★ The 11th NLN ★
International Conference

The Campaign for Lymphedema Care
Perspectives, Evidence & Practices

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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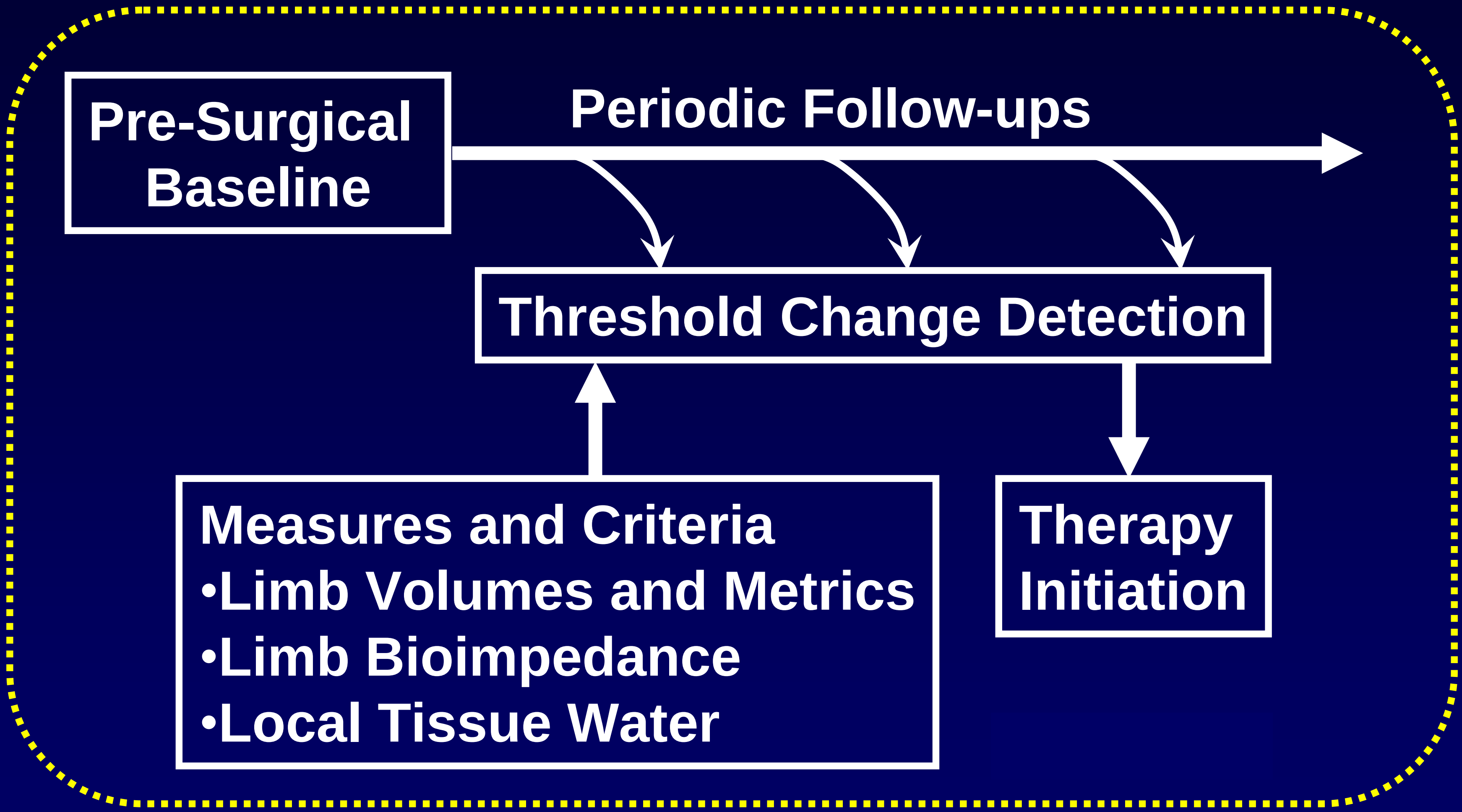
Why Measure/Quantify?

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

Early Detection of Lymphedema



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Methods Applicable to *LIMBS*

Limb Girth (Circumference)

- **Girth → Limb Volume or Sum of Girths** →

Limb Volume

- **Water Displacement → Limb Volume** →

Limb fluid content and its change

- **Bioimpedance → BIA & BIS → Whole Limb** →

- **Tissue Dielectric Constant (TDC) → Local** →

Physical and Structural Properties

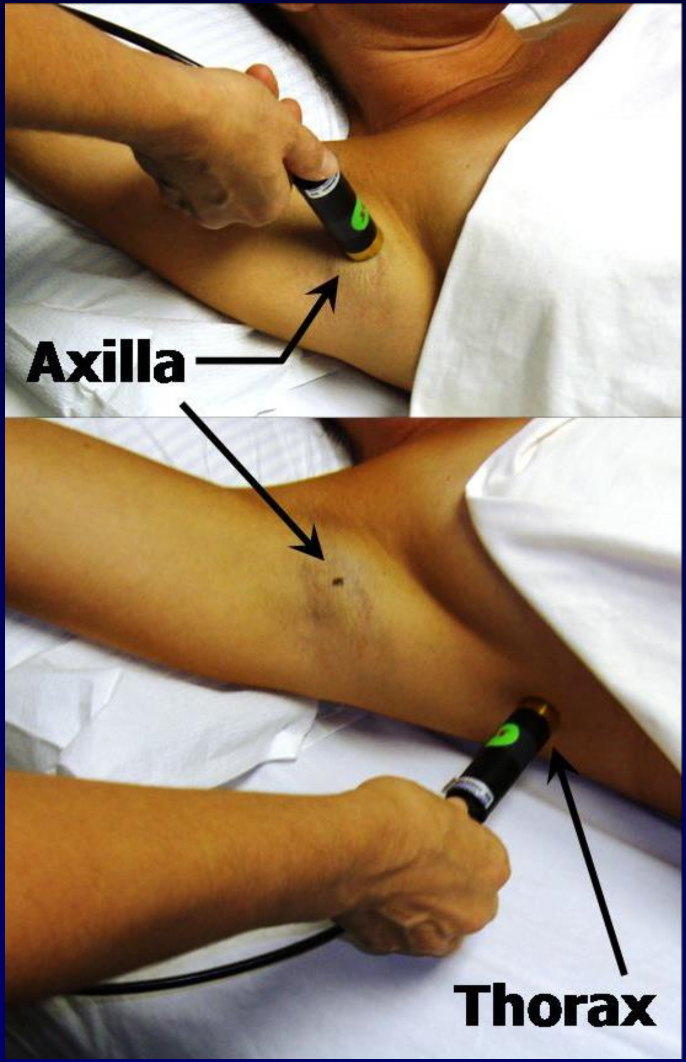
- **Tonometry / Indentometry → Various** →
- **Imaging: Ultrasound - MRI - Other**

Methods Applicable to MOST Sites

Fluid Content (TDC)

Tissue Dielectric Constant

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



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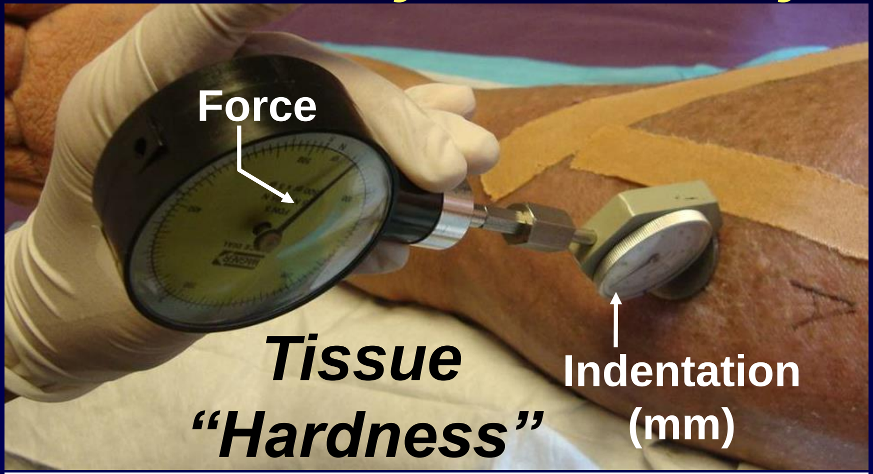
Methods Applicable to MOST Sites

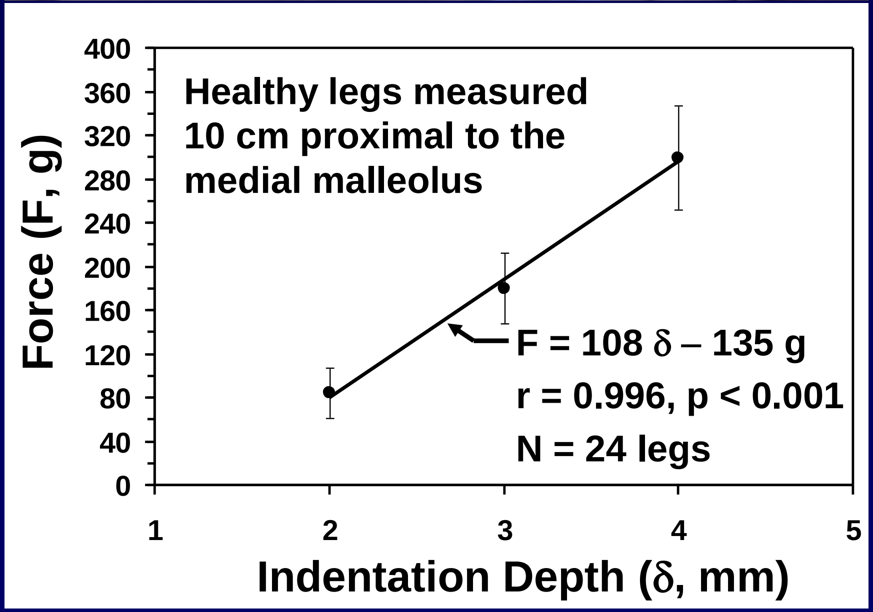
Physical Properties
Tonometry/Identometry

Indent (mm)

↓

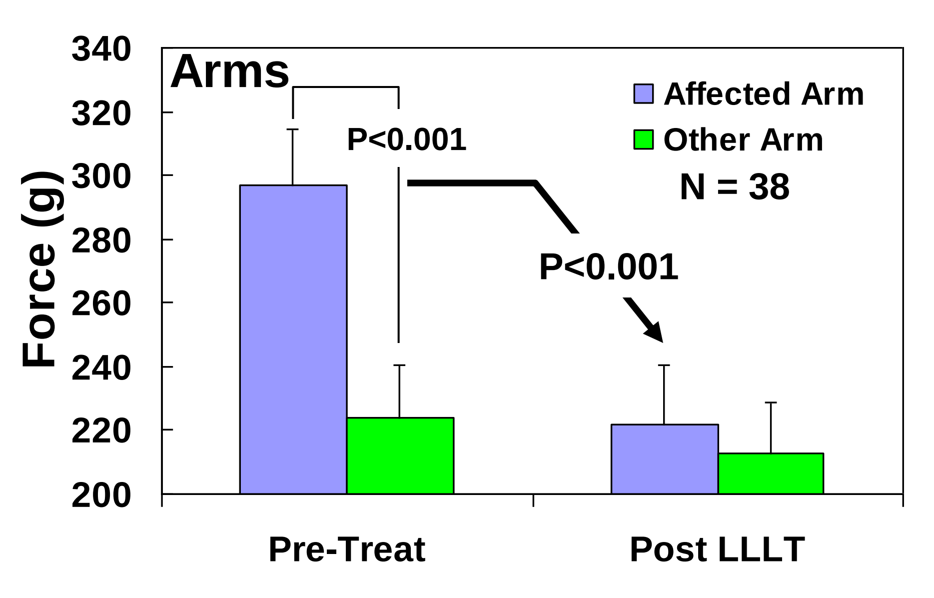
Measure Force

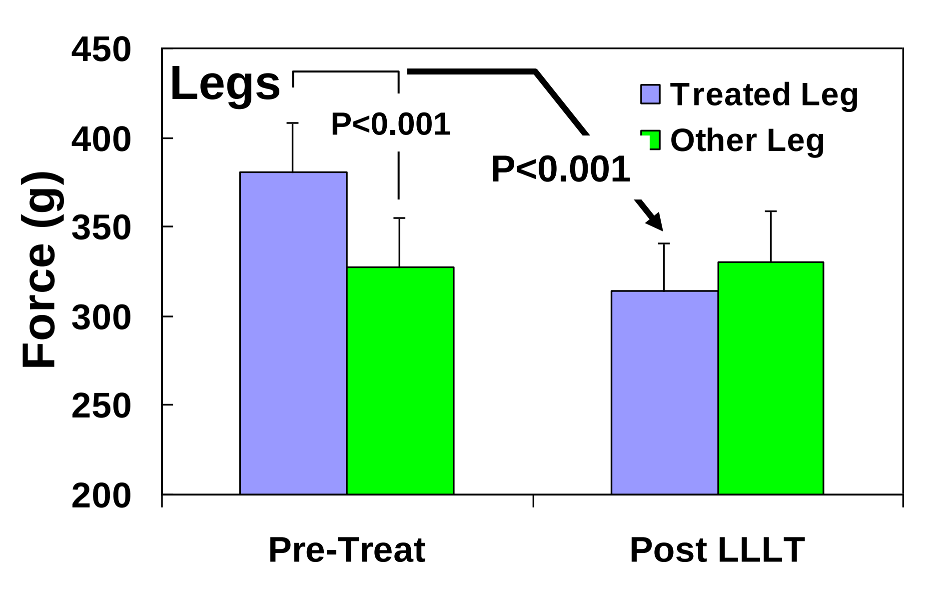


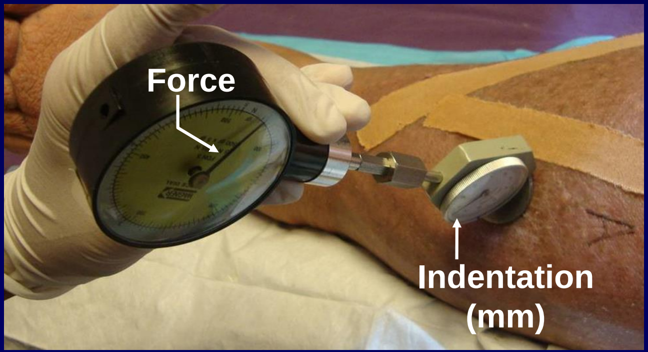


Mayrovitz HN
Lymphology
2009;42:88-98

Hardness Changes with LLLT







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

Commercial Tonometers

Force Applied

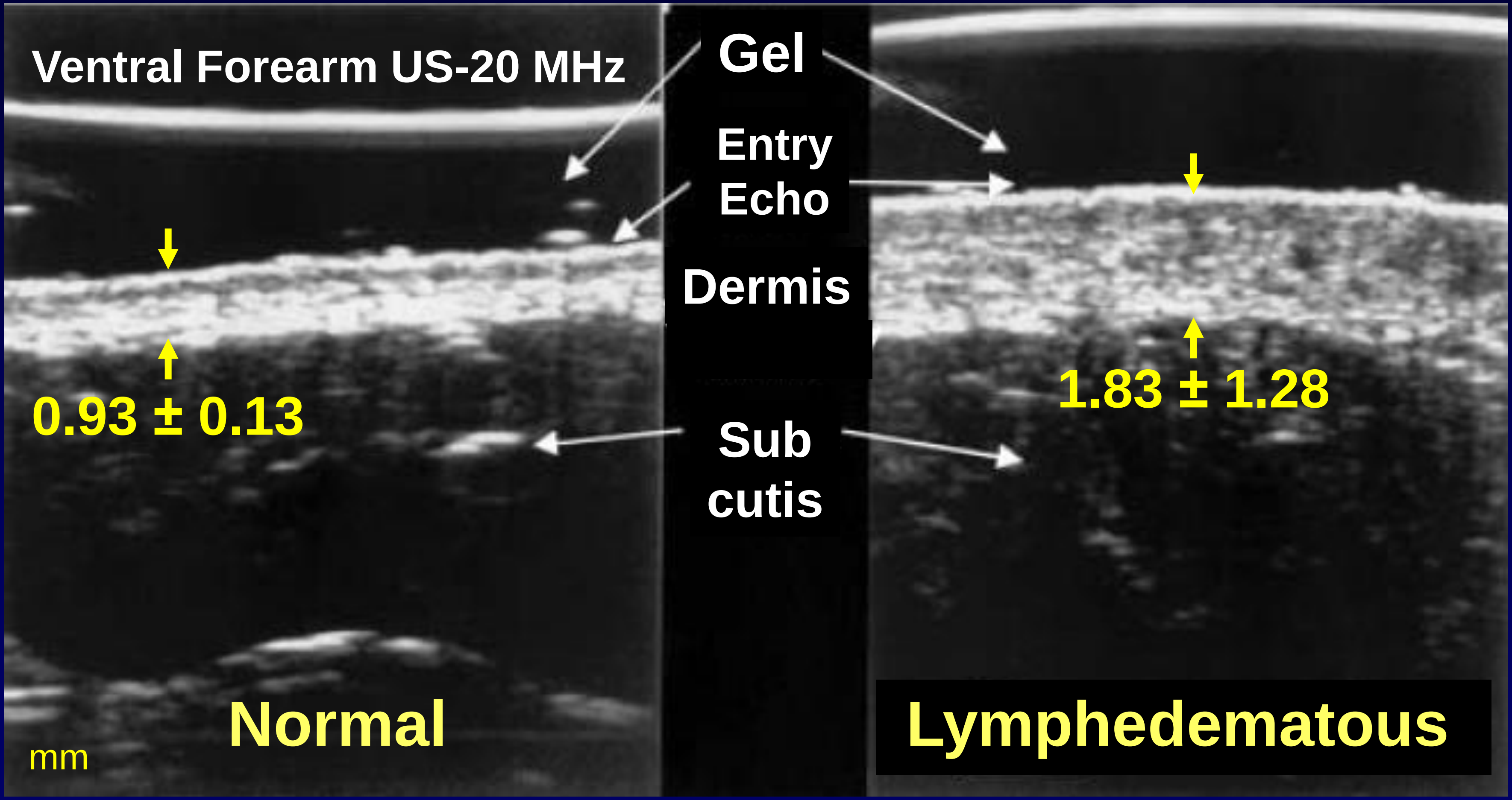
↓

Displacement Determined

Pallota O. J Lymphoedema 2011;6:34-41

Methods Applicable to MOST Sites

Imaging → Ultrasound → MRI → Other



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

Metric Measures for LIMBS

Tape Measure Girth at multiple points

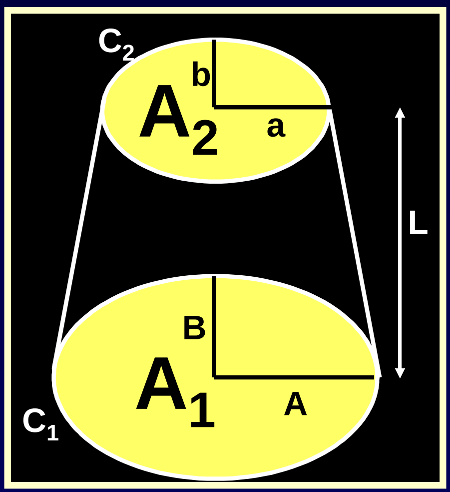
- **Measure both limbs**
  - → **Inter-limb differentials and sequential changes**
- **Measure one limb**
  - → **Sequential data but miss systemic changes**

Segment Length

Limb Girth → Volume

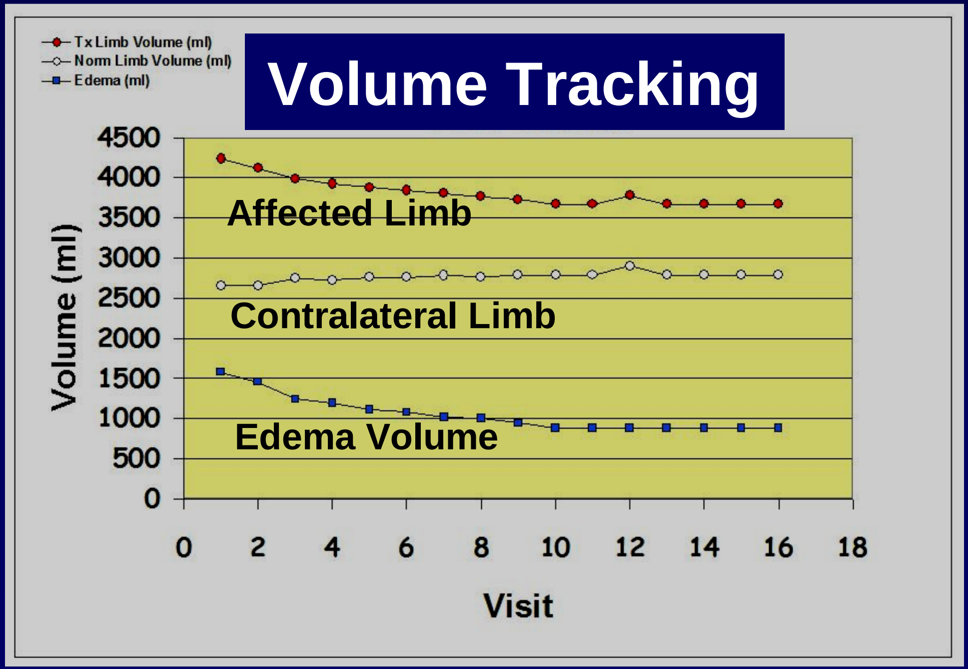
Geometric Model or Algorithm ← **Circumferences @ 4 – 12 cm intervals** ←

Manual

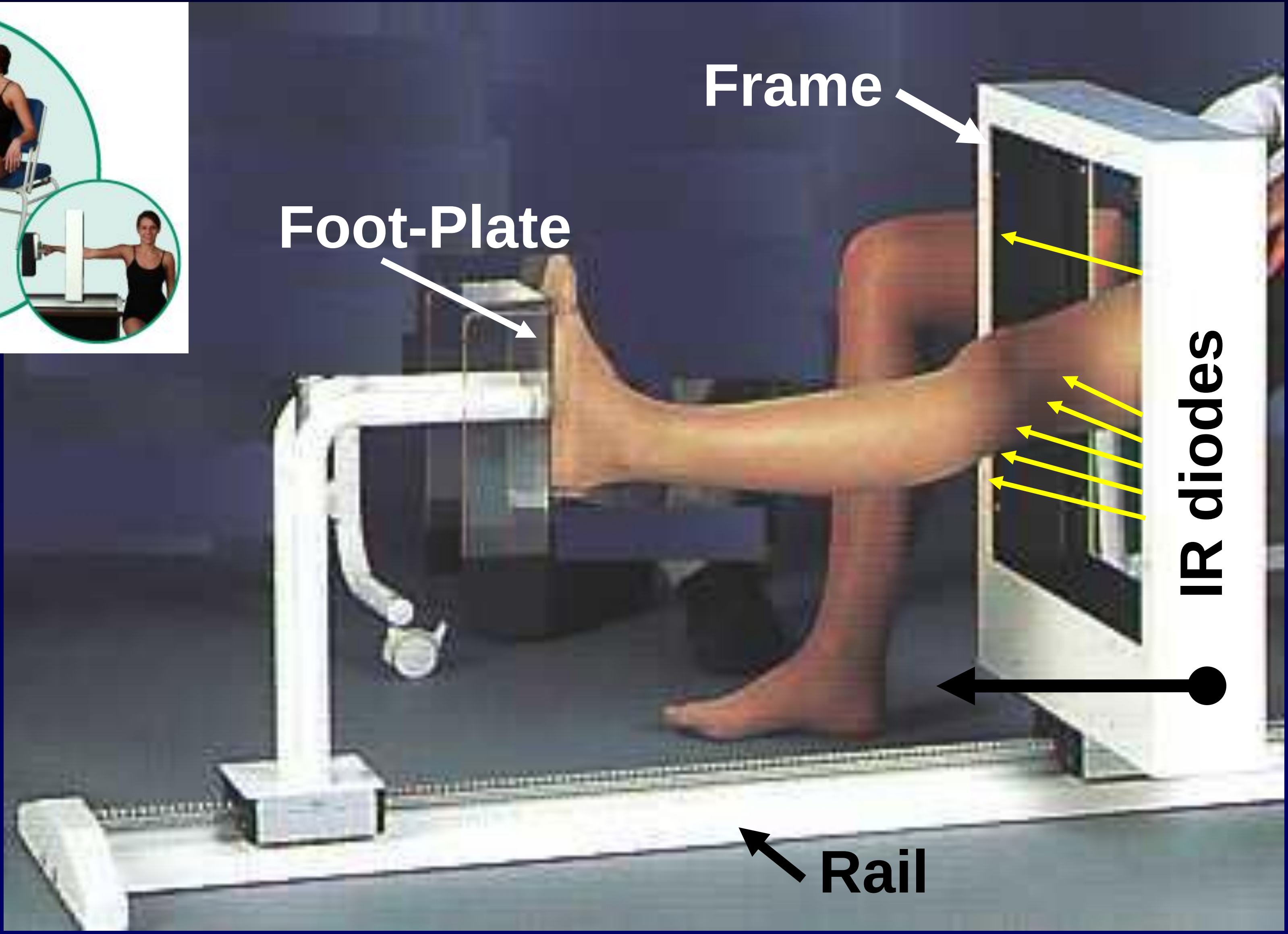


General Frustum Calculation Model

$$V = L/3\,(A_1 + A_2 + (A_1A_2)^{1/2})$$

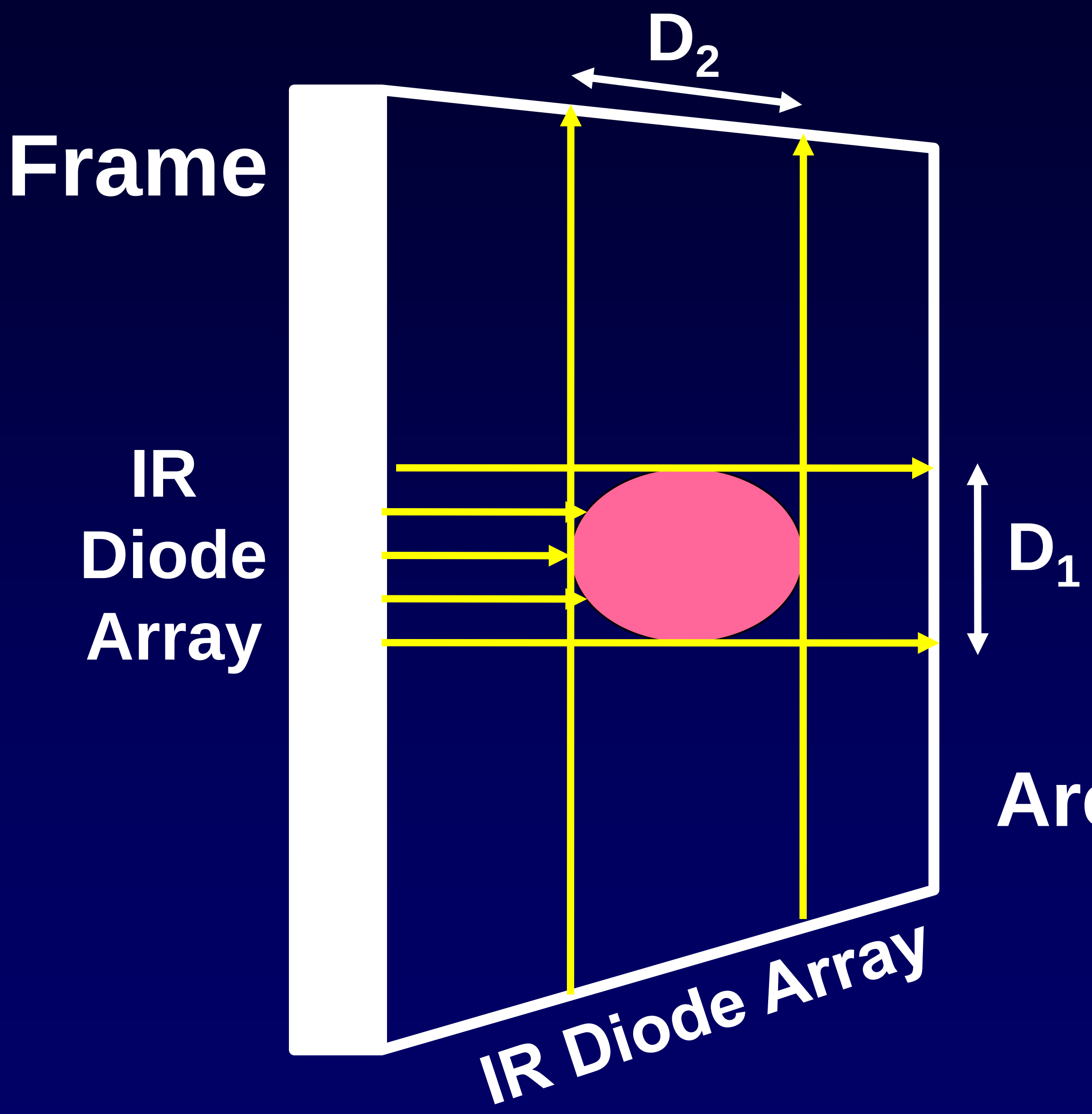


Perometer: Girth → Volume



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

Perometer: Basic Principle



Area = KD_1D_2

Limb Girth & Volume LE Thresholds

Manual

Automated

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

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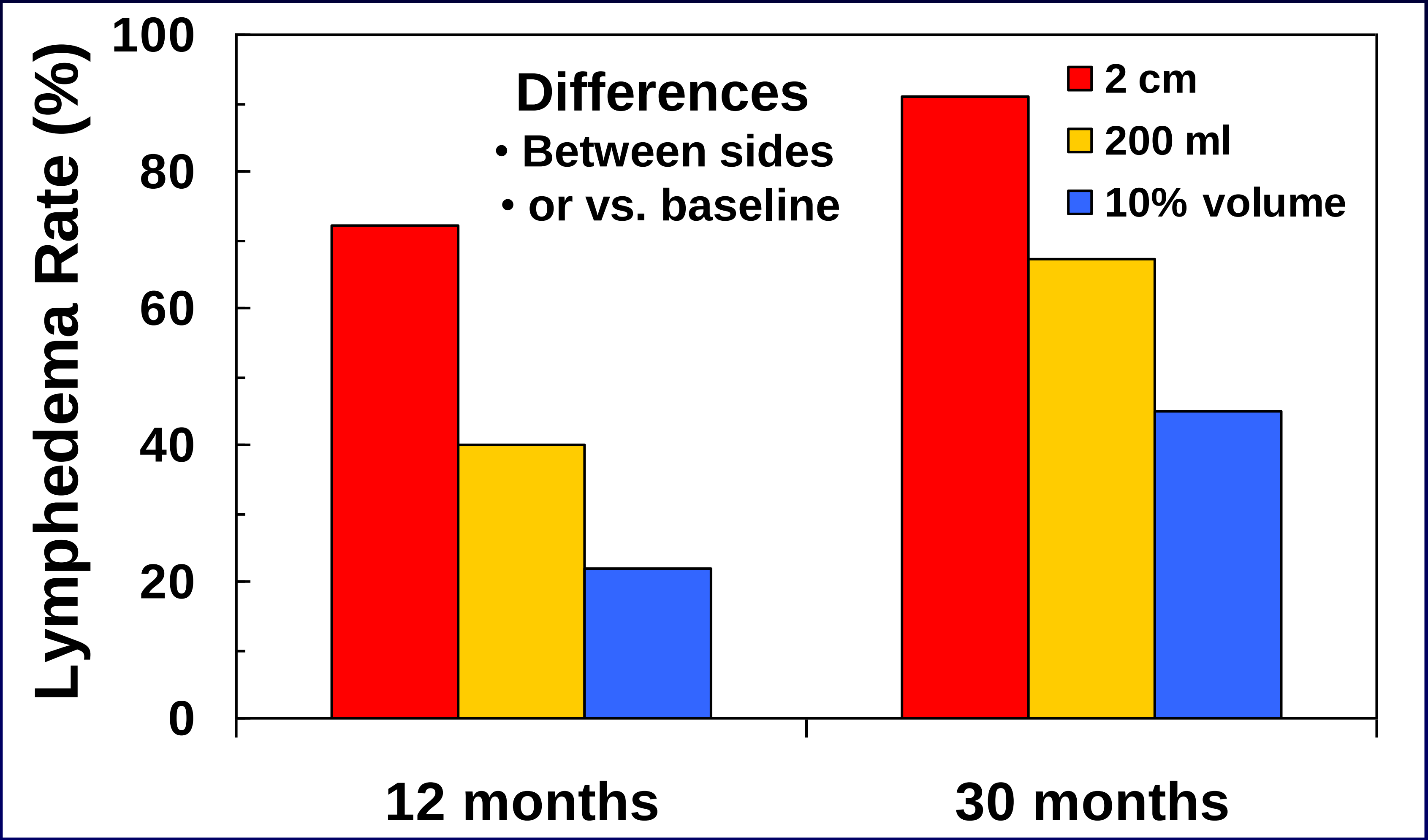
Arm Lymphedema Metric Criteria

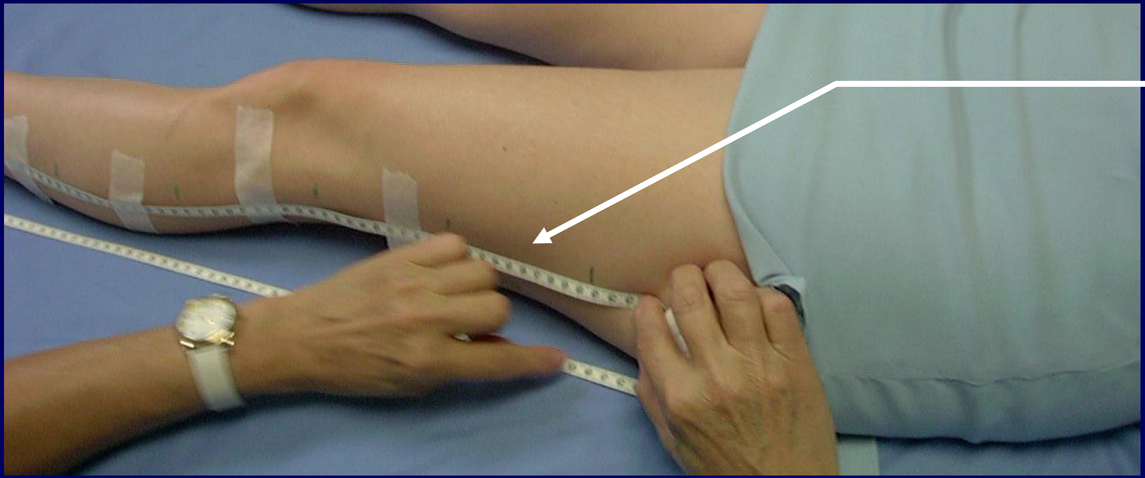
LE rate dependent on criteria used



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

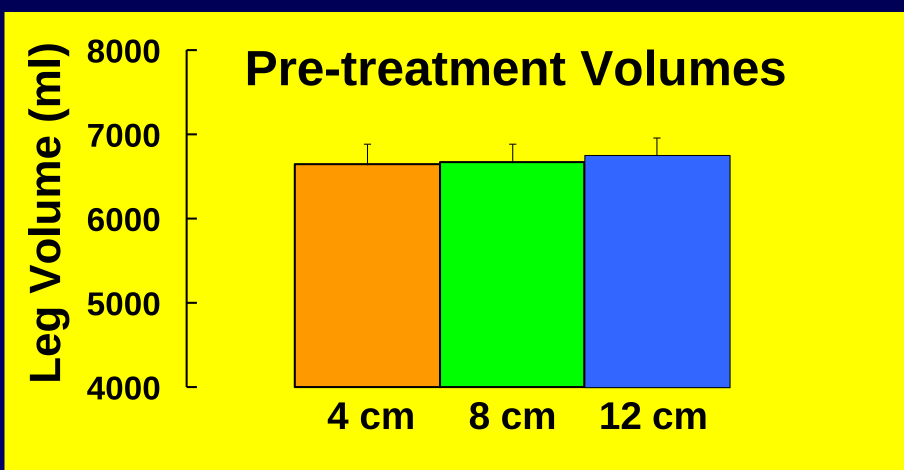
Source of large
Follow-up error

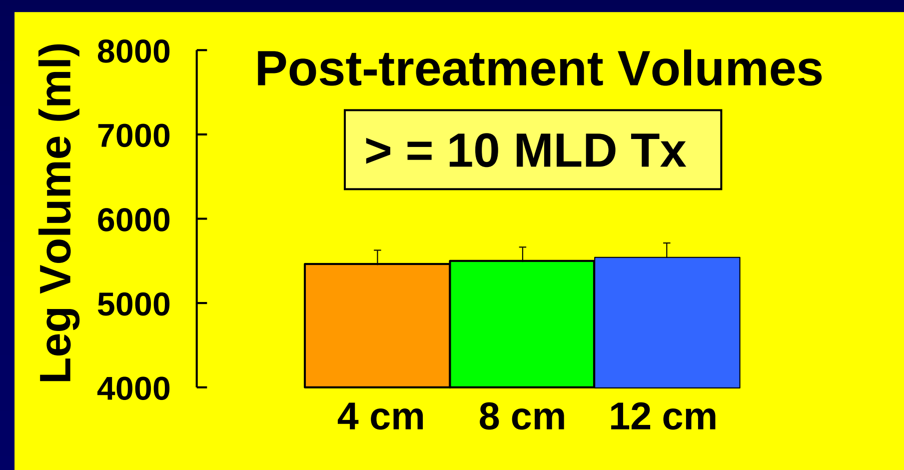
What Segment Length to Use?

Bilateral lower extremity lymphedema

Segment Length	Volume Reduction (ml)	Volume Reduction (%)
4 cm	1183 ± 778	17.2 ± 7.1
8 cm	1180 ± 782	17.1 ± 7.2
12 cm	1202 ± 781	17.4 ± 7.0

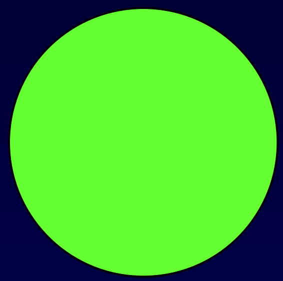
N = 70



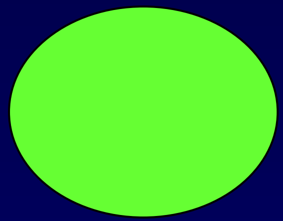


Mayrovitz et al. Physical Therapy 2007; 87: 1362-1368

Limb Shape as a Factor



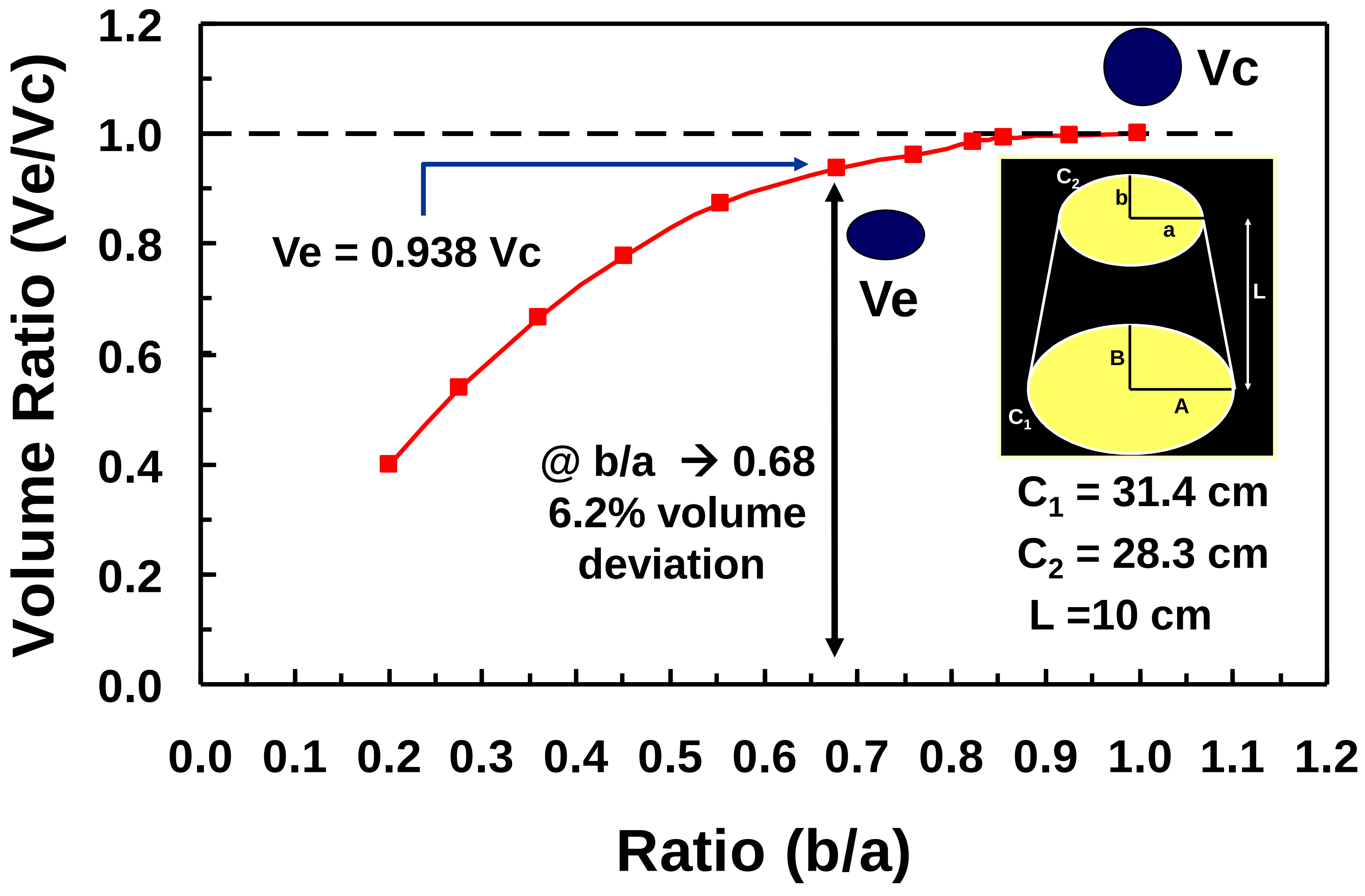
If you calculate
on the basis of
THIS



and its really more like
THIS

Then you obtain a volume
greater than the true value

Limb Shape as a Factor



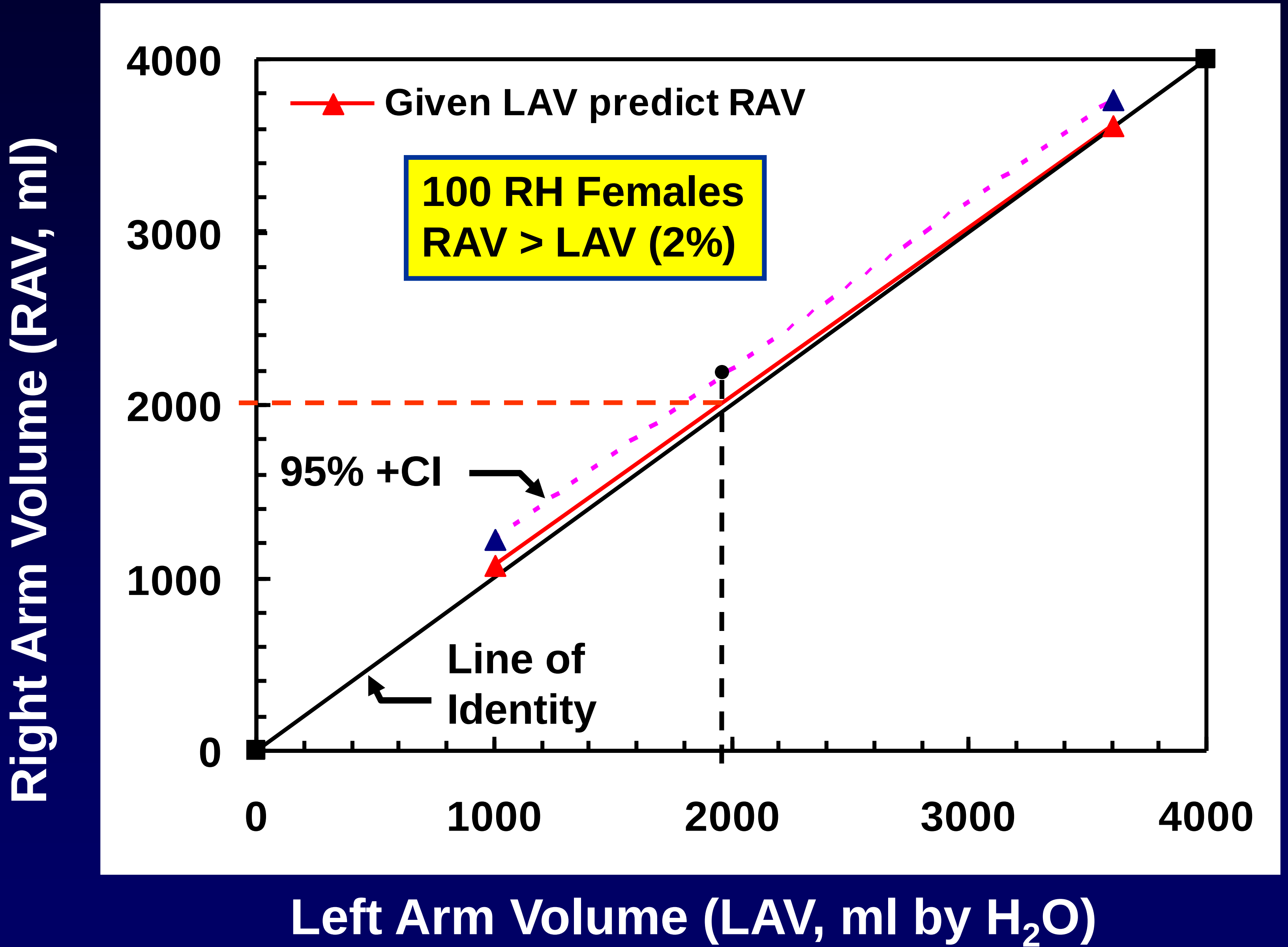
Data from: Mayrovitz HN, Lymphology 2003;31:140-143

Volumes via H_2O Displacement

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

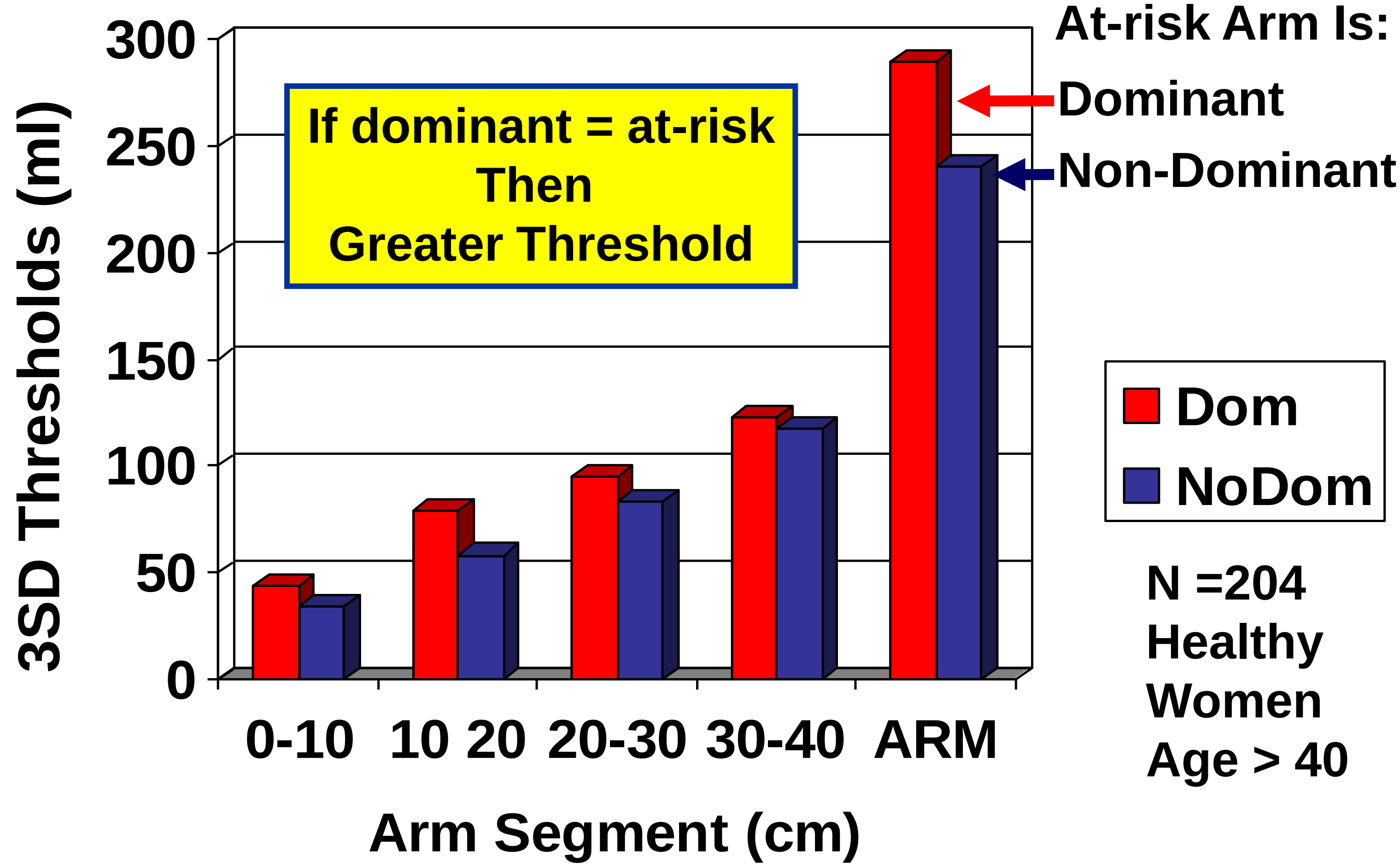
Photo from: K. Johansson & E Branje Acta Oncologica 2010;49:166-173
Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis
LE if change in edema volume >= 5% from pre-surgery

Normal Arm Volume Differentials



Data from Gebruers N et al . Clin Physiol Funct Imaging 2007; 27:17-22

Normal Arm Volume Differentials

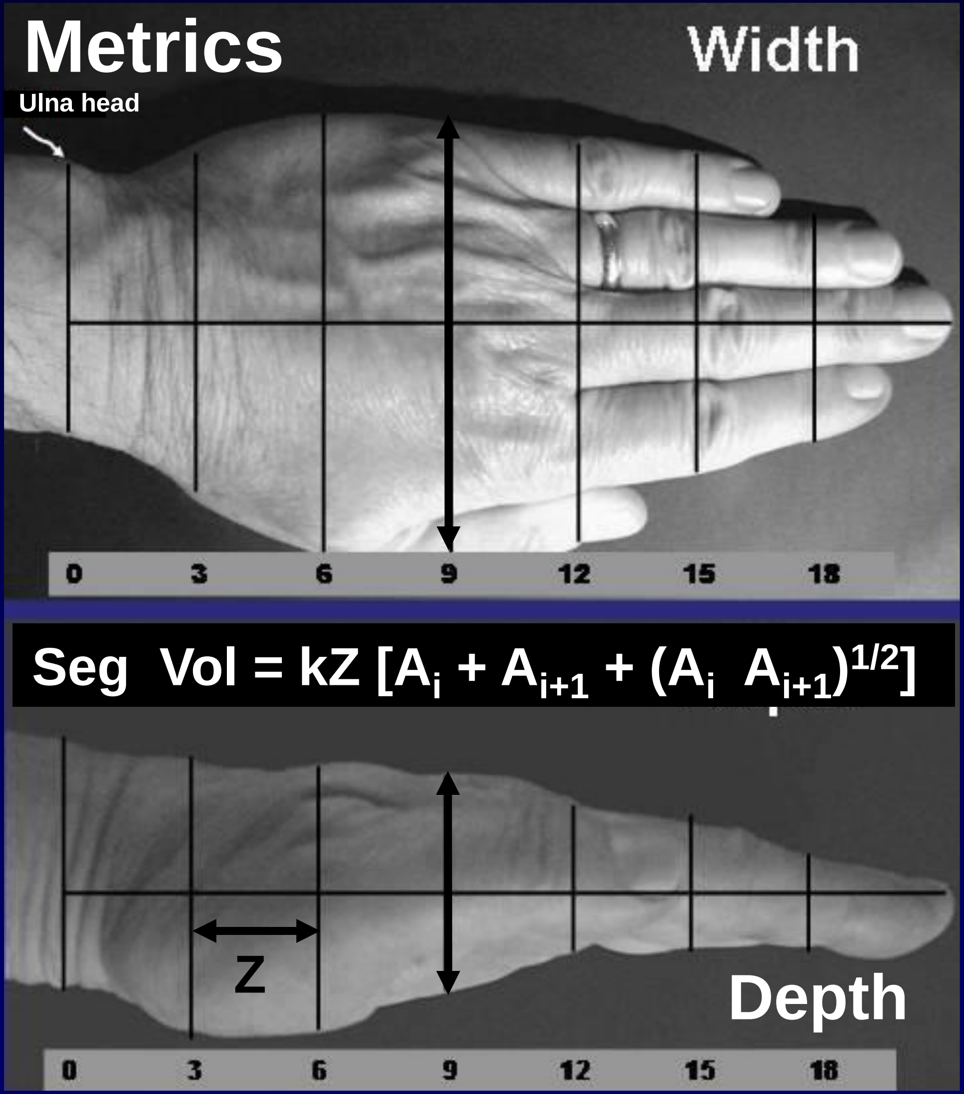


N =204
Healthy
Women
Age > 40

Girths via Perometer → Volumes via frustum calculation

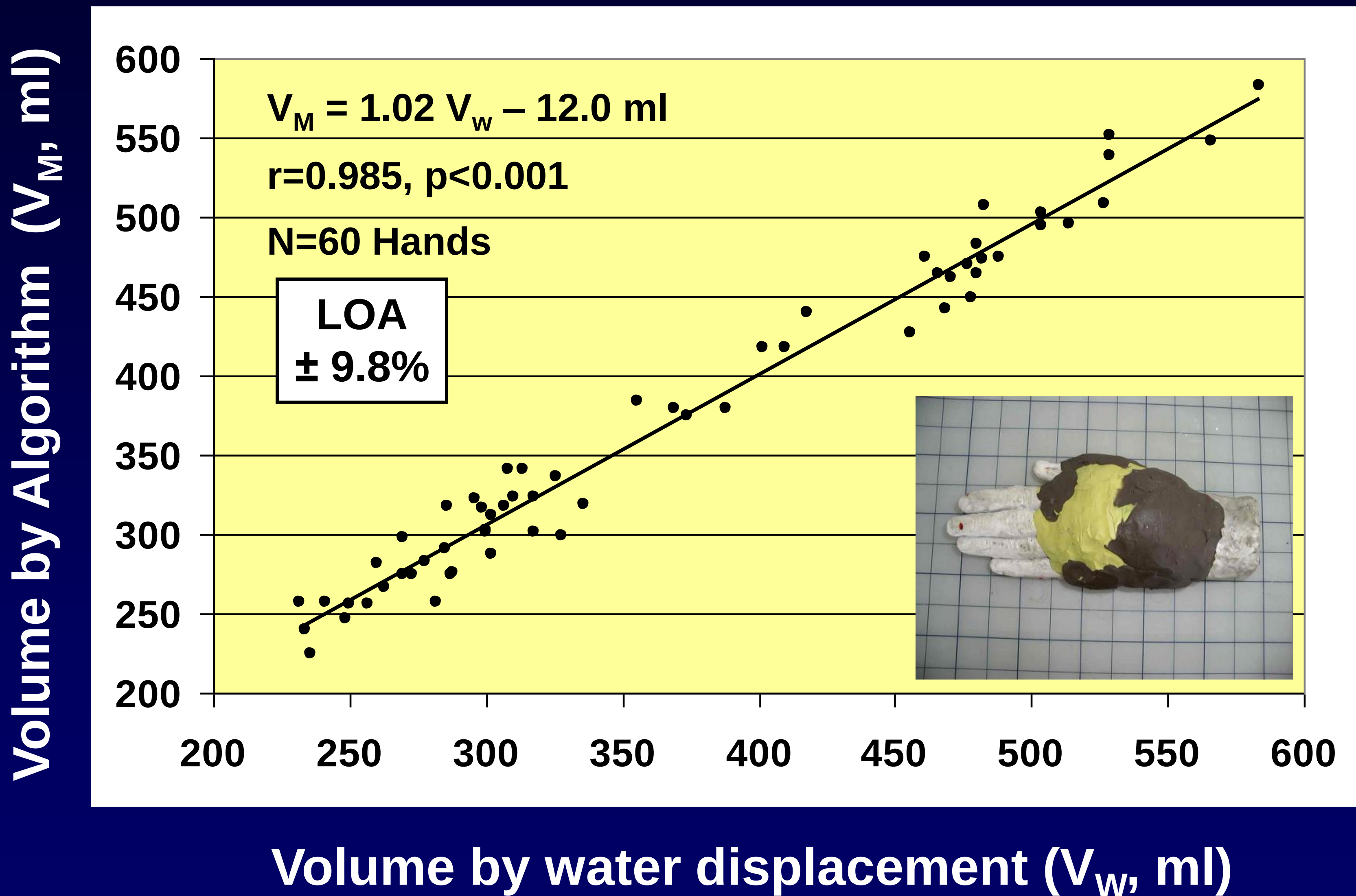
Data from: Dylke ES et al Lymphatic Res Biology 2012;10:182-188

Hand Volume: H_2O Displacement



From: Mayrovitz HN et al. Lymphology 2006;39:95-103

Algorithm vs. Water Displacement



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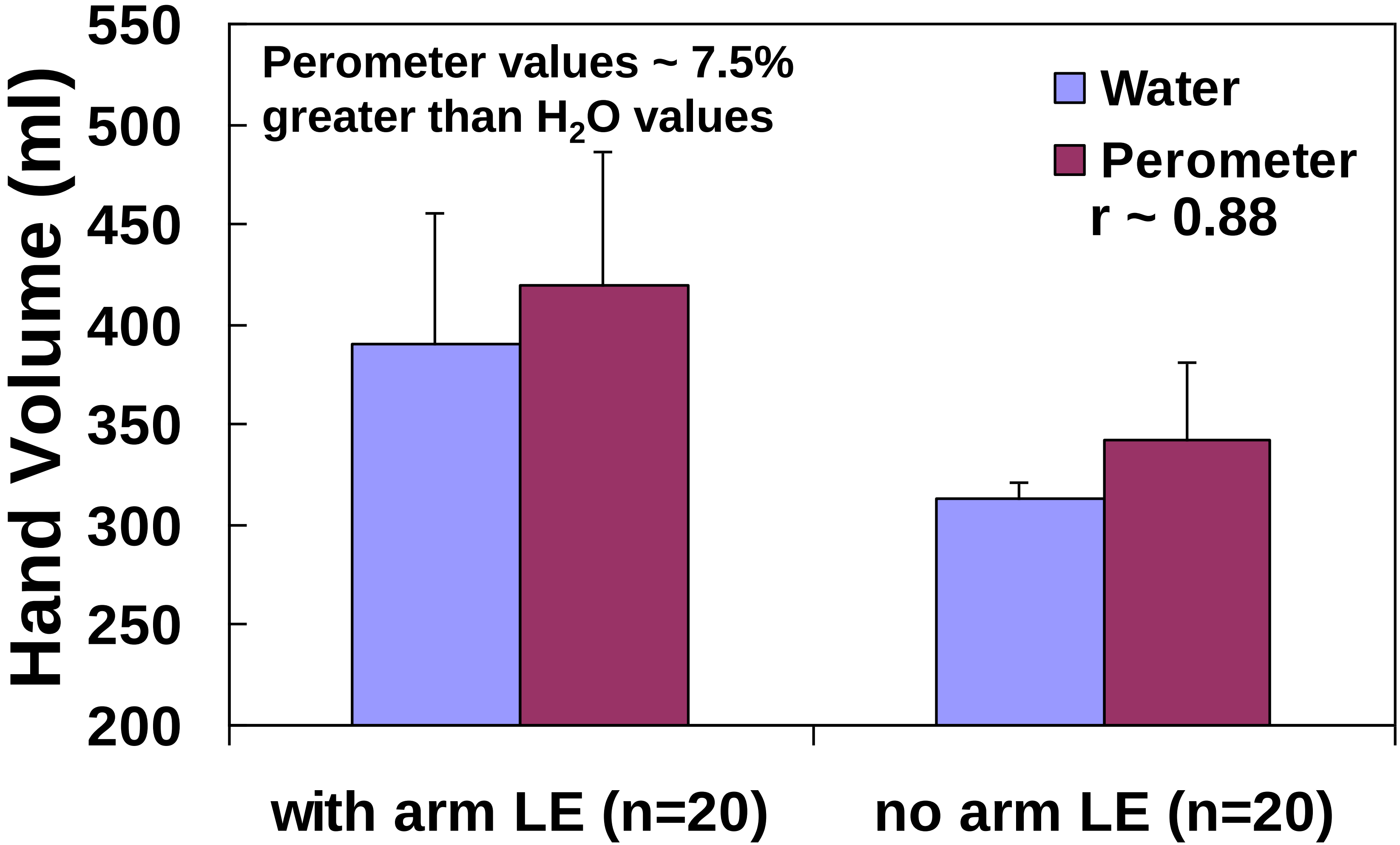
Hand Volume: H_2O vs. Perometer



Data from: Lee MJ et al. Lymphatic Research Biology 2011;9:13-18

Figure-of-Eight: Hand volume Surrogate

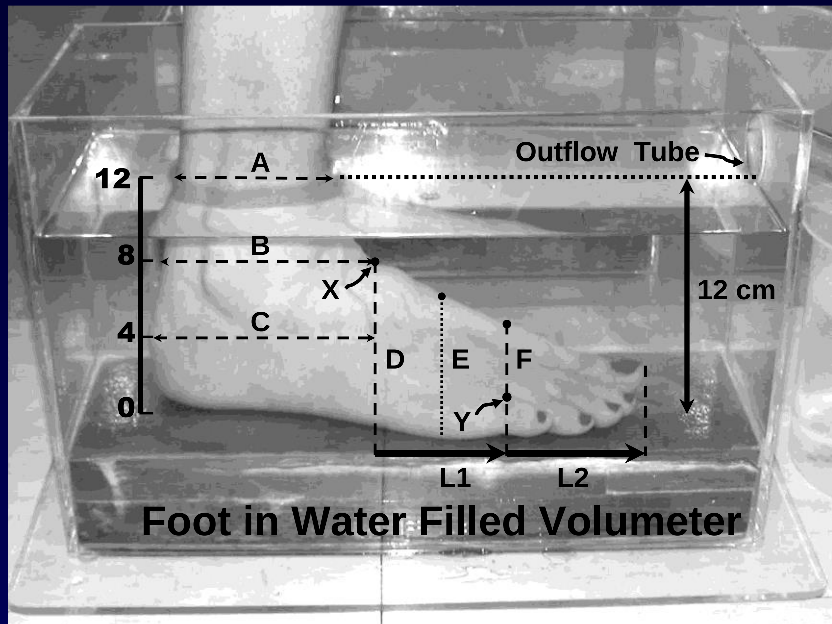
Pellecchia GL J Hand Therapy 2003;16:300-304

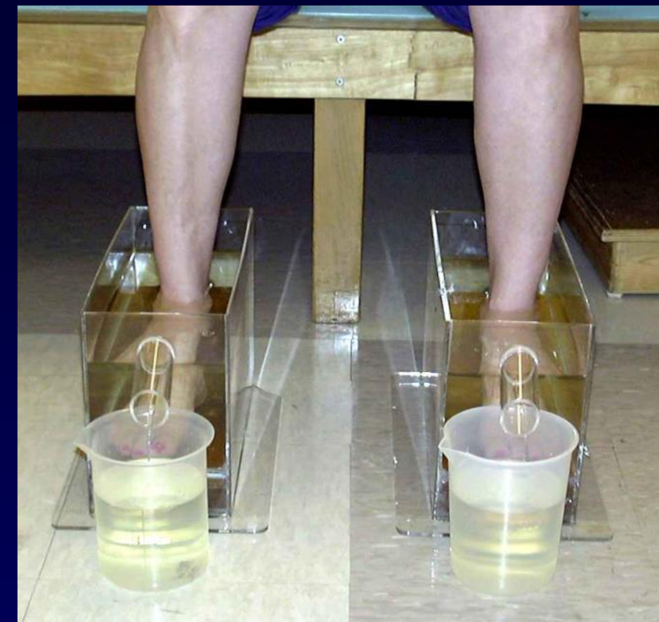
Maihafer GC J Hand Therapy 2003;16:305-310

cm (fig-8) vs. H_2O displacement (ml)

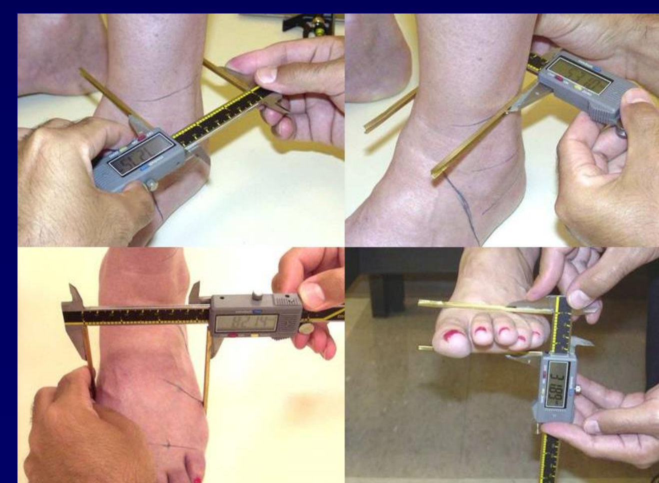
R = 0.94-0.95 but only normal hands
Tracking ability unproven

Foot Volume: H_2O Displacement



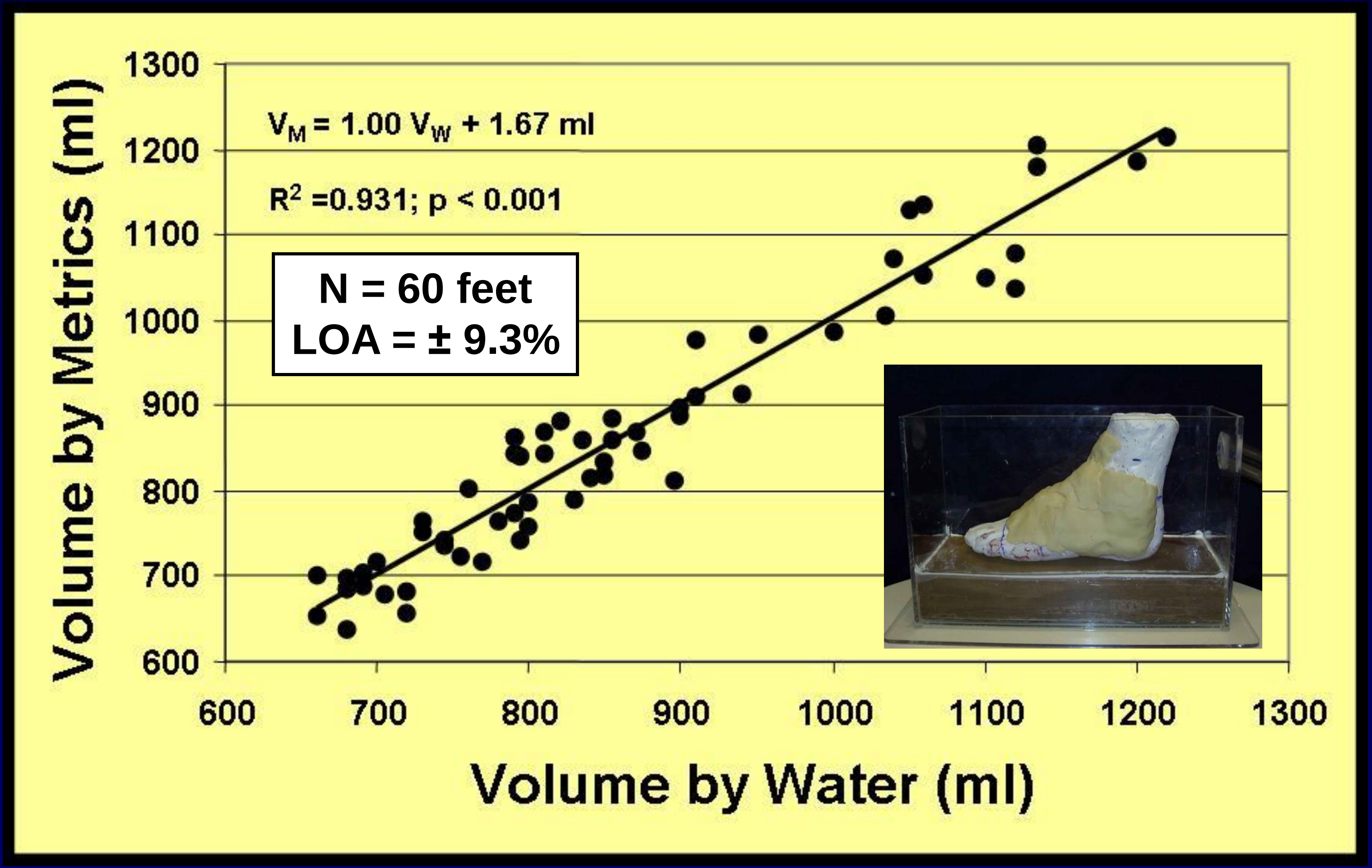


Water Displacement Compared to Metric Measures

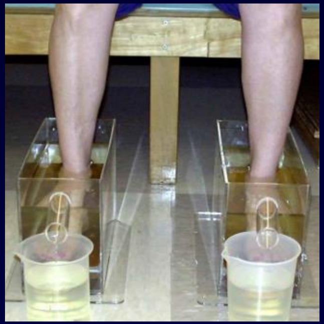


Mayrovitz HN et al. Lymphology 2005;38:20-27

Algorithm vs. Water Displacement



Mayrovitz HN et al. Lymphology 2005;38:20-27

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

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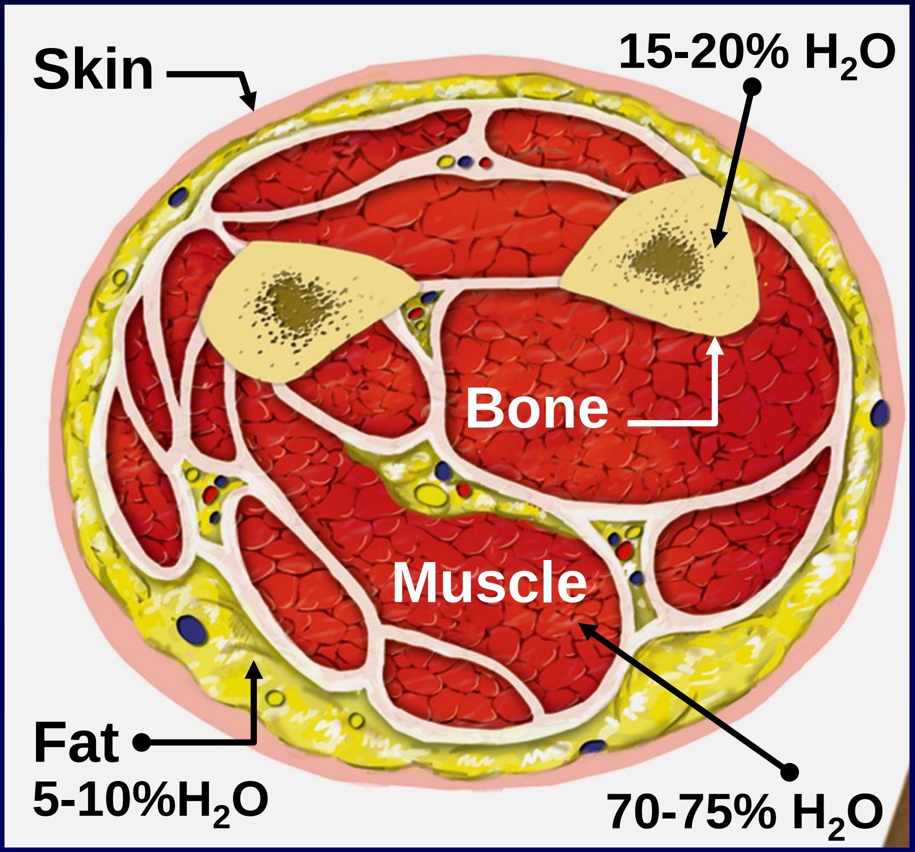
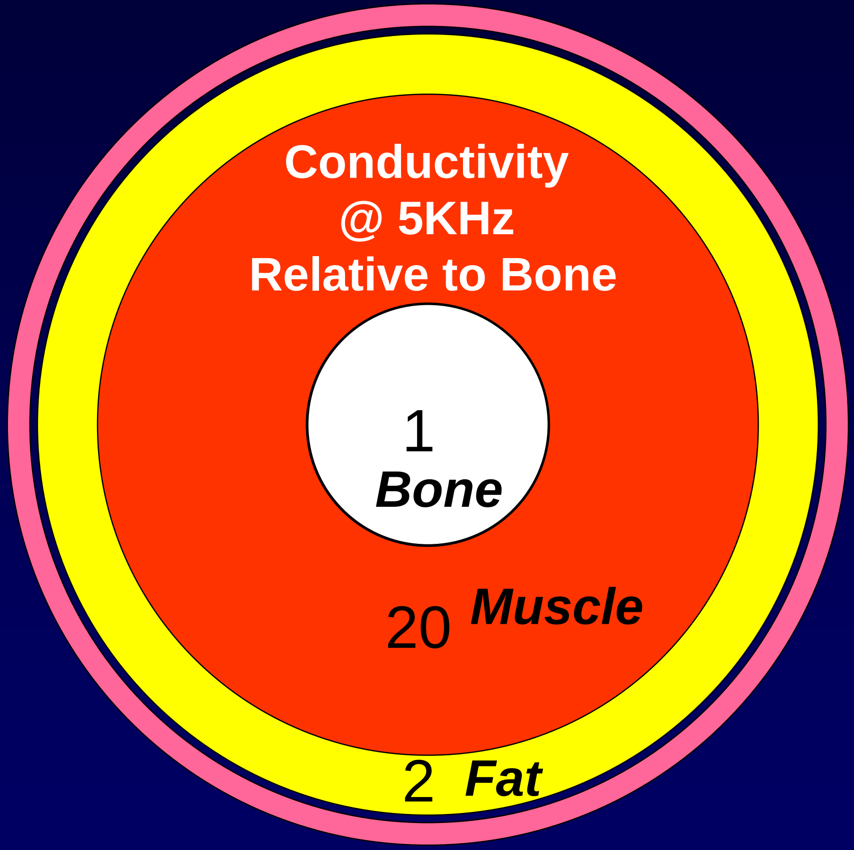
Bioimpedance Analysis

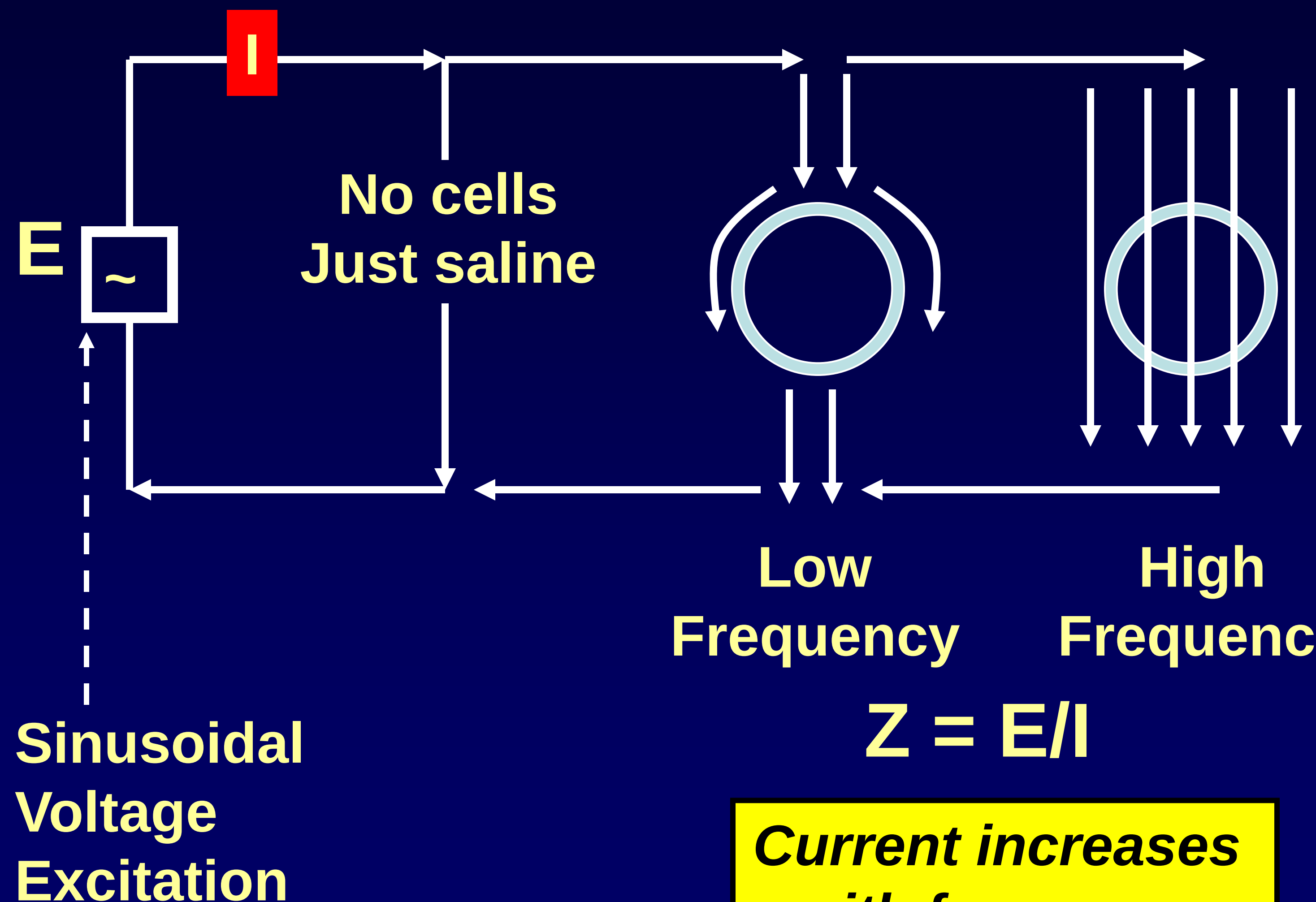
- Electrical Impedance of a limb depends on the limb's volume and constituents
- Lymphedema → increase in low resistance fluid content of the limb
  - Bioimpedance (BIOZ)
  - Bioimpedance Spectroscopy (BIS)
  - Bioimpedance Analysis (BIA)
  - Single Frequency BIA = SFBIA
  - Multi-Frequency BIA = MFBIA

Limb Conducting Structures





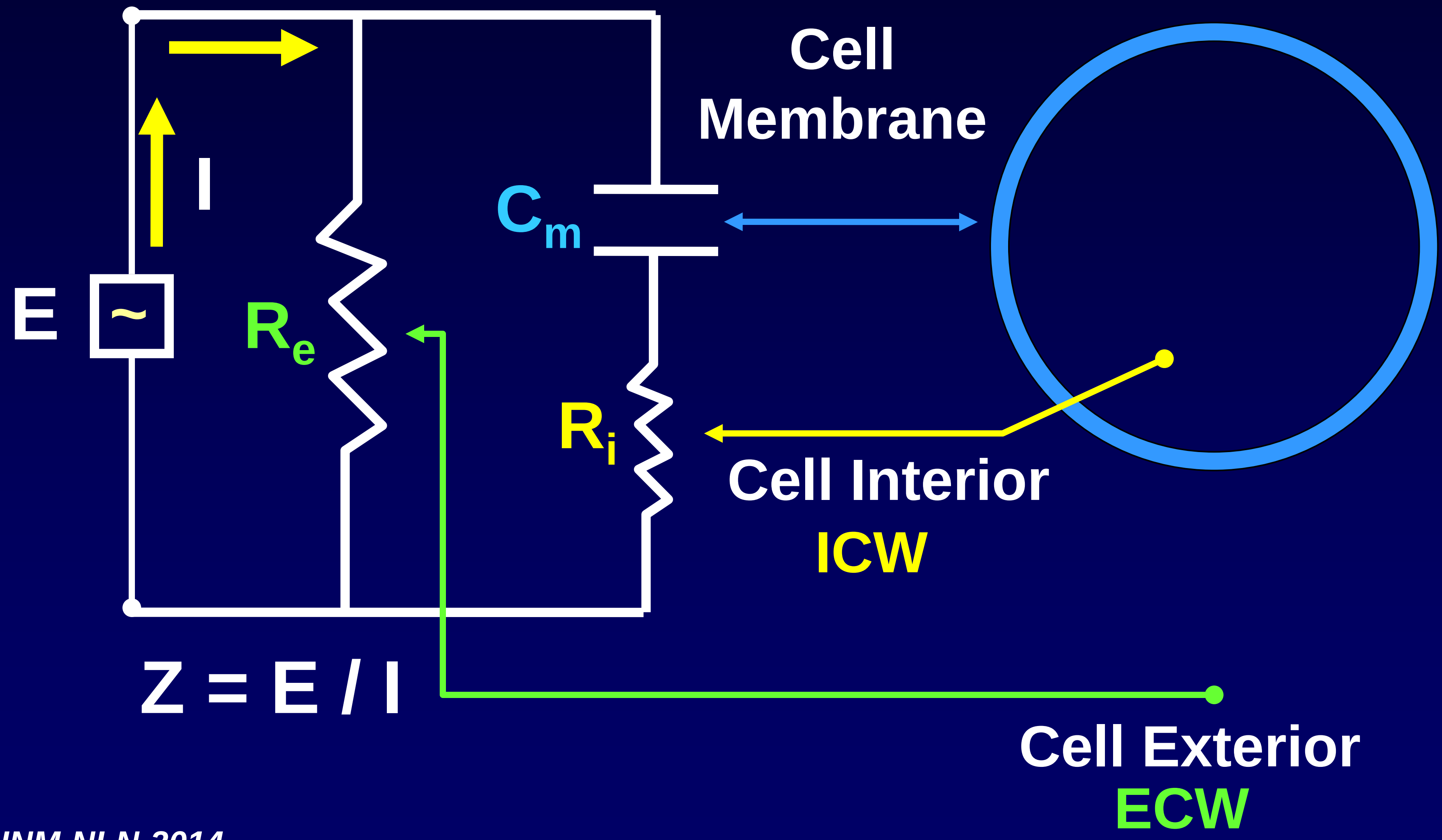
Basic Operating Principle



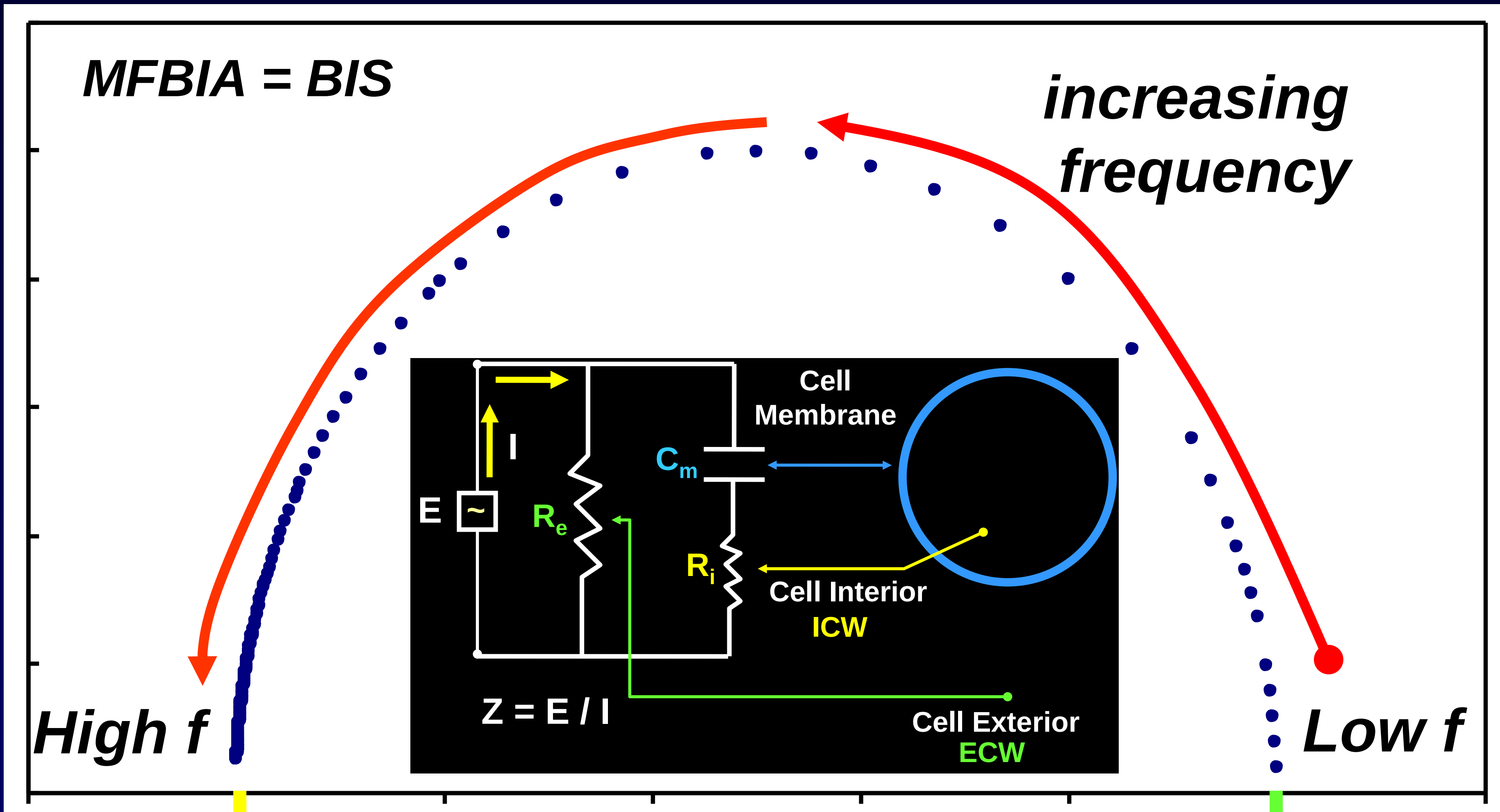
$$Z = E/I$$

Current increases with frequency

Frequency Analysis Basis



Cole-Cole Plot: estimate parameters



R_∞ R_0

$R_iR_e/(R_i + R_e)$ → ECW + ICW ECW ← R_e

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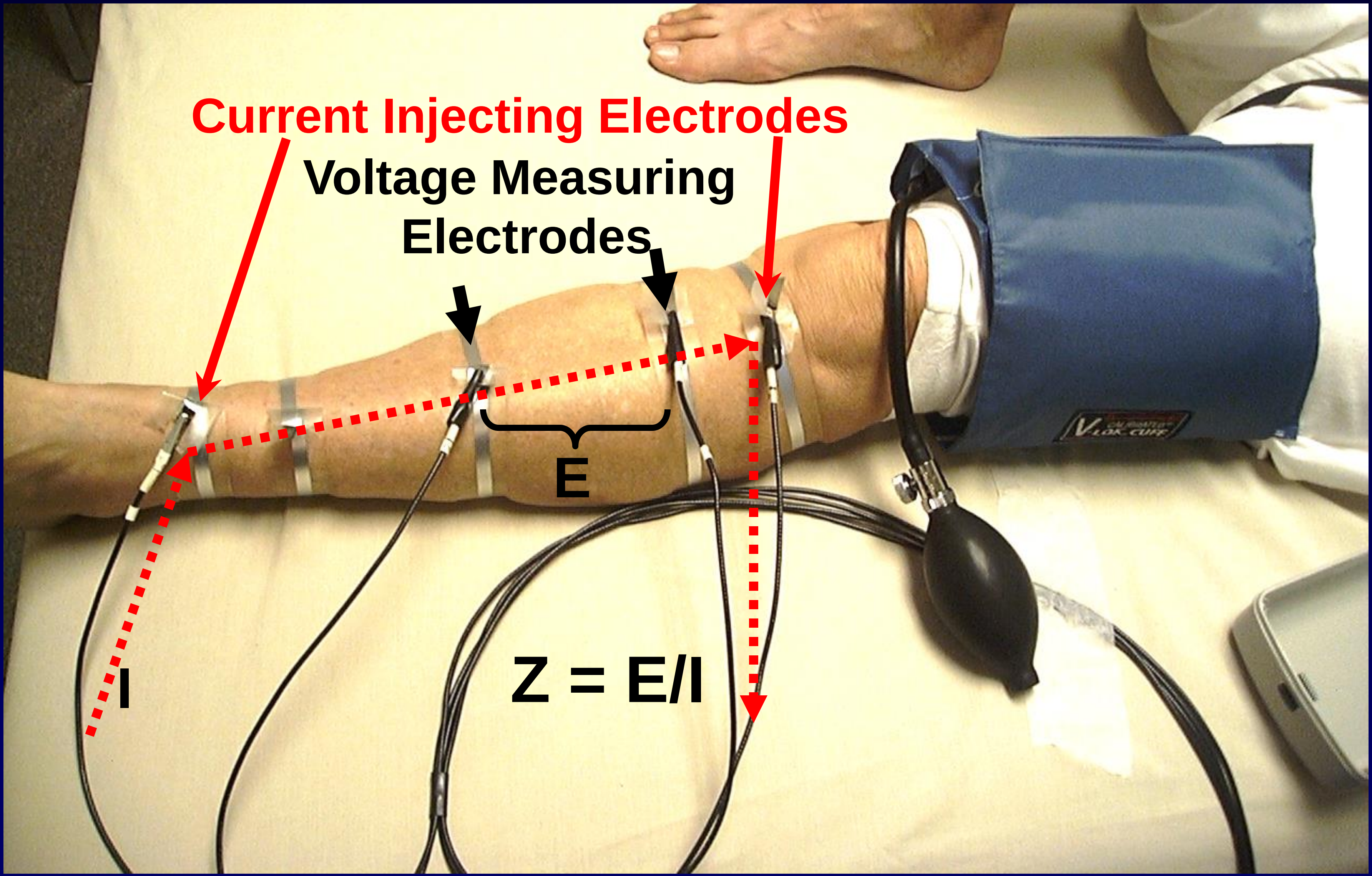
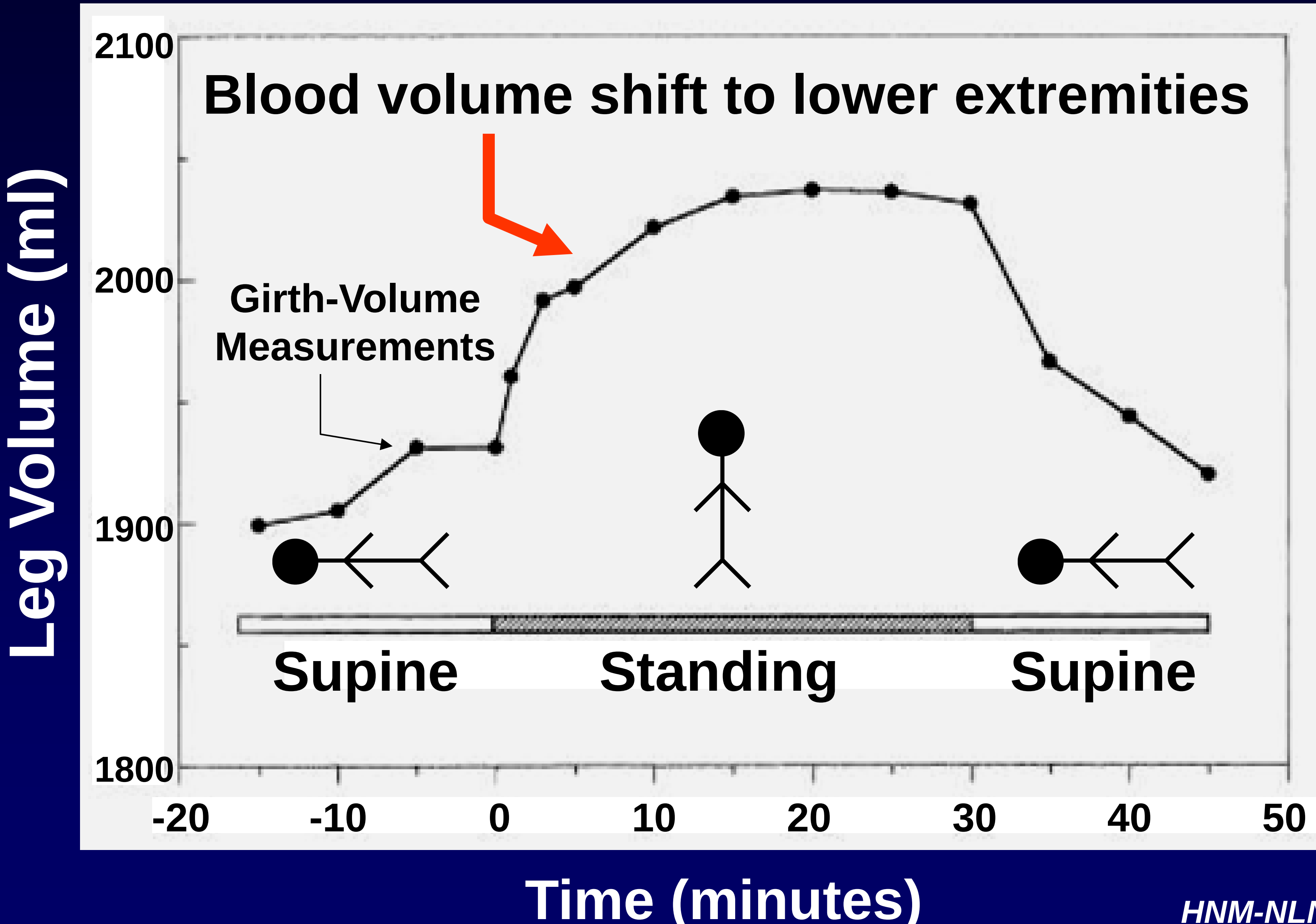
Basic Operating Principle



Mayrovitz HN Clinical Physiology 1998;18:234-242

Leg Volumes: Supine → Stand



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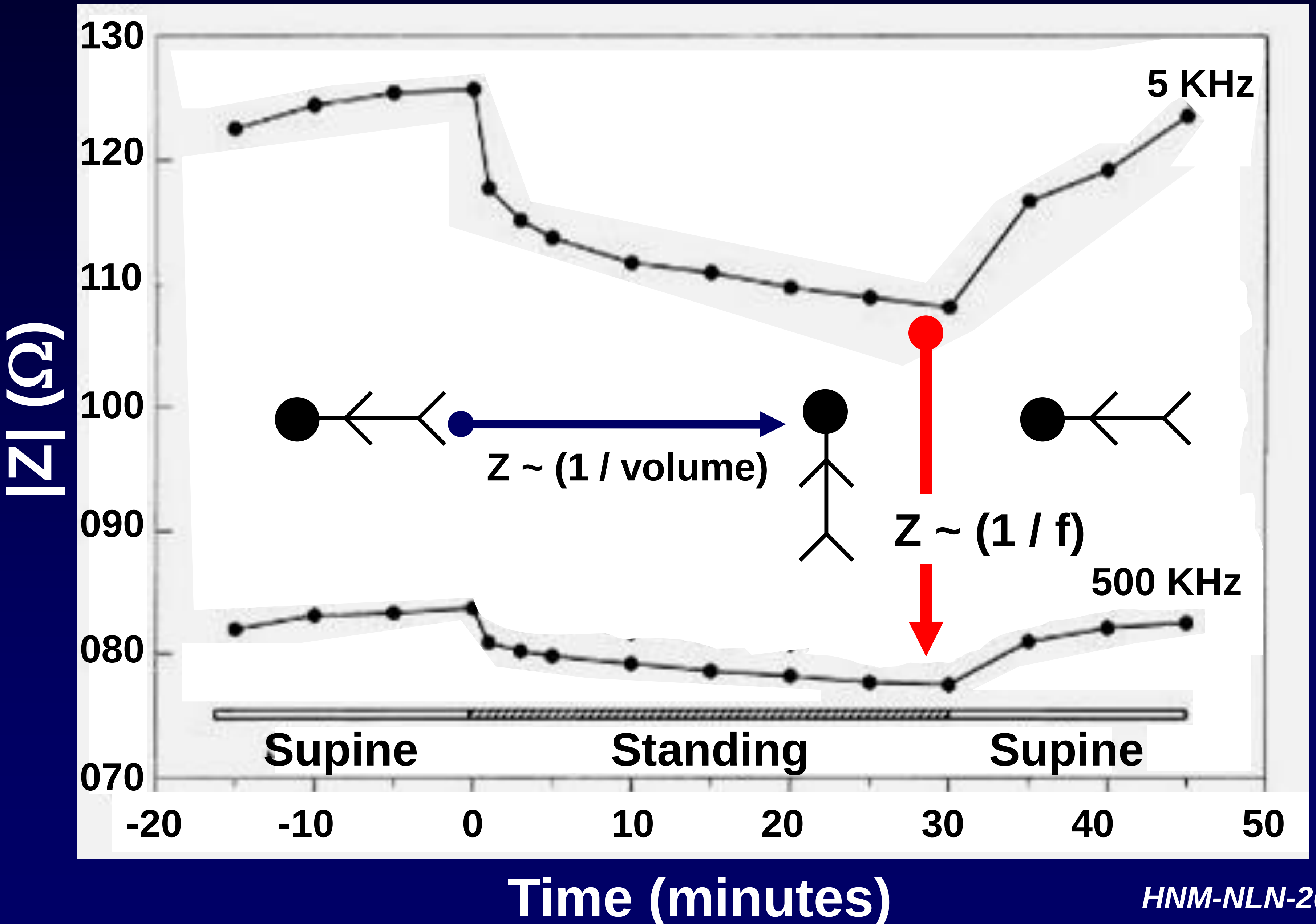
Z Depends on Frequency & Volume



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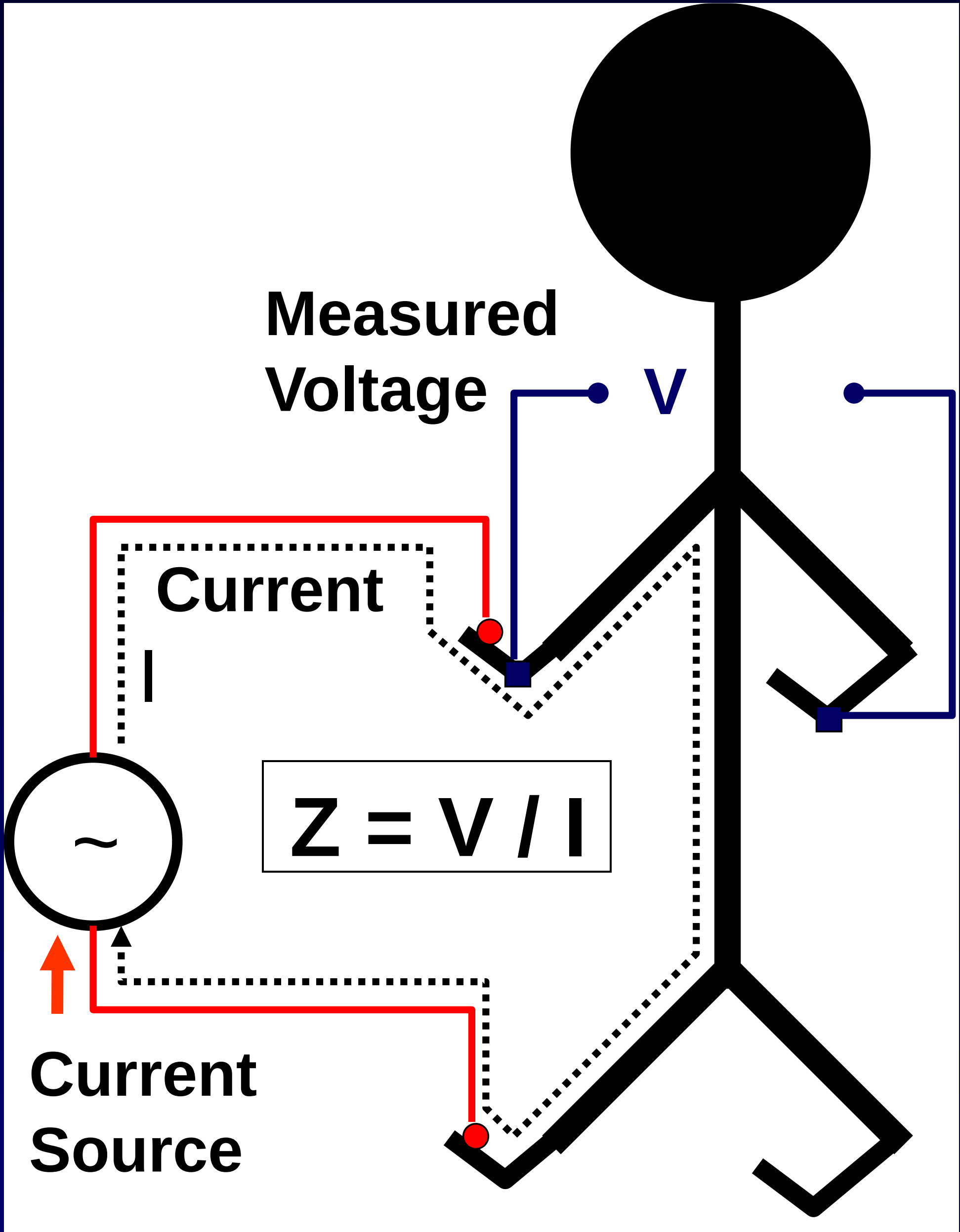
Assessing Arm Lymphedema



Single Frequency BIA → ECW

Multi-Frequency BIA

	Nondomnant	Dominant
R_0	360.1± 45.8	354.8 ± 45.9
R_∞	266.5 ± 39.2	257.8 ± 39.4
R_i	1052.3 ± 276.2	966.7 ± 264.9
$\frac{R_i}{R_0}$	2.988 ± 0.653	2.781 ± 0.595
$\frac{R_{0DOM}}{R_{0NONDOM}}$	0.986 ± 0.040	

172 paired arms

3SD lymphedema thresholds nondom/dom

dom = at-risk

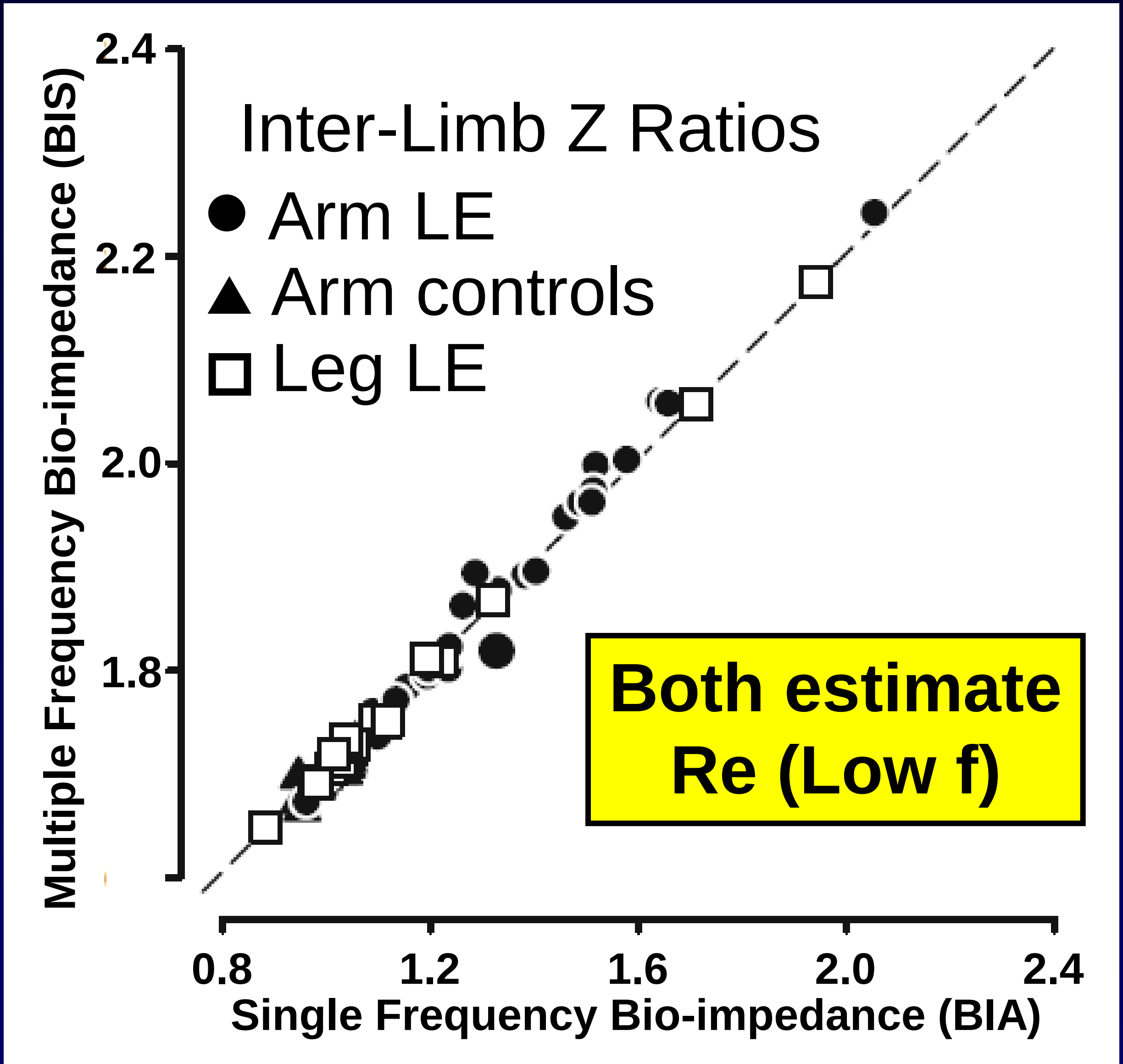
1.134

nondom = at-risk

1.106

Data from: Ward LC et al. Lymphatic Research Biology 2011;9:47-51

SFBIA = MFBIA for estimating ECW



York SL et al. Breast Cancer Res Treat 2009;117:177-182

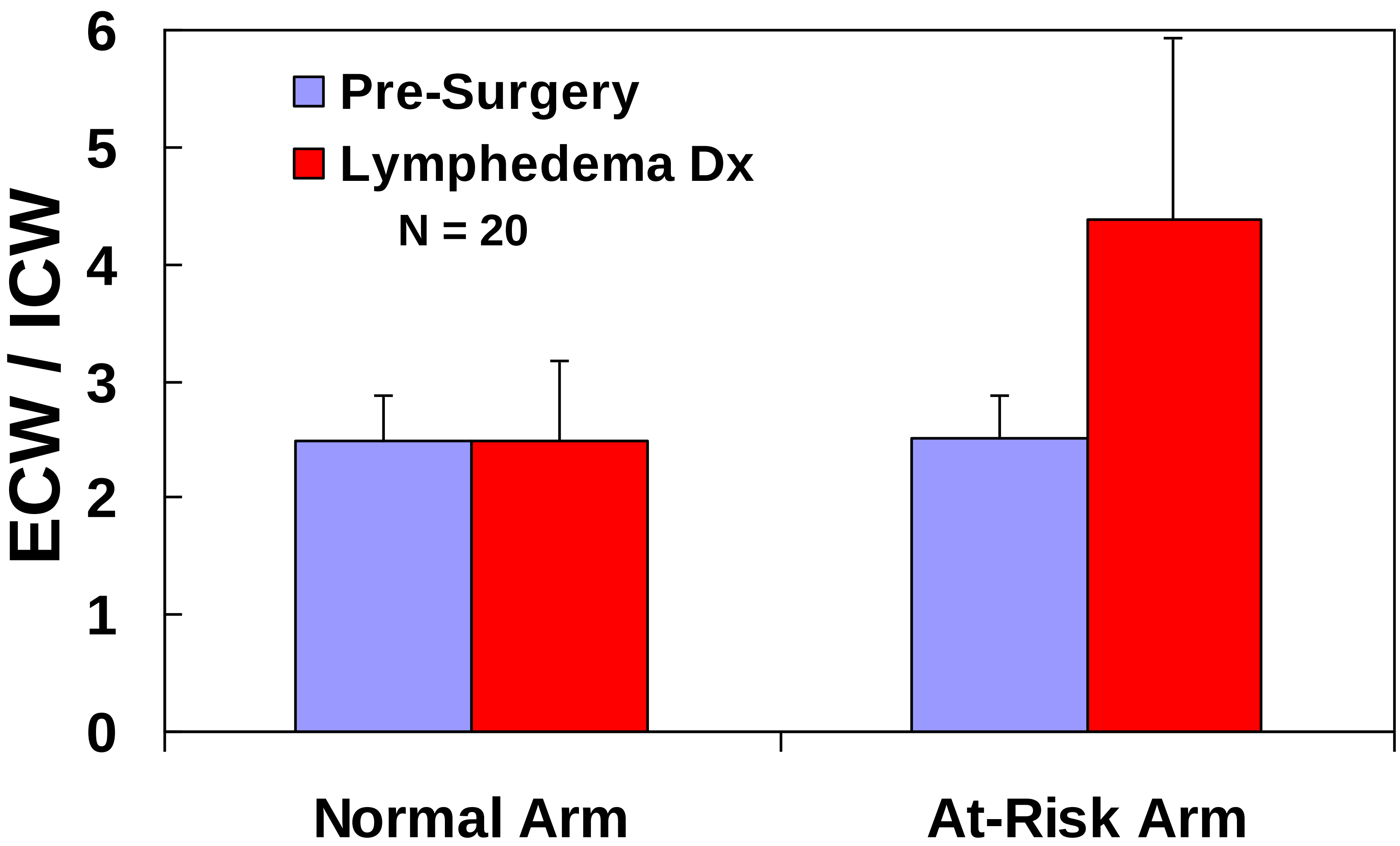
So …. Why use MFBIA (BIS)?

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

$$\frac{ECW}{ICW}$$

ECW / ICW Ratios



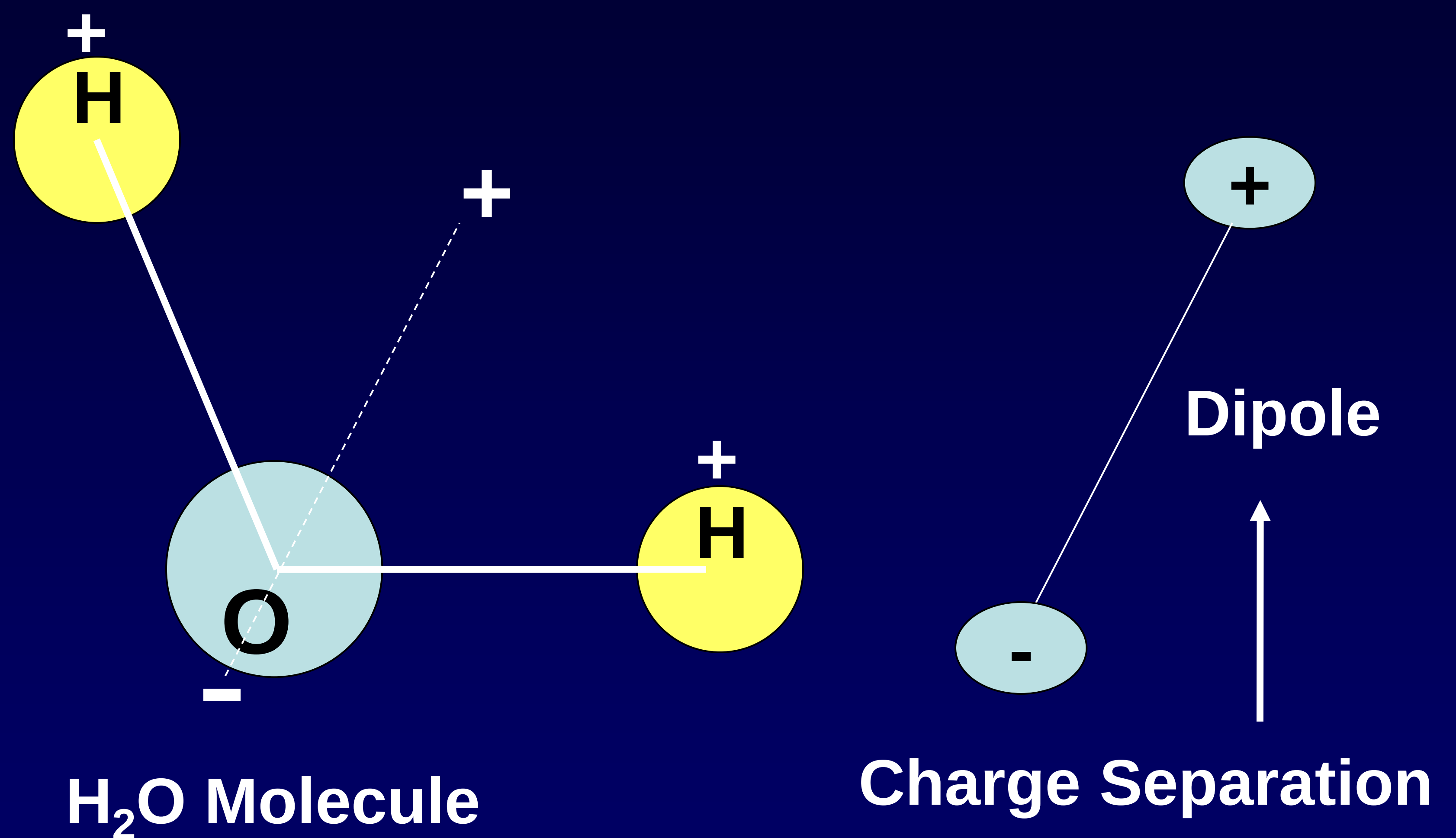
Data from: Cornish BH et al. Angiology 2002;53:41-47

Local Tissue Water Assessment

Tissue Dielectric Constant (TDC)
Relative Permittivity (ε_r)

PRINCIPLE

What is Dielectric Constant?



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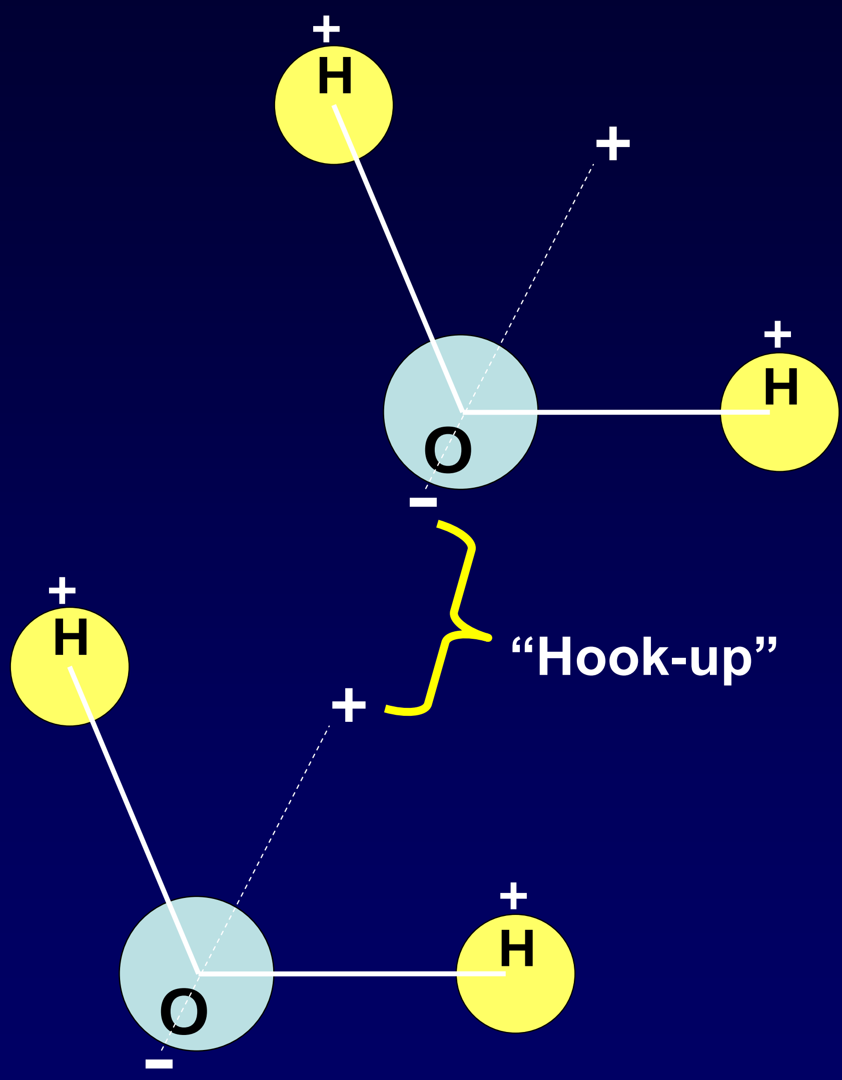
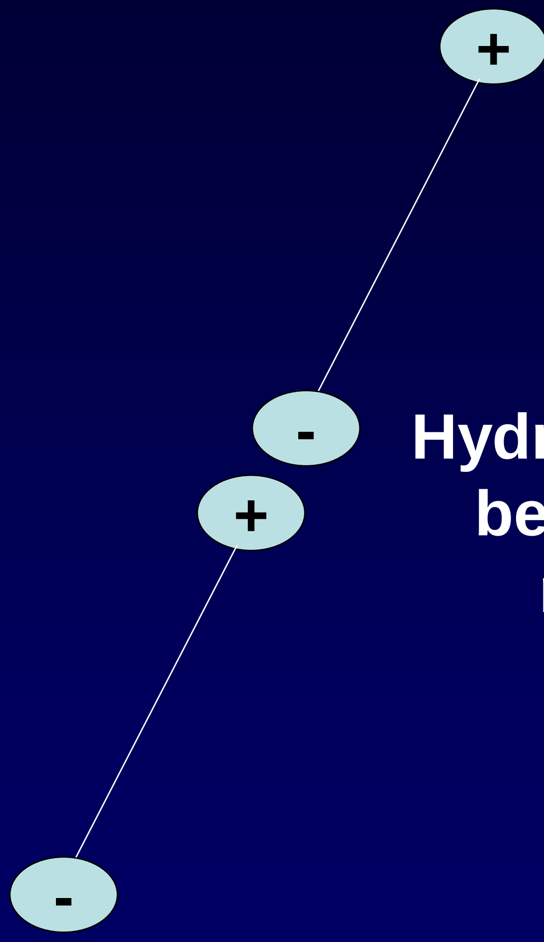
What is Dielectric Constant?



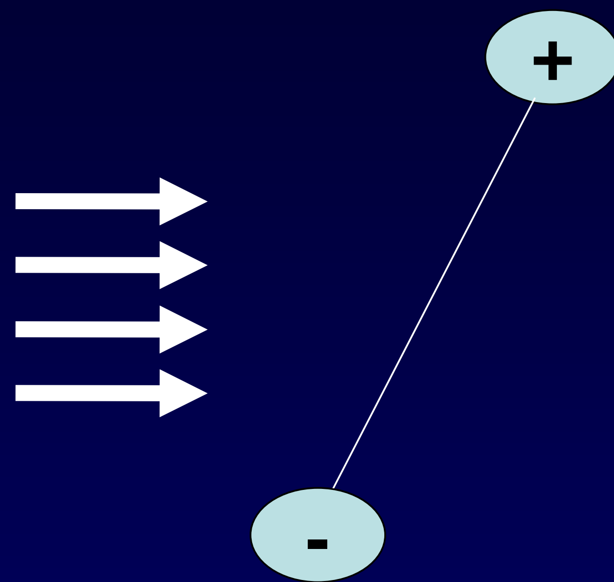
2 molecules



Hydrogen bonding between water molecules

What is Dielectric Constant?

Time varying electric field of force - E



Dipole movement Displacement - D of various types

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

Dielectric Constant

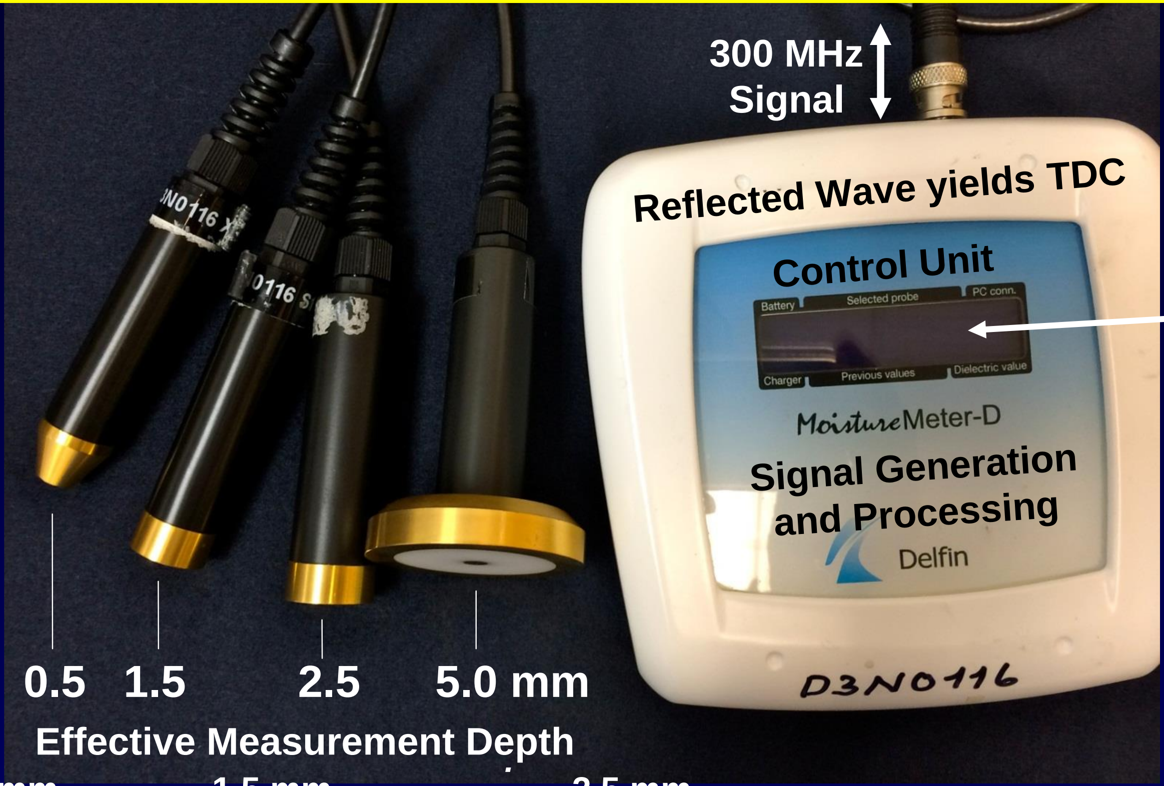
H_2O @ 32ºC → $\varepsilon_r = 76$

ε_r = ratio $\varepsilon/\varepsilon_0$ = TDC

Measurement Devices

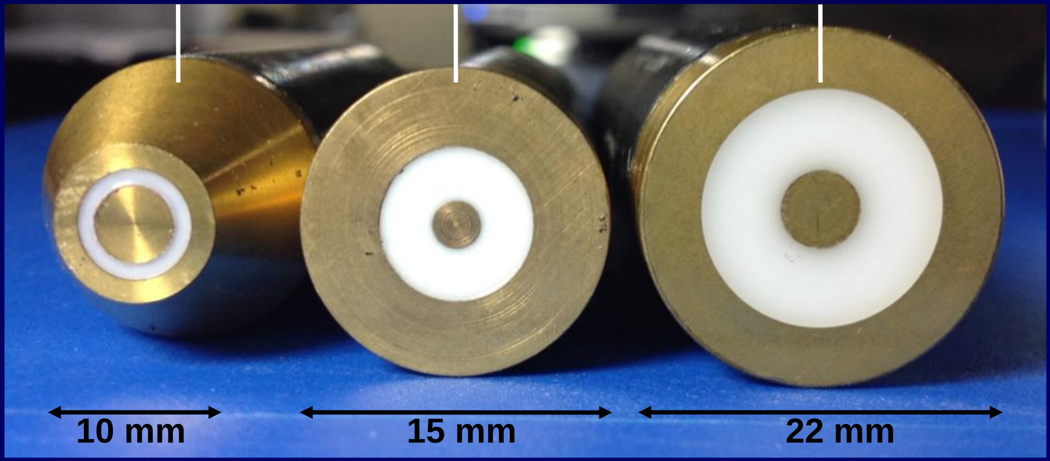
- Multi-Probe
- Single Probe (compact)

Multi-Probe

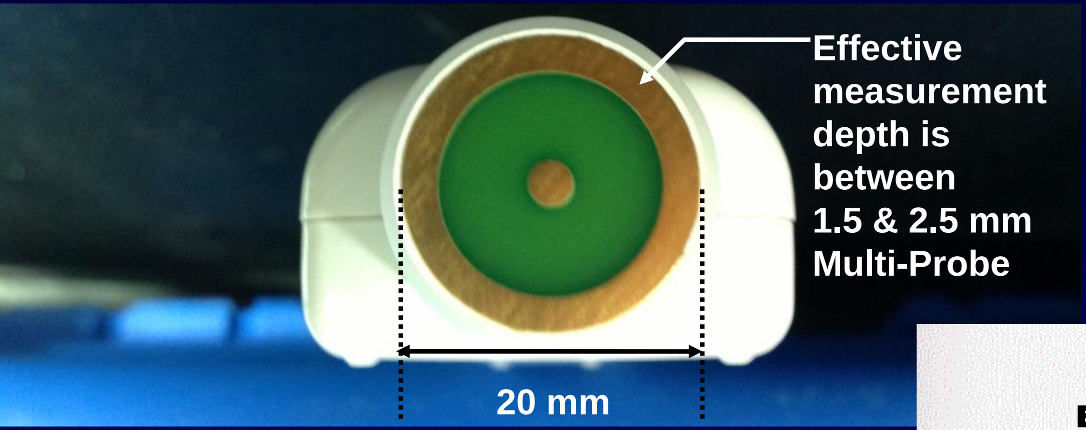


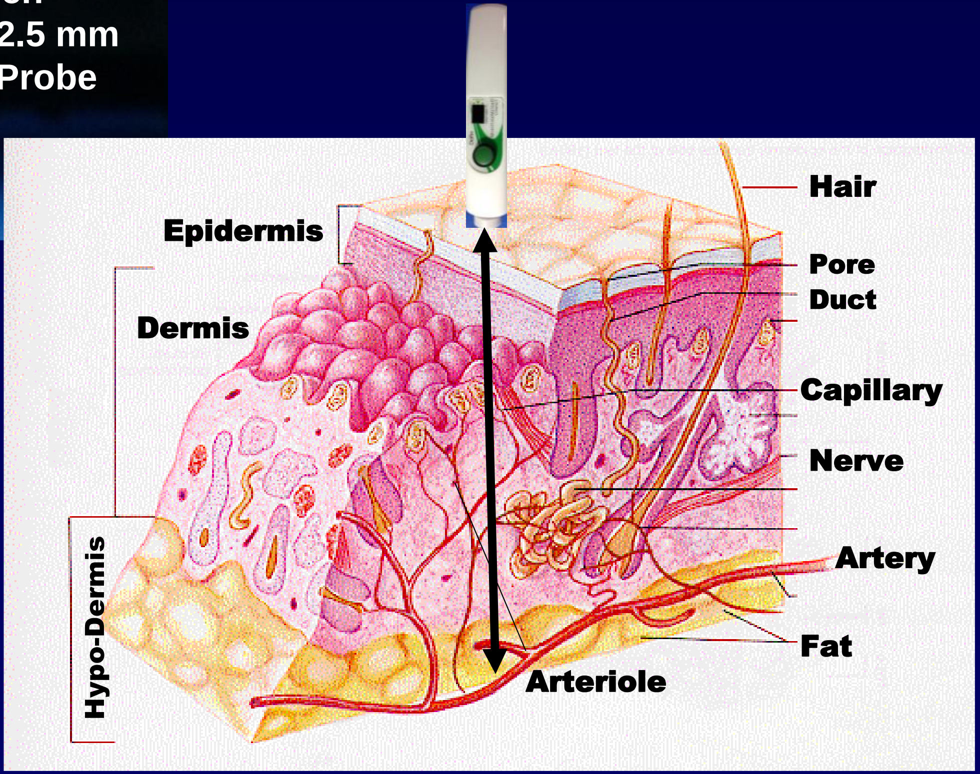
TDC
readout

0.5 mm 1.5 mm 2.5 mm

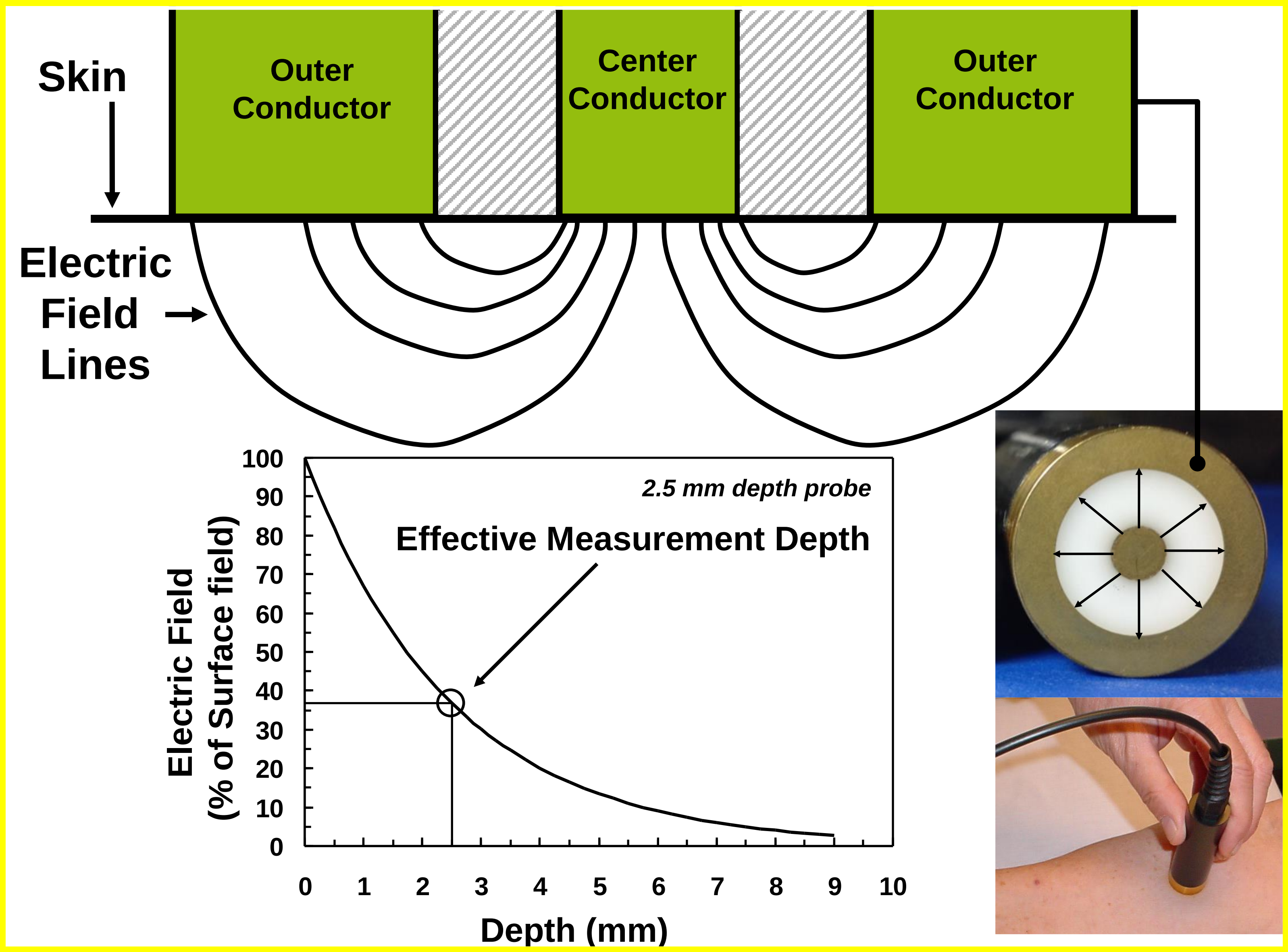


Single Probe (Compact)

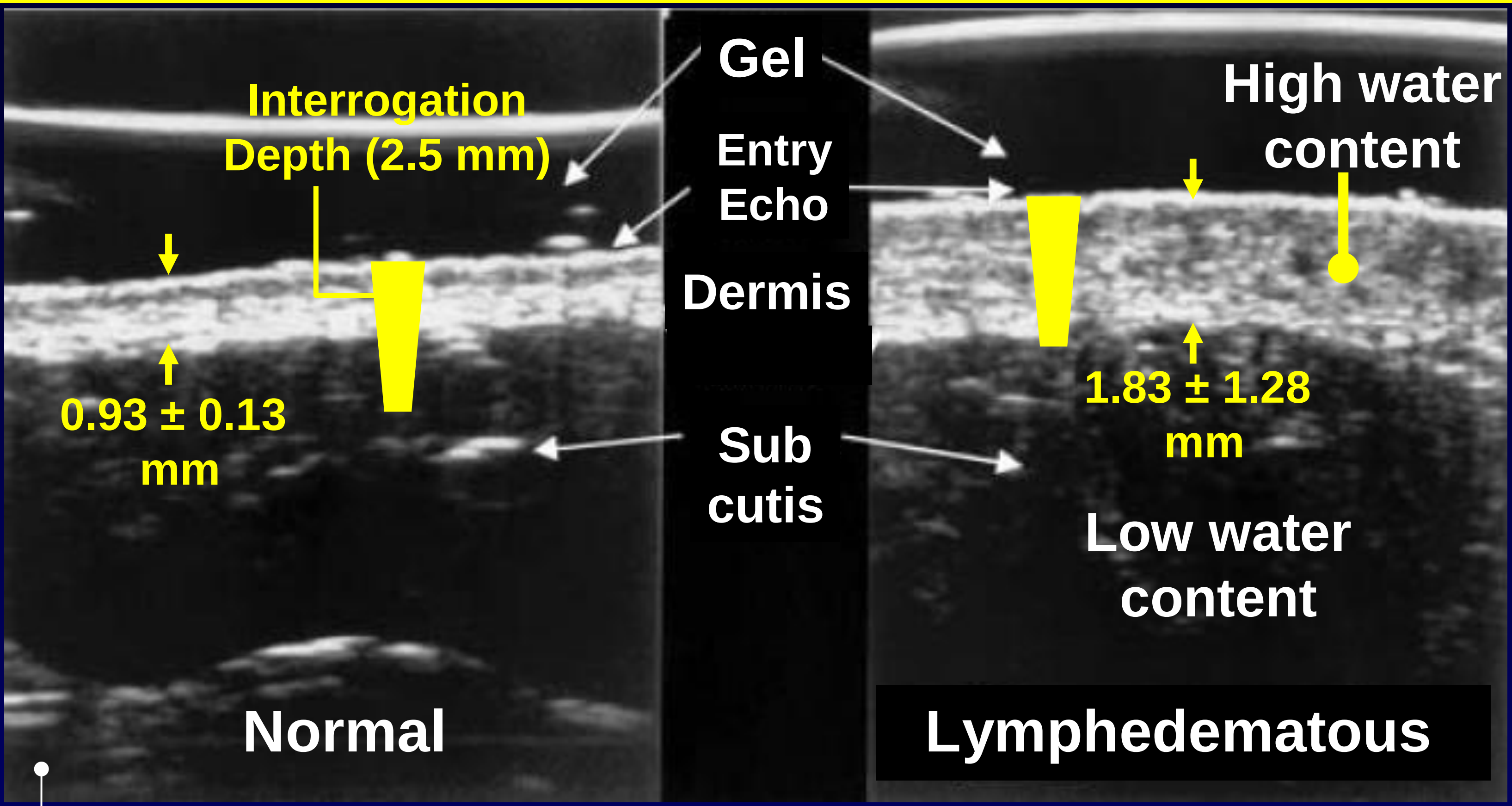




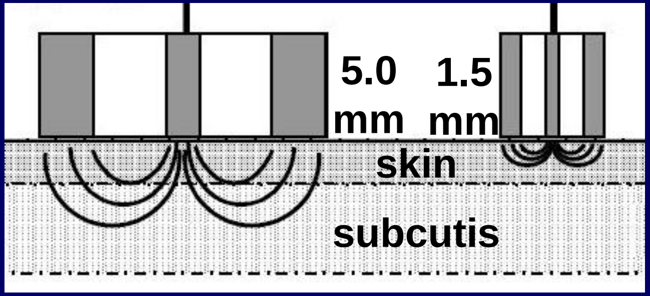
Effective Measurement Depth



Effective Measurement Depth

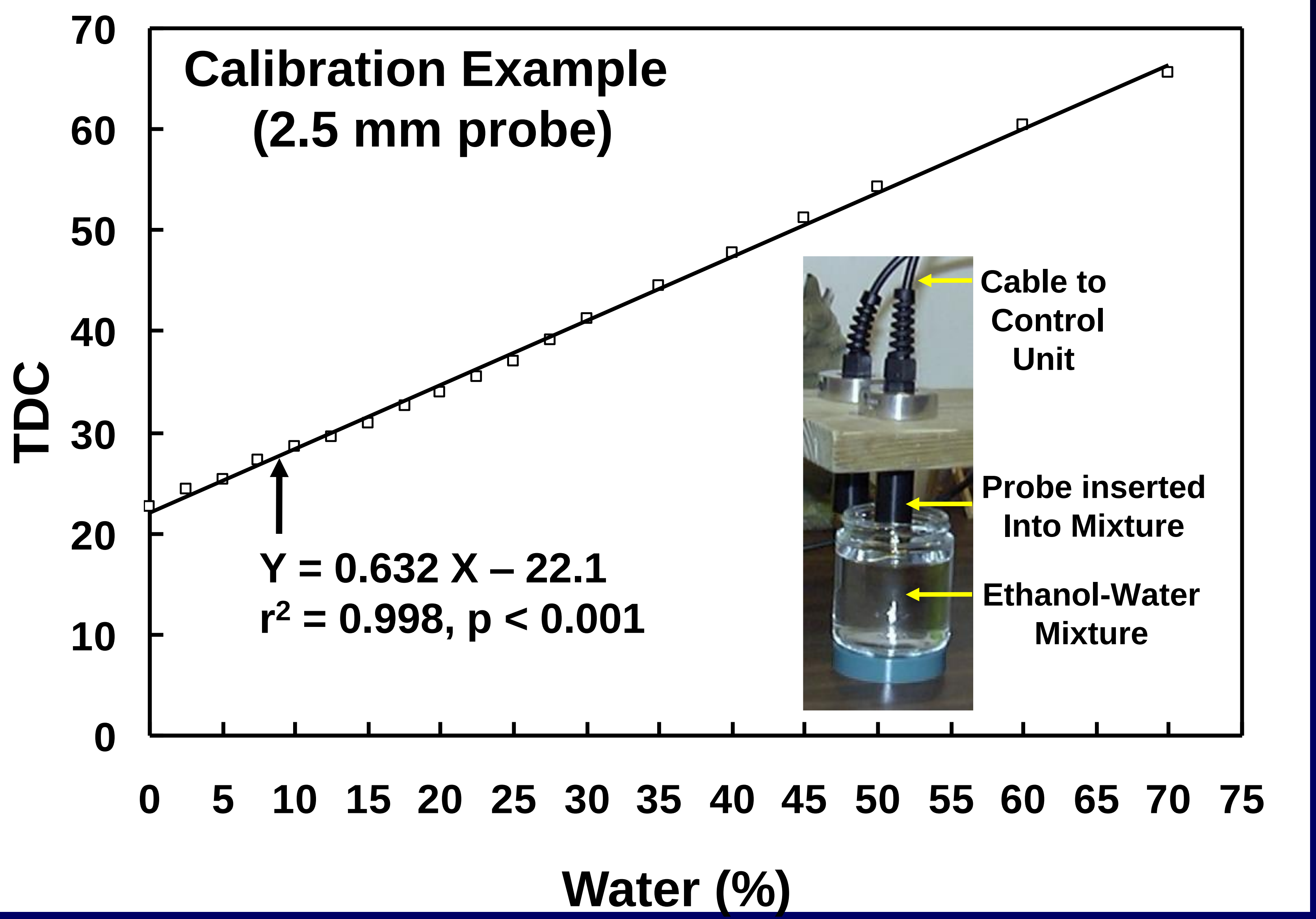


Ventral Forearm

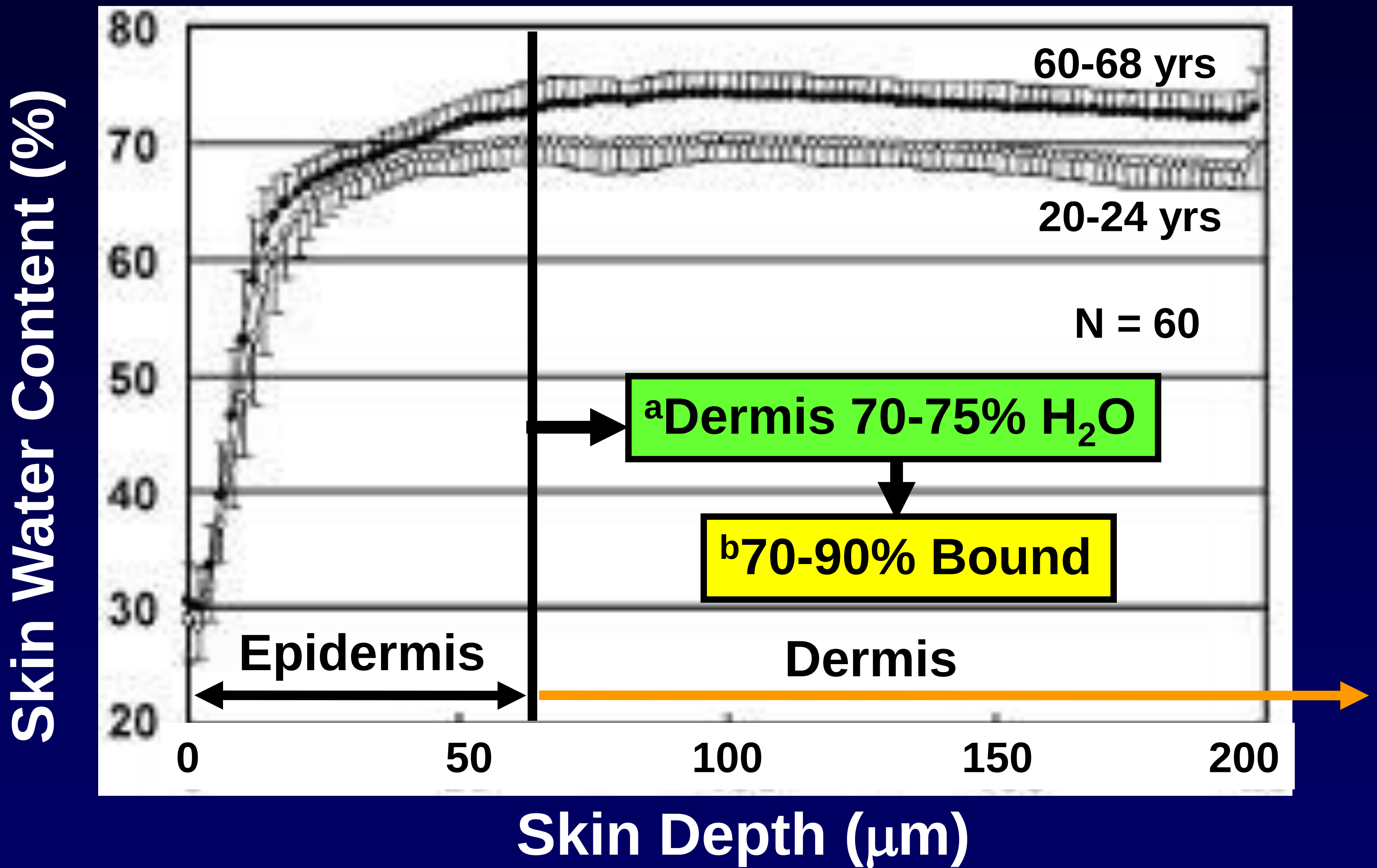


Modified from Mellor et al. The Breast J. 2004;10:496-503

TDC dependence on H_2O



Skin Water Distribution



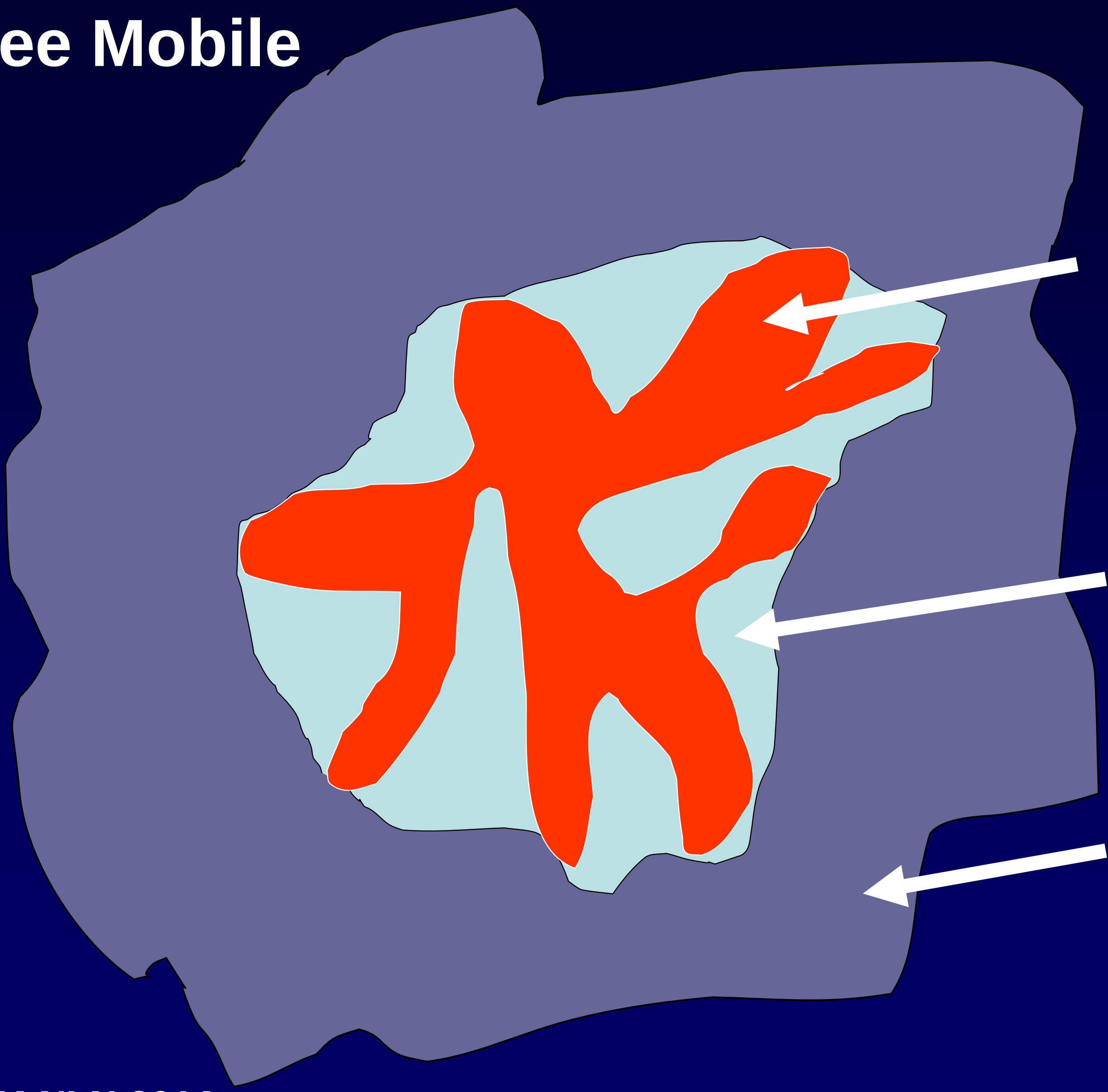
[a]*Data: Nakagawi N et al. SRT, 2010:16:137-141; Confocal Raman Spectroscopy*

[b]*Data: Gniadecka et al. J Invest Dermatol 1998: 110:393-398 NIR-Raman Spec*

Free and Bound Water

Free Mobile

Free Mobile



Protein
(1 g)

Bound H_2O
(0.2 – 0.5 g)

Limited
Mobility H_2O
~ 20 g

Free Mobile

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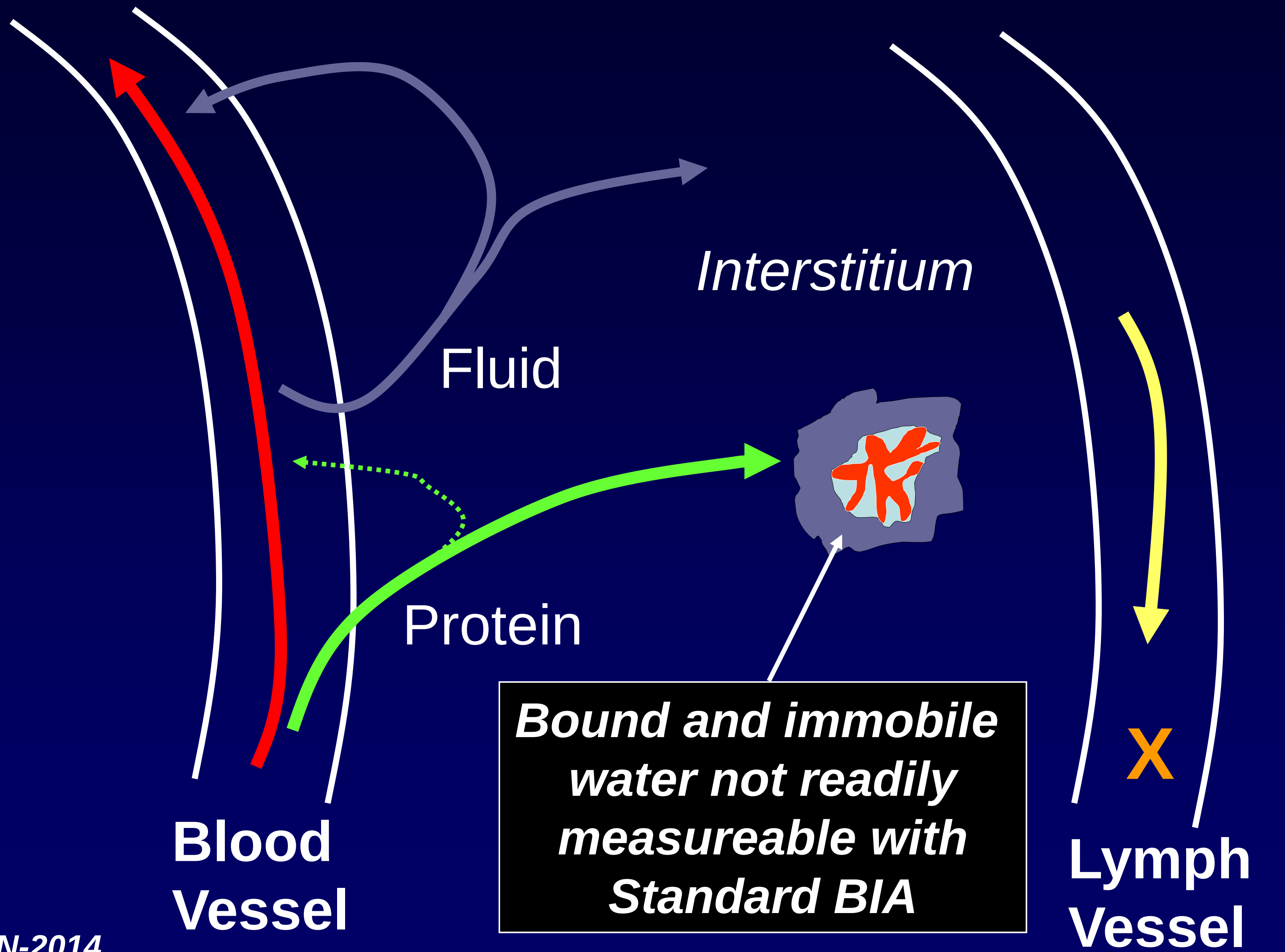
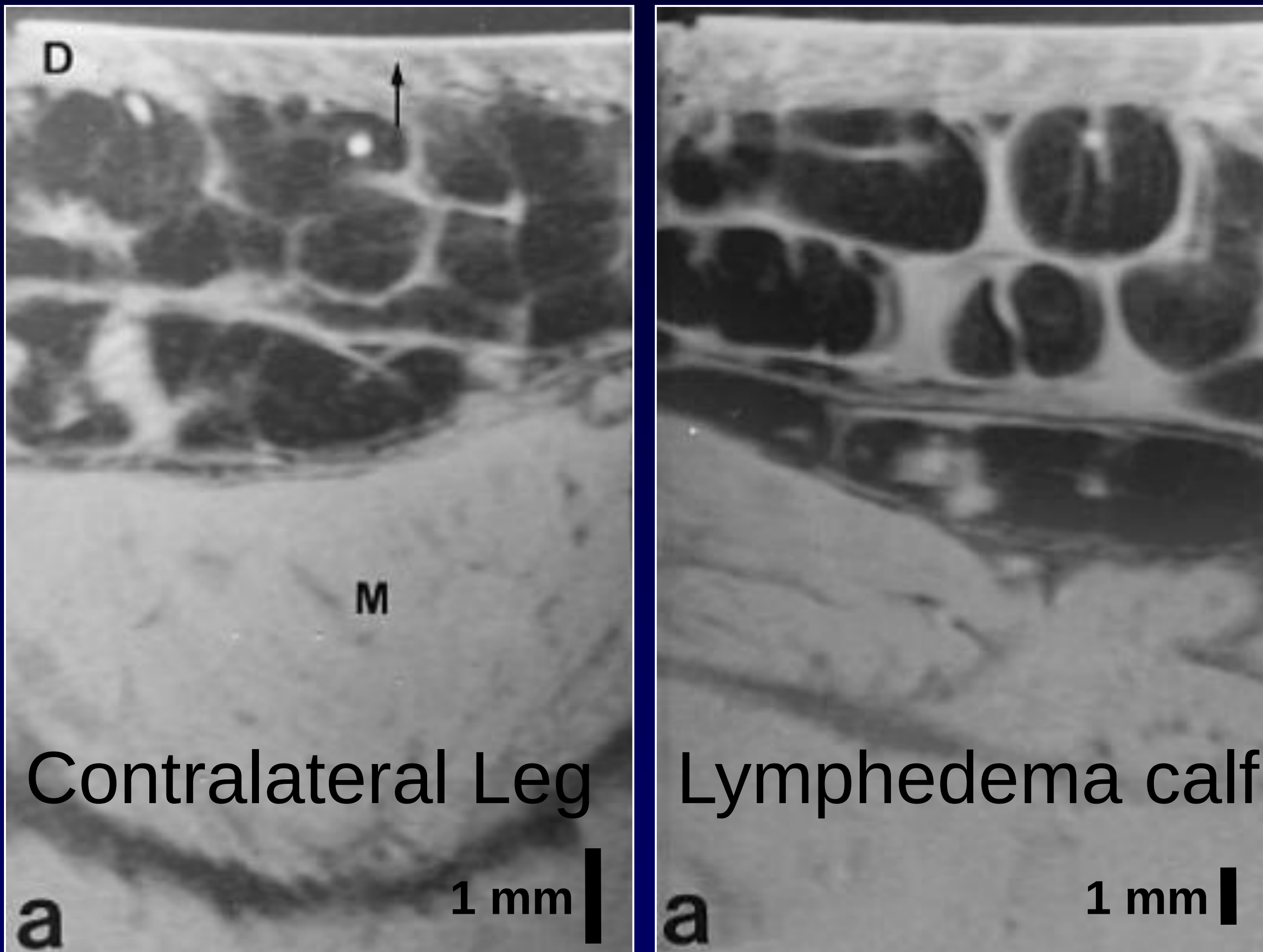
Lymphatic Dysfunction



Dermal Water in Lymphedema



40% increase in Calf Dermal Water in Lymphedema

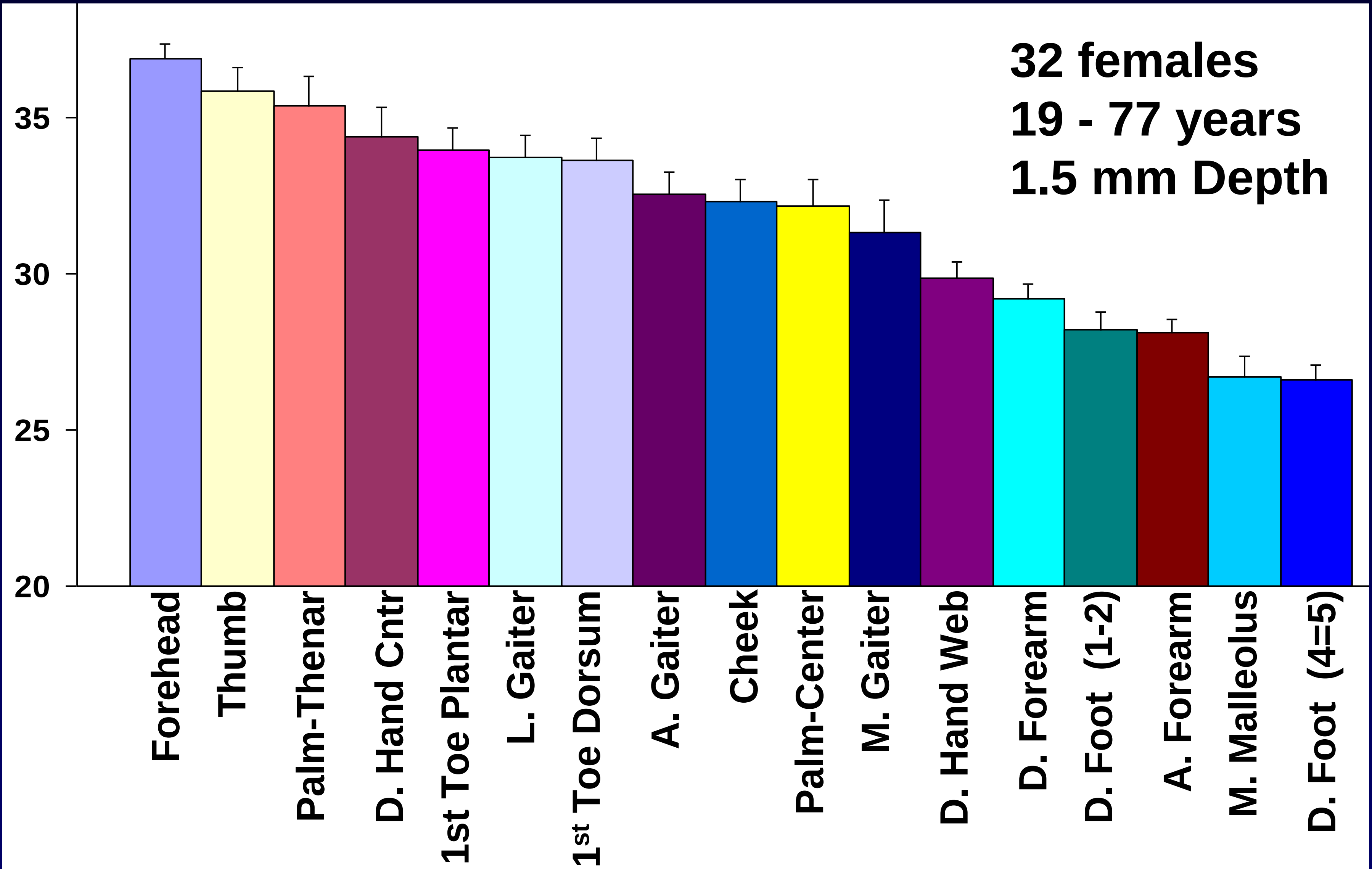
11 primary LE
10 secondary LE

Mobile water shows intense

Data: Idy-Peretti et al. Int J Dermatol 1998;110:782-787 Hi-Res MRI N=21

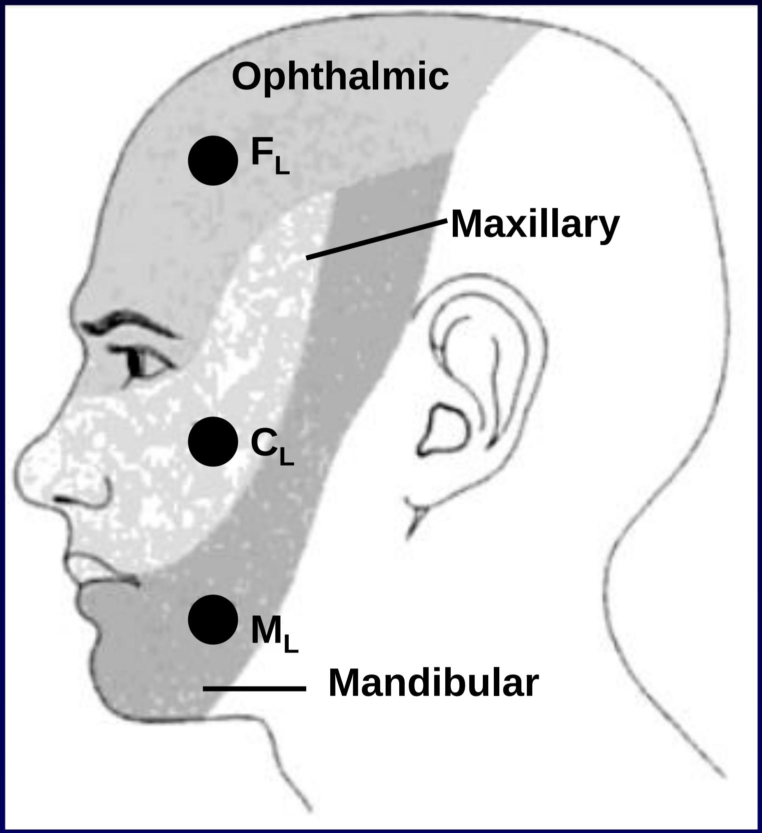
TDC Features and Applications

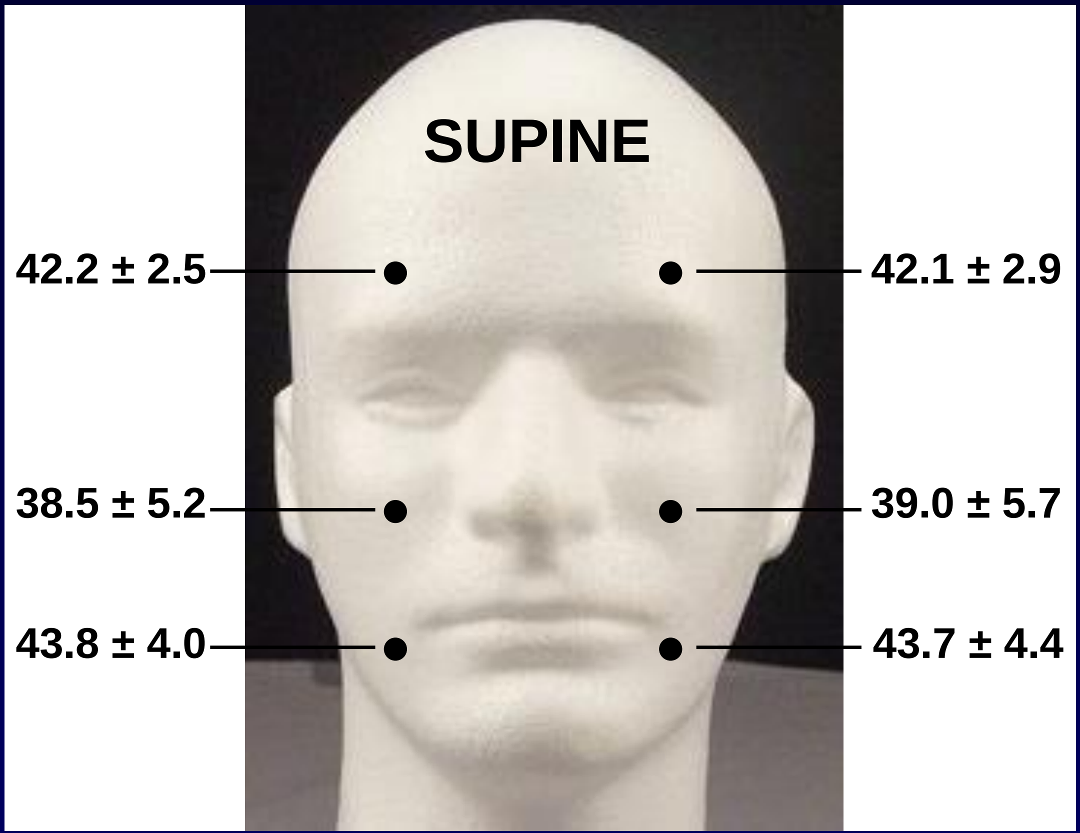
TDC Site Variability



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

TDC Site Variability

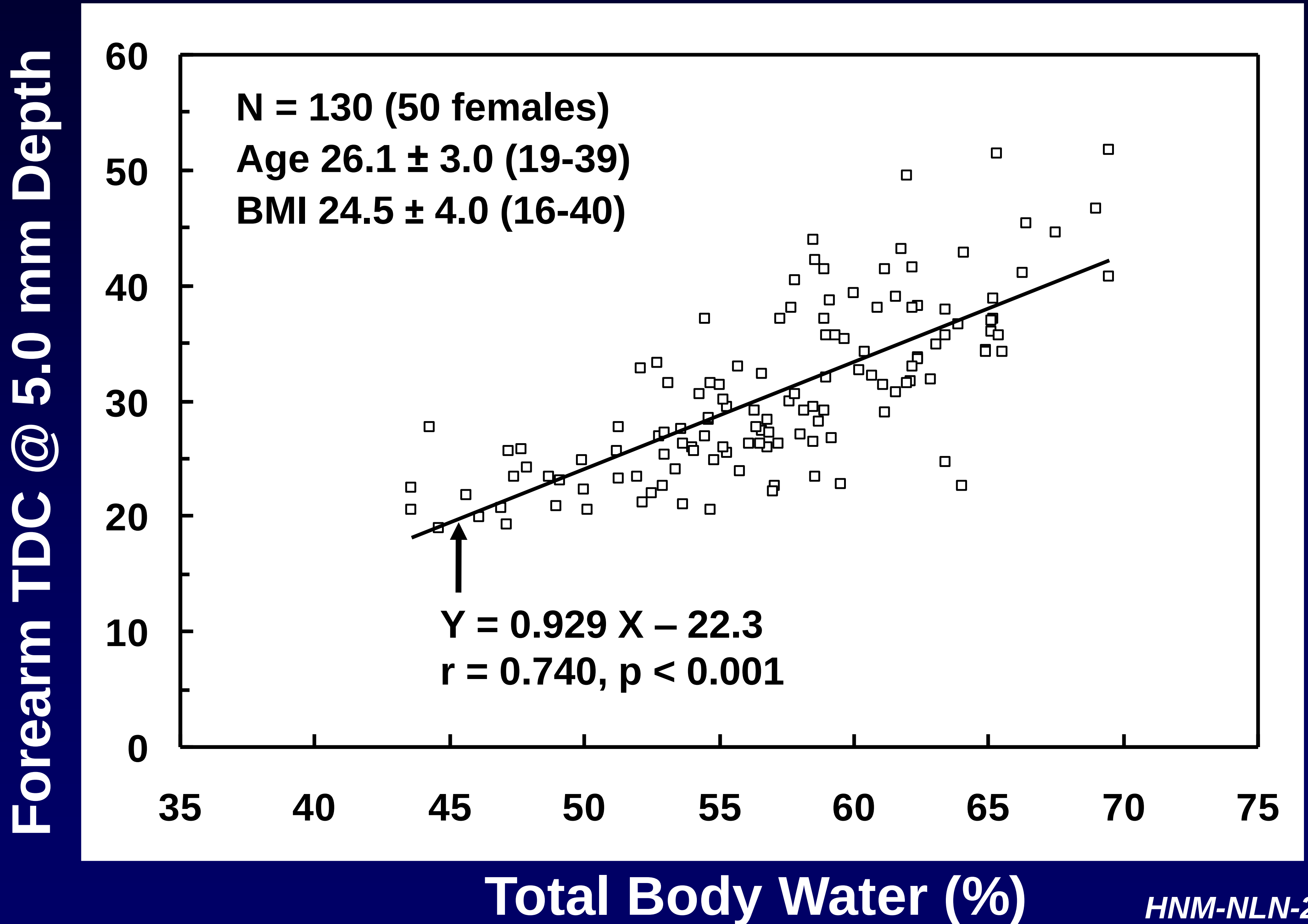




N = 30 young adult males (25.0 ± 2.5 years) @ 1.5 mm depth

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

Correlation with Total Body Water



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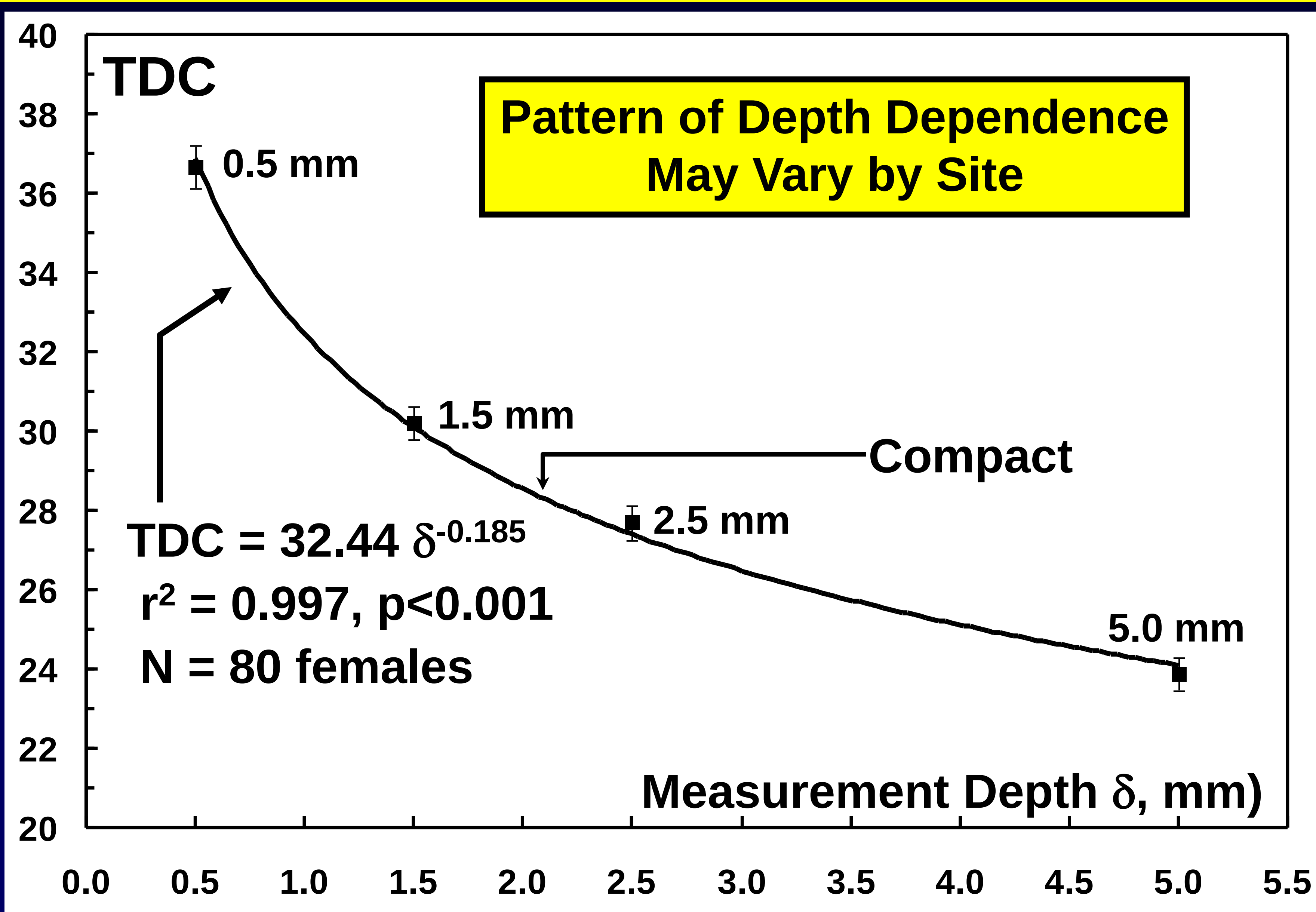
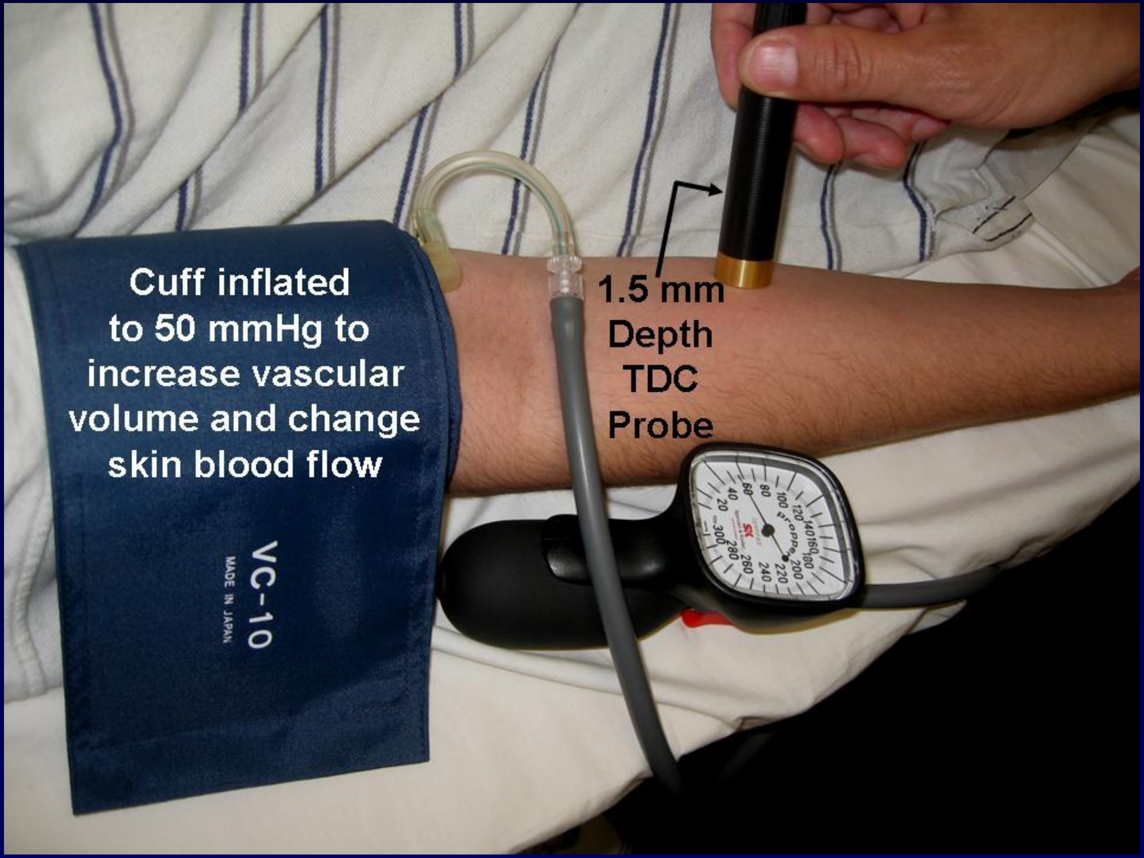
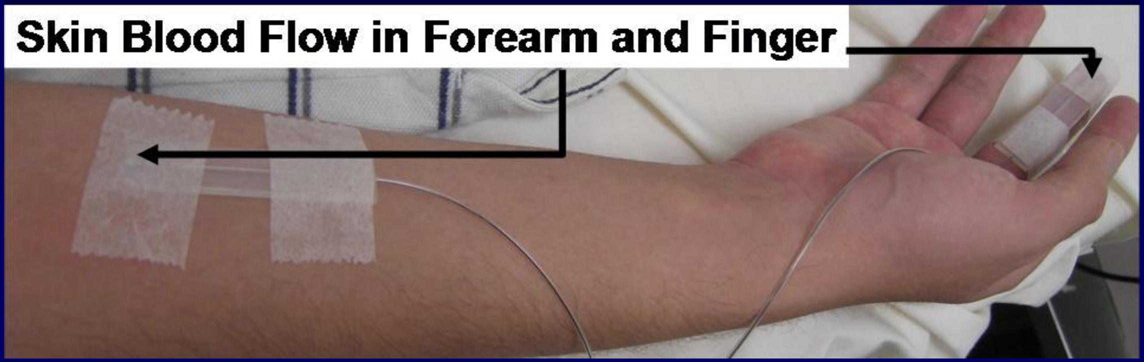
TDC Depth Dependence: Forearm

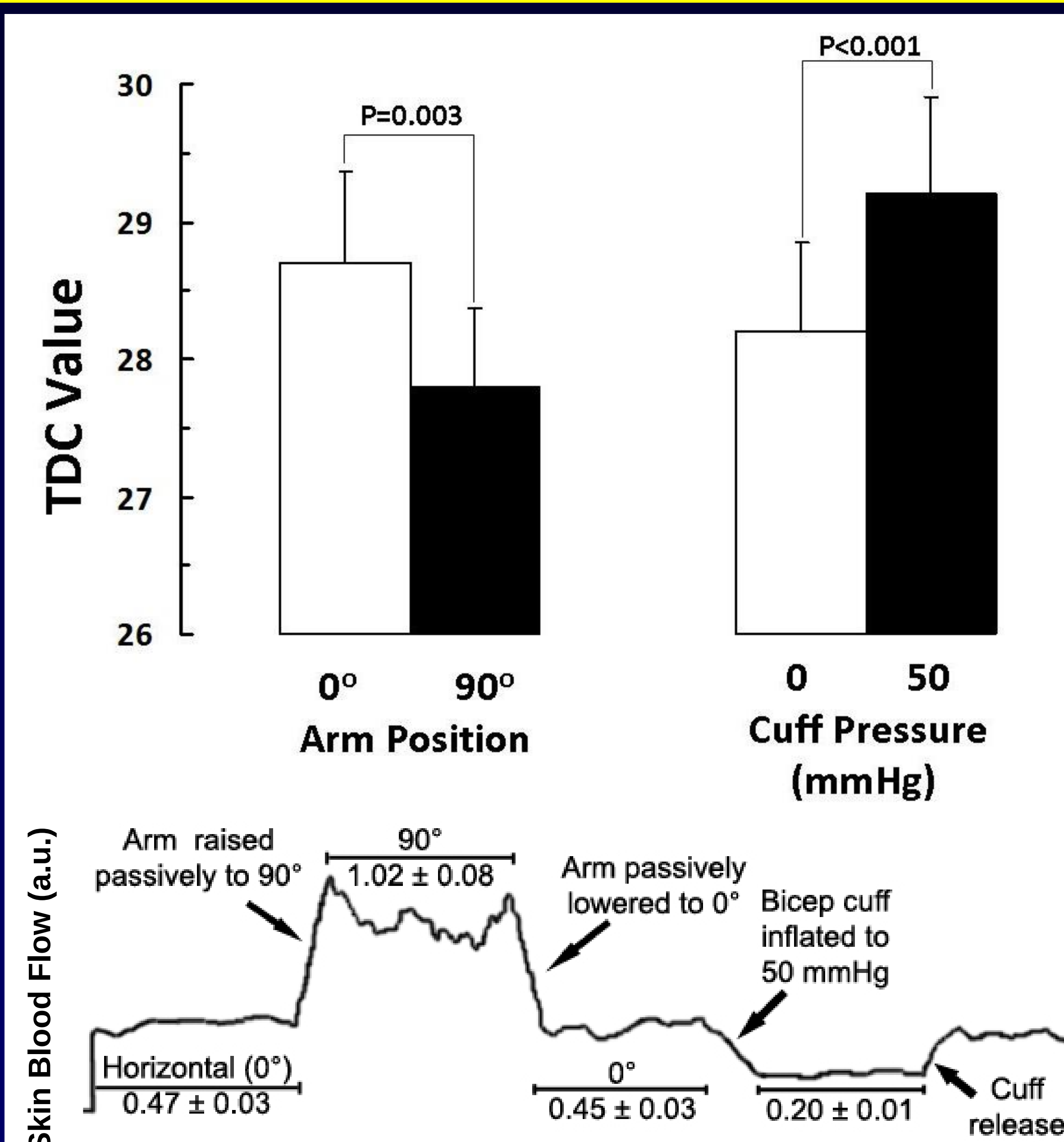


TDC Vascular Component





TDC Vascular Component



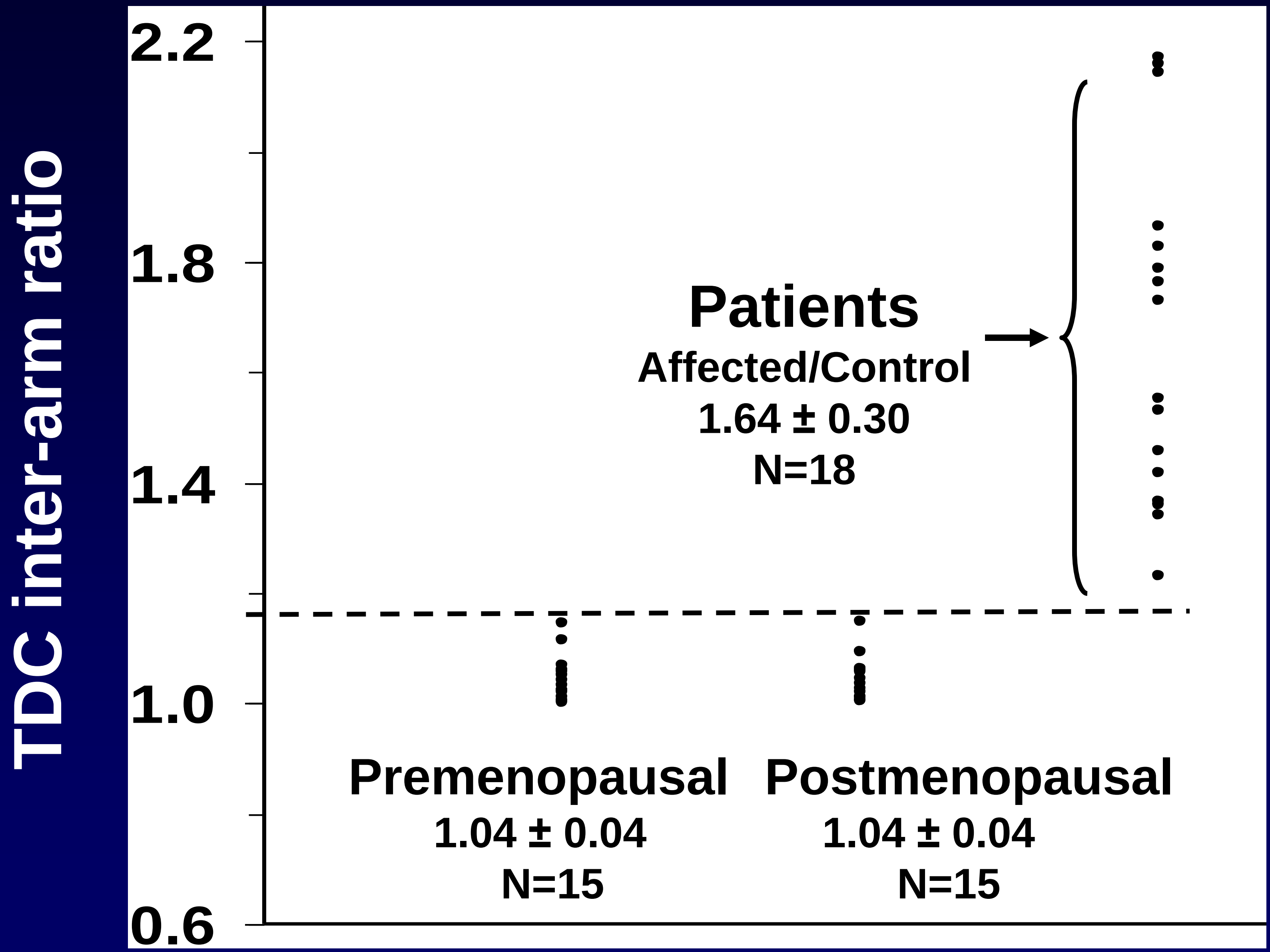
Large vascular blood volume & flow changes

↓

Minor changes in TDC values

From: Mayrovitz HN et al. Clinical Physiology and Functional Imaging 2013;33:55-61

TDC Lymphedema Discriminations



Mayrovitz HN Lymphology 2007;40:87-94

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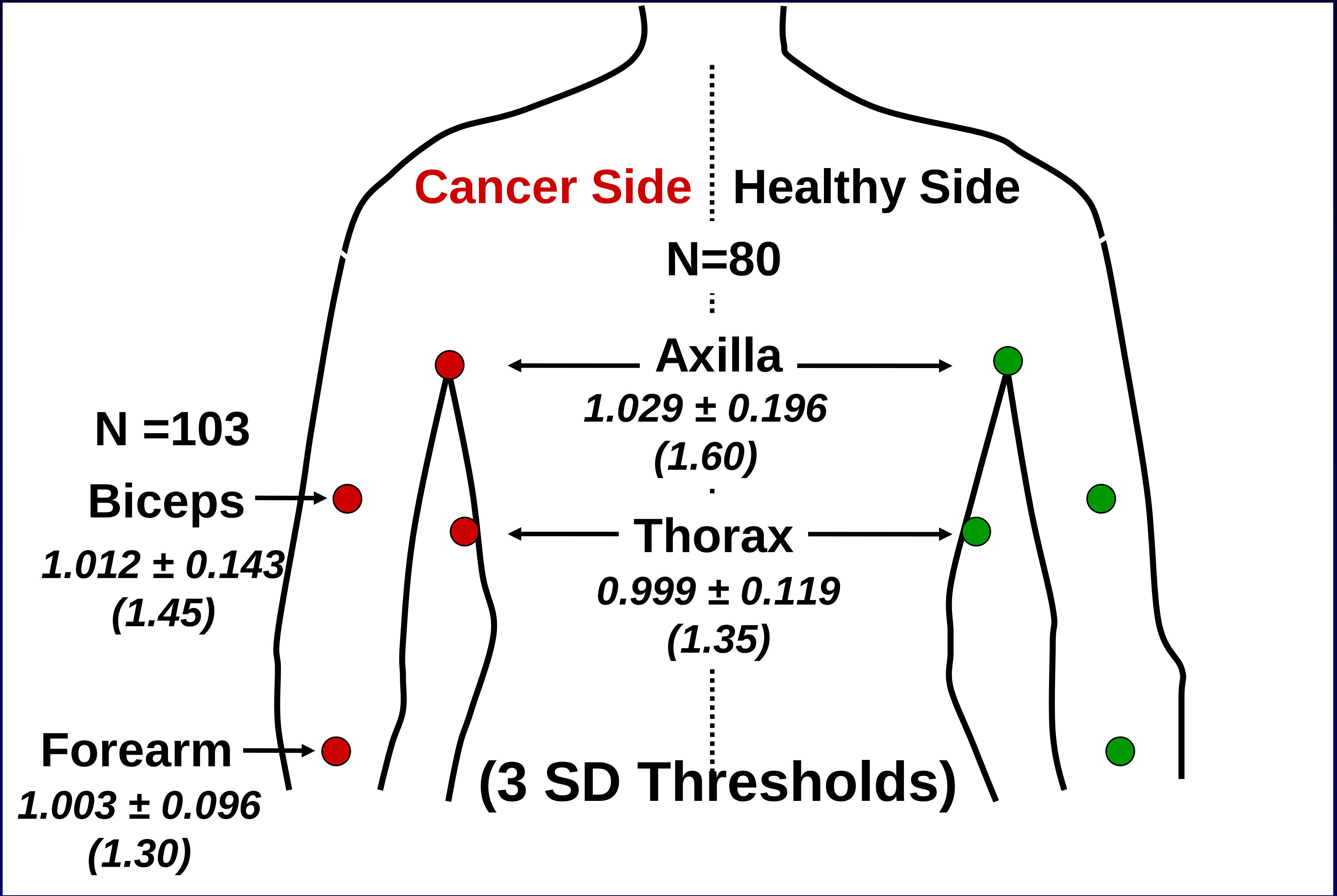
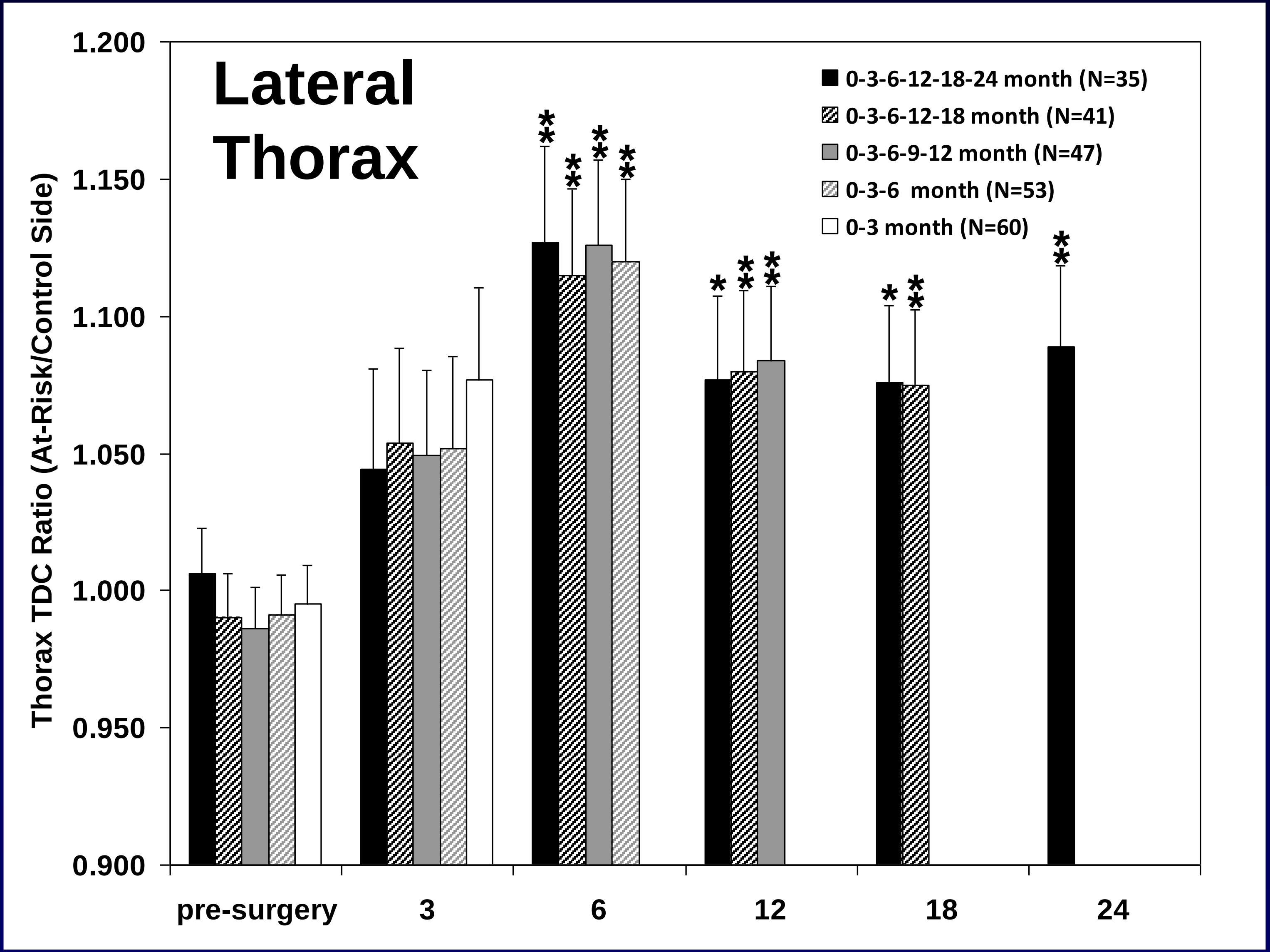
Pre-Surgery Reference TDC Ratios



Sequential TDC Ratio Changes



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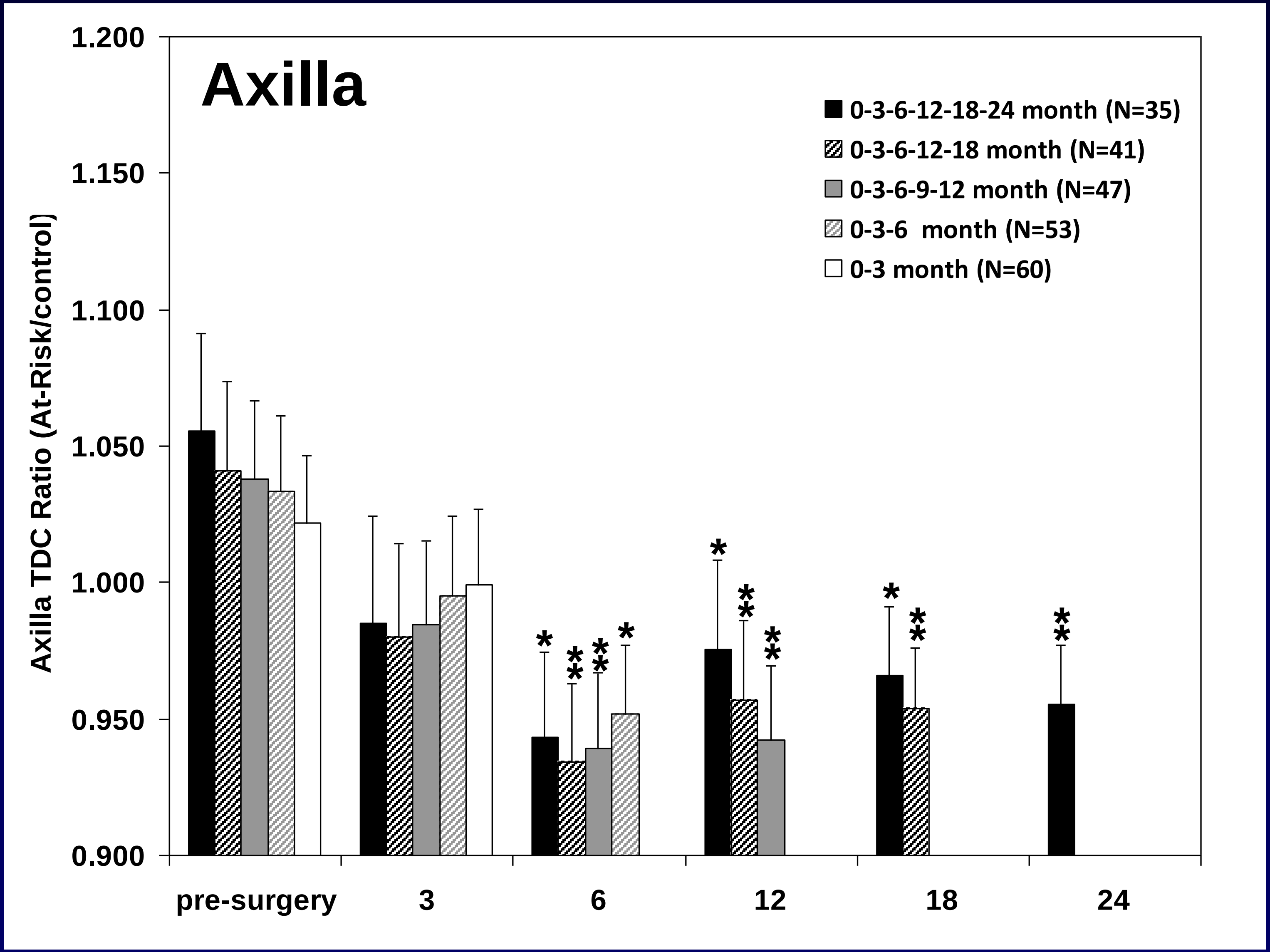
Sequential TDC Ratio Changes



Methods Features Comparison

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