>
<td>N = 103</td>
<td>N = 80</td>
</tr>
<tr>
<td>Biceps</td>
<td>Thorax</td>
</tr>
<tr>
<td>1.012 ± 0.143 (1.45)</td>
<td>0.999 ± 0.119 (1.35)</td>
</tr>
<tr>
<td>Forearm</td>
<td></td>
</tr>
<tr>
<td>1.003 ± 0.096 (1.30)</td>
<td></td>
</tr>
</tbody>
</table>

(3 SD Thresholds)
Sequential TDC Ratio Changes

Lateral Thorax

Thorax TDC Ratio (At-Risk/Control Side)

- 0-3-6-12-18-24 month (N=35)
- 0-3-6-12-18 month (N=41)
- 0-3-6-9-12 month (N=47)
- 0-3-6 month (N=53)
- 0-3 month (N=60)
Sequential TDC Ratio Changes

**Axilla**

- 0-3-6-12-18-24 month (N=35)
- 0-3-6-12-18 month (N=41)
- 0-3-6-9-12 month (N=47)
- 0-3-6 month (N=53)
- 0-3 month (N=60)
## Methods Features Comparison

<table>
<thead>
<tr>
<th></th>
<th>TDC (Delfin Technologies Ltd)</th>
<th>BIA/BIS (Impedimed Ltd)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operating principle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequency applied</strong></td>
<td>EMF 300 MHz</td>
<td>4 - 1000 kHz</td>
</tr>
<tr>
<td><strong>Current flowing in the body</strong></td>
<td>Very Localized</td>
<td>Much of the body</td>
</tr>
<tr>
<td><strong>Number of electrodes / probes</strong></td>
<td>1 probe</td>
<td>4 electrodes</td>
</tr>
<tr>
<td><strong>Total single measurement time</strong></td>
<td>~ 8 sec</td>
<td>~ 60 sec</td>
</tr>
<tr>
<td><strong>Measurement Depth</strong></td>
<td>0.5 – 5 mm</td>
<td>Undefined</td>
</tr>
<tr>
<td><strong>Measurement quantity</strong></td>
<td>Tissue dielectric constant</td>
<td>Resistance</td>
</tr>
<tr>
<td><strong>Measurement parameter</strong></td>
<td>Skin-to-fat tissue fluid</td>
<td>Parameter ~ to ECF</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>Practically all body sites</td>
<td>Limbs</td>
</tr>
<tr>
<td><strong>Patient preparation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient position</strong></td>
<td>Any body position</td>
<td>Supine</td>
</tr>
<tr>
<td><strong>Arm-leg skin contact</strong></td>
<td>No effect</td>
<td>Limbs must be abducted</td>
</tr>
<tr>
<td><strong>Arm and hand position</strong></td>
<td>No restriction</td>
<td>Palms flat on surface</td>
</tr>
<tr>
<td><strong>Shoe and socks removal</strong></td>
<td>Not needed to remove</td>
<td>Must be removed</td>
</tr>
<tr>
<td><strong>Bladder emptying necessary</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Dominant side affects</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Measurement sites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hairy skin shaving</strong></td>
<td>Yes (very hairy)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Precautions for measurement</strong></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Patient metal contact problem</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>