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

Dr. HN Mayrovitz

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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

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Methods Applicable to MOST Sites

**Physical Properties**
*Tonometry/Identometry*

<table>
<thead>
<tr>
<th>Force (F, g)</th>
<th>Indentation Depth (δ, mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>280</td>
<td>280</td>
</tr>
<tr>
<td>320</td>
<td>320</td>
</tr>
<tr>
<td>360</td>
<td>360</td>
</tr>
<tr>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

*Healthy legs measured 10 cm proximal to the medial malleolus*

$F = 108 \delta – 135$ g

$r = 0.996, \ p < 0.001$

$N = 24$ legs

---

Mayrovitz HN
*Lymphology*
2009;42:88-98

*HNM-NLN-2014*
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

mm


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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

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Limb Girth $\rightarrow$ Volume

Geometric Model or Algorithm $\rightarrow$ Circumferences @ 4 – 12 cm intervals

General Frustum Calculation Model

$V = \frac{L}{3} \left( A_1 + A_2 + (A_1 A_2)^{1/2} \right)$

Volume Tracking

- Affected Limb
- Contralateral Limb
- Edema Volume

Manual

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Perometer: Girth $\rightarrow$ Volume

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

Frame

IR Diode Array

IR Diode Array

Area = KD_1 D_2
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

Manual

Automated

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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

Practical Aspects of Limb Girth
For Reproducibility: Mark along flat

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What Segment Length to Use?

Segment Length
4 cm
8 cm
12 cm

Volume Reduction
(ml) (%)
1183 ± 778 17.2 ± 7.1
1180 ± 782 17.1 ± 7.2
1202 ± 781 17.4 ± 7.0

N = 70

Bilateral lower extremity lymphedema

Pre-treatment Volumes

Post-treatment Volumes

>= 10 MLD Tx

Mayrovitz et al. Physical Therapy 2007; 87: 1362-1368

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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**

![Graph showing volume ratio (Ve/Vc) vs. ratio (b/a).]

- **Volume Ratio (Ve/Vc)**
- **Ratio (b/a)**

Data from: Mayrovitz HN, Lymphology 2003;31:140-143

Ve = 0.938 Vc

@ b/a → 0.68

6.2% volume deviation

C₁ = 31.4 cm
C₂ = 28.3 cm
L = 10 cm

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Volumes via H$_2$O 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

Given LAV predict RAV

Left Arm Volume (LAV, ml by H₂O)

Right Arm Volume (RAV, ml)

100 RH Females
RAV > LAV (2%)

95% +CI

Line of Identity

Normal Arm Volume Differentials

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

If dominant = at-risk
Then
Greater Threshold

Data from: Dylke ES et al Lymphatic Res Biology 2012;10:182-188

- Girths via Perometer → Volumes via frustum calculation

N =204
Healthy
Women
Age > 40
Hand Volume: H$_2$O Displacement

Displaced H$_2$O in recovery container

Seg Vol = kZ [$A_i + A_{i+1} + (A_i A_{i+1})^{1/2}$]

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

Volume by Algorithm ($V_M$, ml) vs. Volume by water displacement ($V_W$, ml)

- $V_M = 1.02 V_W - 12.0$ ml
- $r = 0.985$, $p < 0.001$
- $N = 60$ Hands

LOA $\pm 9.8\%$

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Hand Volume: H₂O vs. Perometer

Perometer values ~ 7.5% greater than H₂O values


Water
Perometer
r ~ 0.88
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

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Foot Volume: H$_2$O Displacement

Water Displacement Compared to Metric Measures

Algorithm vs. Water Displacement

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

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

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

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


HNM-NLN-2014
<table>
<thead>
<tr>
<th>Method</th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Displacement</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></td>
<td></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>

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Bioimpedance Analysis

- Electrical Impedance of a limb depends on the limb’s volume and constituents
- Lymphedema → 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

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Limb Conducting Structures

- Skin
- 15-20% H₂O
- Fat
- 5-10% H₂O
- Muscle
- 70-75% H₂O
- Bone
- 90-95% H₂O

Conductivity @ 5KHz Relative to Bone

1 Bone
20 Muscle
2 Fat

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Basic Operating Principle

Sinusoidal Voltage Excitation

No cells
Just saline

Low Frequency

High Frequency

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

Current increases with frequency

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Frequency Analysis Basis

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

Cell Membrane

Cell Interior ICW

Cell Exterior ECW

\[ E \]

\[ R_e \]

\[ C_m \]

\[ R_i \]
Cole-Cole Plot: estimate parameters

$MFBIA = BIS$

Increasing frequency

$Z = E / I$

$R_{\infty}$

$R_i R_e / (R_i + R_e) \rightarrow ECW + ICW$

$R_e \rightarrow ECW$

$R_0$

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Current Injecting Electrodes

Voltage Measuring Electrodes

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

Blood volume shift to lower extremities

Girth-Volume Measurements

Legend:
- Supine
- Standing
- Supine

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Leg Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1900</td>
</tr>
<tr>
<td>10</td>
<td>1800</td>
</tr>
<tr>
<td>20</td>
<td>1800</td>
</tr>
<tr>
<td>30</td>
<td>1900</td>
</tr>
<tr>
<td>40</td>
<td>2000</td>
</tr>
<tr>
<td>50</td>
<td>2100</td>
</tr>
</tbody>
</table>
Z Depends on Frequency & Volume

\[ Z \sim \frac{1}{\text{volume}} \]

\[ Z \sim \frac{1}{f} \]

Supine               Standing              Supine

-20         -10            0            10          20           30          40            50

5 KHz

500 KHz

\[ HNM-NLN-2014 \]
Assessing Arm Lymphedema

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nondominant</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>$R_0\text{DOM}$</td>
<td>2.988 ± 0.653</td>
<td>2.781 ± 0.595</td>
</tr>
<tr>
<td>$R_0\text{NONDOM}$</td>
<td>0.986 ± 0.040</td>
<td></td>
</tr>
</tbody>
</table>

3SD lymphedema thresholds

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


172 paired arms

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SFBIA = MFBIA for estimating ECW

Inter-Limb Z Ratios

- Arm LE
- Arm controls
- Leg LE

Both estimate Re (Low f)

So …. Why use MFBIA (BIS)?

Proposed Concept

- If 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 ICW is associated with muscle

ECW

ICW

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ECW / ICW Ratios

Data from: Cornish BH et al. Angiology 2002;53:41-47

N = 20
Local Tissue Water Assessment

Tissue Dielectric Constant (TDC) Relative Permittivity ($\varepsilon_r$)

PRINCIPLE
What is Dielectric Constant?

H₂O Molecule

Charge Separation

Dipole
What is Dielectric Constant?

Hydrogen bonding between water molecules

“Hook-up”

2 molecules
What is Dielectric Constant?

Time varying electric field of force - $E$

Dipole movement Displacement - $D$

Various types

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

$H_2O @ 32^\circ C \rightarrow \varepsilon_r = 76$

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

Dielectric Constant

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• Multi-Probe
• Single Probe (compact)
Multi-Probe

300 MHz Signal

Effective Measurement Depth

0.5 mm                1.5 mm                         2.5 mm

Reflected Wave yields TDC

TDC readout

0.5 mm                1.5 mm                         2.5 mm
Single Probe (Compact)

Display has pressure bar indicator during measurement

Effective measurement depth is between 1.5 & 2.5 mm Multi-Probe

20 mm

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Effective Measurement Depth

Skin

Electric Field Lines

Conductor

Outer Conductor

Center Conductor

Outer Conductor

Electric Field Lines

Depth (mm)

Effective Measurement Depth

2.5 mm depth probe

Electric Field (% of Surface field)

0 10 20 30 40 50 60 70 80 90 100

0 1 2 3 4 5 6 7 8 9 10

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Effective Measurement Depth

- Interrogation Depth (2.5 mm)
- Dermis
- Subcutis
- Gel Entry Echo

Normal:
- 0.93 ± 0.13 mm

Lymphedematous:
- 1.83 ± 1.28 mm

Low water content
- 1.5 mm

High water content
- 5.0 mm

Ventral Forearm

Modified from Mellor et al. The Breast J. 2004;10:496-503

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TDC dependence on $H_2O$

Calibration Example
(2.5 mm probe)

$Y = 0.632X - 22.1$

$r^2 = 0.998, p < 0.001$

Cable to Control Unit
Probe inserted into Mixture
Ethanol-Water Mixture
Skin Water Distribution

Skin Water Content (%)

Skin Depth (μm)

Epidermis

Dermis

60-68 yrs

20-24 yrs

N = 60

aDermis 70-75% H₂O

b70-90% Bound

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

Free and Bound Water

- Protein (1 g)
- Bound H₂O (0.2 – 0.5 g)
- Limited Mobility H₂O ~ 20 g
Lymphatic Dysfunction

Bound and immobile water not readily measurable with Standard BIA
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

- Forearm
- Biceps
- Axilla
- Thorax
- Foot Dorsum

Signal Generation and Processing
TDC Value Display

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TDC Site Variability

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

N = 30 young adult males (25.0 ± 2.5 years) @ 1.5 mm depth

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

Pattern of Depth Dependence May Vary by Site

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

$\text{r}^2 = 0.997, \ p<0.001$

N = 80 females

Compact
Cuff inflated to 50 mmHg to increase vascular volume and change skin blood flow

Skin Blood Flow in Forearm and Finger
Skin Blood Flow (a.u.)

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
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Pre-Surgery Reference TDC Ratios

Cancer Side | Healthy Side

Axilla
N = 103
Biceps
1.012 ± 0.143 (1.45)

Thorax
1.029 ± 0.196 (1.60)
N = 80

Forearm
1.003 ± 0.096 (1.30)

(3 SD Thresholds)

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Sequential TDC Ratio Changes

Lateral Thorax

- 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)

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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)

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