Quantifying Lymphedema with Non-invasive Methodology

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Plan: Four Major Areas

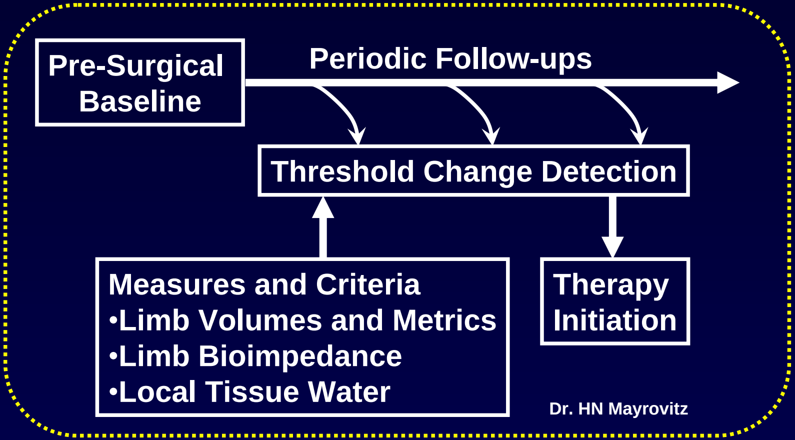
1. Measurement Considerations
   - A. Why measure / quantify?
   - B. Reliability/Repeatability
2. Measurement Methods
   - A. Limb girth and volume
   - B. Tissue Properties
   - C. Limb Bioimpedance
   - D. Tissue Dielectric Constant
3. Measurement Principles
4. Measurement Threshold Issues

Presentation slides will be available for download!

1. Measurement Considerations

A. Why Measure/Quantify?

- Evaluate at-risk patients
- Early detection → Early Tx



- Stratify LE severity
- Track Tx outcomes
- Documentation needs

- Research and Other Clinically Related Purposes

B. Measurement Reliability

- What constitutes a "real" or "trustable" Difference or Change?

I Like

↓

Minimal Detectible Change (MDC)

Example: Arm Girth Test-Retest for MDC

Arm Girth (cm)

Subject	Test1
1	20.6
2	24.3
3	27.3
4	21.2
5	22.7
6	21.6
7	27.3
8	21.2
9	20.5
10	24.7
11	24.6
12	25.3

Example: Arm Girth Test-Retest for MDC

Arm Girth (cm)

Subject	Test1	Test2
1	20.6	20.1
2	24.3	24.8
3	27.3	26.8
4	21.2	21.7
5	22.7	22.2
6	21.6	22.1
7	27.3	26.8
8	21.2	21.7
9	20.5	20.0
10	24.7	25.2
11	24.6	24.1
12	25.3	25.8

Example: Arm Girth Test-Retest for MDC

Arm Girth (cm)

Subject	Test1	Test2	Difference (T2 – T1)
1	20.6	20.1	-0.5
2	24.3	24.8	0.5
3	27.3	26.8	-0.5
4	21.2	21.7	0.5
5	22.7	22.2	-0.5
6	21.6	22.1	0.5
7	27.3	26.8	-0.5
8	21.2	21.7	0.5
9	20.5	20.0	-0.5
10	24.7	25.2	0.5
11	24.6	24.1	-0.5
12	25.3	25.8	0.5
AVG	23.4	23.4	0.0
SD	2.48	2.45	0.5

SD_d

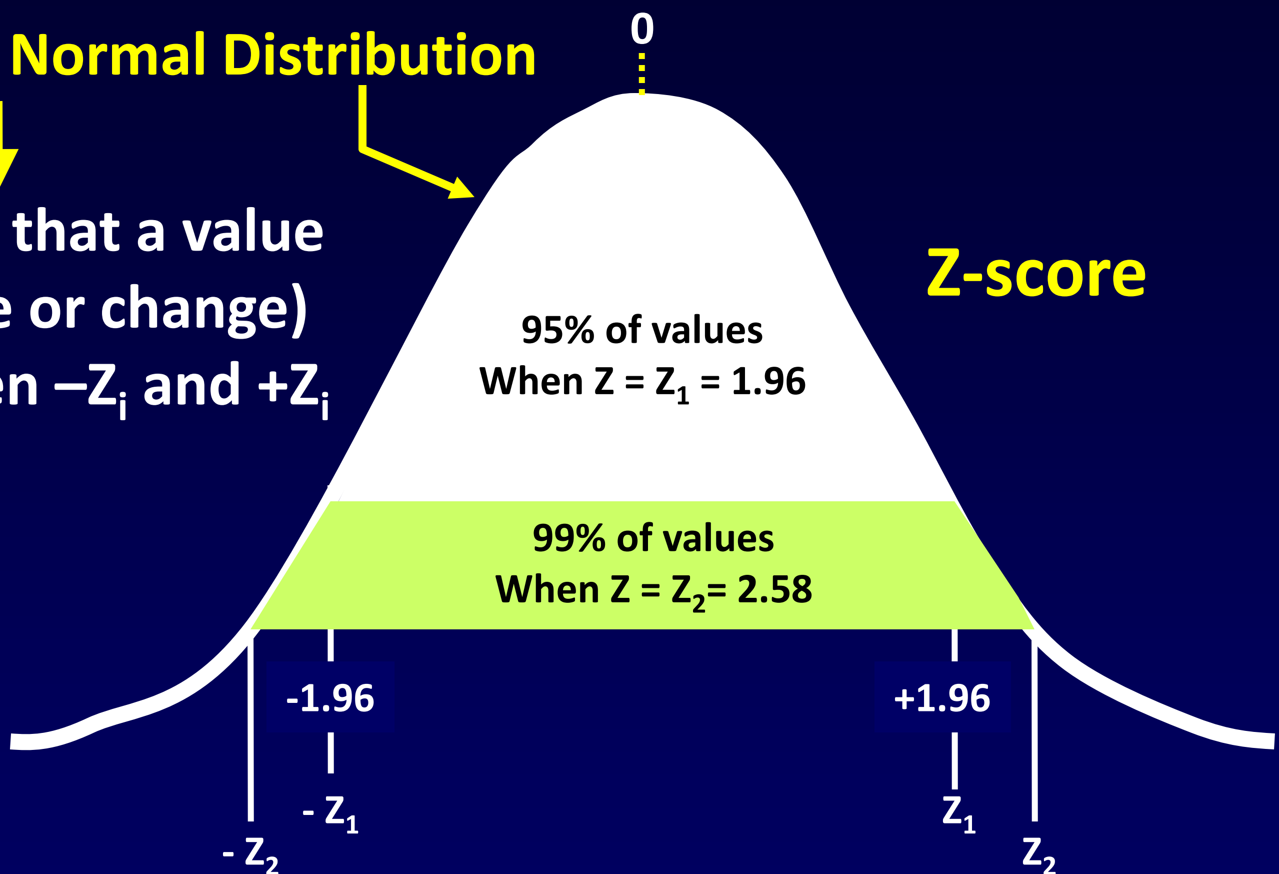
$$MDC \approx Z \times SD_d$$

Z-score

Example: Arm Girth Test-Retest for MDC

Standardized Normal Distribution

Probability that a value (difference or change) lies between $-Z_i$ and $+Z_i$



Z-score

Z's are Z-scores

Prob that a value lies between a Z score of ± 1.96 = 0.95

Prob that a value lies between a Z score of ± 2.58 = 0.99

Example: Arm Girth Test-Retest for MDC

Arm Girth (cm)

Subject	Test1	Test2	Difference (T2 – T1)
1	20.6	20.1	-0.5
2	24.3	24.8	0.5
3	27.3	26.8	-0.5
4	21.2	21.7	0.5
5	22.7	22.2	-0.5
6	21.6	22.1	0.5
7	27.3	26.8	-0.5
8	21.2	21.7	0.5
9	20.5	20.0	-0.5
10	24.7	25.2	0.5
11	24.6	24.1	-0.5
12	25.3	25.8	0.5
AVG	23.4	23.4	0.0
SD	2.48	2.45	0.5

SD_d → (SD of Difference)

$$MDC \approx Z \times SD_d$$

$$MDC = 1.96 \times 0.5 \approx 1 \text{ cm}$$
@ 95% confidence

- Any change ≥ MDC is considered "real" @ 95% CI
- Of N persons who on a <u>subsequent</u> test, show a change ≥ MDC, then 95% of these are "real" changes

Take Home Messages

- Consider the purpose of the measurements being made
- Be informed as to the measurement method reliability

2. Measurement Methods

Methods Applicable *JUST* to *LIMBS*

Limb Girth (Circumference)

- Girth → Limb Volume or Sum of Girths

  Manual - Optoelectronic →

Manual

Optoelectronic

Limb Volume

- Water Displacement → Volume

  Hand – Foot – Arm - Leg →

Limb fluid content and its change

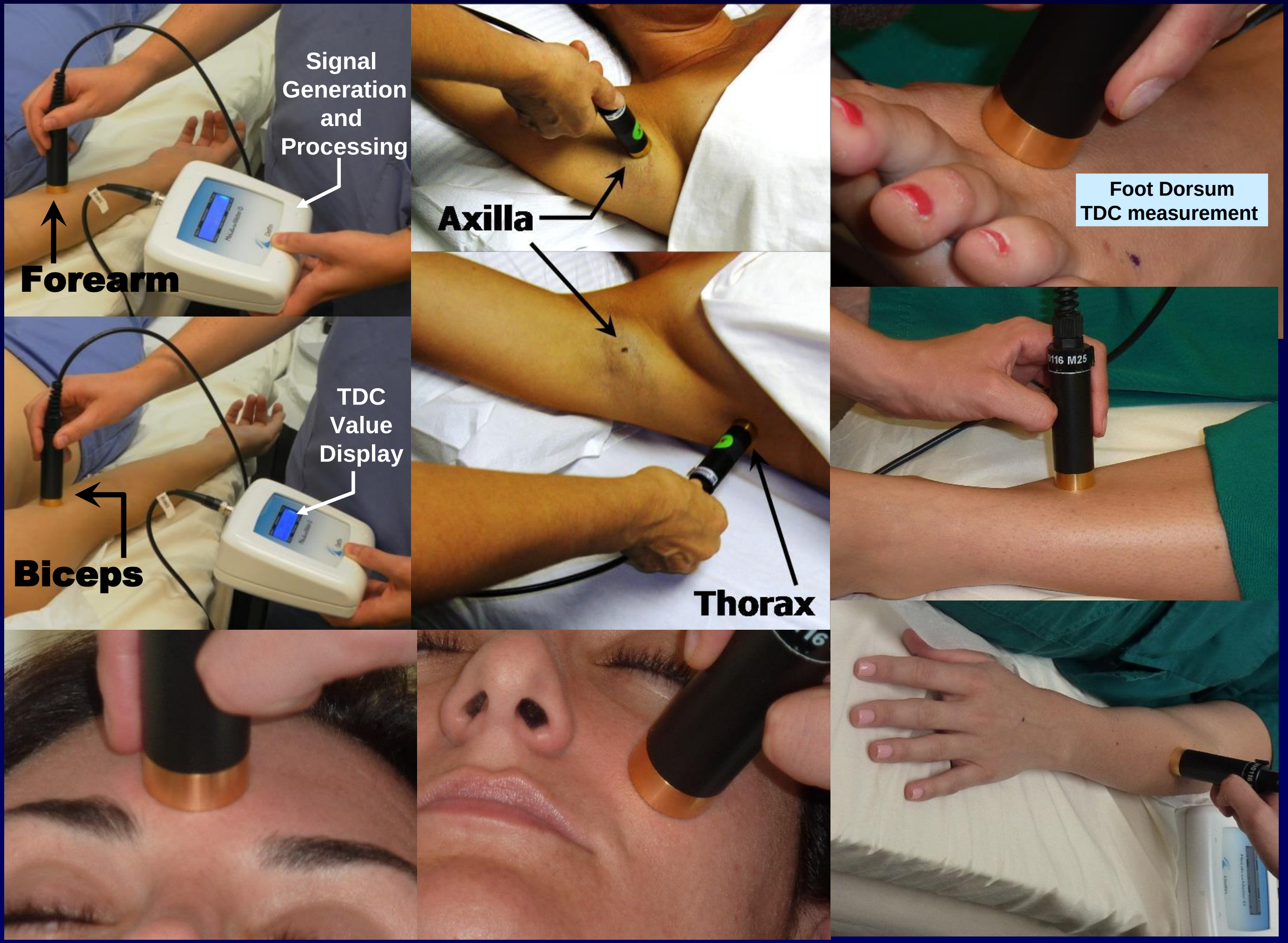
- Bioimpedance → BIA & BIS

  → Whole Limb →

Methods Applicable to *ANY* Location

- ***Fluid Content via Tissue Dielectric Constant (TDC)***

- Head
- Face
- Neck
- Breast
- Trunk
- Foot
- Toe
- Arm
- ETC



- ***Imaging: Ultrasound - MRI – Etc. → Dr. Emily Iker***

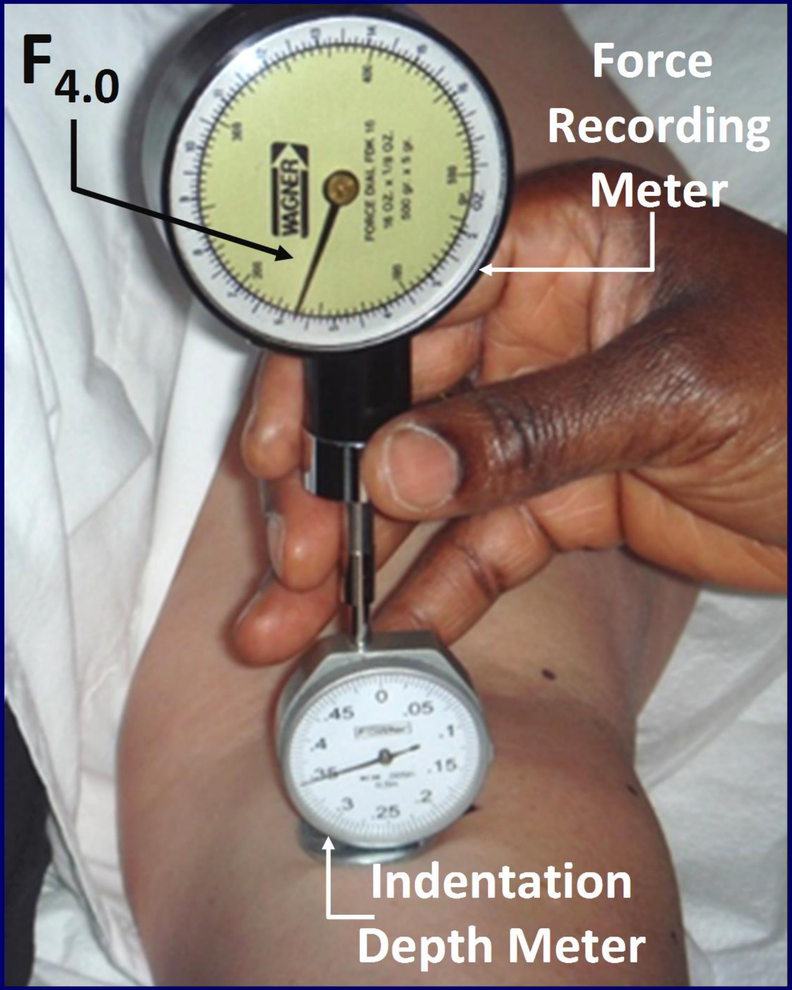
Methods Applicable to *MANY* Locations

- ***Tissue Properties: Tonometry / Indentometry***

Fixed Indentation Depth

↓

Force Measured



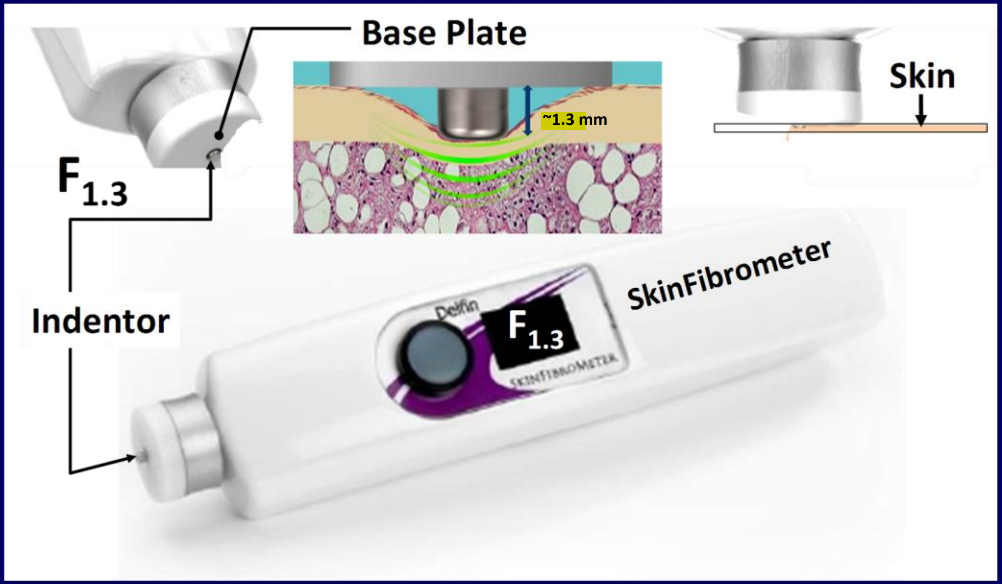
Methods Applicable to *MANY* Locations

- ***Tissue Properties: Tonometry / Indentometry***

Fixed Indentation Depth

↓

Force Measured



n = 89 forearms in N = 62 subjects
Age = 28.1 ± 7.1 yrs, seated - relaxed
$F_{1.3}$ = 56.6 ± 18.3 mN

Methods Applicable to *SOME* Locations

- ***Tissue Properties: Tonometry / Indentometry***

Fixed Force or Load

↓

Indentation Measured

High CV% 26.7-32%[a]

Pallota O. J Lymphoedema 2011;6:34-41
Vanderstelt et al. LRB 2015;13(2)131-136[a]

Tissue Properties: Example Usages

Tissue Properties: Example Usages

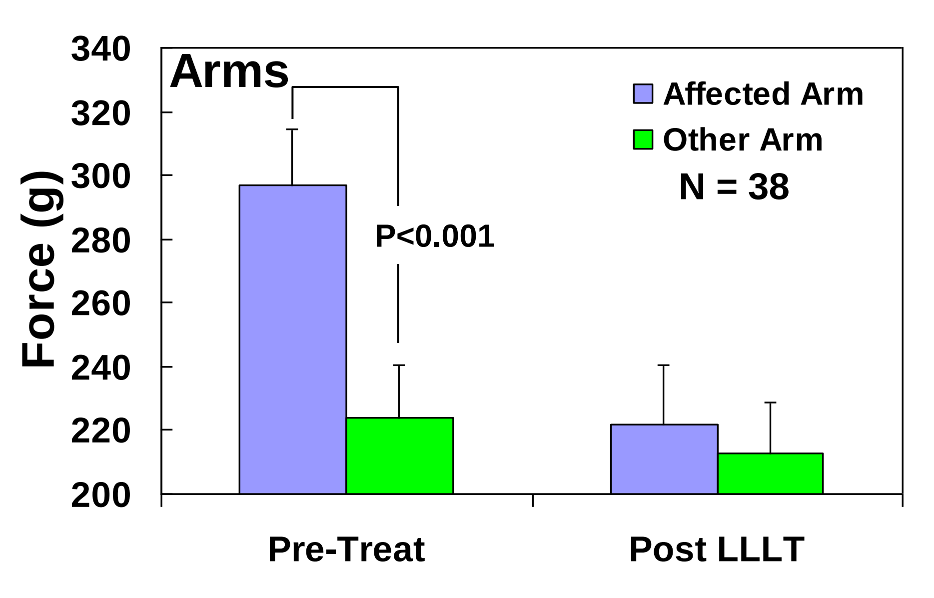
- ***Help characterize ISL Staging***

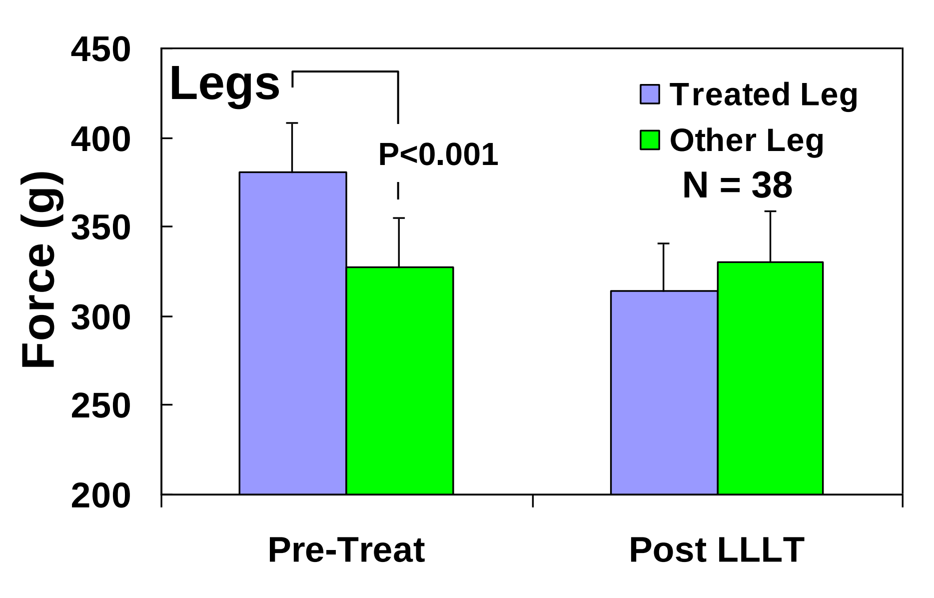
Stage I → no fibrosis

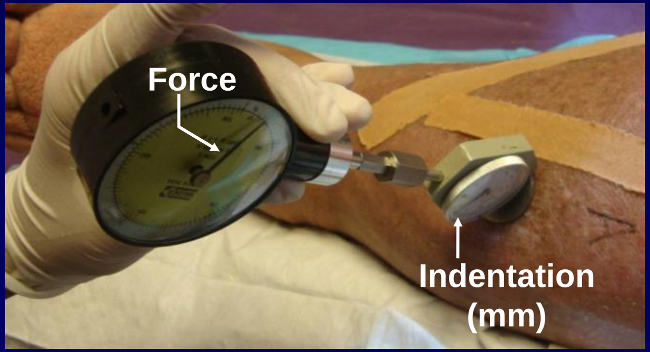
Stage II → some fibrosis → How much?

- ***Assess treatment affects on fibrosis***

Hardness Changes with LLLT

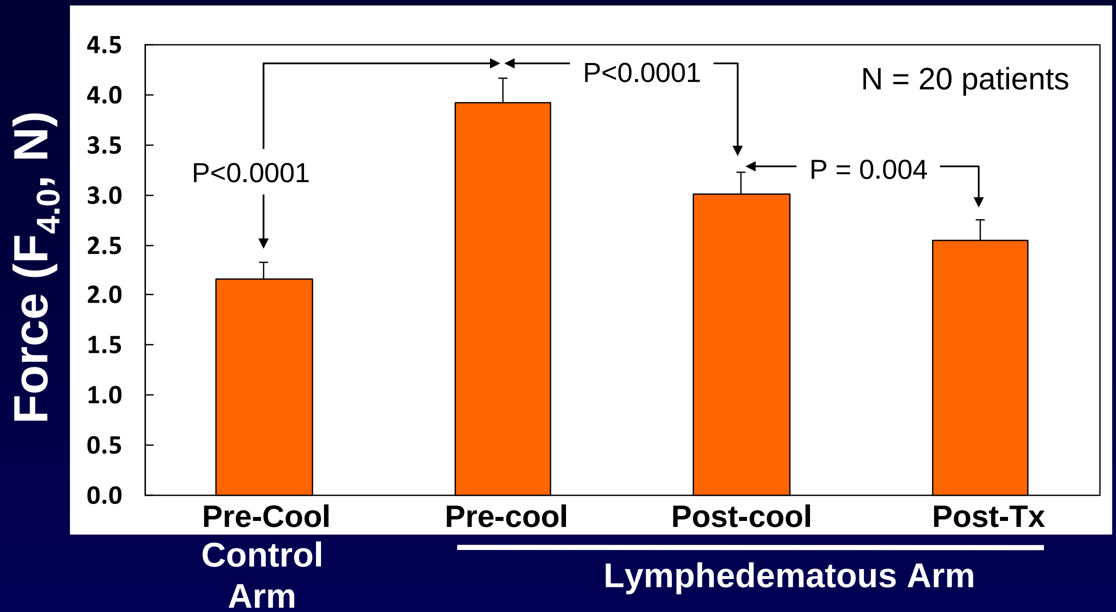


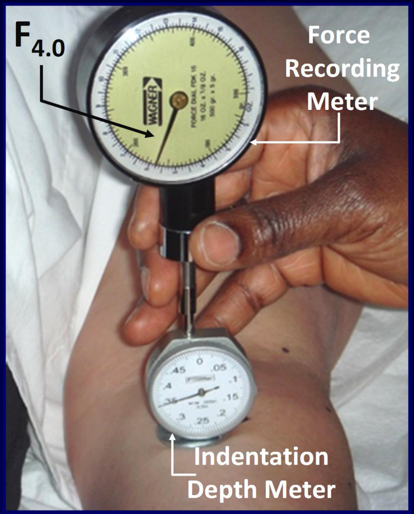


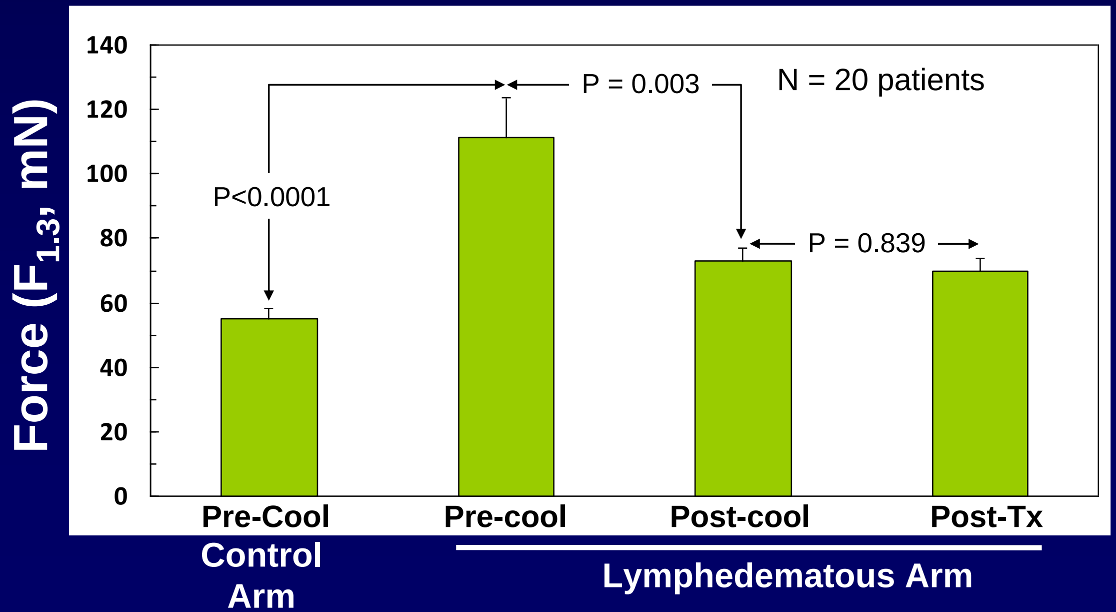


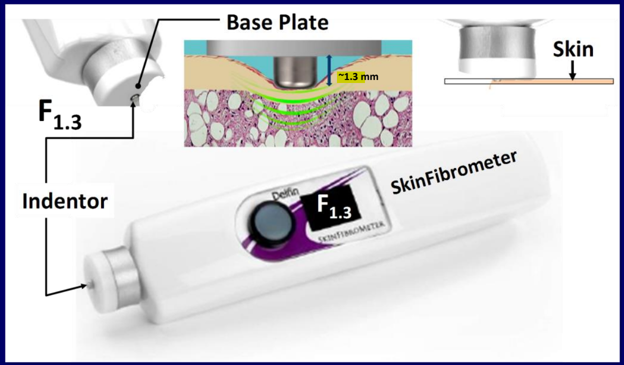
Data from:
Mayrovitz HN & Davey S.
Lymphology 2011;44:168-177

Assessing Fibrotic Tissue Changes



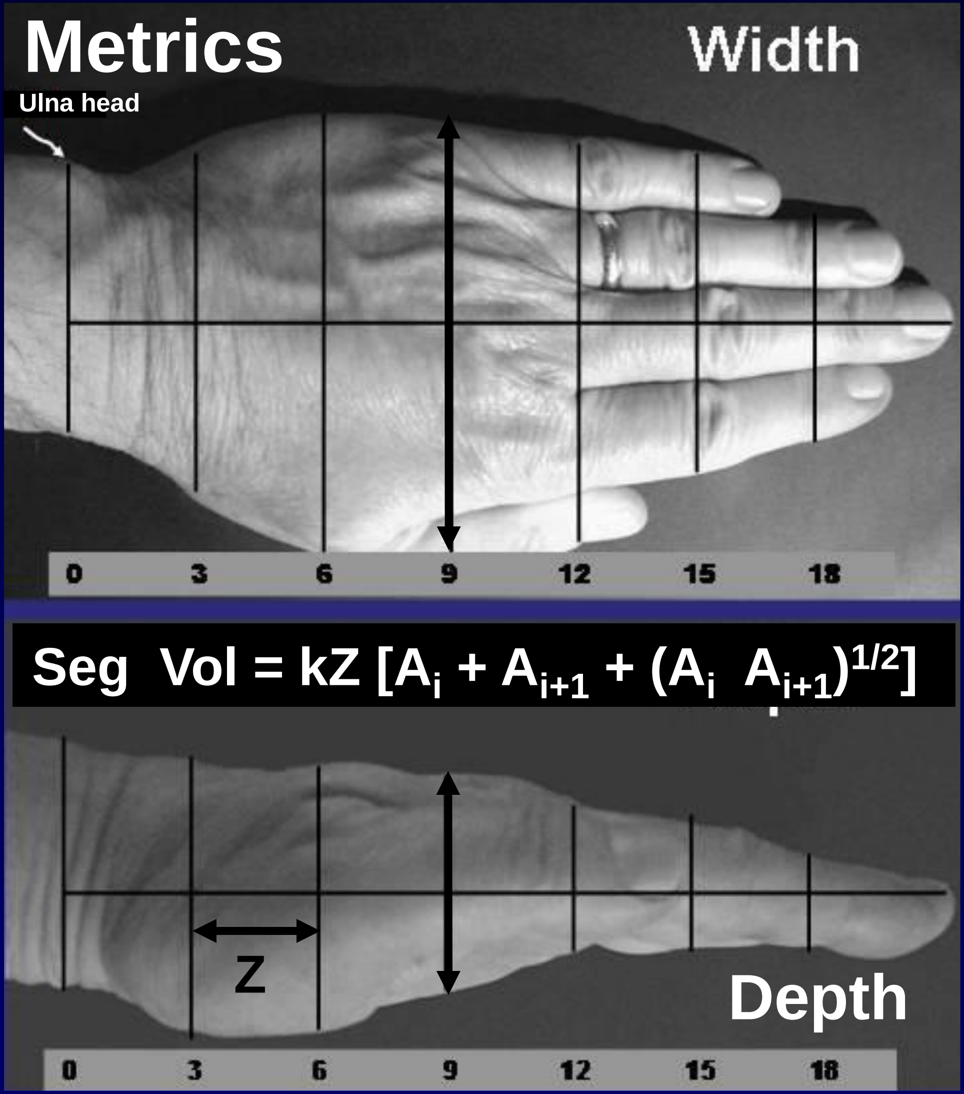






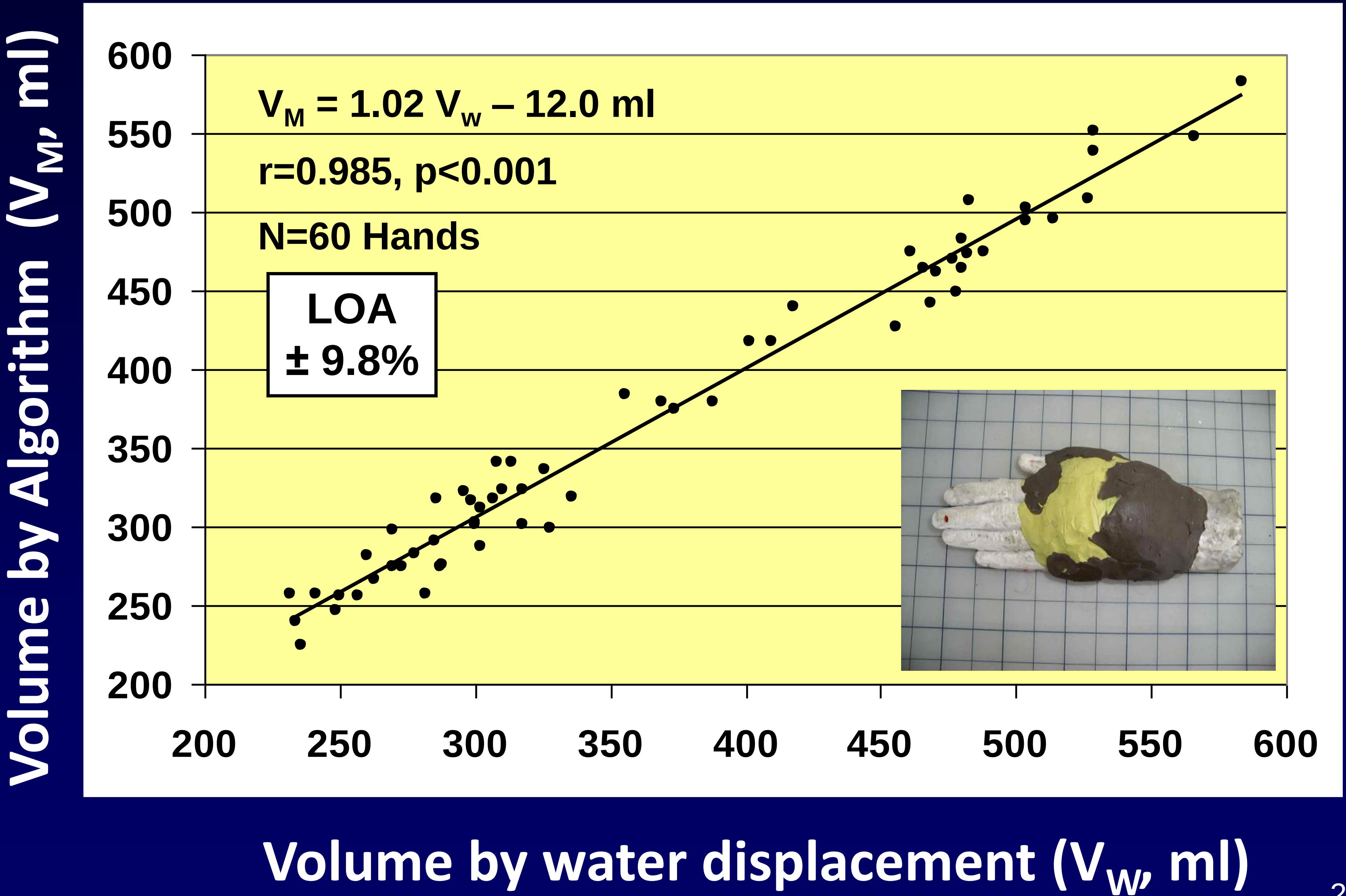
Hand and Foot Volumes

Hand Volume: H_2O Displacement

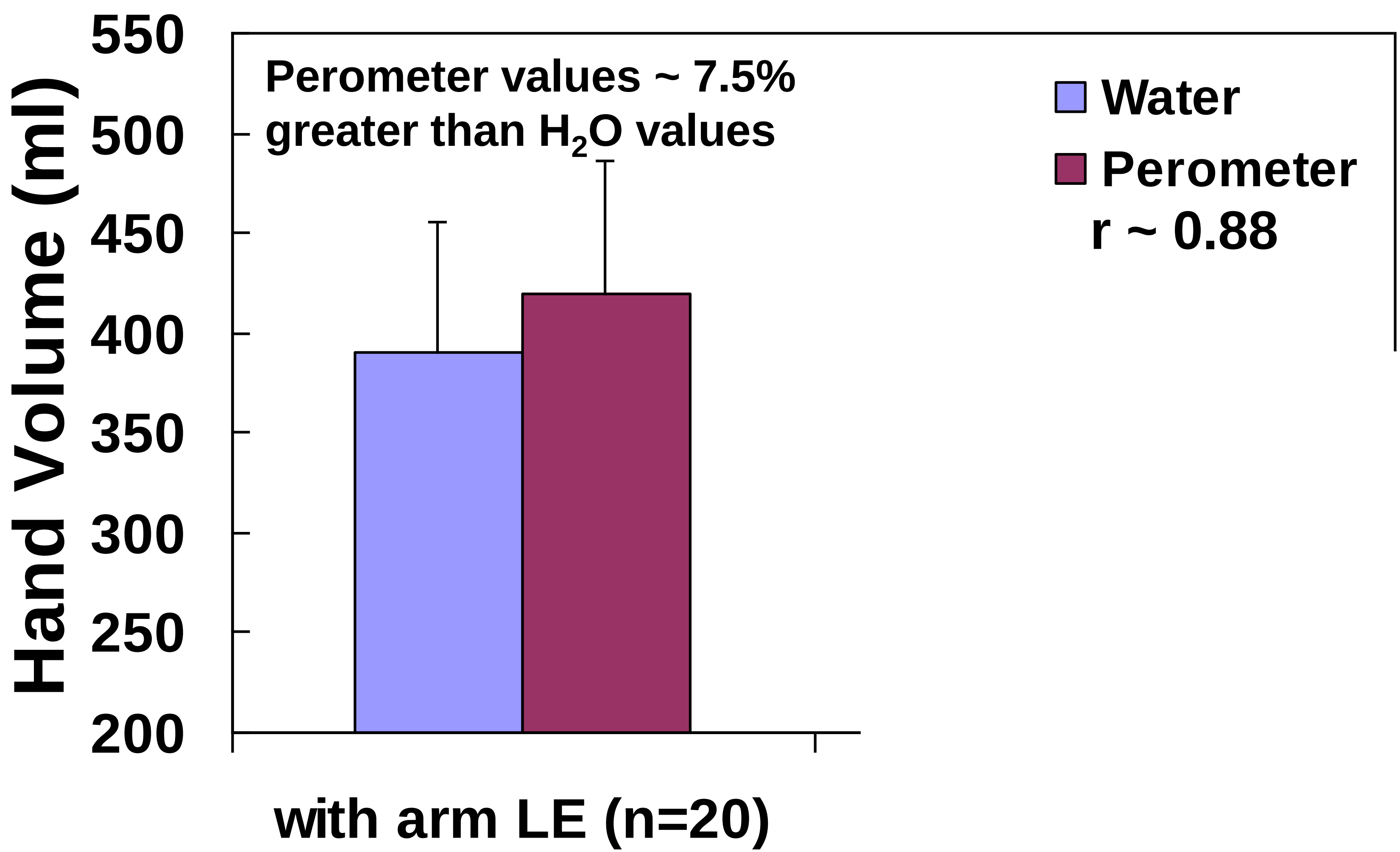


From: Mayrovitz HN et al. Lymphology 2006;39:95-103

Algorithm vs. Water Displacement

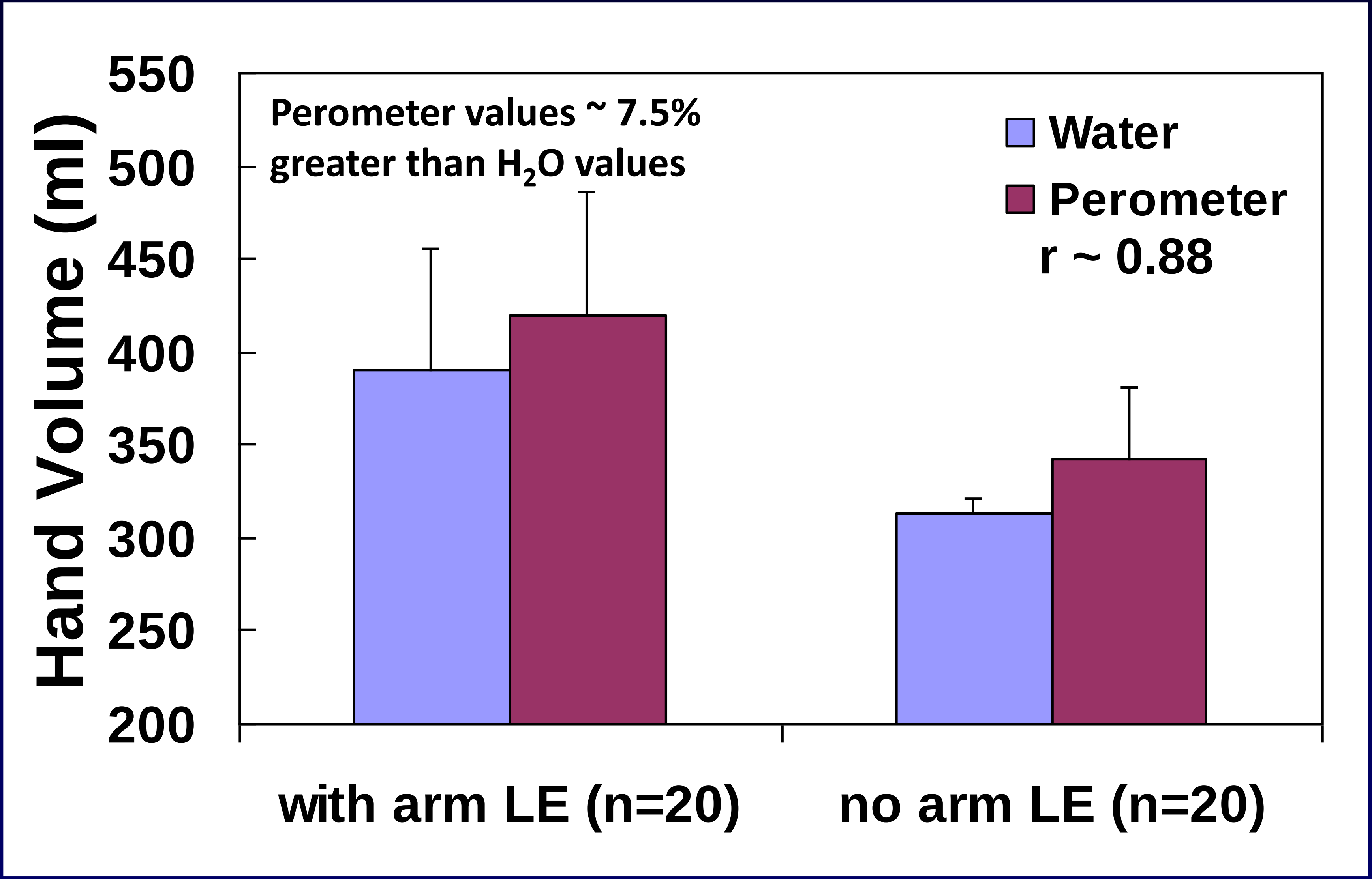


Hand Volume: H_2O vs. Perometer



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

Hand Volume: H_2O vs. Perometer



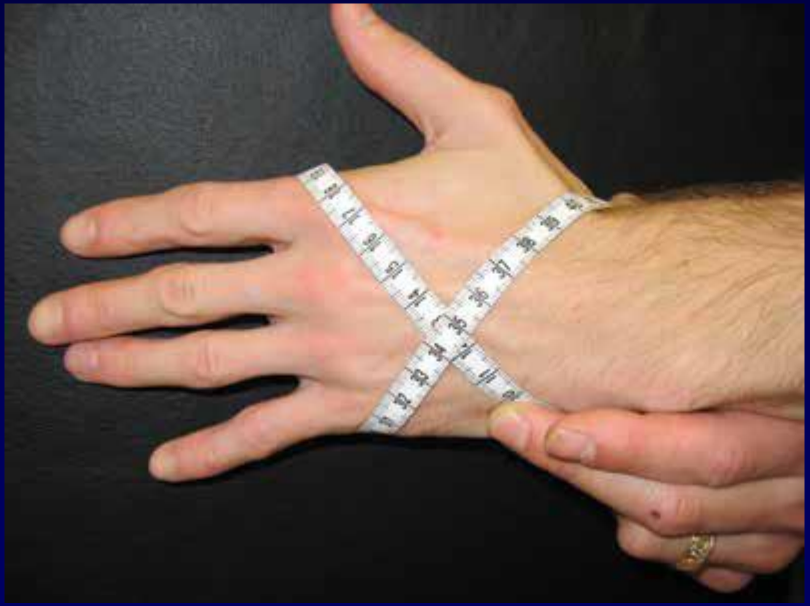
Data from: Lee MJ et al. Lymphatic Research Biology 2011;9:13-18

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)

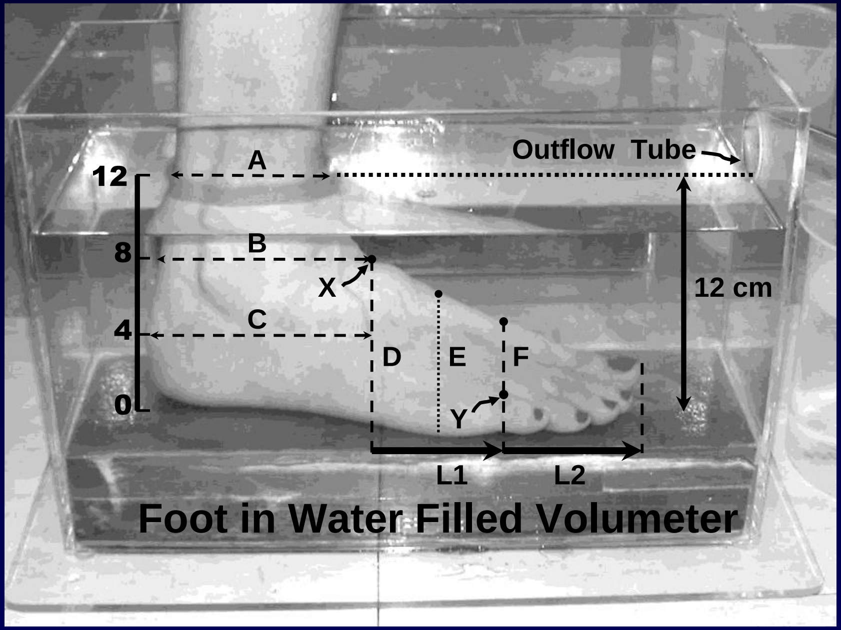


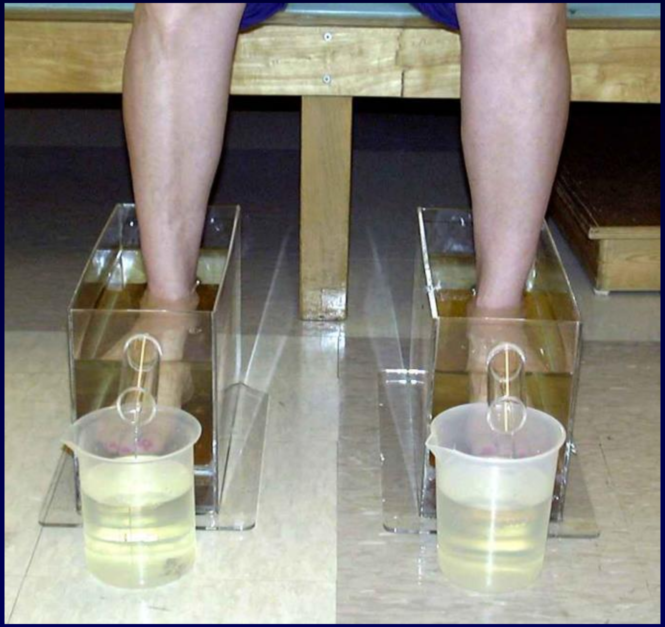
R = 0.94-0.95 but only normal hands

Tracking ability unproven

Foot Volume: H_2O Displacement

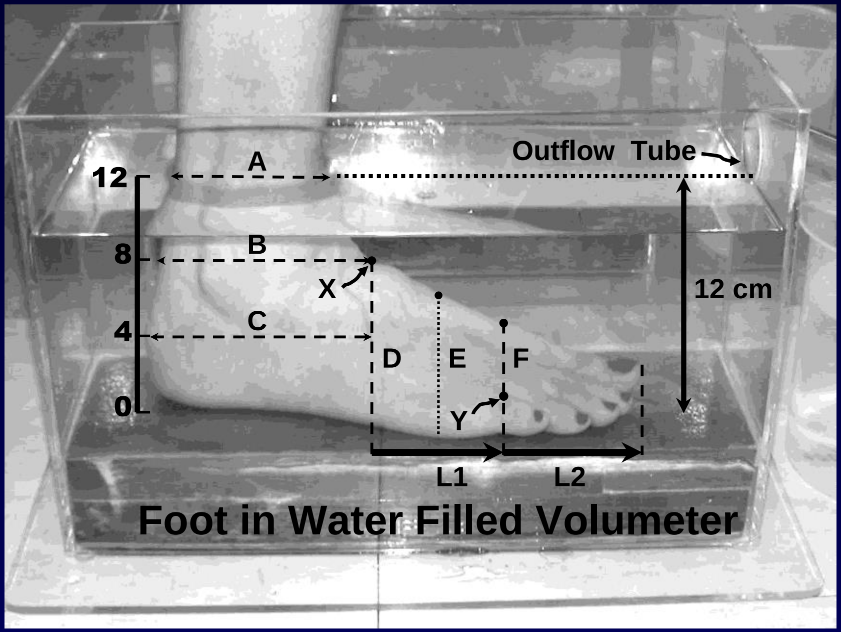
Water Displacement

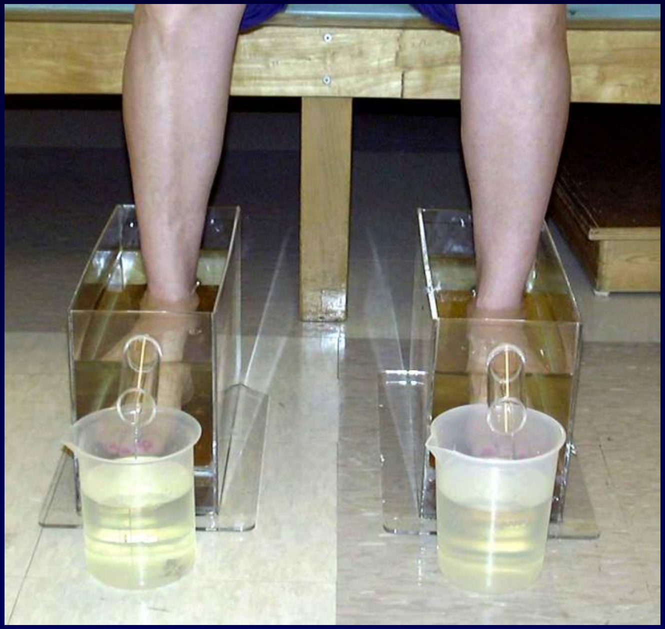




Mayrovitz HN et al. Lymphology 2005;38:20-27

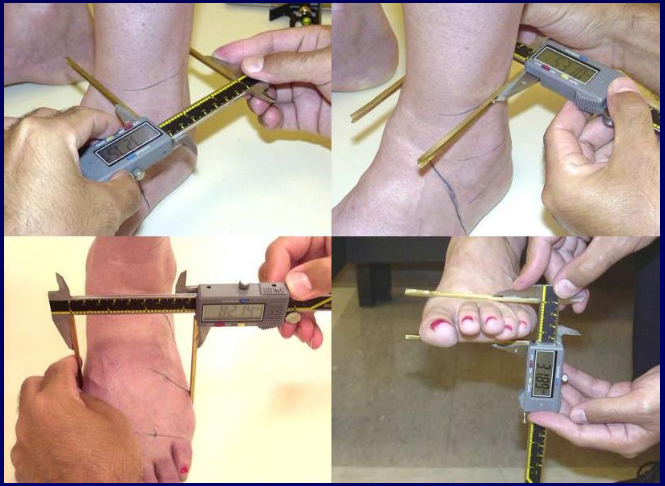
Foot Volume: H_2O Displacement





Water Displacement

Metric Measures



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

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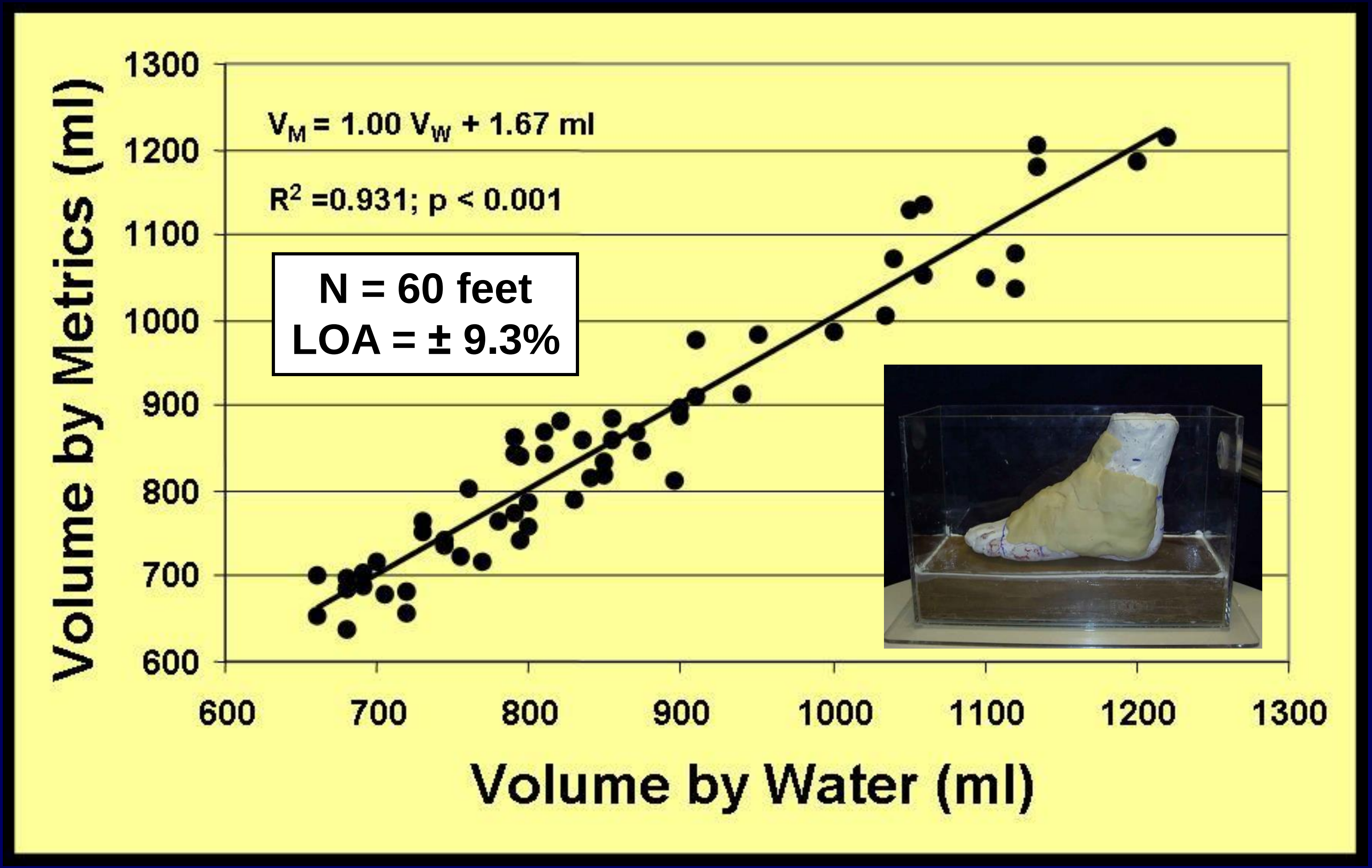


Mayrovitz HN et al. Lymphology 2005;38:20-27

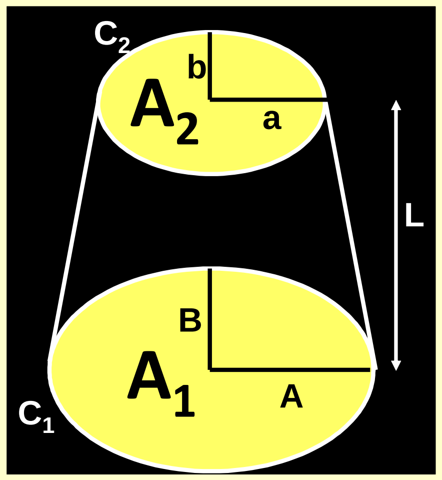
	PRO	CON
Water Displacement 	• Direct – Accurate Limb/Hand/Foot volumes • Especially for irregularly shaped limbs	• Impractical for whole limbs • Bulky equipment • sterilization procedures • Patient mobility • Patient flexibility • Open wounds
Manual Girth 	• Low cost • Portable • Easy to use • Whole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

3. Measurement Principles

Limb Girth → Volume

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

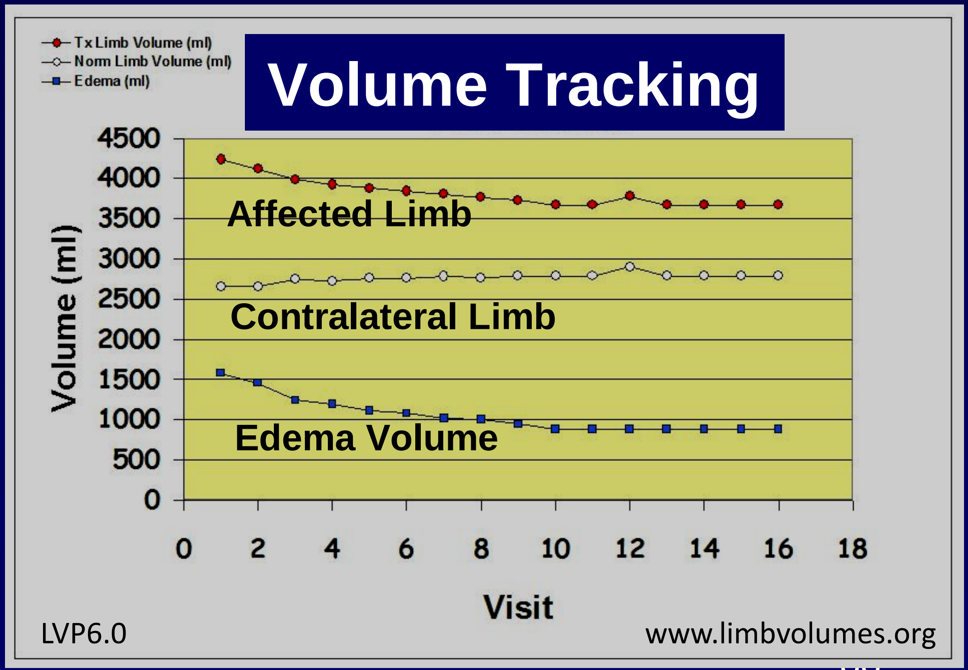
Manual



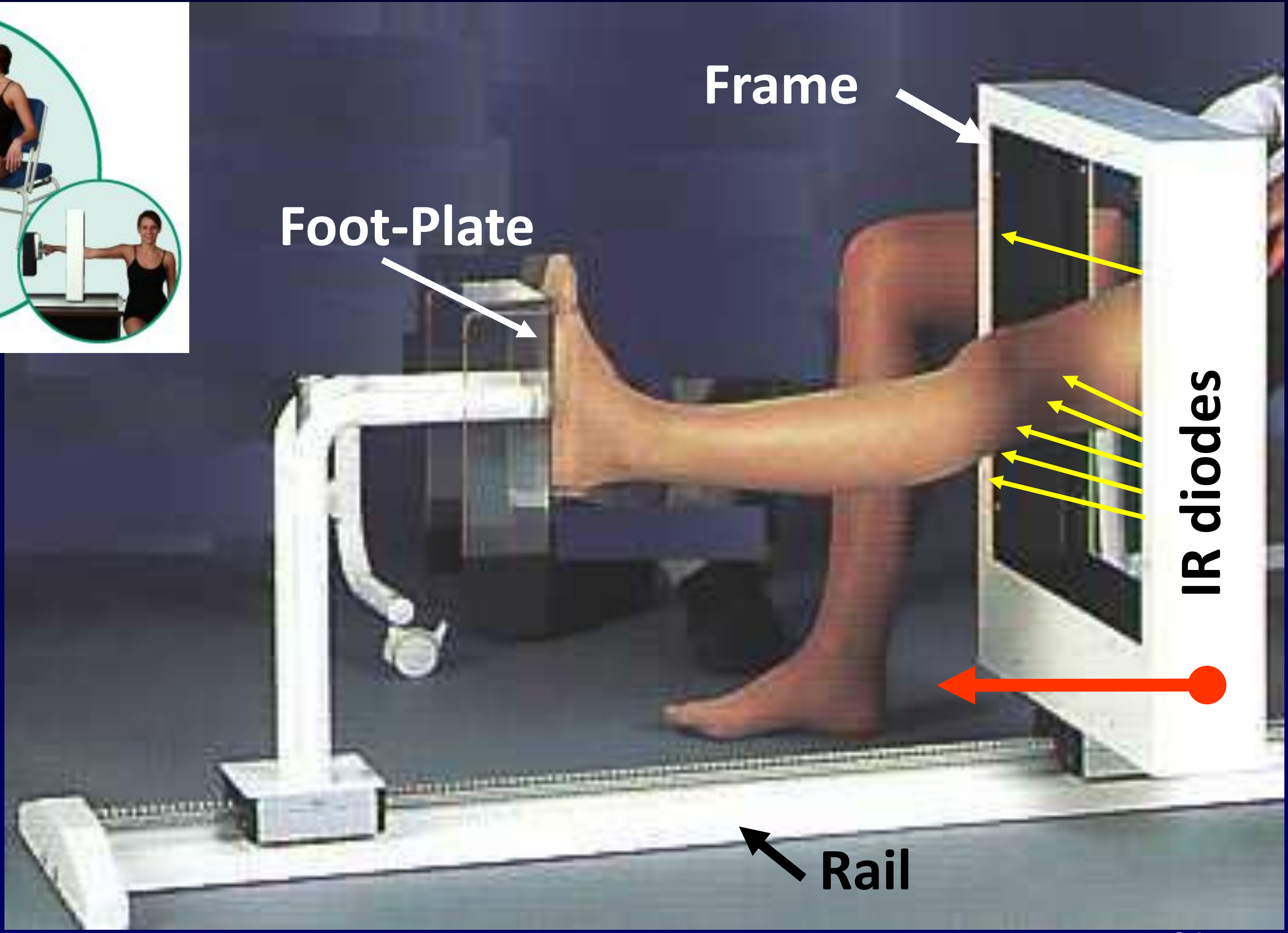
General Frustum Calculation Model

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

$$= \pi L/2\ [AB + ab + (abAB)^{1/2}]$$

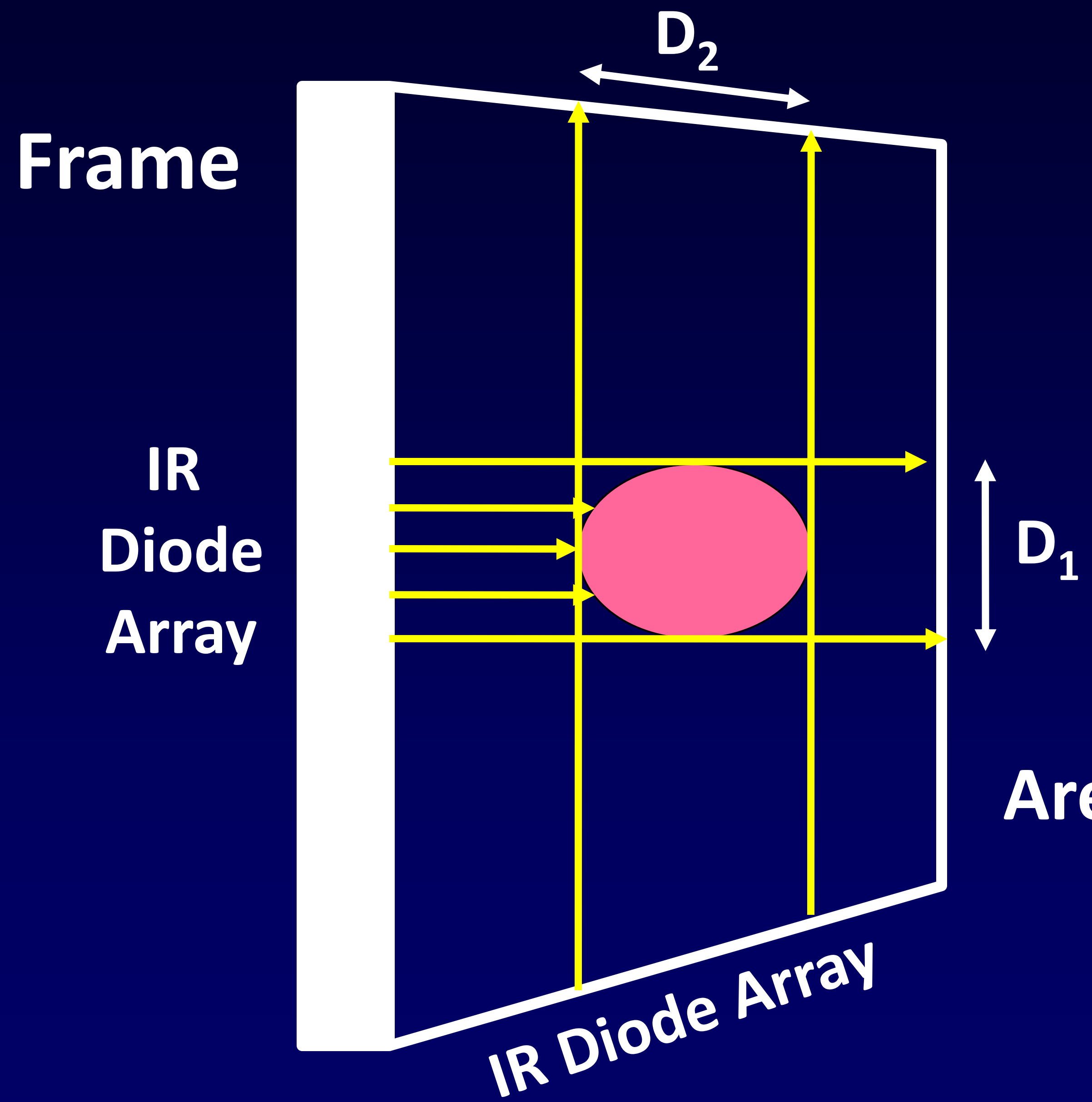


Perometer: Girth → Volume



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

Perometer: Basic Principle

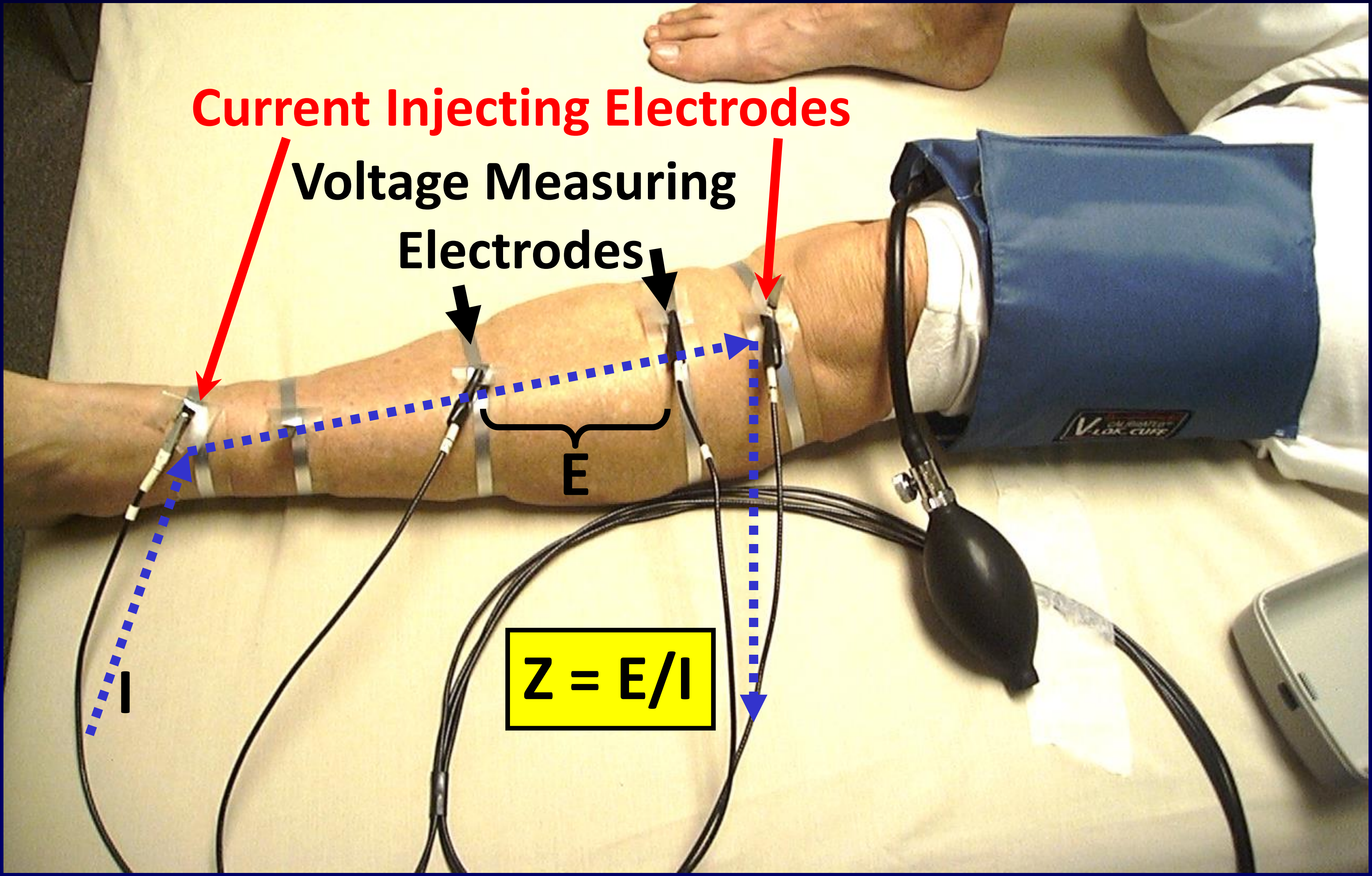


Area = KD_1D_2

Bioimpedance Analysis

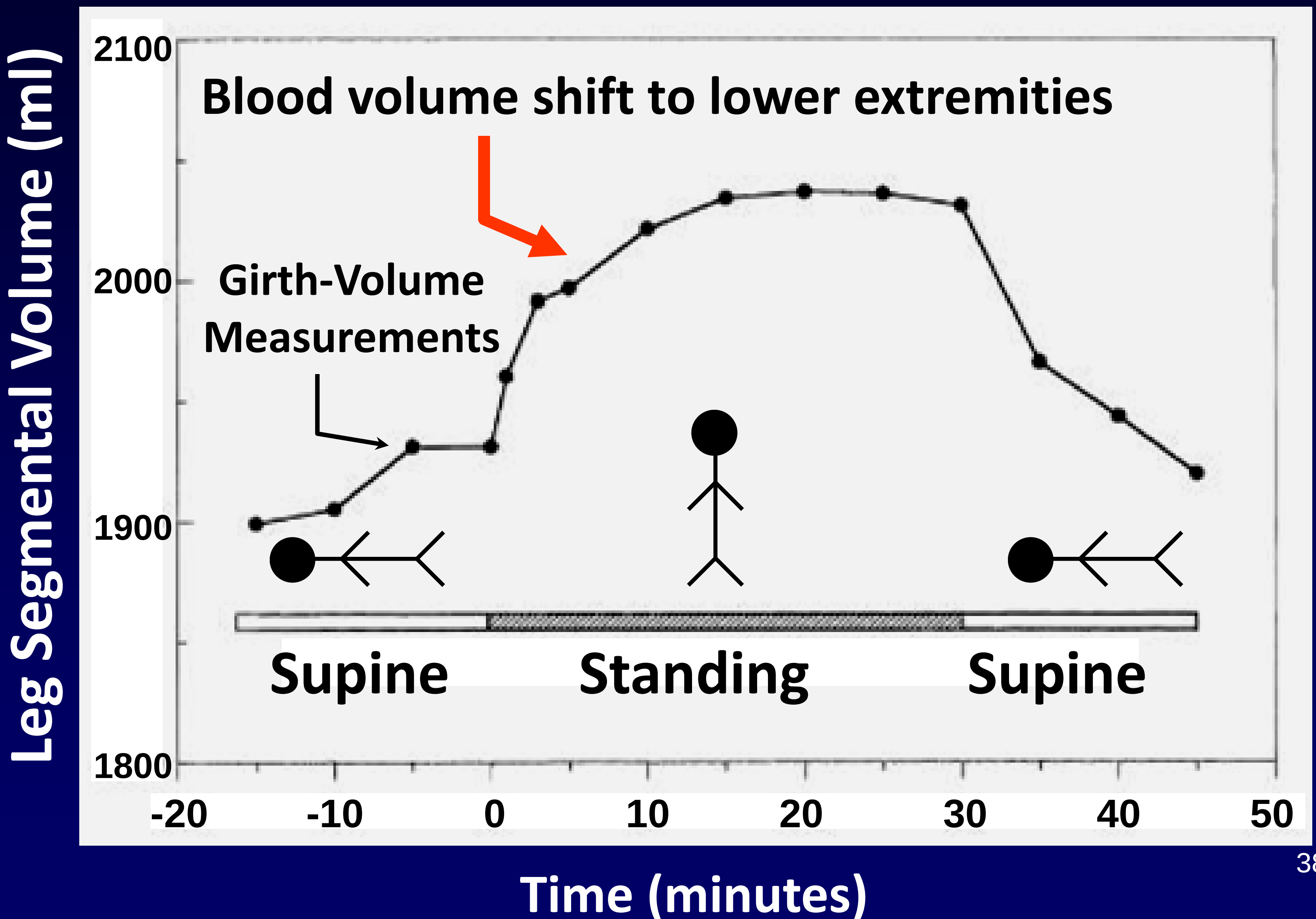
- Bioimpedance (BIOZ)
- Bioimpedance Spectroscopy (BIS)
- Bioimpedance Analysis (BIA)
- Single Frequency BIA = SFBIA
- Multi-Frequency BIA = MFBIA

Basic Operating Principle

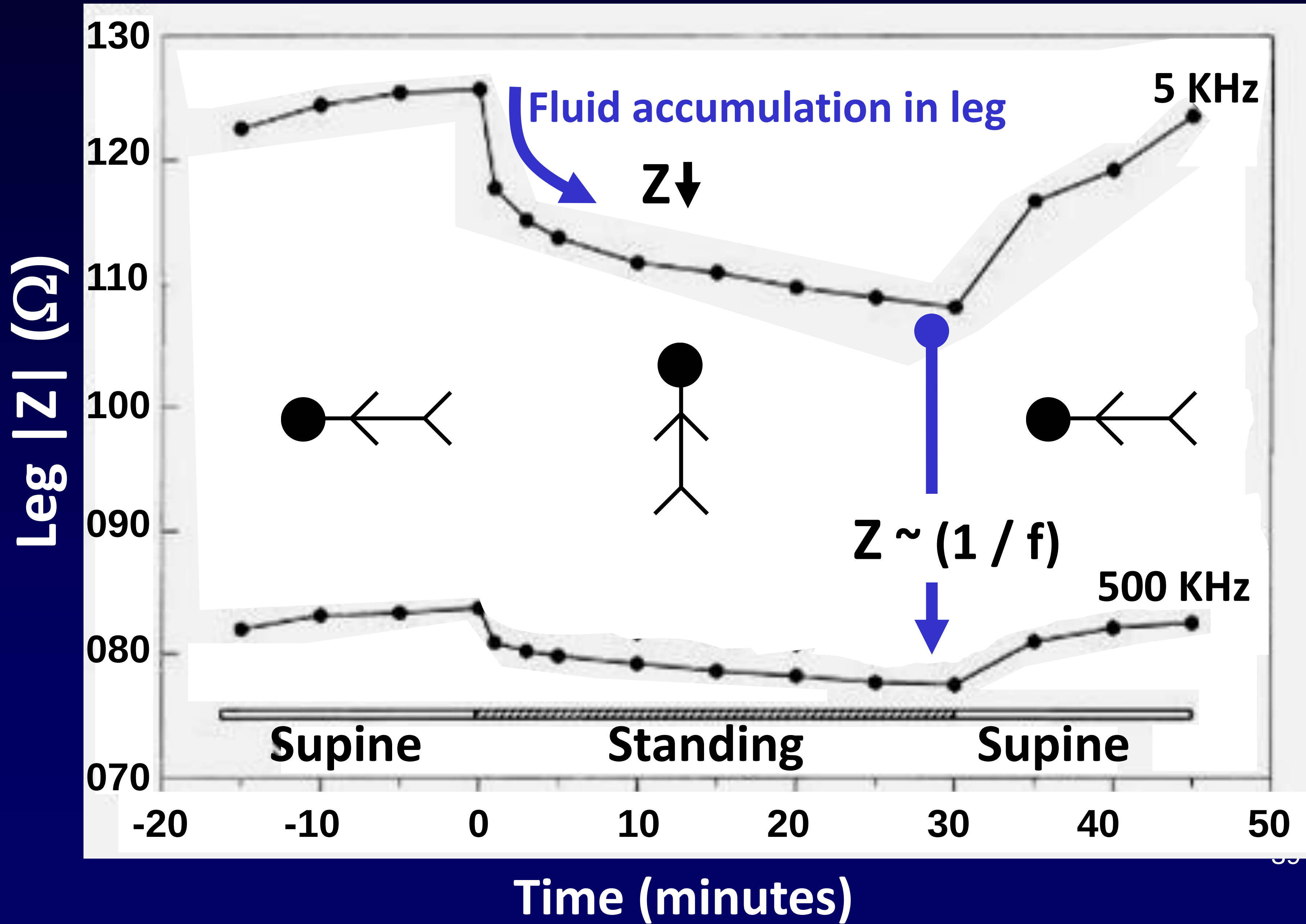


Mayrovitz HN Clinical Physiology 1998;18:234-242

Example: Leg Volumes: Supine → Stand

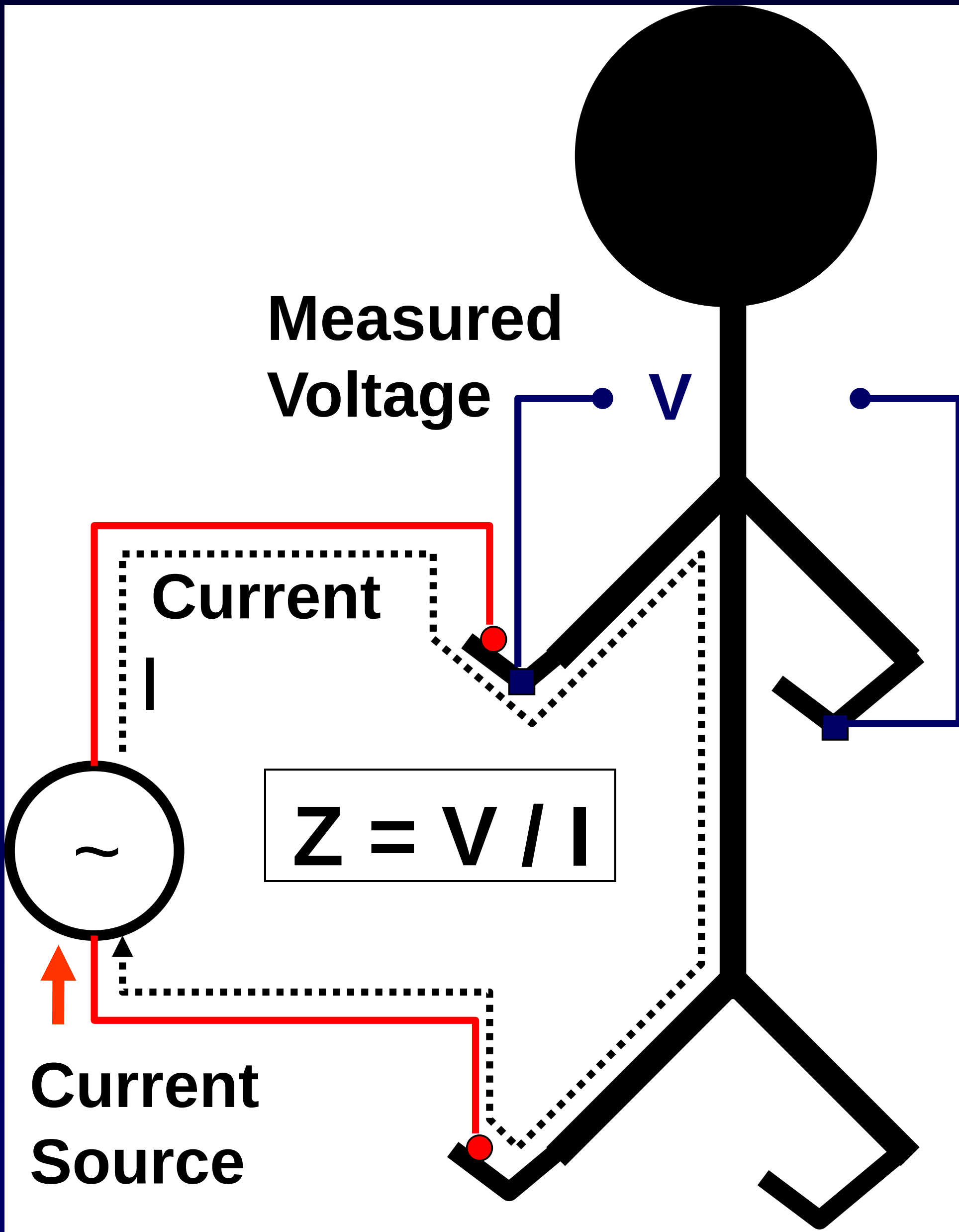


Z Depends on Frequency & Volume



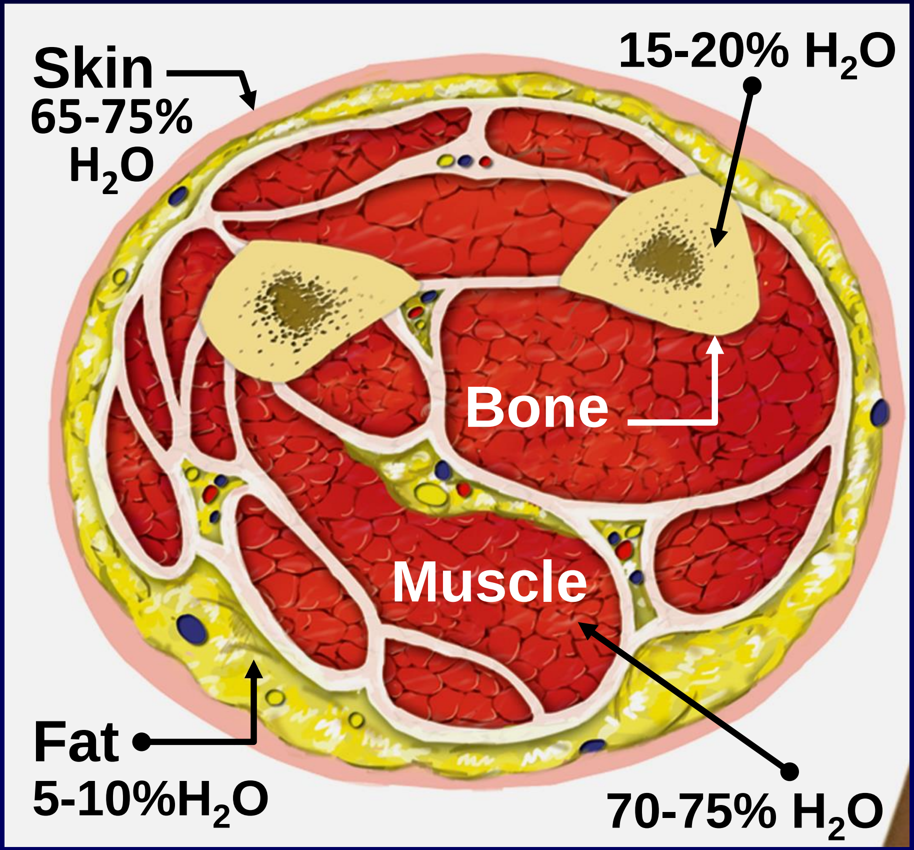
Bioimpedance Analysis
Applied to Lymphedema

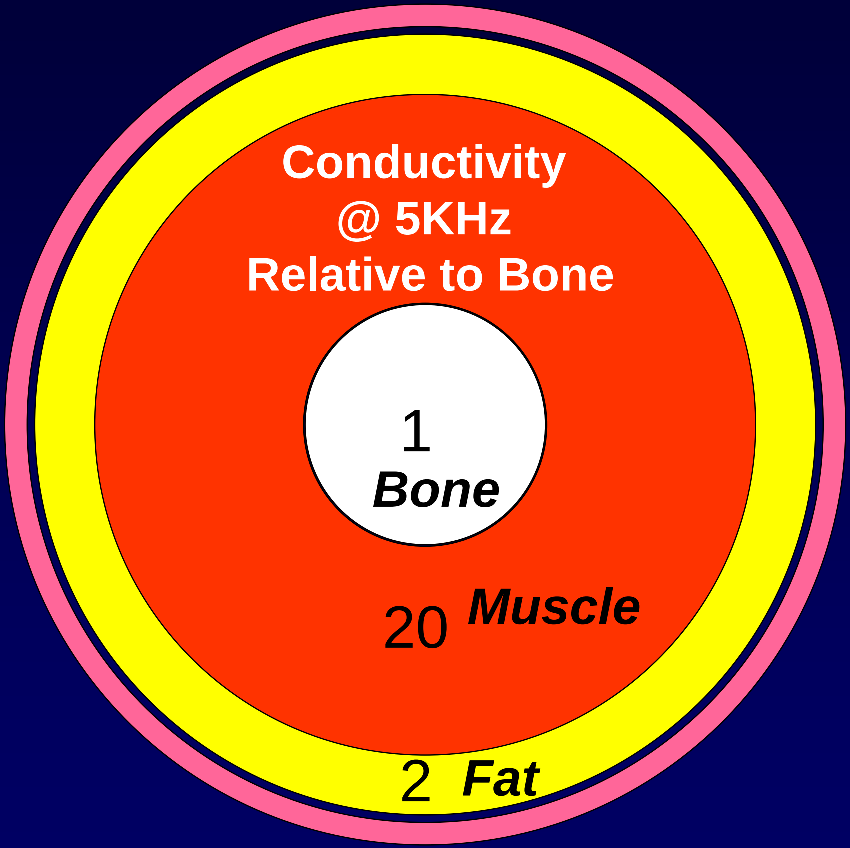
Assessing Arm Lymphedema



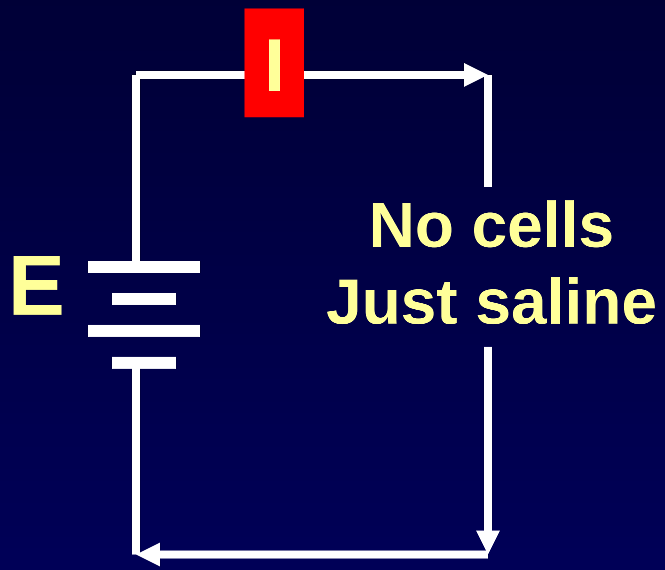
Single Frequency BIA → ECW

Limb Electrically Conducting Structures



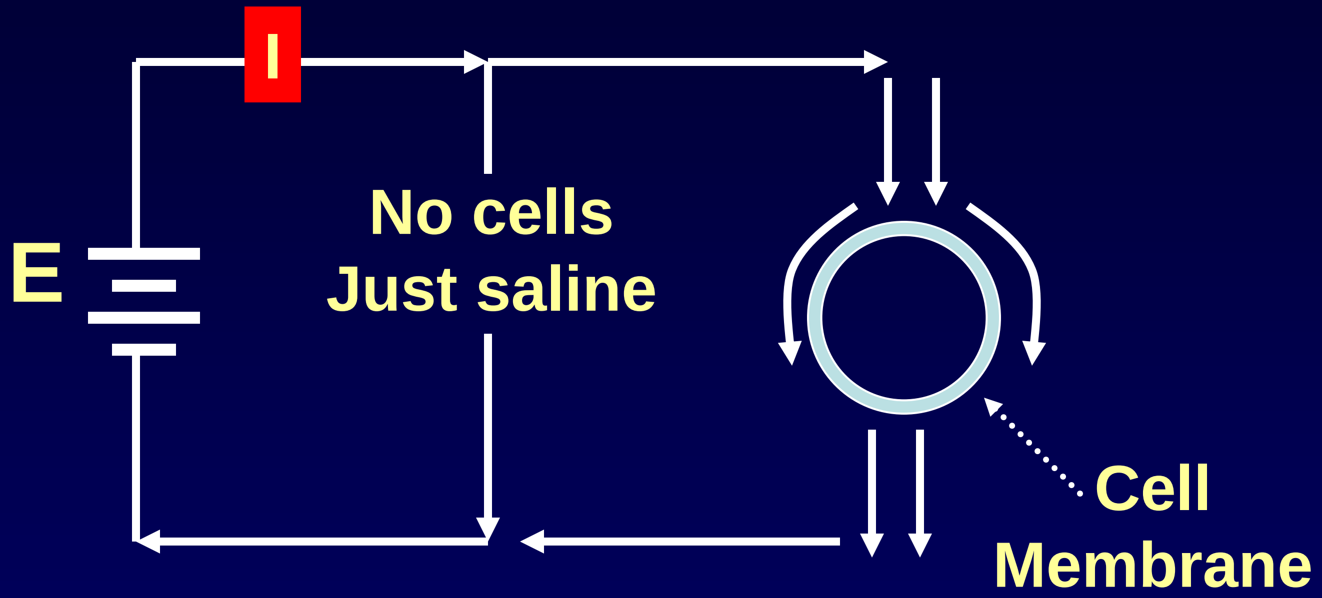


Basic Operating Principle



$$R = E/I$$

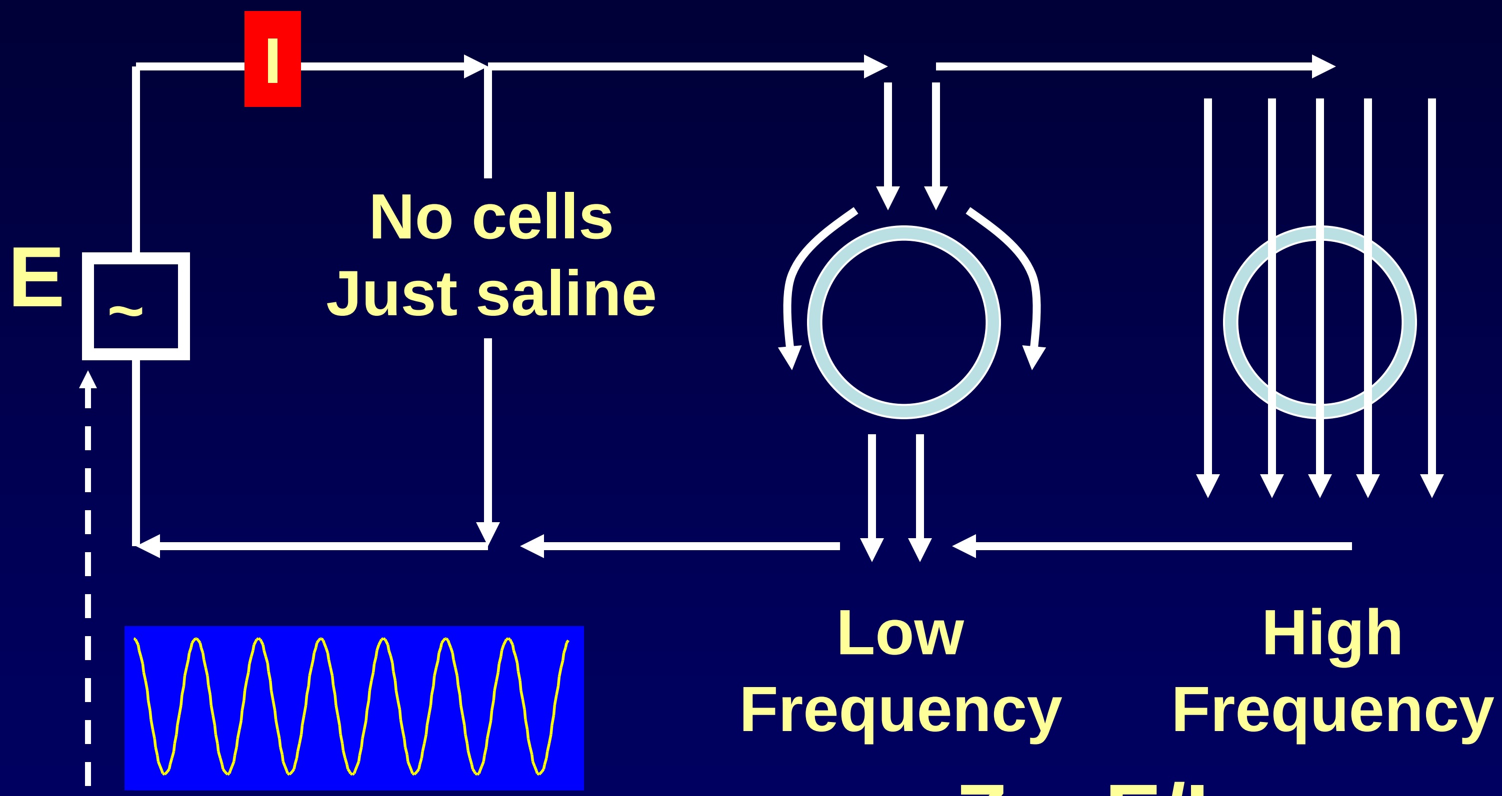
Basic Operating Principle



R = E/I

- *Polarized*
- *Charge Separation*
- *Electrical Capacitance*

Basic Operating Principle

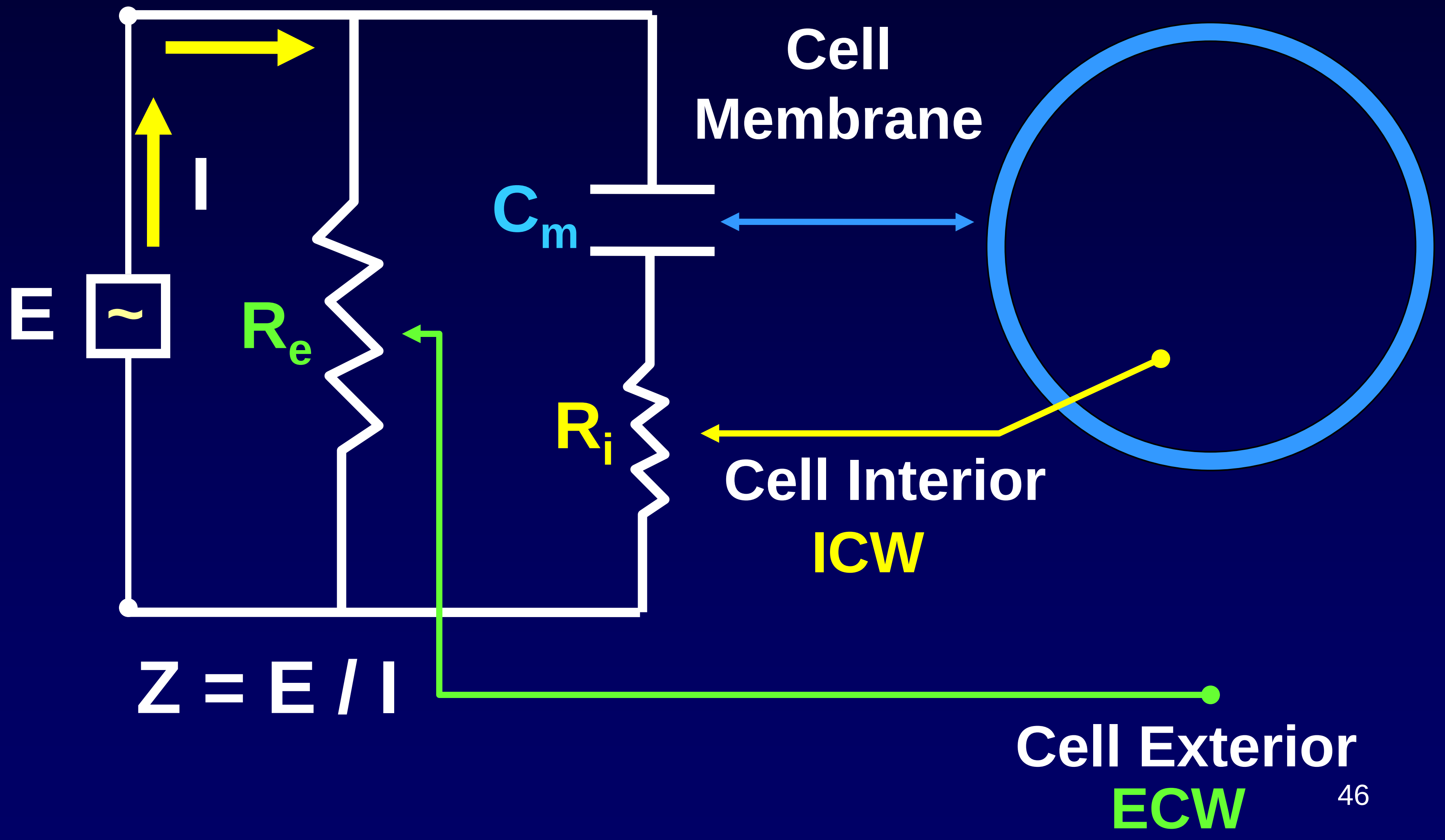


Sinusoidal
Voltage
Excitation

$$Z = E/I$$

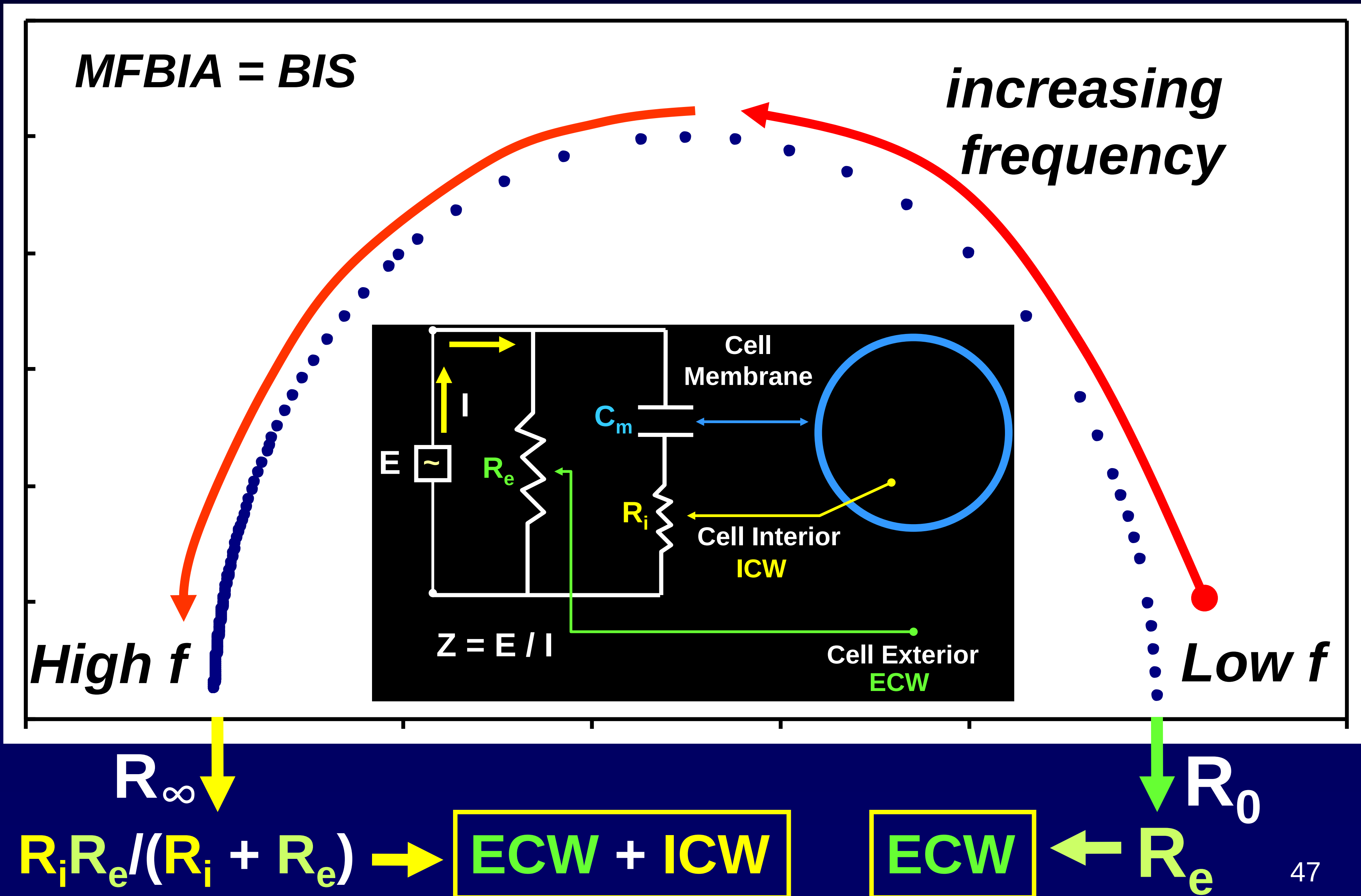
Current increases with frequency

Multi-Frequency Analysis Basis

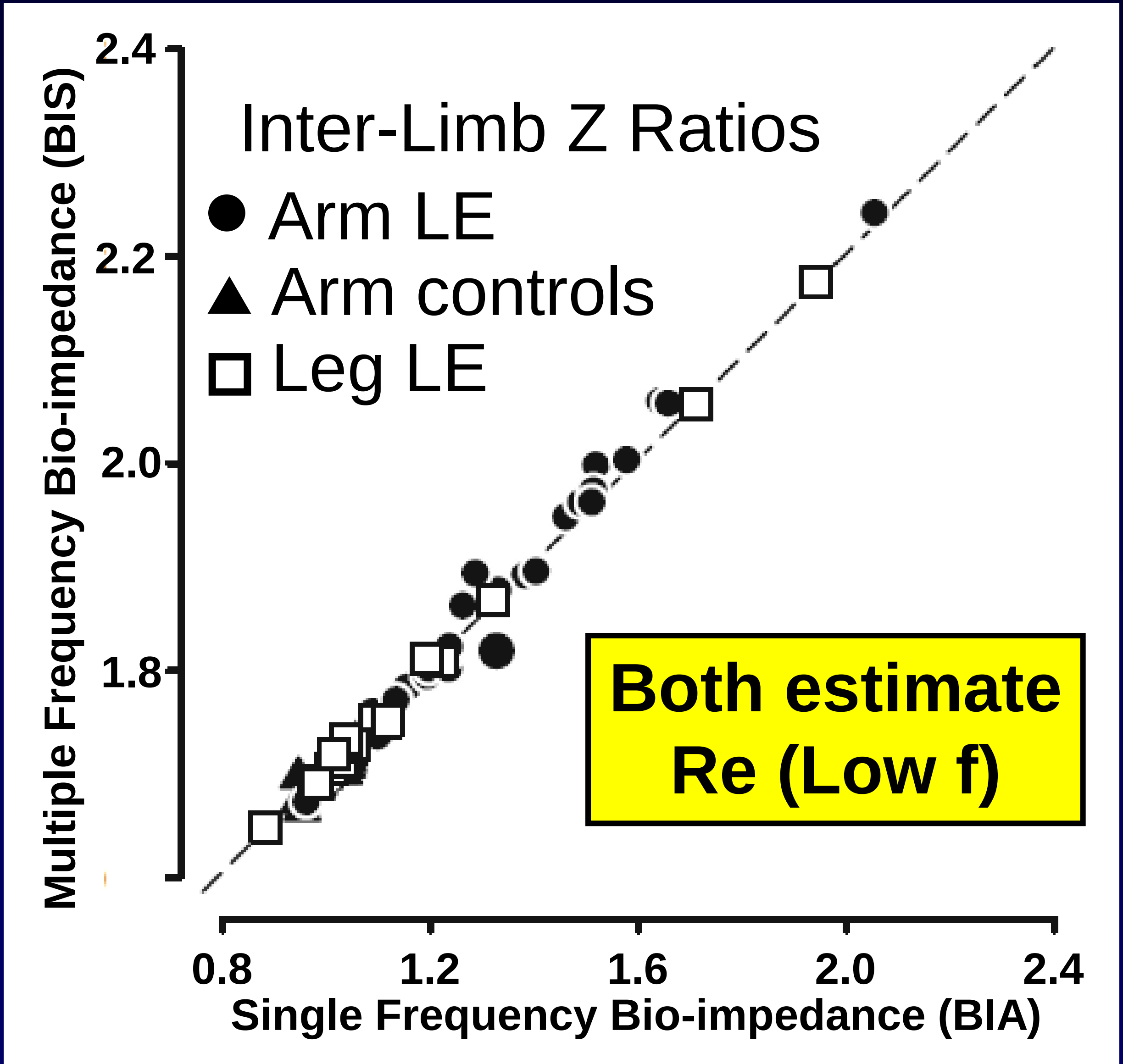


$Z = E / I$

Cole-Cole Plot: Estimate Parameters



SFBIA = MFBIA for estimating ECW



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

So …. Why use MFBIA (BIS)?

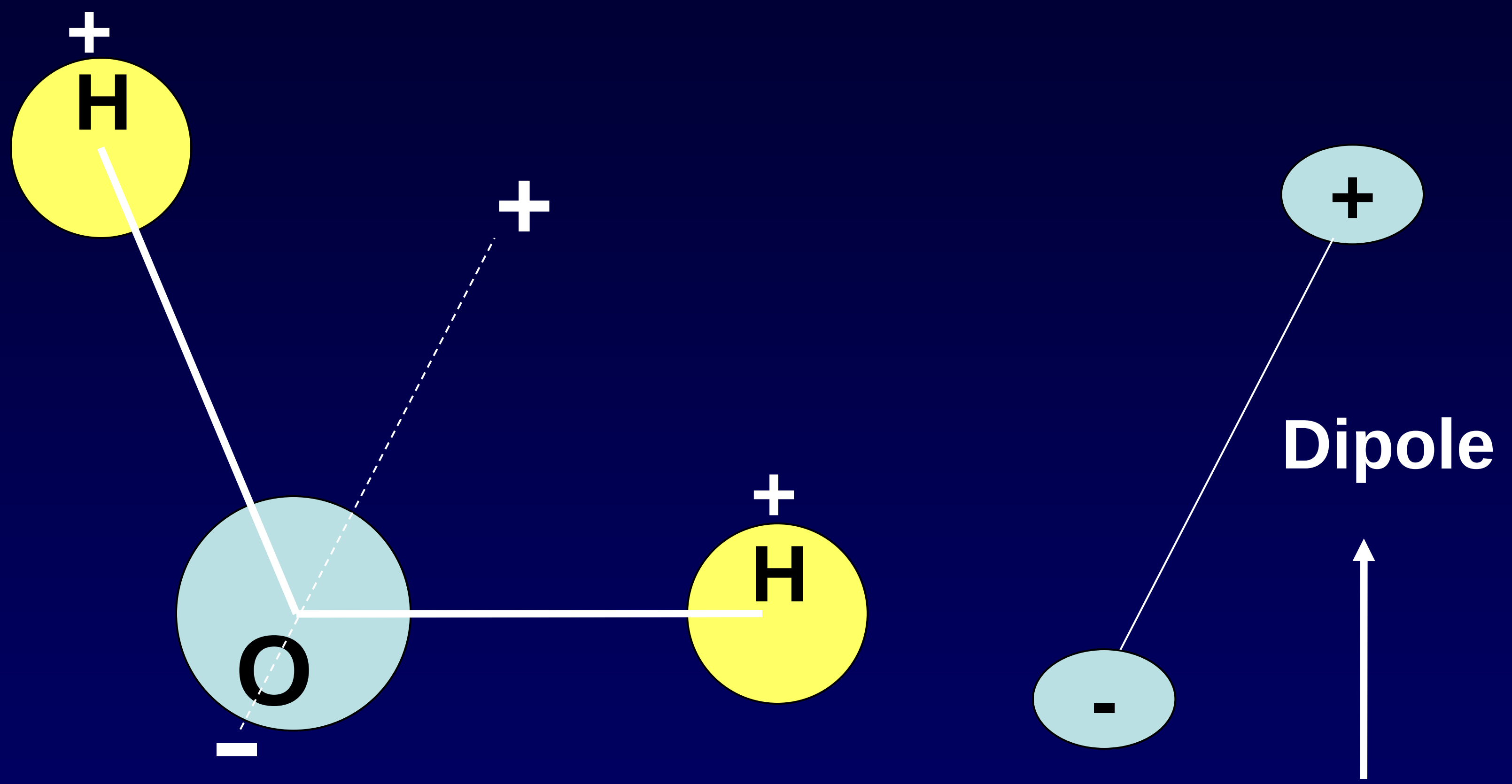
Proposed Concept

- 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

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

Local Tissue Water Assessment: Tissue Dielectric Constant (TDC) Relative Permittivity (ε_r)

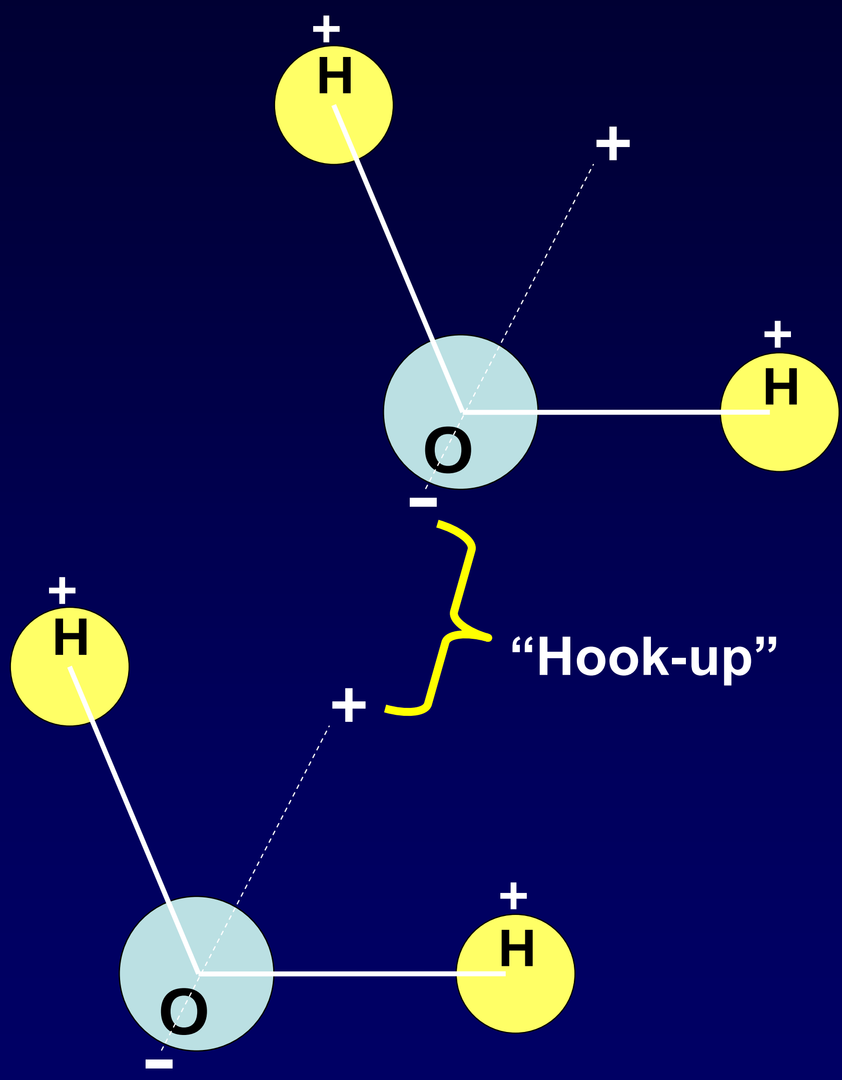
What is Dielectric Constant?

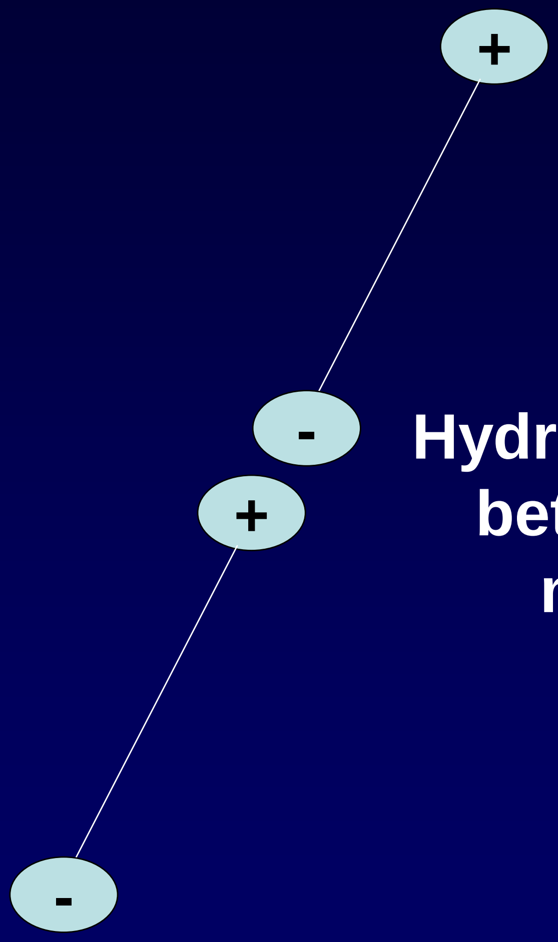


H_2O Molecule

Charge Separation

What is Dielectric Constant?



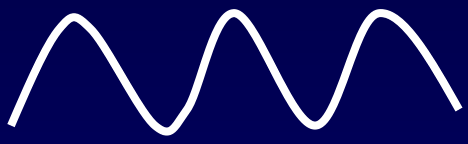


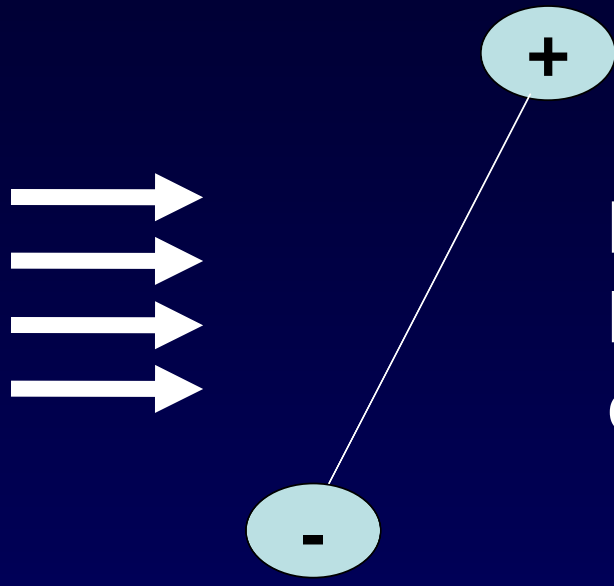
Hydrogen bonding between water molecules

2 H_2O molecules

What is Dielectric Constant?

Time varying electric field of force - E





Dipole movement Displacement - D of various types

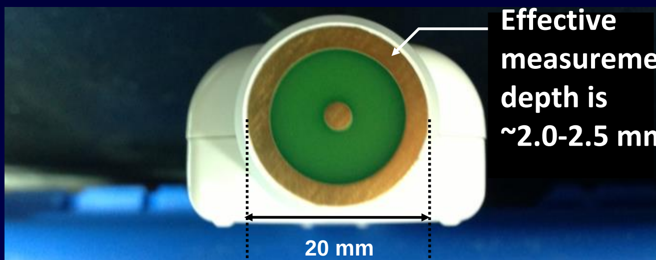
$$D = \varepsilon E = \varepsilon_r \varepsilon_0 E$$

H_2O @ 32°C → $\varepsilon_r = 76$

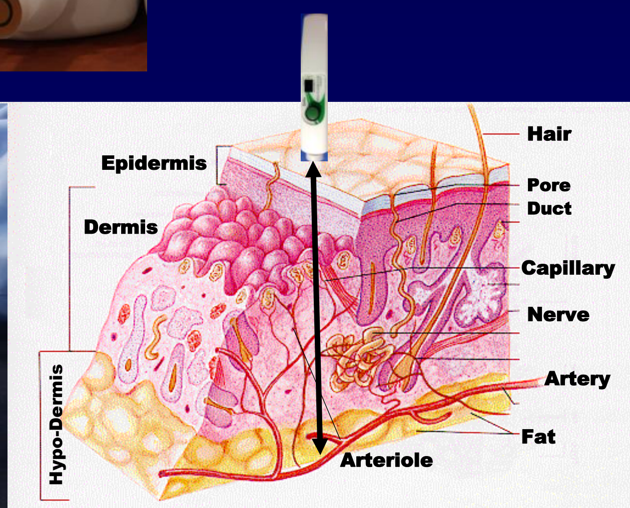
Dielectric Constant

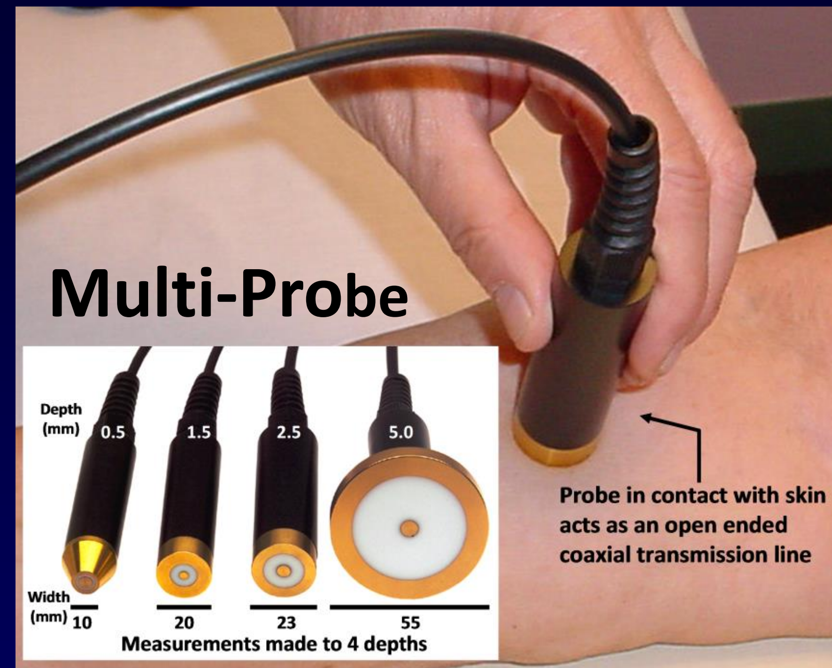
ε_r = ratio $\varepsilon / \varepsilon_0$ = TDC

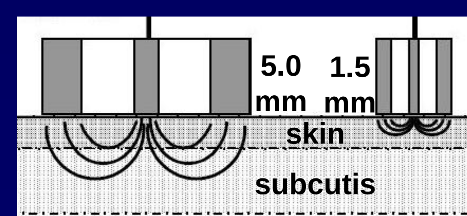
Measurement Devices



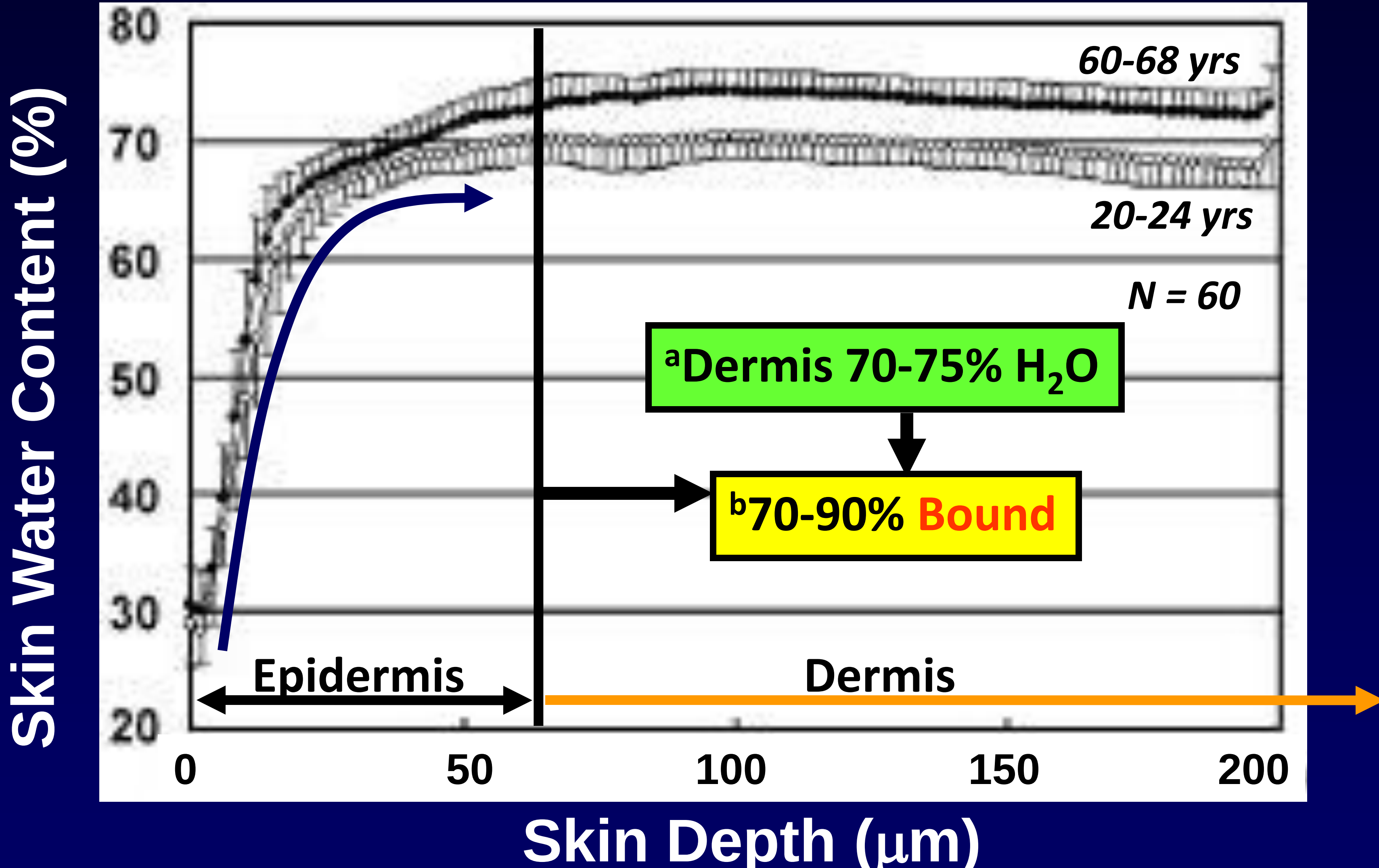
Compact







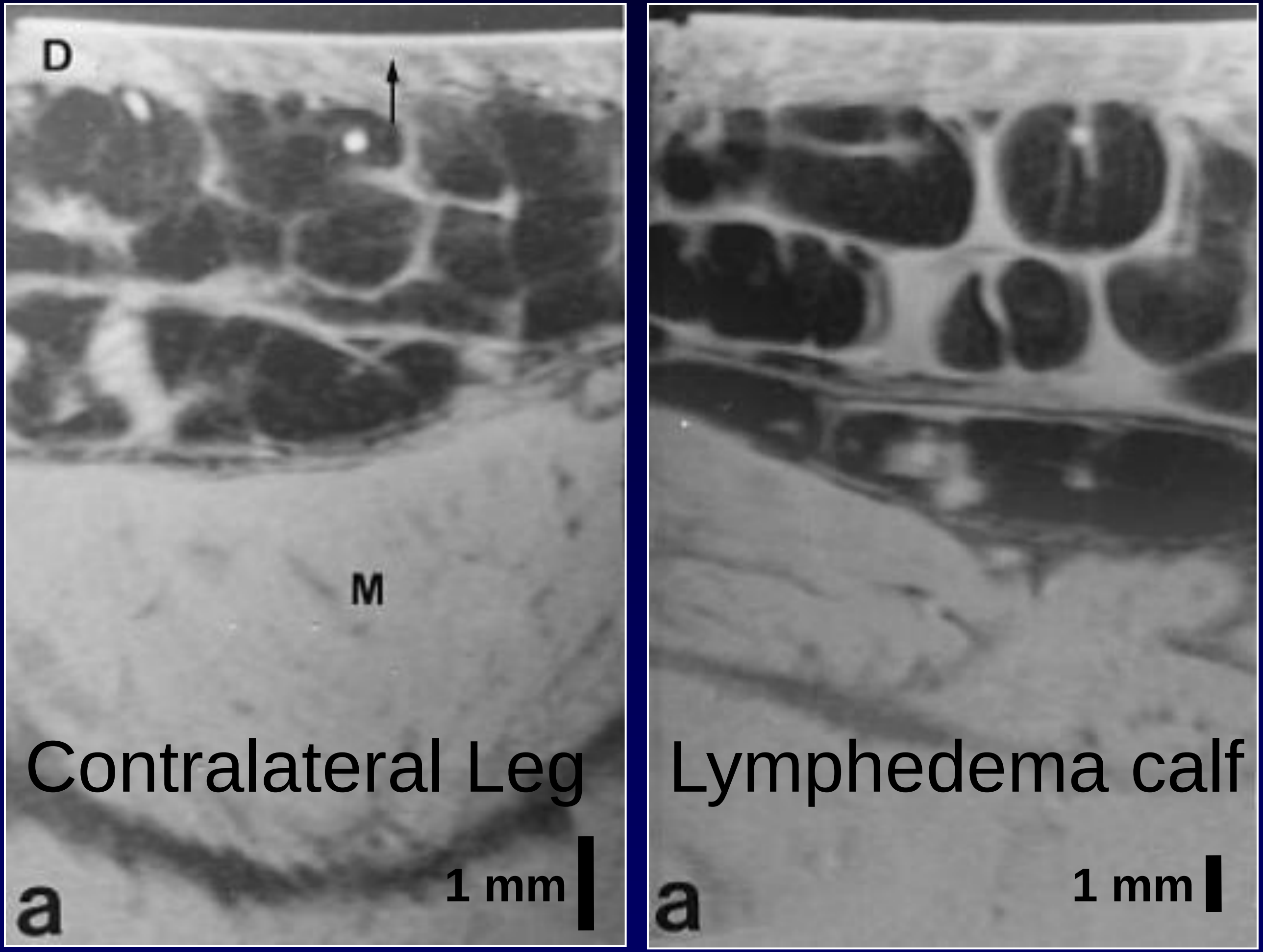
Skin Water Distribution



[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*

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

Effective Measurement Depth

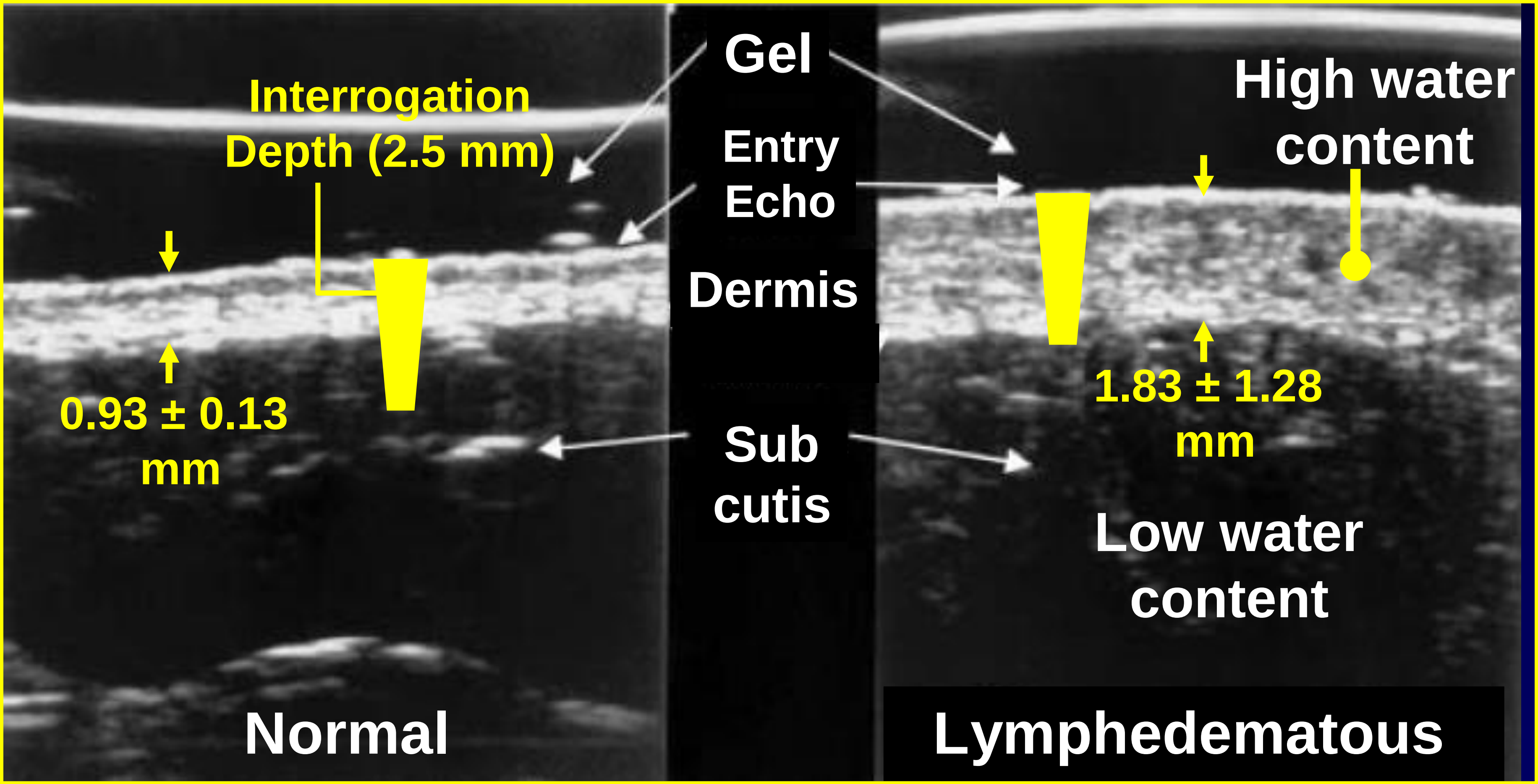
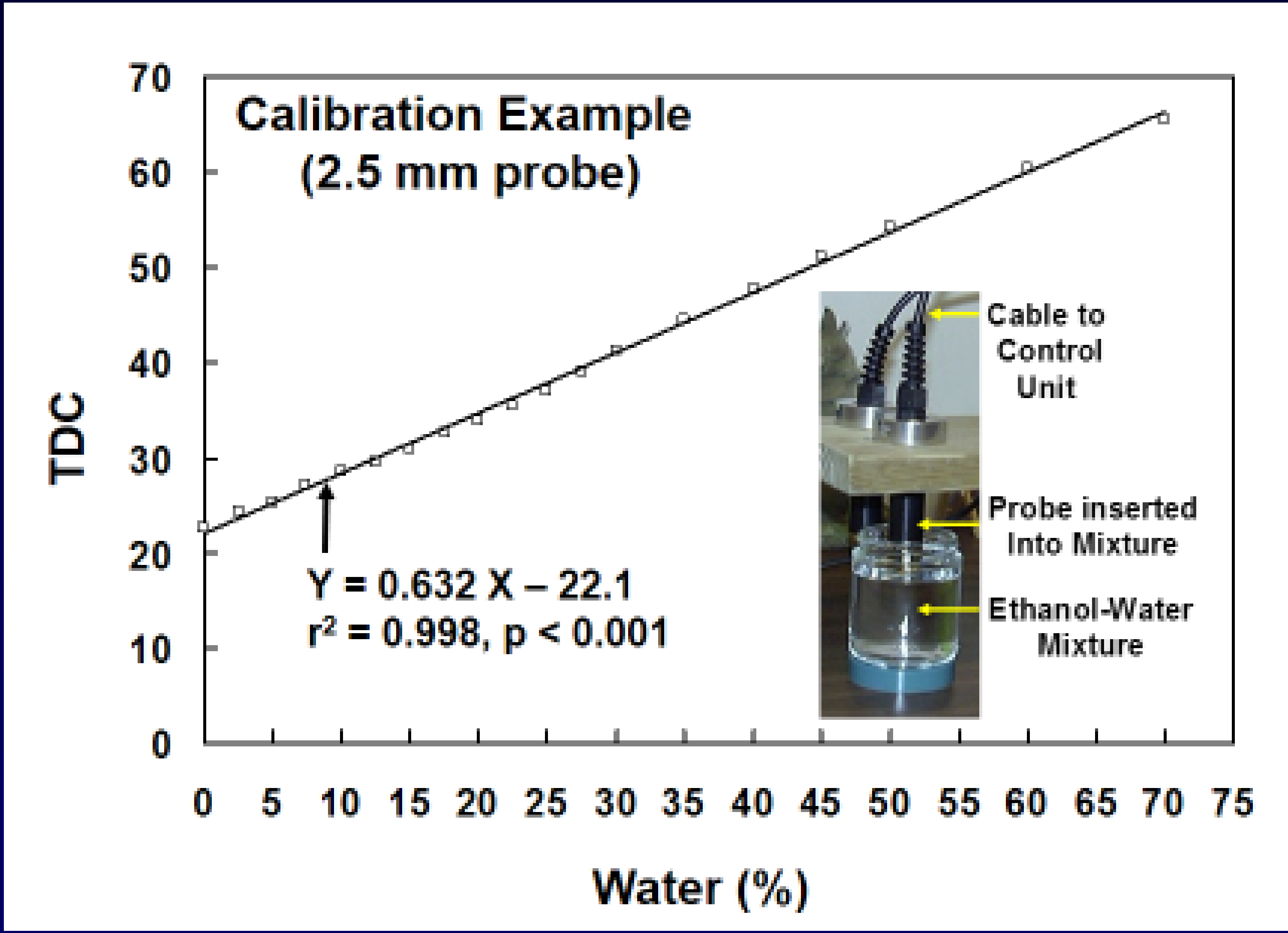


Image modified from Mellor et al. The Breast J. 2004;10:496-503

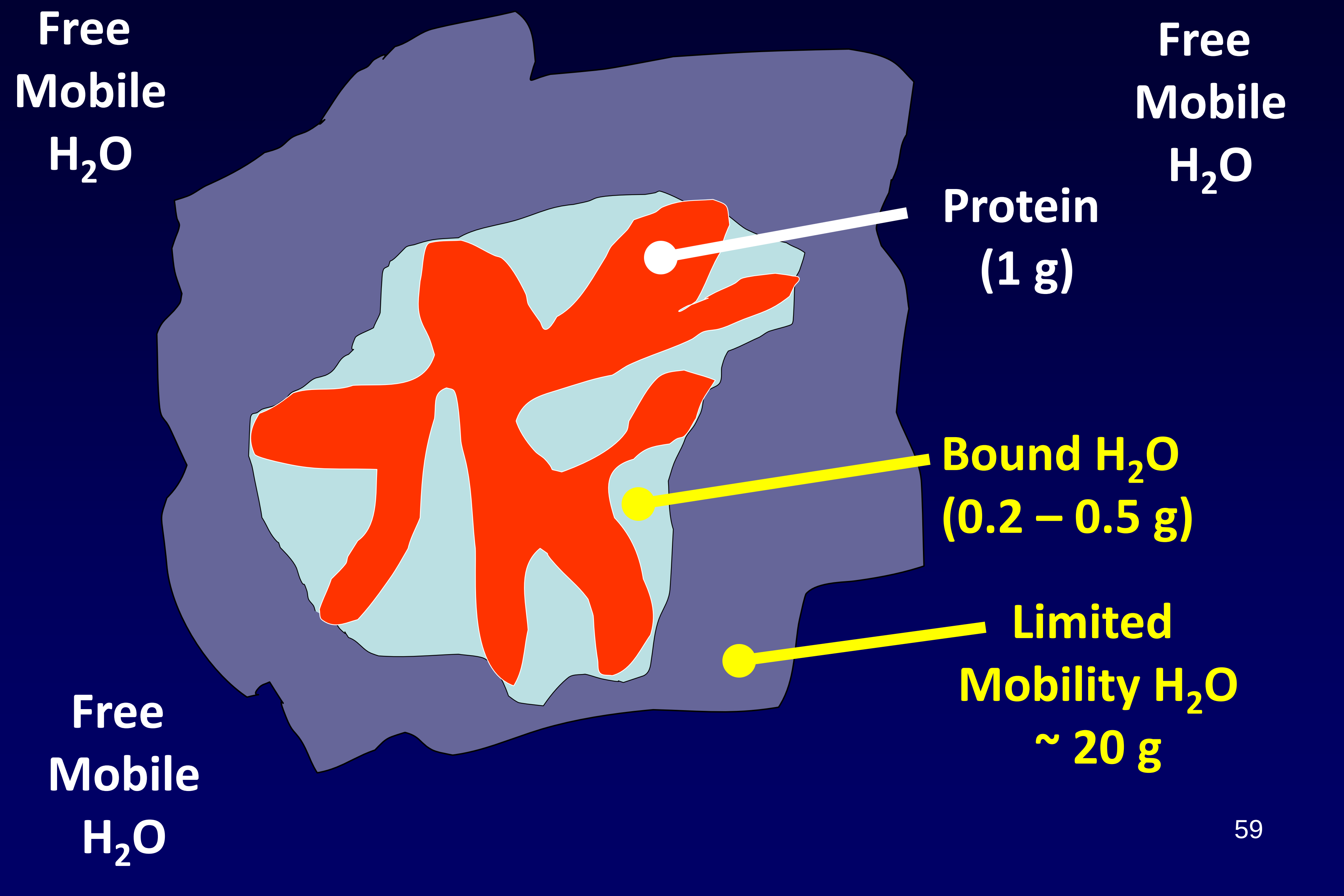
Anterior Forearm

TDC: Linear with Water Content

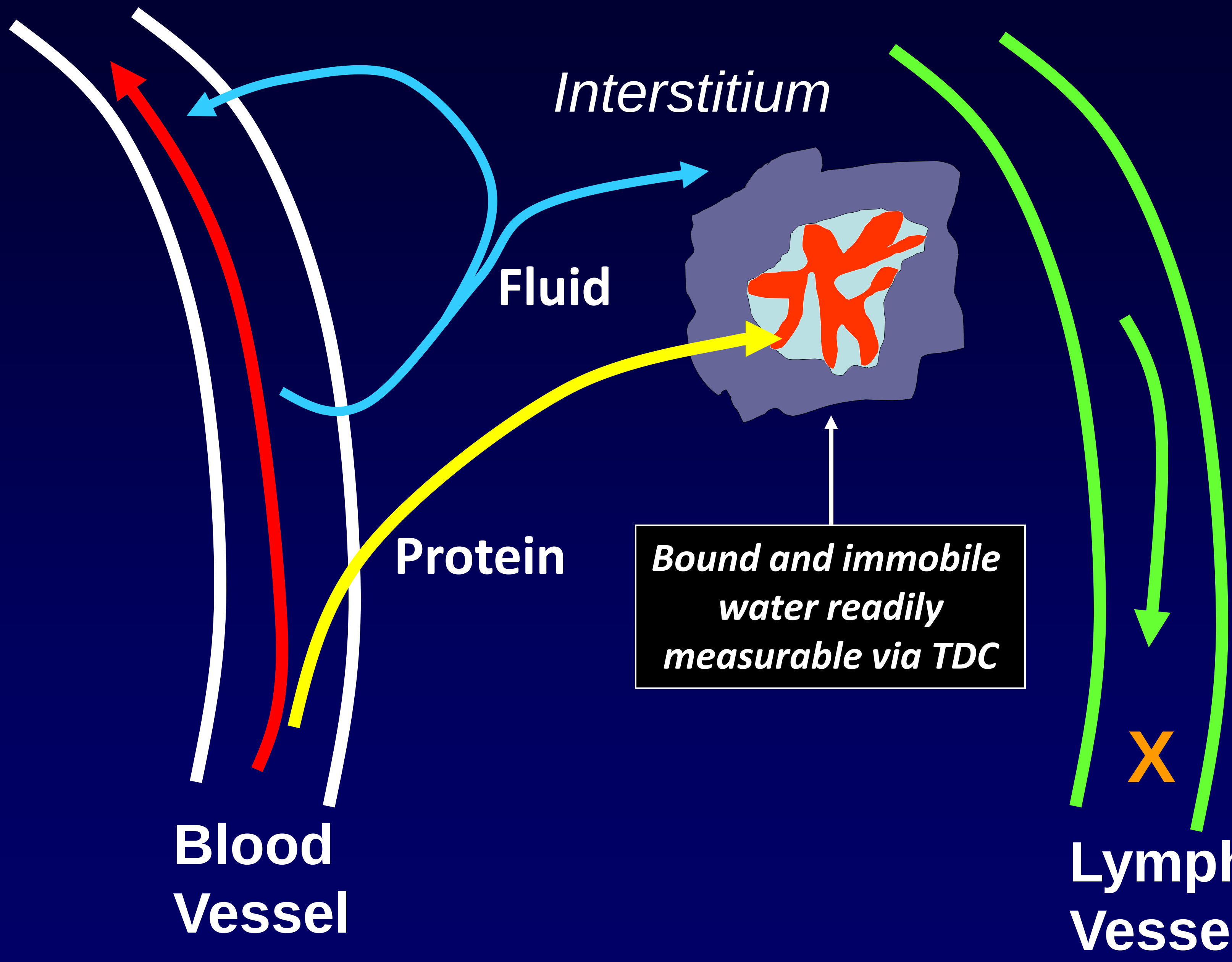


- Thresholds

Free and Bound Water



Bound H_2O -Lymphatic Dysfunction



4. Measurement Threshold Issues

- Girth and Volume Thresholds
- Volume Thresholds S
- Volume Thresholds F
- Bioimpedance Thresholds
- TDC Thresholds
- End

Girth and Volume Thresholds

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 > γ

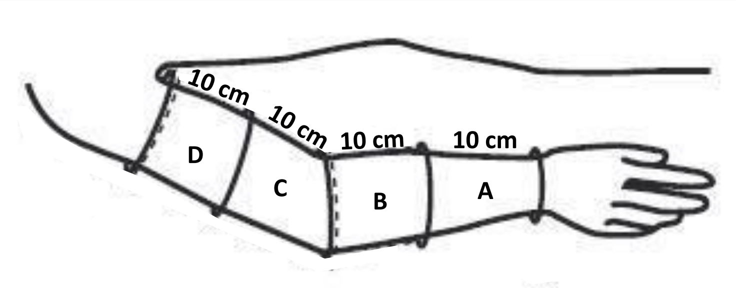
if unilateral or bilateral then

- change from pre-surgery > V_2 ml

Normal Arm Volume Differentials

185 healthy females > 40 years

Dom > NonDom (1.8%)[1]



- **Girths by Perometer**
- **Volumes by frustum**

[1]Dylke ES et al. Lymphatic Research and Biology 2012;10:182-188

100 healthy females: 50.6 ± 18.2 years

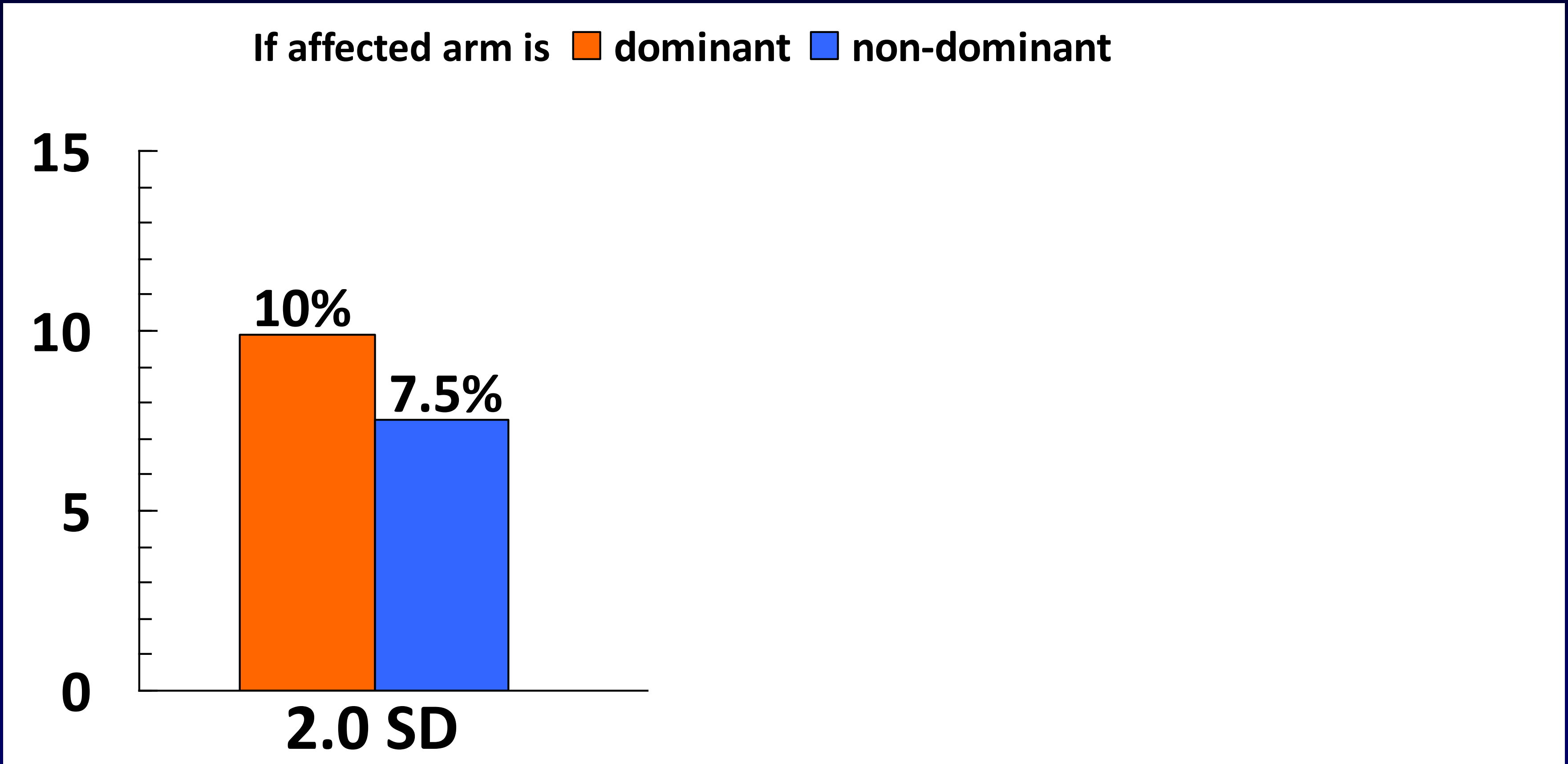
Volumes by water displacement

Dom > NonDom (2.0%)[2] @ 2300 ml

***Dom = 0.979NonDom + 97 ml (*± 149 ml)**

[2]Gebruers N et al . Clin Physiol Funct Imaging 2007; 27:17-22

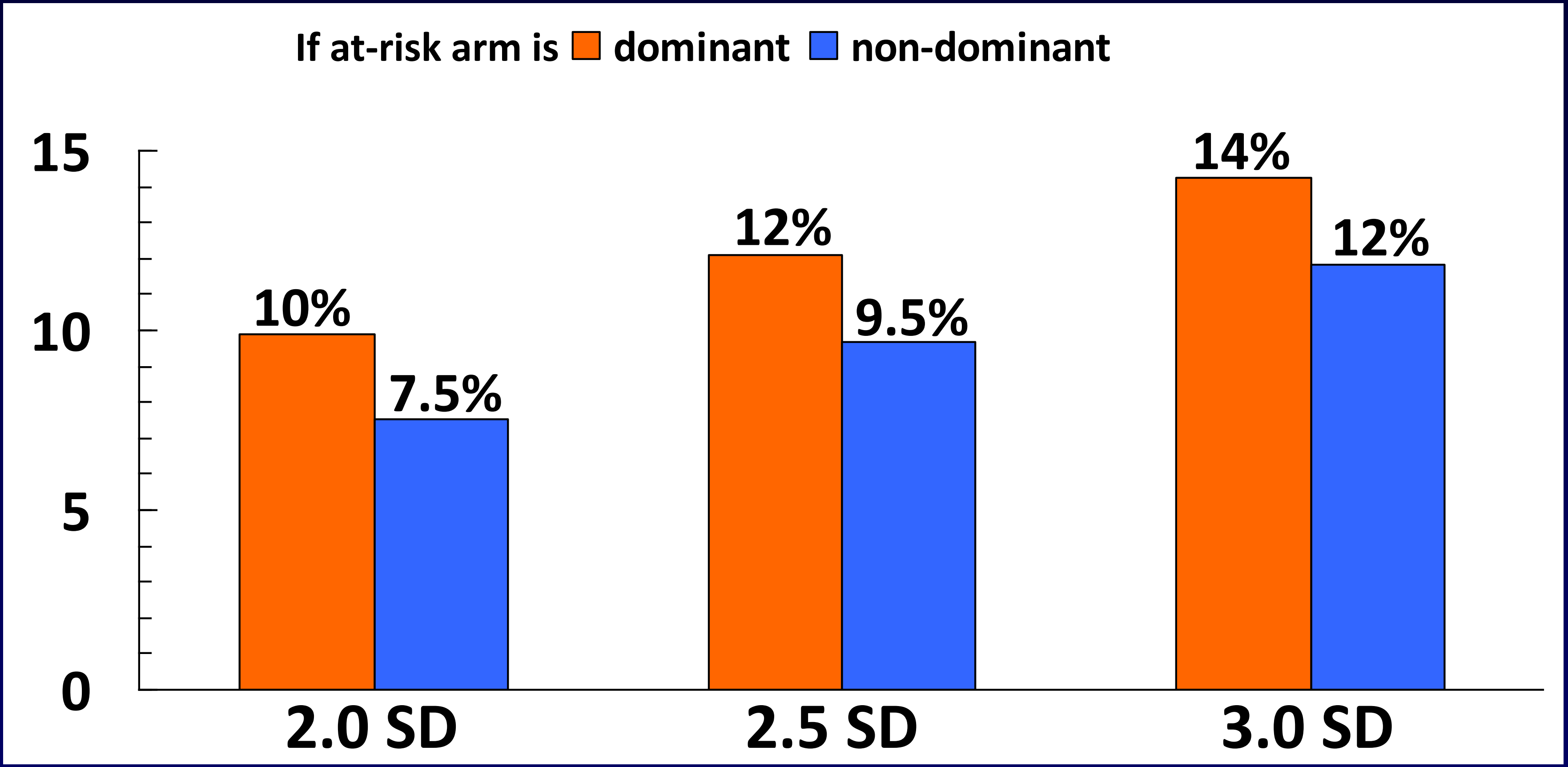
Volume Thresholds: %Differences between Arms to be Judged as Lymphedema



% of cases 95.4%

Calculated based on bilateral measurements of 185 healthy (non-lymphedematous) women age >40 with girths measured via Perometer but volumes determined via truncated cone at 10 cm intervals
Dylke ES et al. Lymphatic Research and Biology 2012;10:182-188

Volume Thresholds: %Differences between Arms to be Judged as Lymphedema

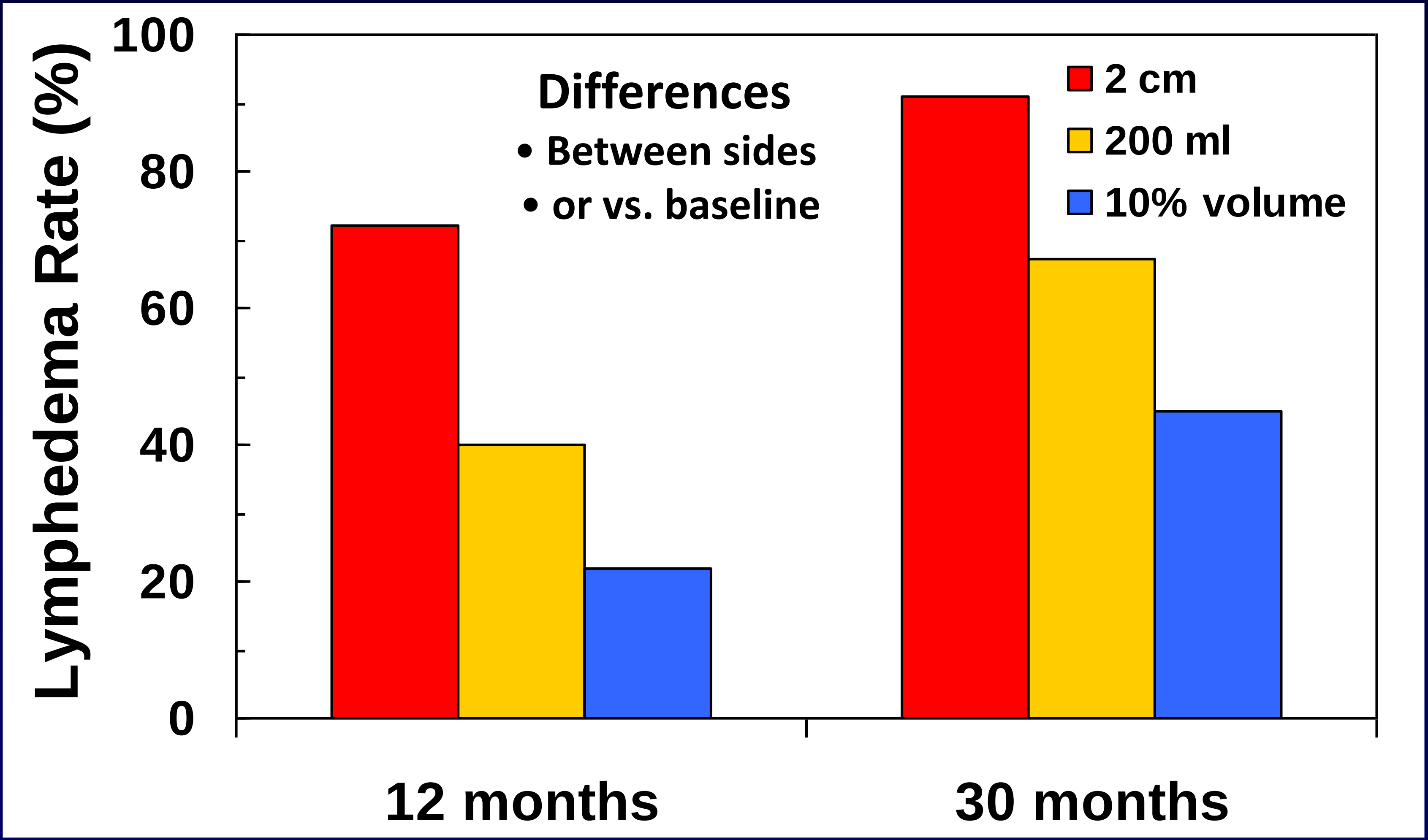


% of cases 95.4% 98.7% 99.7%

Calculated based on bilateral measurements of 185 healthy (non-lymphedematous) women age >40 with girths measured via Perometer but volumes determined via truncated cone at 10 cm intervals
Dylke ES et al. Lymphatic Research and Biology 2012;10:182-188

Arm Lymphedema Metric Criteria

LE rate dependent on criteria used



Data from: Armer et al. J. Lymphoedema 2009;4:14-18

Bioimpedance Thresholds

Bioimpedance Thresholds: Inter-arm ratios Judged to Detect Lymphedema

	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 Non-Dom / Dom

Dom = at-risk

1.134

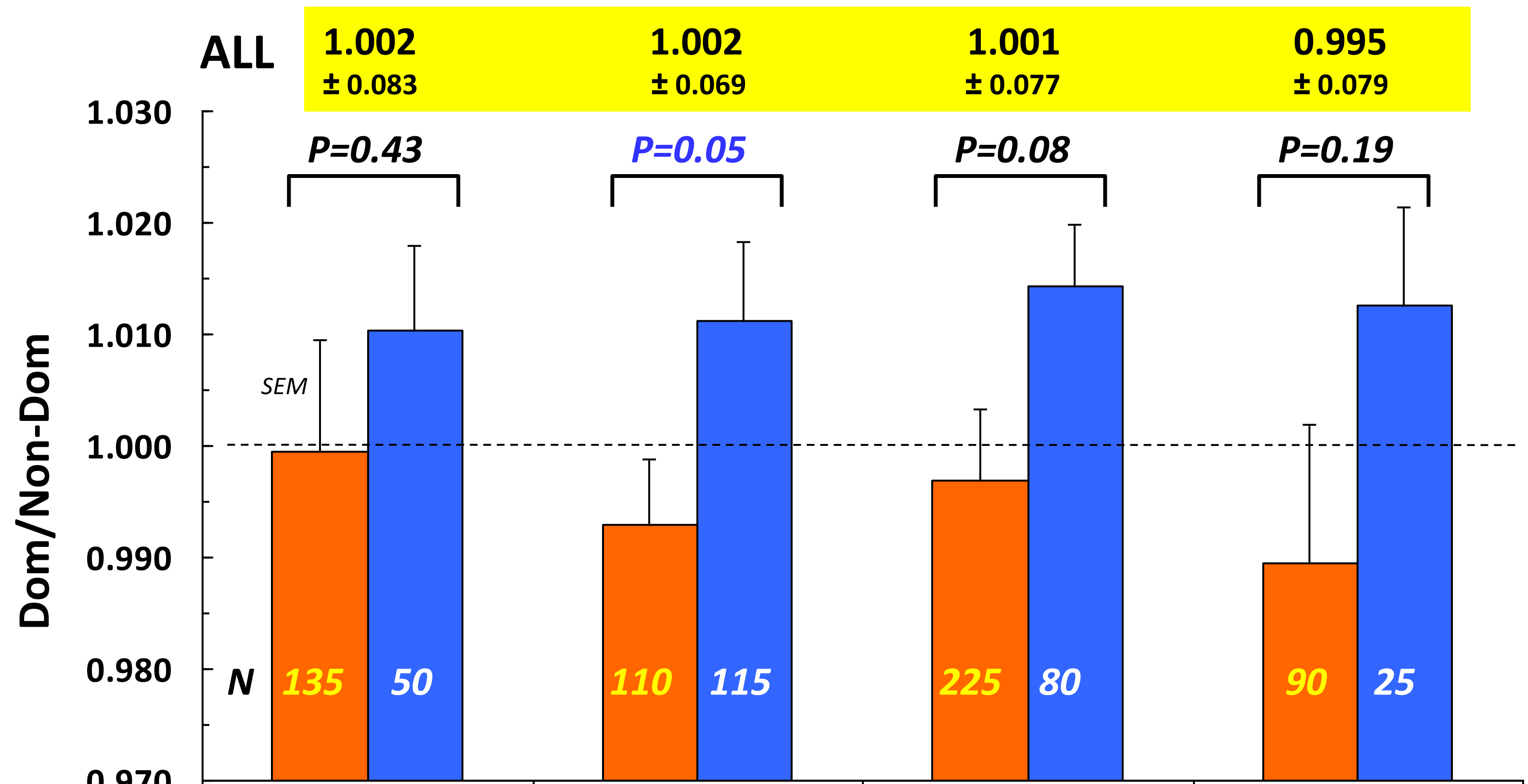
Non-Dom = at-risk

1.106

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

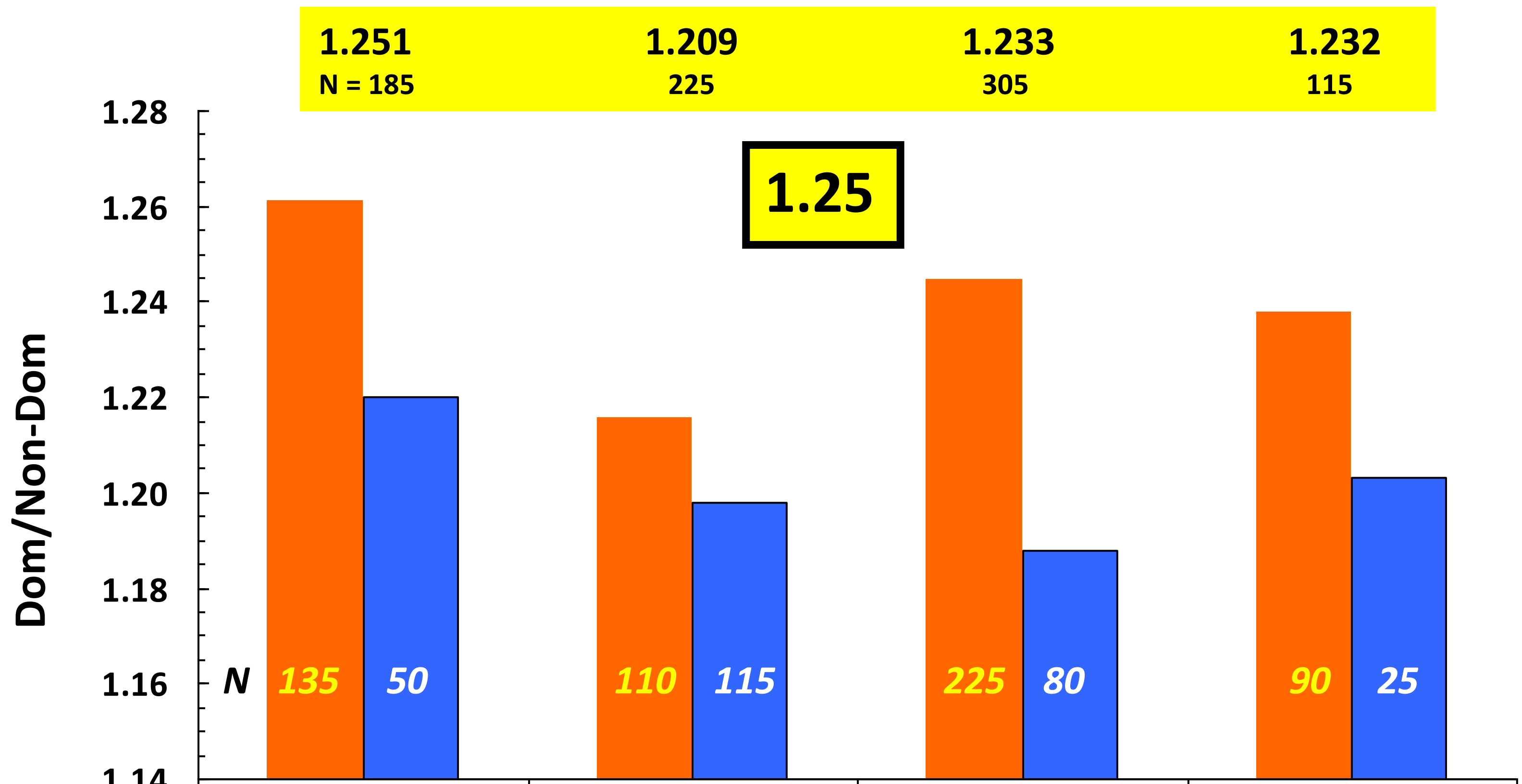
TDC Thresholds

TDC Ratios: Inter-arm (Forearm)
Slight Age Difference Tendency



Depth	0.5 mm	1.5 mm	2.5 mm	5.0 mm
Age > 40	0.999	0.993	0.997	0.989
Age <=40	1.010	1.011	1.014	1.013

TDC Thresholds: Inter-arm ratios (Forearm) Judged to Detect Lymphedema at 3SD



Depth	0.5 mm	1.5 mm	2.5 mm	5.0 mm
Age > 40	1.26	1.22	1.24	1.24
Age <=40	1.22	1.20	1.19	1.20

Thanks to my many student collaborators and thanks to ALL OF YOU FOR YOUR ATTENTION