Multiparametric ultrasound imaging of the diaphragm
-
Muscle volume estimation based on bioelectrical impedance measurements

LIBM seminar

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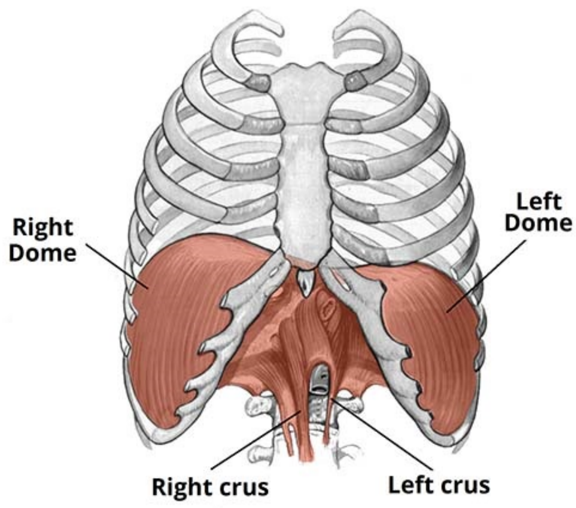
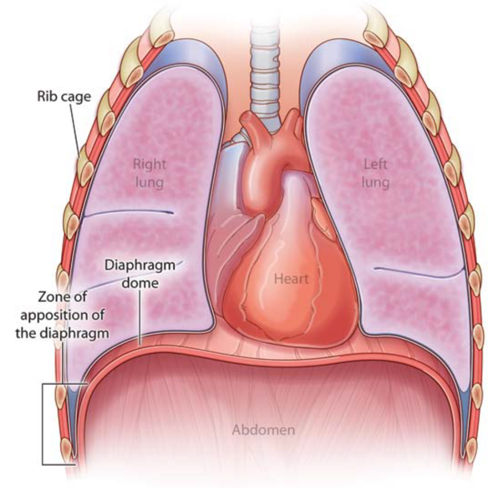
Overview

Multiparametric ultrasound imaging of the diaphragm

- The diaphragm
- Diaphragm dysfunction
- Assessment of diaphragm function in humans
- Novel developments and application of multiparametric ultrasound imaging for assessing diaphragm

The diaphragm





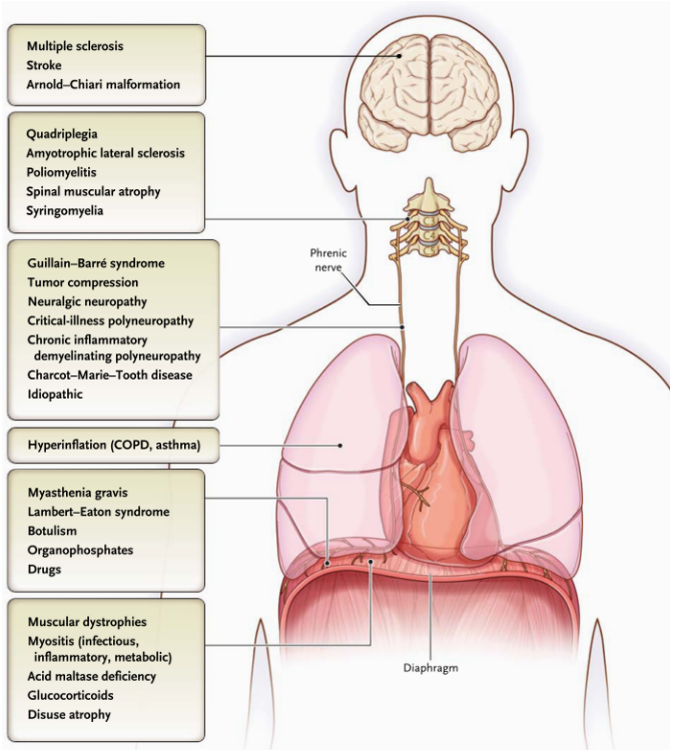
- The main inspiratory muscle
- 20 000 daily contractions
- Innervation: phrenic nerves nerve roots at C3-C5 nerve roots
- Inspiratory contraction:
  - Flattens and enlarge the rib cage
  - Lowers pressure in the thoracic cavity

Diaphragm dysfunction

- Disease processes that interfere with
  - Diaphragmatic innervation
  - Contractile properties
  - Mechanical coupling

  ➔ **Diaphragm dysfunction**
- Dyspnea
- Decreased exercise performance
- Sleep-disordered breathing
- Constitutional symptoms
- Hypersomnia
- Reduced quality of life
- Atelectasis

➔ **Respiratory failure**



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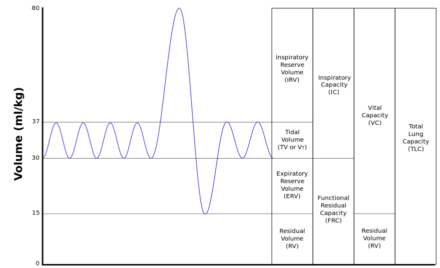
[1] *Mc Cool et al. 2012*

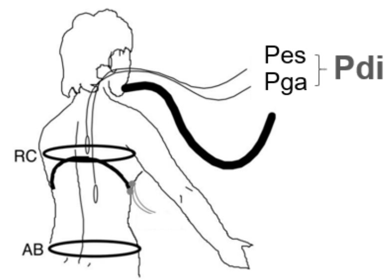
Assessment of diaphragm function in humans

- Flows and volumes
- External pressures (mouth, nasal)
- Internal pressures
  - Esophageal pressure
  - Gastric pressure
  - **Transdiaphragmatic pressure**
    - gold standard
    - **invasive**
    - **equipment** & **expertise**

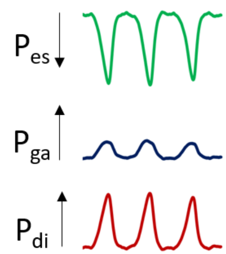
➔ Diaphragm dysfunction is **underdiagnosed**

➔ Monotoring diaphragm function is **challenging**

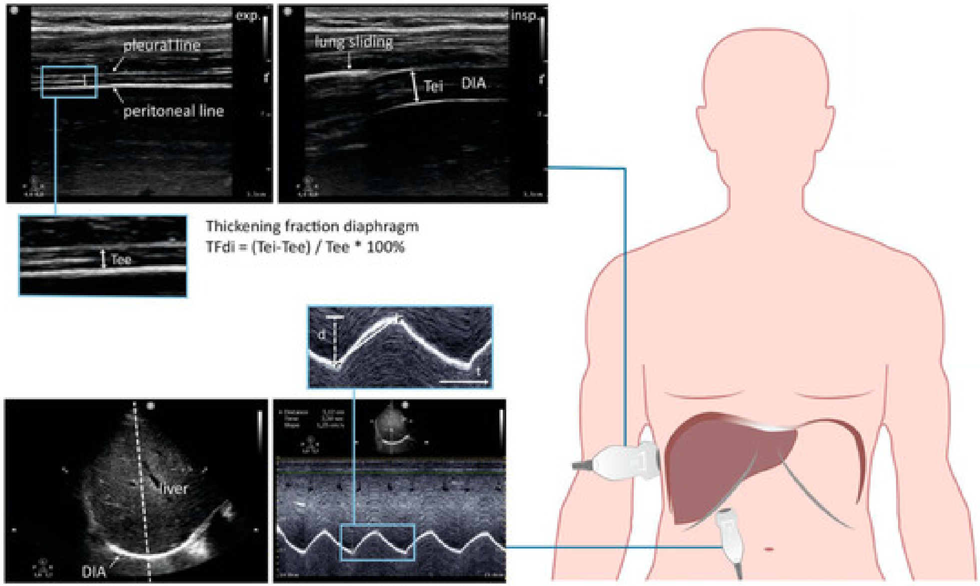




(Similowski et al., Reanimation, 2003)



Conventional diaphragm ultrasound imaging



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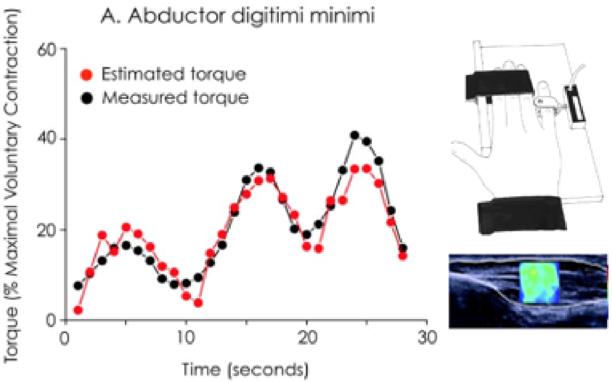
- Portable - direct visualization
  - Intercostal scanning: thickness, thickening fraction (TFdi)
  - Subcostal scanning: excursion
- Ability for gauging diaphragm effort ➔ controversial
- Limited frame rate (~60 Hz)

[1] *Tuinman et al. 2020*

Novel developments and applications for multiparametric ultrasound imaging of the diaphragm

Active muscle mechanics using shear wave elastography (SWE)

Muscle shear modulus measured using SWE provides reliable estimates of **force output** in the skeletal muscle.



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Can changes in diaphragm shear modulus (SMdi) be assessed using SWE ?

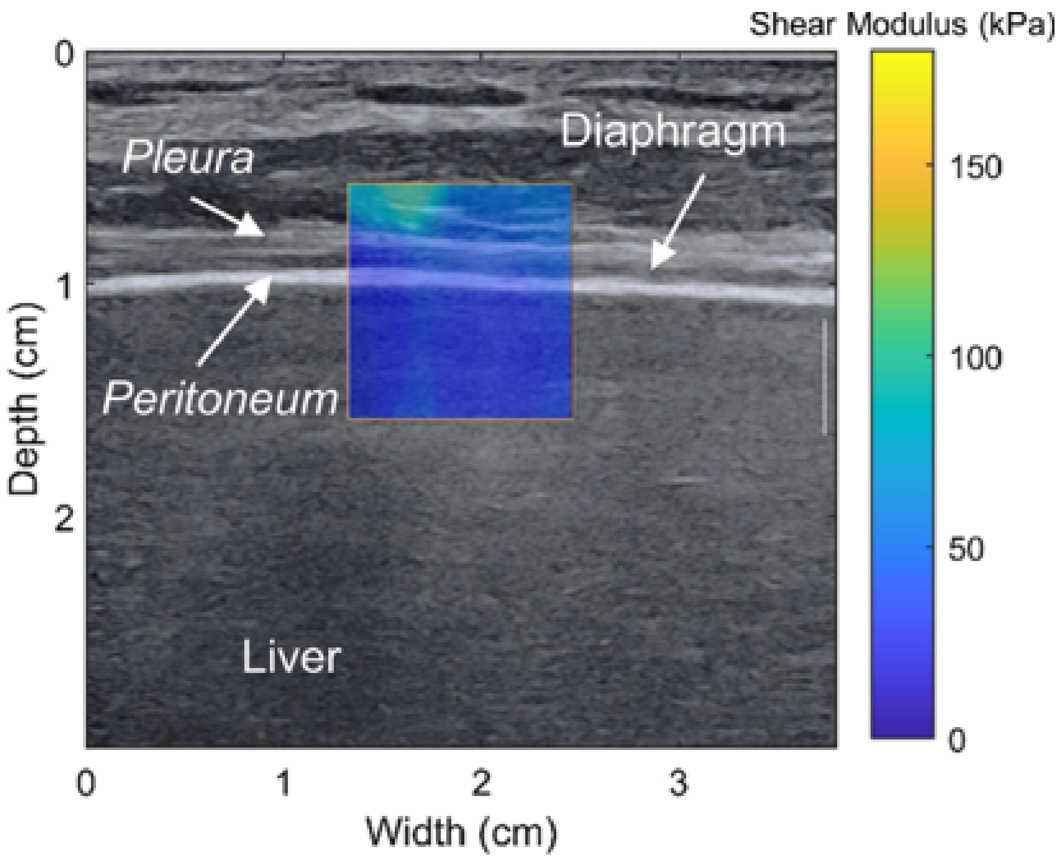
What is the relationship between SMdi and Pdi ?

[1] Ates et al. 2015, JEK

Diaphragm SWE

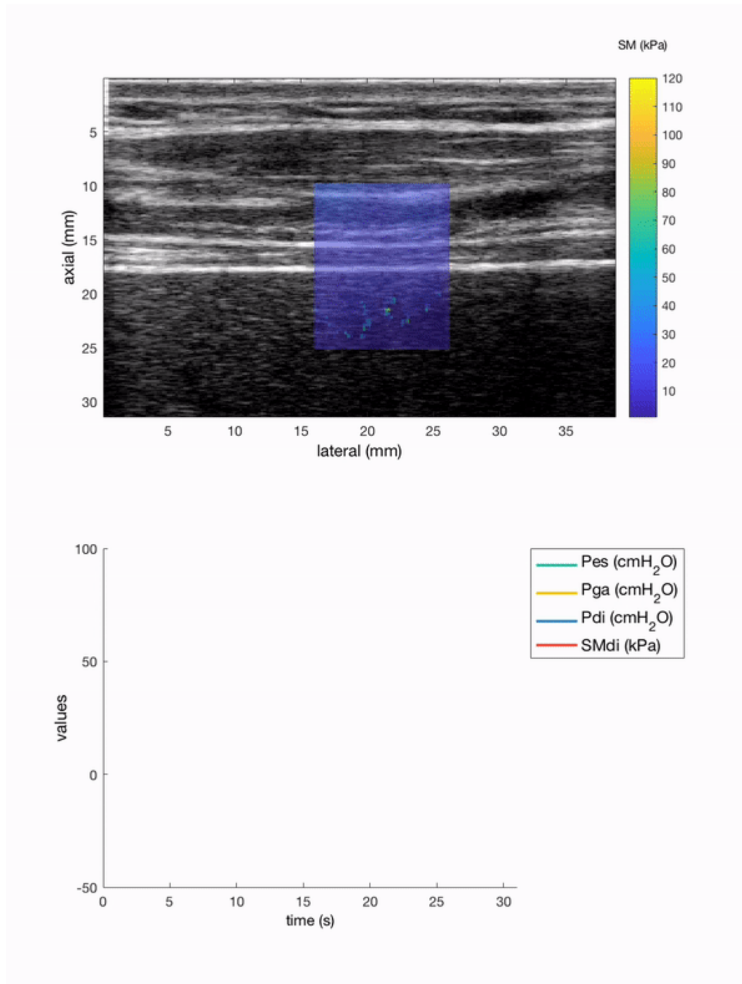
- 15 healthy participants (11 men, 4 women)
- Stepwise inspiratory loading protocol
  - 0 to 50% of maximal inspiratory pressure
    - Closed-airways inspiratory efforts
    - Ventilation against inspiratory loading
- SL 10-2 (6 MHz) driven by an Aixplorer ultrasound scanner (Supersonic Imagine)

Diaphragm SWE

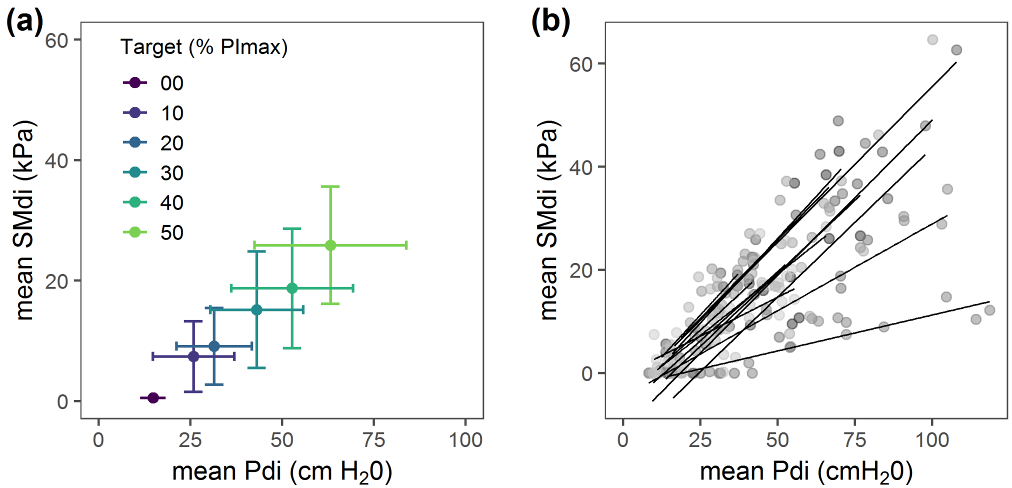


Diaphragm shear modulus (SMdi) measured over the right zone of apposition

Closed-airways inspiratory effort



Closed-airways inspiratory effort



- Mean Pdi correlated to mean SMdi in 14/15 participants (r = -0.60-0.92, all $p < 0.05$)
- Group level: R = 0.76, 95% CIs [0.69, 0.82], $p < 0.001$

Bachasson et al. 2019, J Appl Physiol, PMID: 30730816

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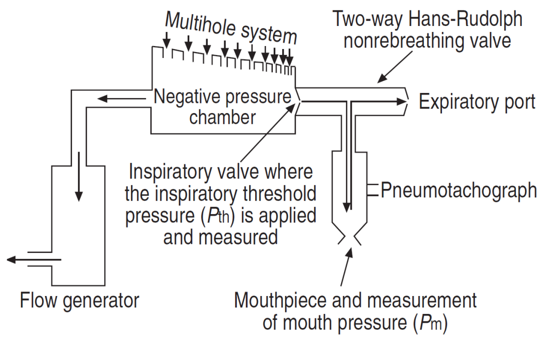
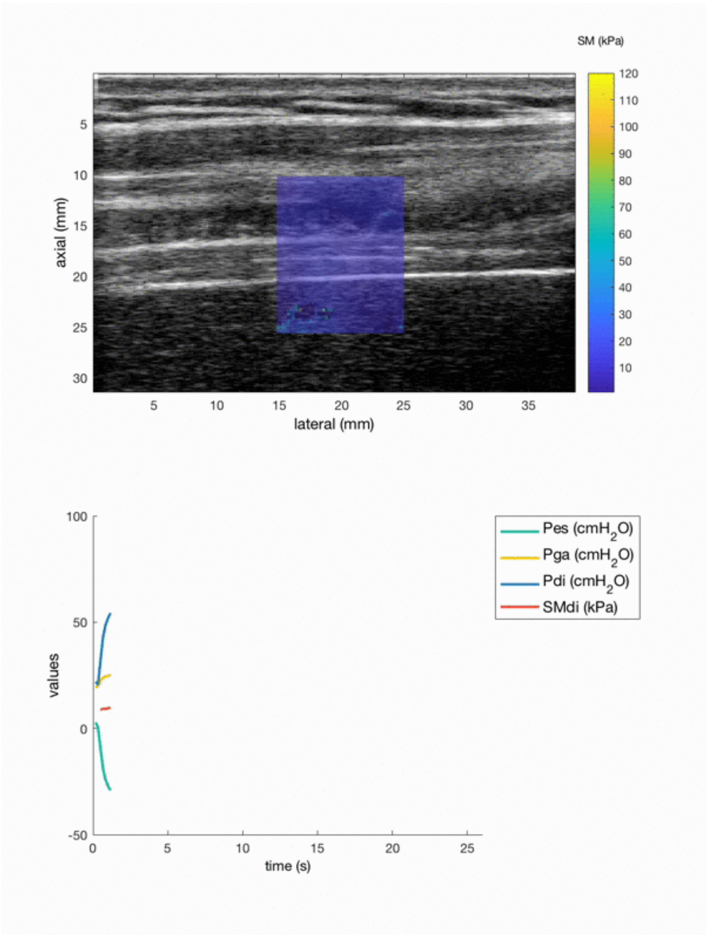
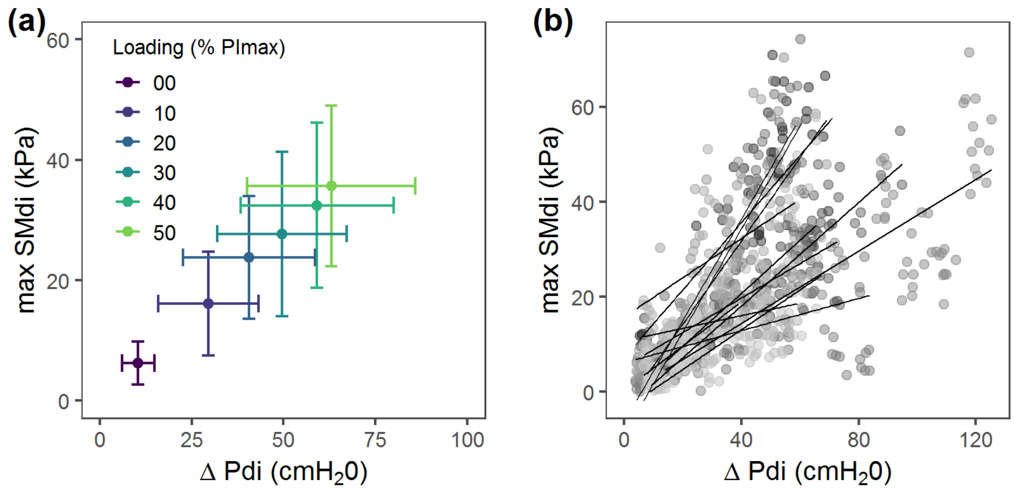
Inspiratory loading





Inspiratory loading

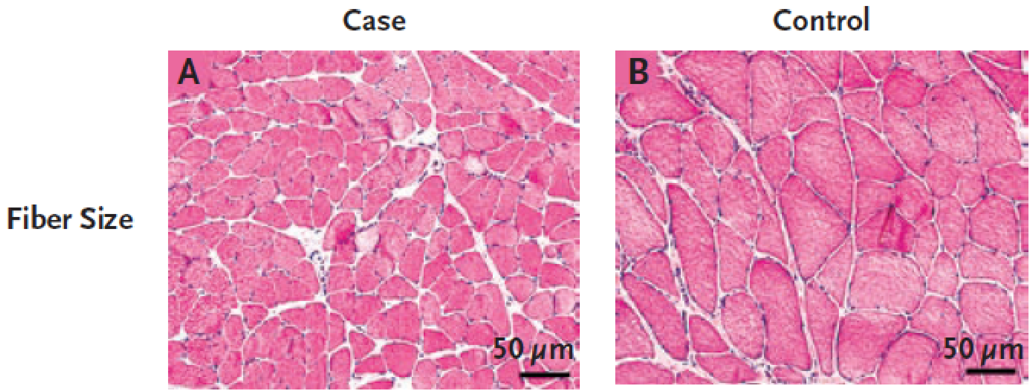


- ΔPdi correlated to max SMdi in all participants ($r = 0.32$-0.95, all $p < 0.01$)
- Group level: $R = 0.71$, 95% CIs [0.68, 0.74], $p < 0.001$

➔ SMdi = novel noninvasive and specific metric of diaphragm effort

? Applicability in the mechanically-ventilated patients ?

Ventilator-Induced Diaphragm Dysfunction



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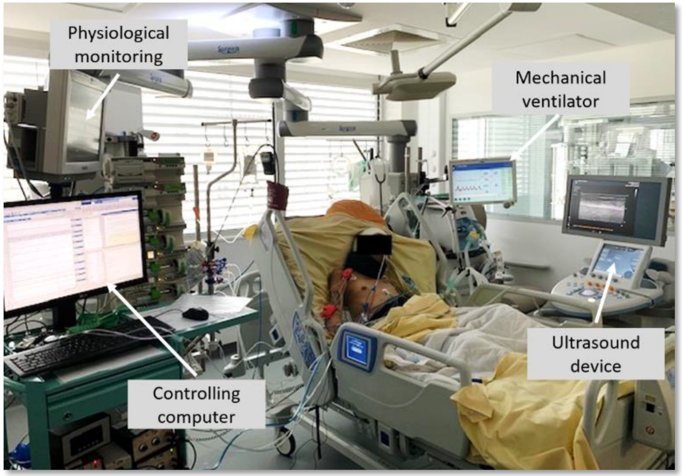
- Marked atrophy of human diaphragm myofibers > **72h** of ventilation [1]
- Impairment of diaphragm pressure-generating capacity[2]
  - Increase duration of mechanical ventilation, prolong weaning, increase mortality

➔ **Protective ventilation** requires **reliable** and **easy accessible** methods for monitoring diaphragm effort

[1] Levine et al. 2008, NEMJ [2] Hermans et al. 2010, Crit Care

Diaphragm SWE in mechanically-ventilated patients

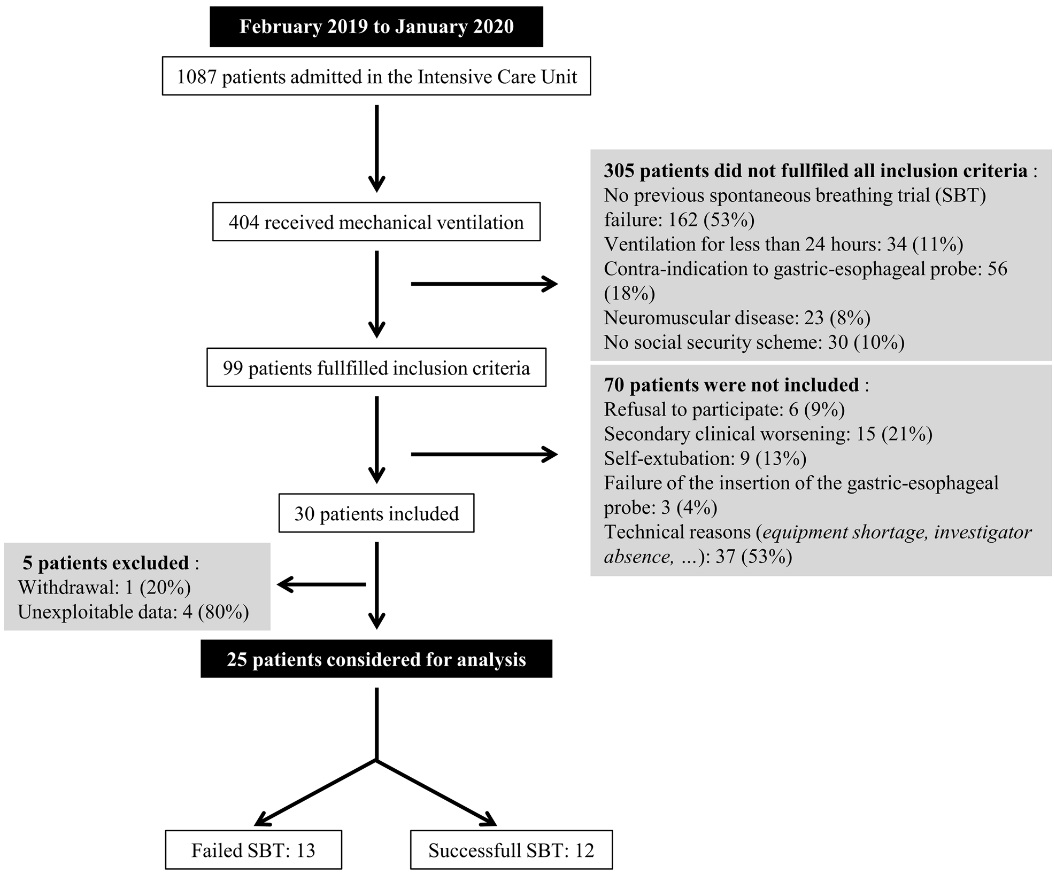


- 25 mechanically ventilated patients
- Changes in ventilator settings for modulating diaphragm effort
- Spontaneous breathing-trial
- Monitoring of Pdi and ultrasound recordings **simultaneously**

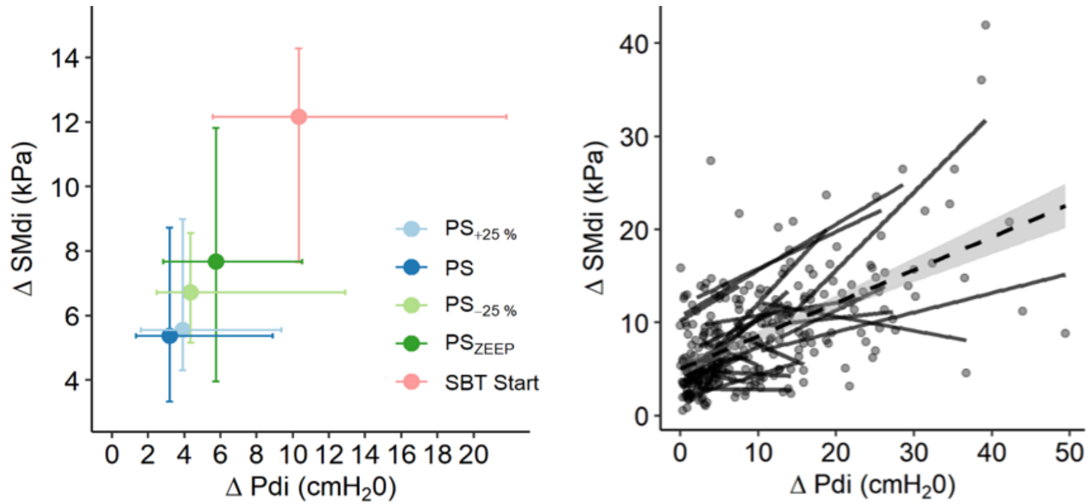
? Relationship between Pdi and SMdi ?

? Ability of SMdi to capture changes in diaphragm effort ?

Diaphragm SWE in mechanically-ventilated patients



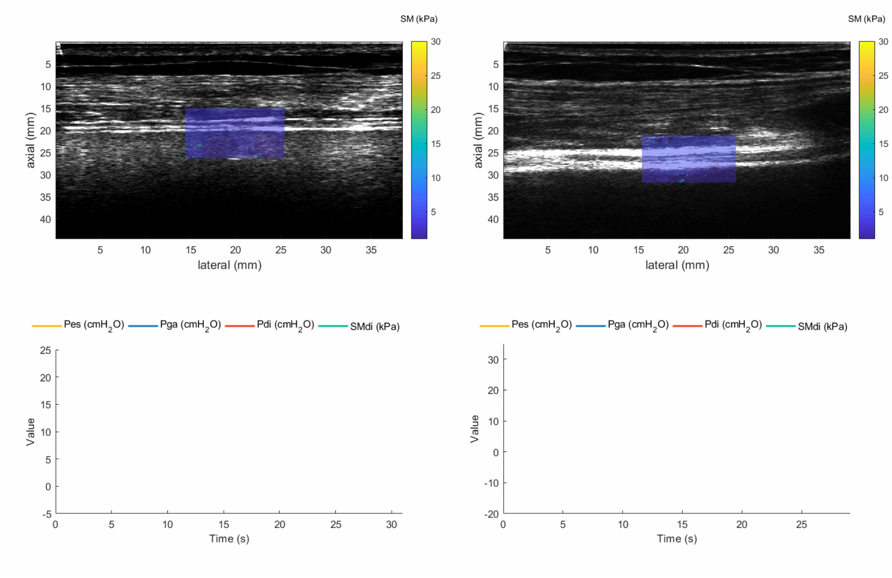
Diaphragm shear modulus vs transdiaphragmatic pressure



- Group level: R = 0.45, 95% CIs [0.35 0.54], $p < 0.001$
- ΔPdi correlated to ΔSMdi in 8/25 patients only

[1] Fossé et al. 2020, Crit Care, PMCID: 7695240

Diaphragm SWE in mechanically-ventilated patients



- Faster respiratory rate in patients with absence of correlation (median (Q1–Q3), 25 (18–33) vs. 21 (15–26) breaths/min)

Perspectives

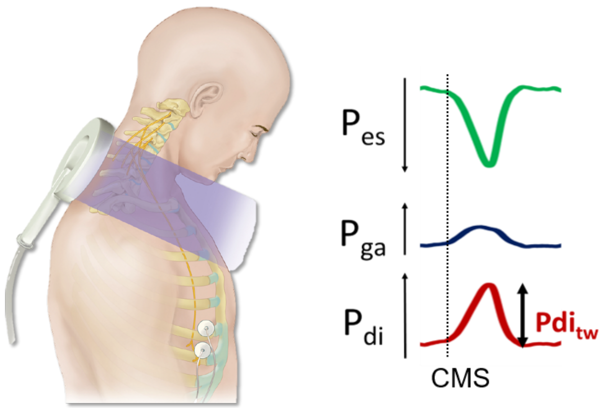
- Technological and methodological developments are required
  - Specific SWE sequences
  - Passive ultrasound elastography
  - 2-points ultrasound elastography
  - Guided shear waves

➔ Ability to improve patient-ventilator interaction ?

➔ Ability to improve weaning strategies ?

Capturing diaphragm evoked responses using ultrafast ultrasound imaging ?

Non-volitional assessment of diaphragm contractility

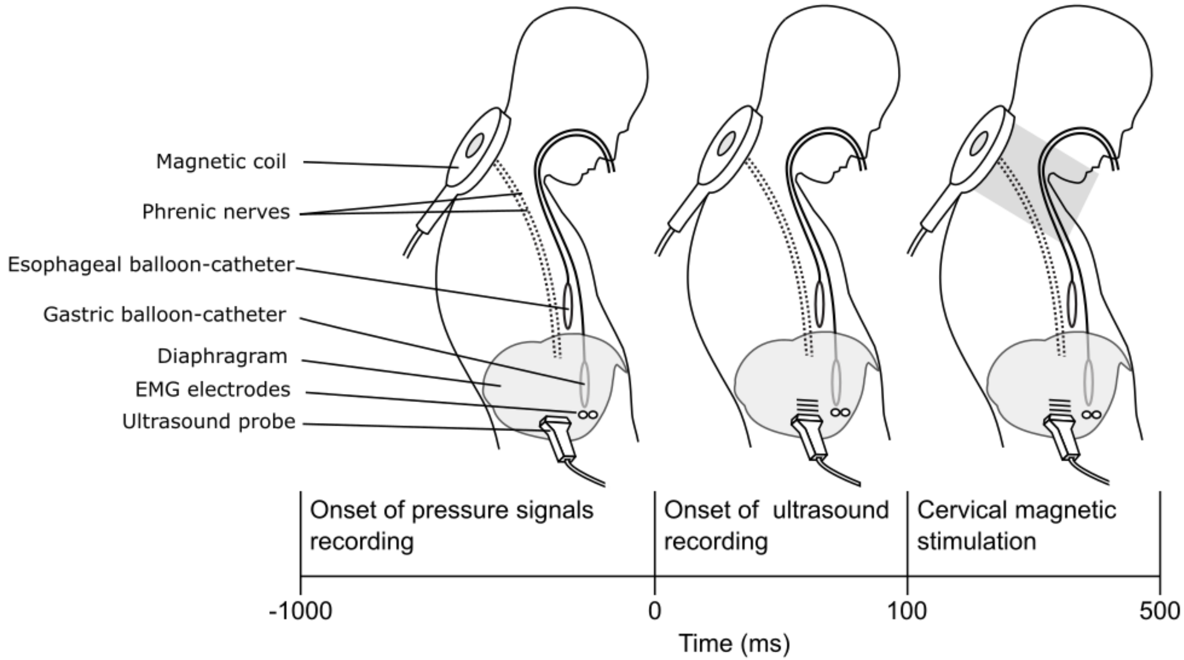


- Cervical magnetic stimulation (CMS)
- Short-lasting event (~300 ms)

? Can Pdi,tw be captured using ultrafast ultrasound ?

? Do metrics derived from ultrafast ultrasound reflect diaphragm contractility ?

Diaphragm ultrafast ultrasound imaging



- 13 healthy volunteers (5 men, 8 women)
- Simultaneous Pdi and ultrasound recordings during CMS
- Variable stimulation intensity

Diaphragm ultrafast ultrasound imaging

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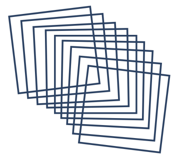
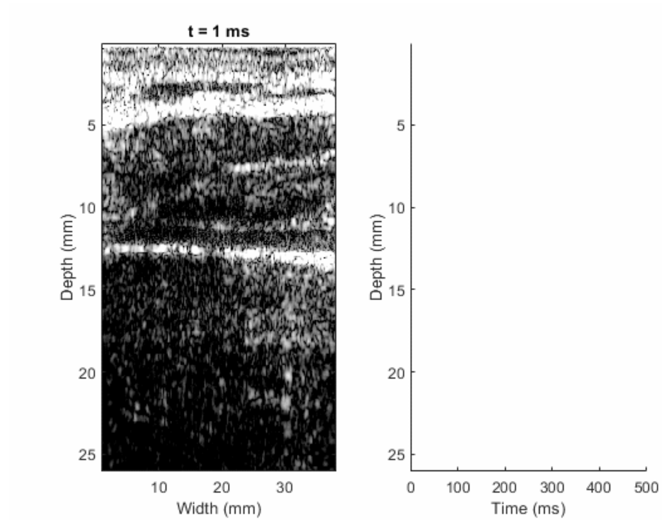
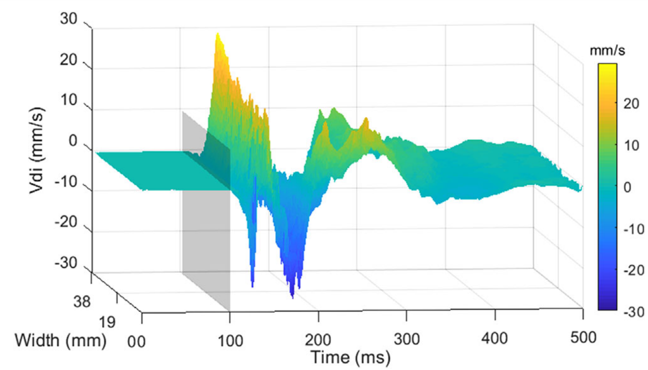
- Ultrafast ultrasound sequence



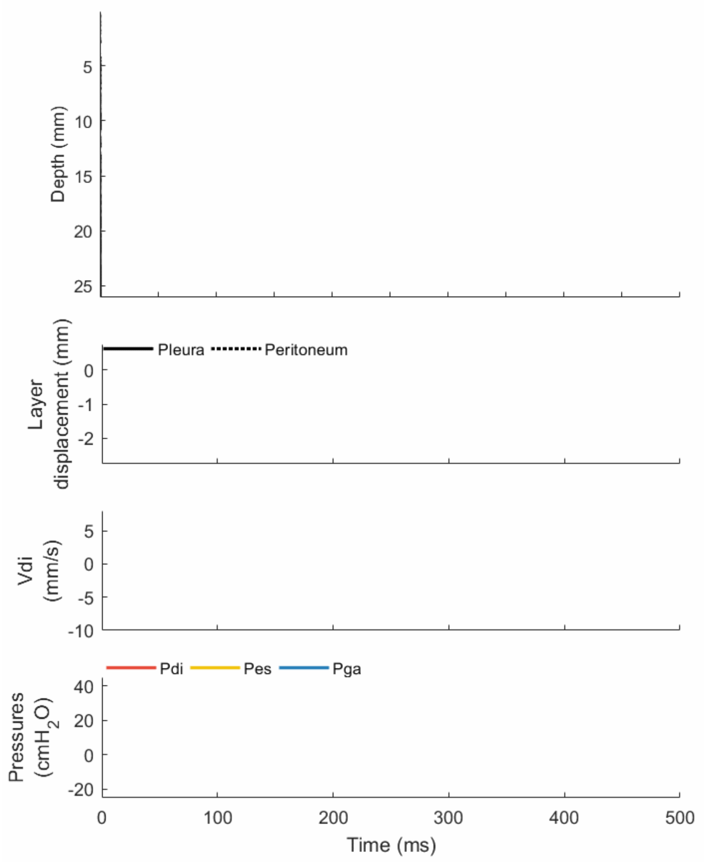
  - nine plane-wave
  - –7°-7° with a 2° increments
  - 9 kHz frame rate
    ➔ compounded frame rate = **1 kHz**
    ➔ duration of **500 ms**

- Vertical speckle tracking:
  ➔ diaphragm **tissue velocity (Vdi,max)**
  ➔ diaphragm **thickening fraction (TFdi,tw)**

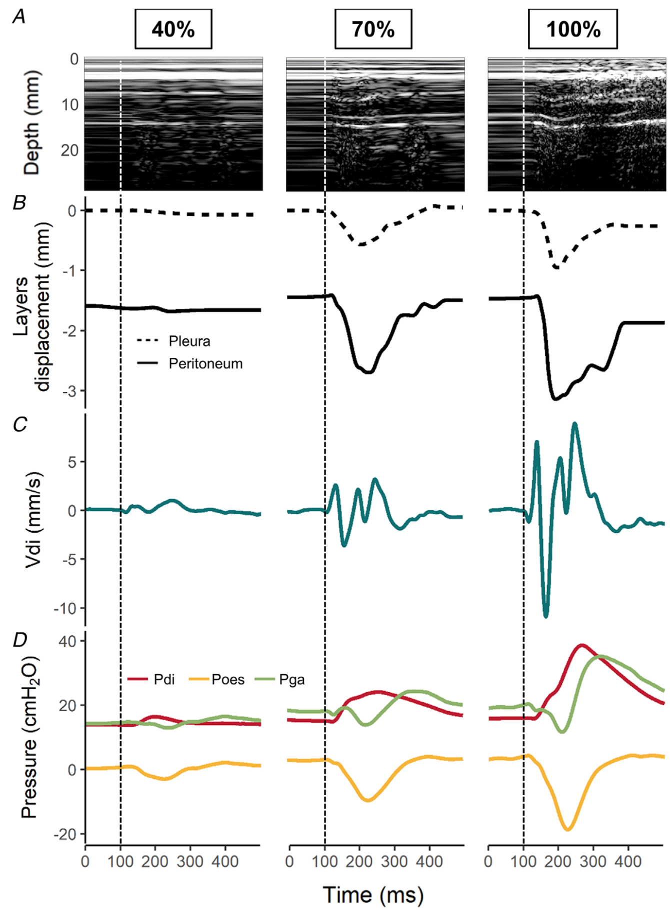




Diaphragm ultrafast ultrasound imaging



Effect of stimulation intensity



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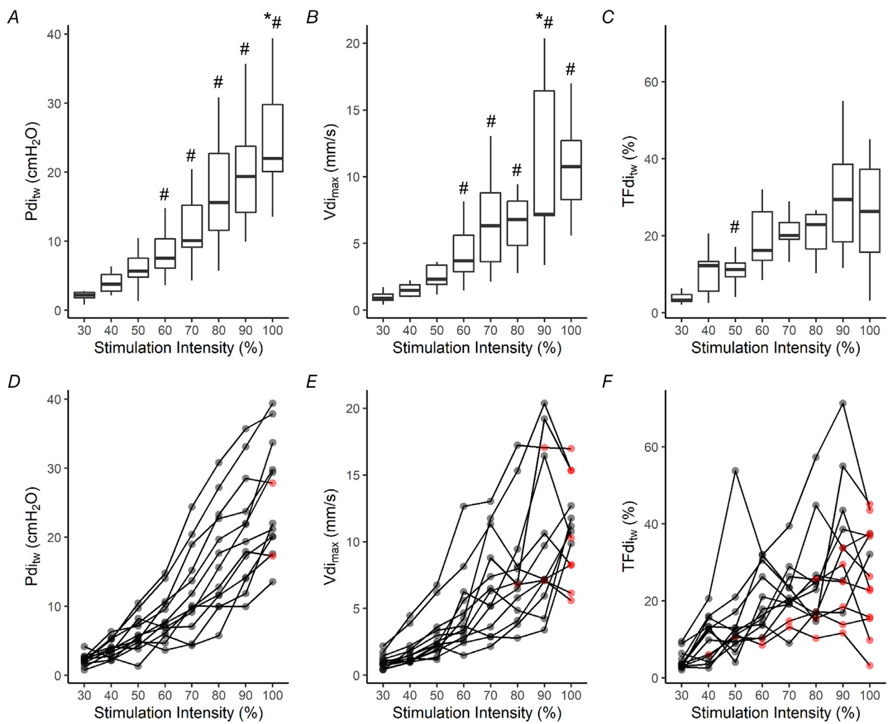
Effect of stimulation intensity



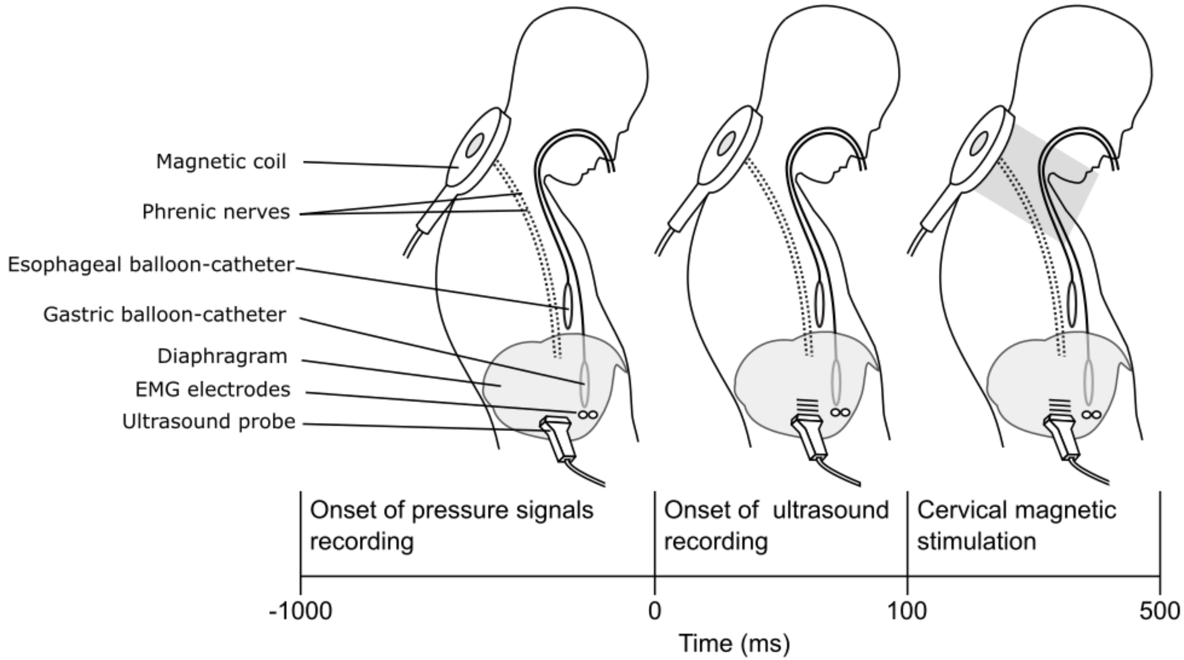
- Vdi,max correlated with Pdi,tw in all subjects ($0.64<\varrho<1.00$, R=0.75; all $P<0.05$).
- TFdi,tw correlated with Pdi,tw in 8/13 subjects ($0.85 < \varrho < 0.93$, R = 0.69; all $P < 0.05$)

Whithin-session reliability

Table 1. Within day reliability of twitch transdiaphragmatic pressure ($P_{di,tw}$), maximal diaphragm tissue velocity ($V_{di,max}$) and diaphragm thickening fraction ($TF_{di,tw}$) for all stimulations. SEM, standard error of measurement; ICC, intraclass correlation coefficient; [95% CI], 95% confidence interval

Variable	Mean (SD)	SEM (95% CI)	ICC (95% CI)
$P_{di,tw}$ (cmH_2O)	11.6 (9.5)	1.55 (1.39, 1.75)	0.97 (0.96, 0.98)
$V_{di,max}$ (mm s^{-1})	5.6 (5.0)	1.89 (1.70, 2.13)	0.86 (0.81, 0.90)
$TF_{di,tw}$ (%)	18.7 (15.6)	10.41 (9.38, 11.76)	0.56 (0.43, 0.66)

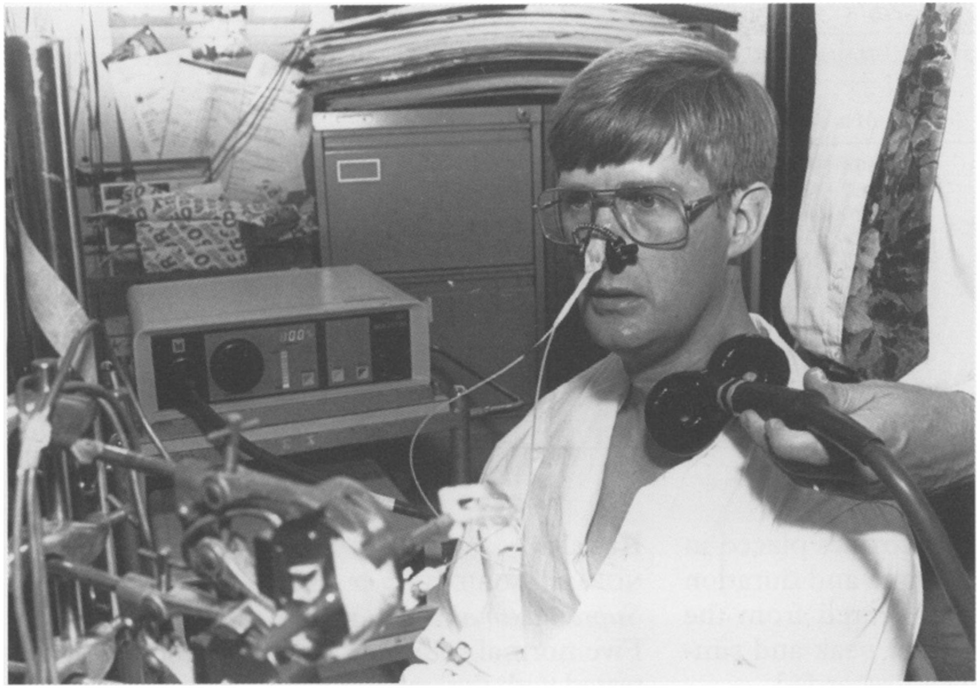
Implications



➔ Fully non-invasive & non-volitional assessment of diaphragm contractility
➔ Bridging the gap between non-volitional and non-invasive methods [1]

[1] Perspective research article from B. Smith 2020, J Physiol, PMCID: 33124690

Getting rid of balloons soon ?



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- ? Sensitivity of Vdi,max to diaphragm fatigue and lung volumes ?
- ? Diagnosis power in patients and potential for follow-up ?

[1] Mills et al. 1995, Thorax

Perspectives for multiparametric ultrasound imaging

- Guidance assistance for probe handling and acquisitions
- Automated post-processing methods
  - Deep learning approaches
- Muscle quality biomarkers
  - Sound speed estimation (fat content)
  - Viscosity
- Ultraportable and wearable solutions

➔ Toward enriched and robust US-based biomarkers of diaphragm structure and function

➔ Toward better diagnosis, prevention, and management of diaphragm dysfunction

Acknowledgments

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All participants that volunteered for participating in these experiments

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Muscle volume estimation based on bioelectrical impedance measurements

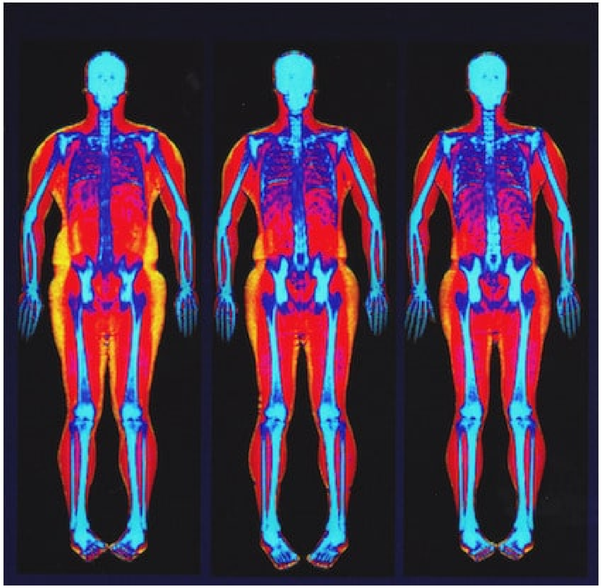
- Context
- Available methods for the assessment of skeletal muscle volume
- Bioelectrical impedance: concepts and state of the art
- Novel developments and application of bioelectrical impedance measurements for estimating regional muscle volume

Context

- We need easy and robust non-invasive methods for estimating **skeletal muscle volume (SMV)** within various physiological and pathophysiological contexts involving muscle remodeling
    - Disuse
    - Neuromuscular disorders
    - Chronic disorders
    - ICU
    - Aging
    - Nutrition
    - Rehabilitation and training
- **Regional SMV** has emerged as an **important hallmark** across the health care continuum

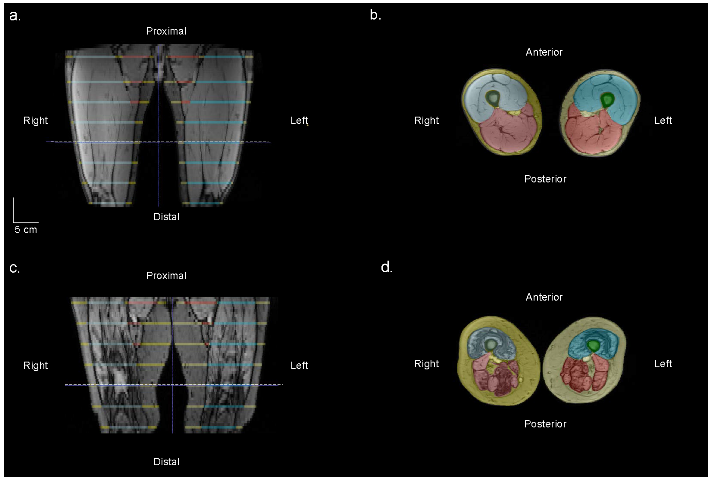
Methods for the assessment of SMV

- Numerous
- Rely on a wide range of physical principles, models, and assumptions
- Dual-energy X-ray absorptiometry (DXA)
  - €, small ☢
  - 2-D ➔ indirect estimation using anatomical models
  -



Methods for the assessment of SMV

- Computerized tomography (CT) and magnetic resonance imaging (MRI)
  - 3-D, muscle fat content
  - MRI non-ionizing but € € €
  - Segmentation ➔ labor-intensive task 🕓 🕓 🕓



[1] Buckinx et al. 2018,J Cachexia Sarcopenia Muscle

Bioelectrical impedance

- Bioimpedance measurements ➔ methods based on the characterization of the **passive electrical properties** of biological tissues/fluids in response to the injection of an external current.

- First works in ~1928 by Kenneth S. Cole (urchins eggs, muscle, ...)

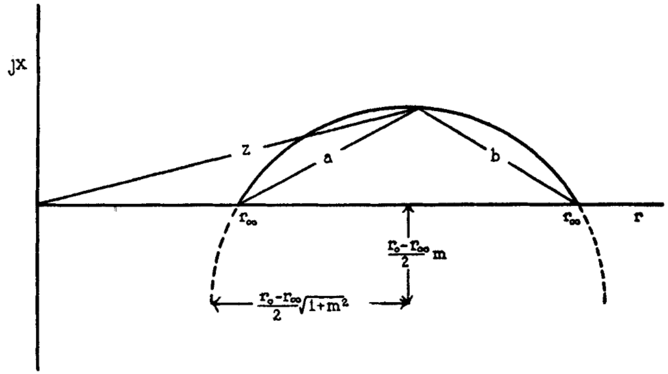
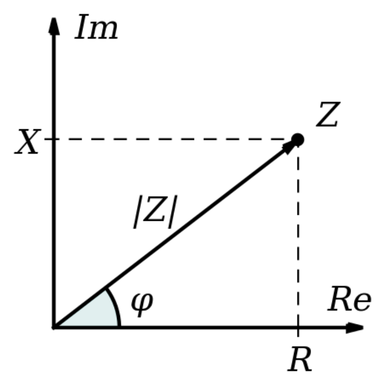


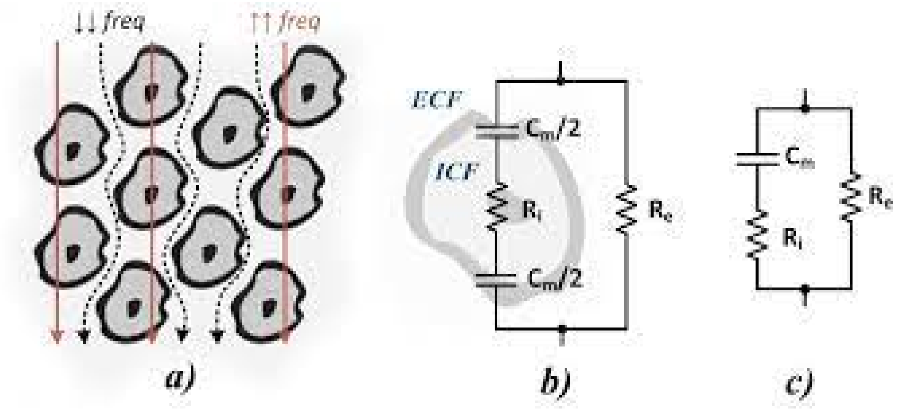
Fig. 3.

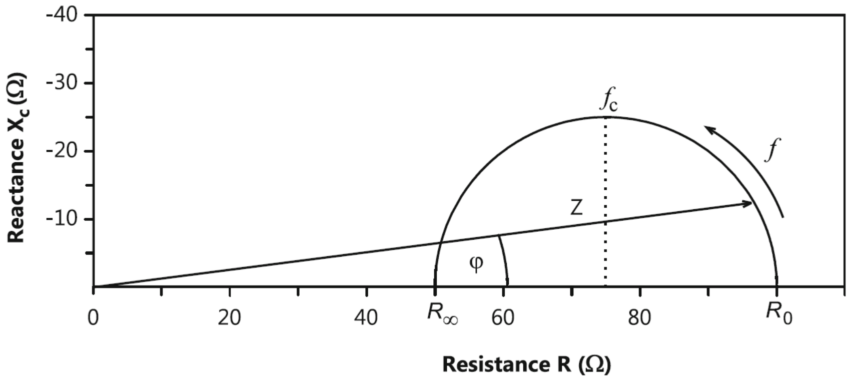
Basic concepts

- Tissue's electrical properties impact the injected current
  - Change in amplitude ➔ resistive components (free water, connective tissue, fat)
  - Time lag ➔ capacitive/reactive components (cell membranes)
- Complex impedance ➔ resistive + capacitive
  - $Z = R + jX$ (resistance (R), reactance (X))
  - Magnitude $|Z| = \sqrt{R^2 + X_c^2}$
  - Phase angle $\varphi = \tan^{-1}\left(\frac{X_c}{R}\right)$



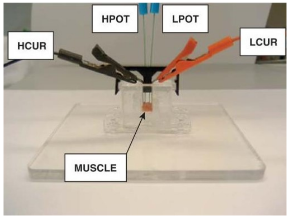
Electrical Equivalent Circuits of Biological Tissue

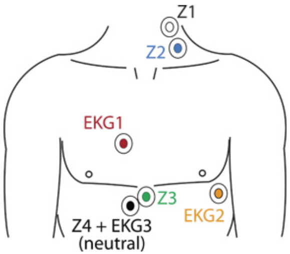


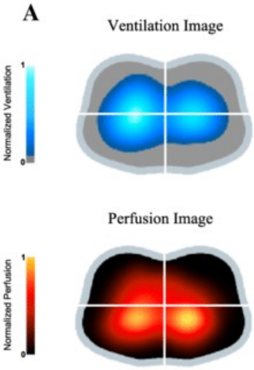


Biomedical applications

- **Tissue level** investigations
- Tomography (cardiac output, lung ventilation/perfusion, abdominal adipose tissue)
- Fluid distribution - hydration, dialysis....
- **Body composition** => BIA (BIS)







BIA

- Non-invasive, nonirradiant, cost-effective, and portable for the assessment of lean mass [1]

Limitations

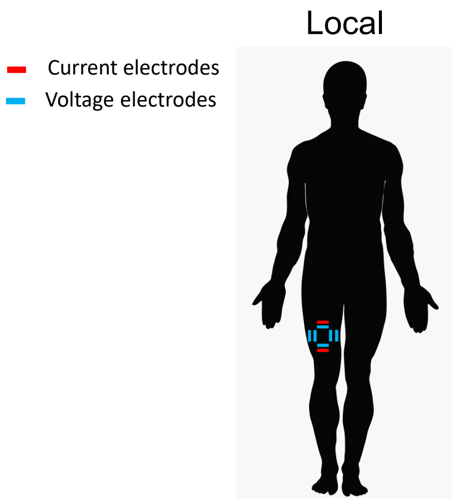
- Prediction algorythm are statistically derived with and highly sample specific [1]
- Mostly single frequency measurement (50 kHz) (prediction based on extracellular space)
- Oversimplification of body geometry => cylinder
- Muscle tissue assumed to be isotropic

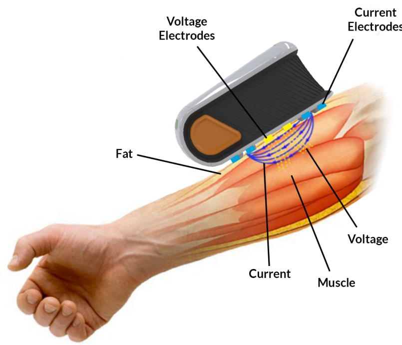
➔ Poor ability to accurately estimate lean regional muscle volume

[1] Janssen et al. 2018, J Cachexia Sarcopenia Muscle [2] Salinari et al. 2002, Am J Physiol Endocrinol Metab

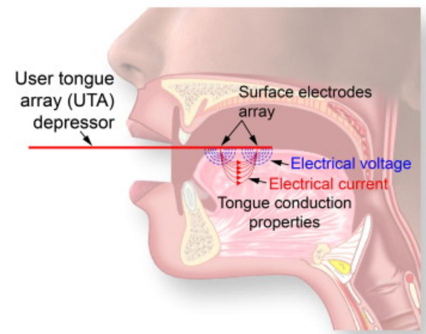
Local approaches

Electrical Impedance Myography (EIM)





[1]



[2]

➔ May provide information regarding pathophysiological processes and change over time using a set of non-specific parameters

➔ Do not provide estimates of regional estimate of skeletal muscle volume

[1] Rutkove et al. 2019, Cold Spring Harb Perspect Med

[2] Luo et al. 2021, Clinical Neurophysiology

Biophysical explanatory models for ovrcoming main BIA drawbacks

Geometrical models based on differential measurements

- Estimating lean muscle volume and for reconstructing the profile of the muscle cross-sectional area along the limb [1]
- Good consistency against DXA and MRI in healthy subjects

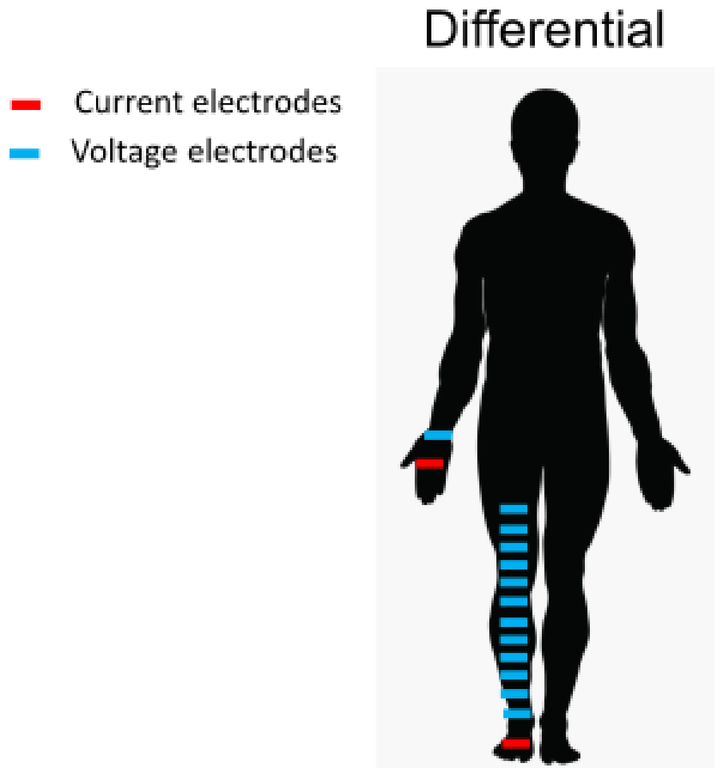
➔ Muscle conductivity constant ?

➔ Applicable with severe wasting and degenerative changes (fatty infiltration)

➔ Applicable in shorter segments (thigh)

➔ Reliability ?

[1] Salinari et al. 2003, J Appl Physiol
[2] Stahn et al. 2007, J Appl Physiol



Participants and study design

- 20 healthy participants
  - 8 women, 12 men
- 20 patients with idiopathic inflammatory myopathies
  - 10 women, 10 men
- MRI
- Differential impedance measurements

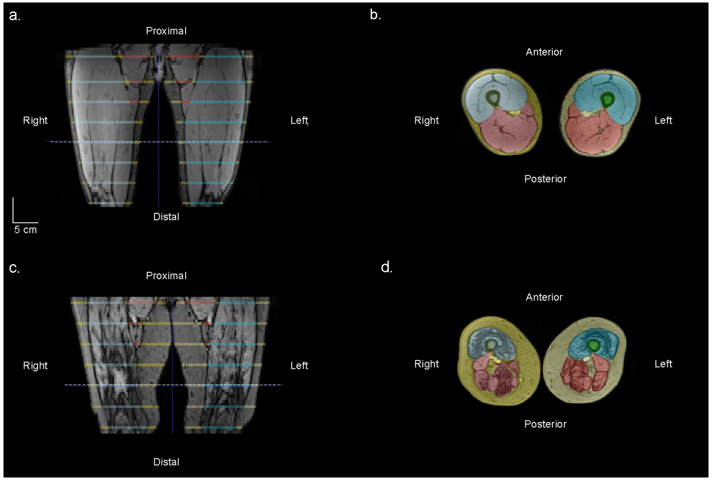
MRI

Acquisition & processing

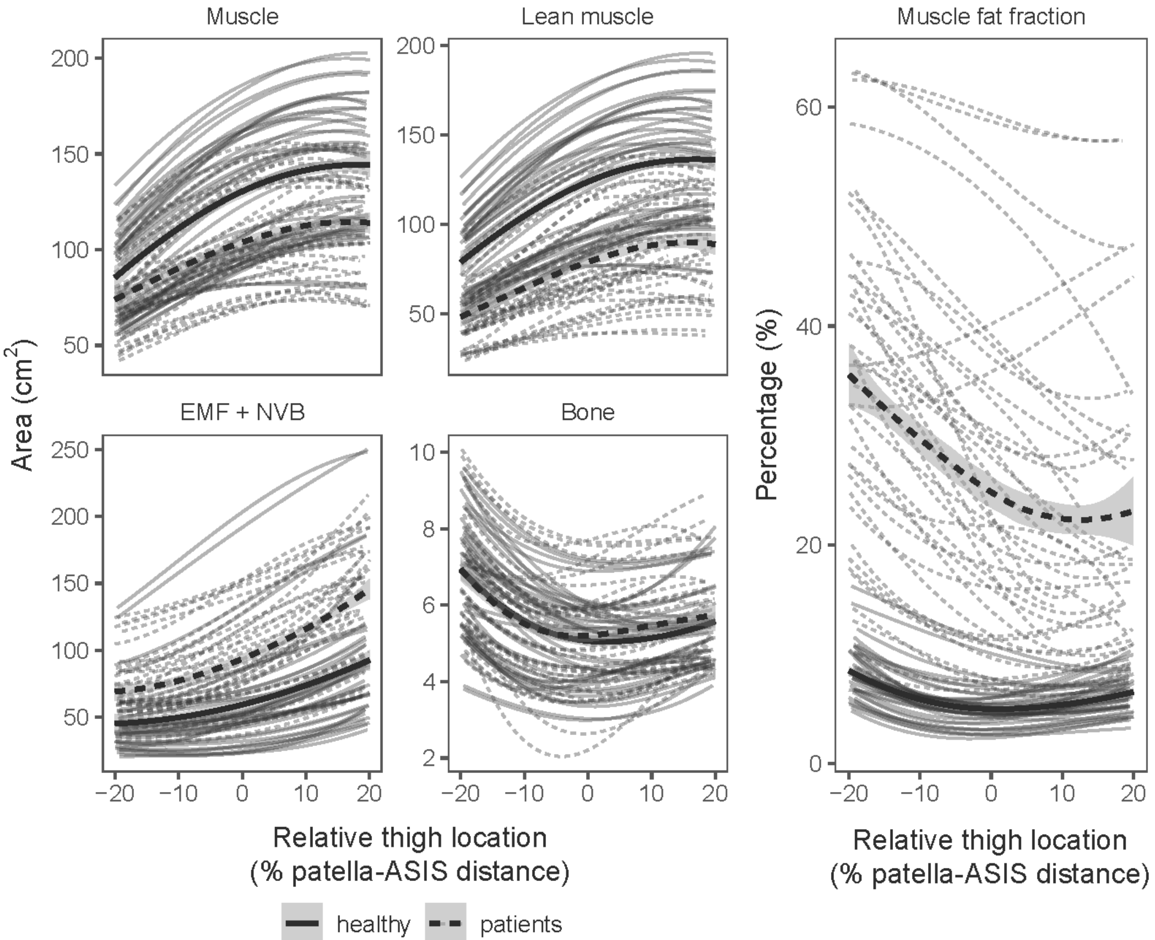
- 3D gradient echo sequence
- 3-point Dixon reconstruction ➔ Water and fat maps

Analysis - segmentation

- Whole muscle (CSA_{MRI})
- Lean muscle ($lCSA_{MRI}$)
- Bone
- Subcutaneous tissue & neurovascular bundles

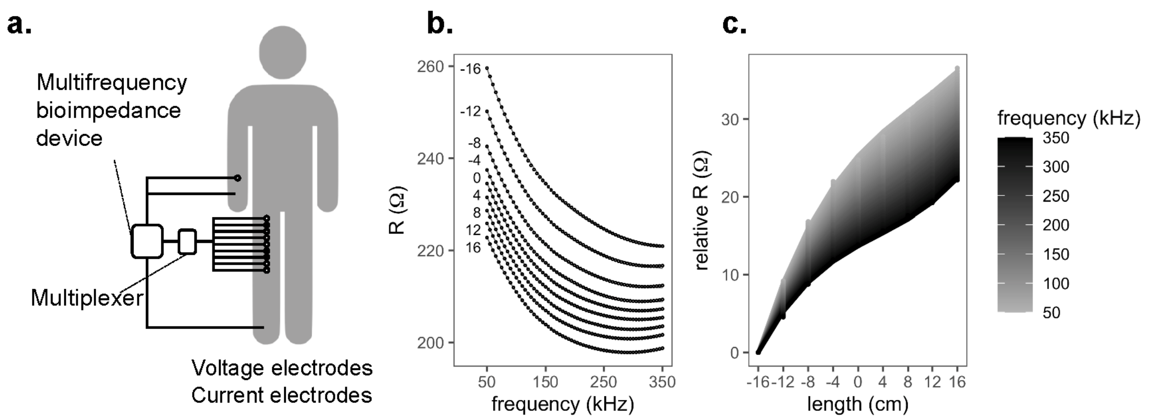


MRI data



Muscle
Lean muscle
Muscle fat fraction
EMF + NVB
Bone
Area (cm²)
Percentage (%)
Relative thigh location
(% patella-ASIS distance)
Relative thigh location
(% patella-ASIS distance)
healthy
patients

Seial bioelectrical impedance measurements

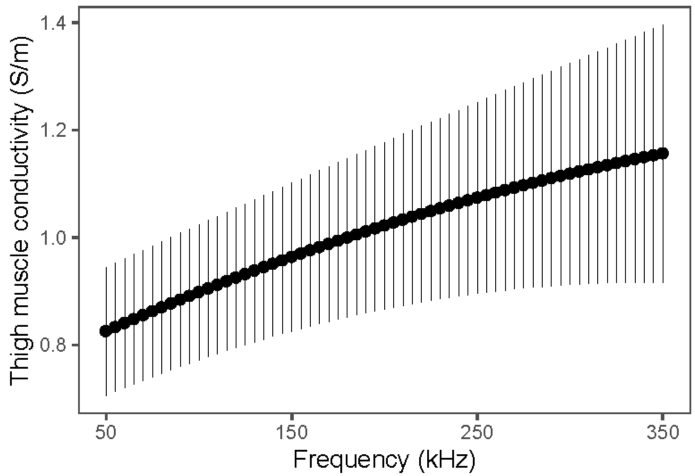


- Apparatus
  - Multifrequency impedance device
  - Arduino driven multiplexer
  - Custom software
- Acquisition
  - After 10-min supine to control fluid shifts
  - Skin preparation
  - Both sides

Seial bioelectrical impedance analysis

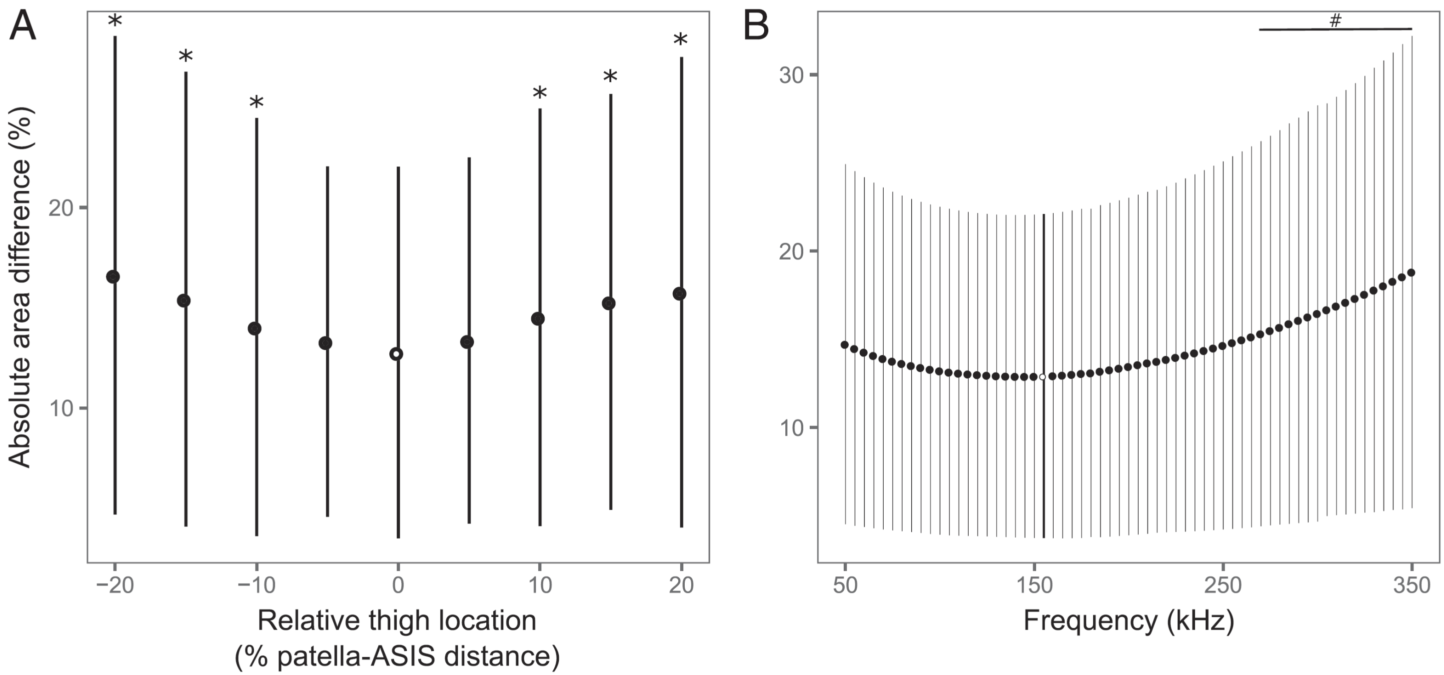
- Purely resistive model
- Computation of thigh muscle conductivity:
  - Right thigh of randomly chosen healthy participants (n = 10, 5 men and 5 women)
  - $\sigma = \frac{1}{\left(\frac{\partial R}{\partial z}\right) \cdot lCSA_{MRI}}$
- Lean CSA estimates ➔ $lCSA_{BIA} = \frac{1}{\left(\frac{\partial R}{\partial z}\right) \cdot \sigma}$

Conductivity constant



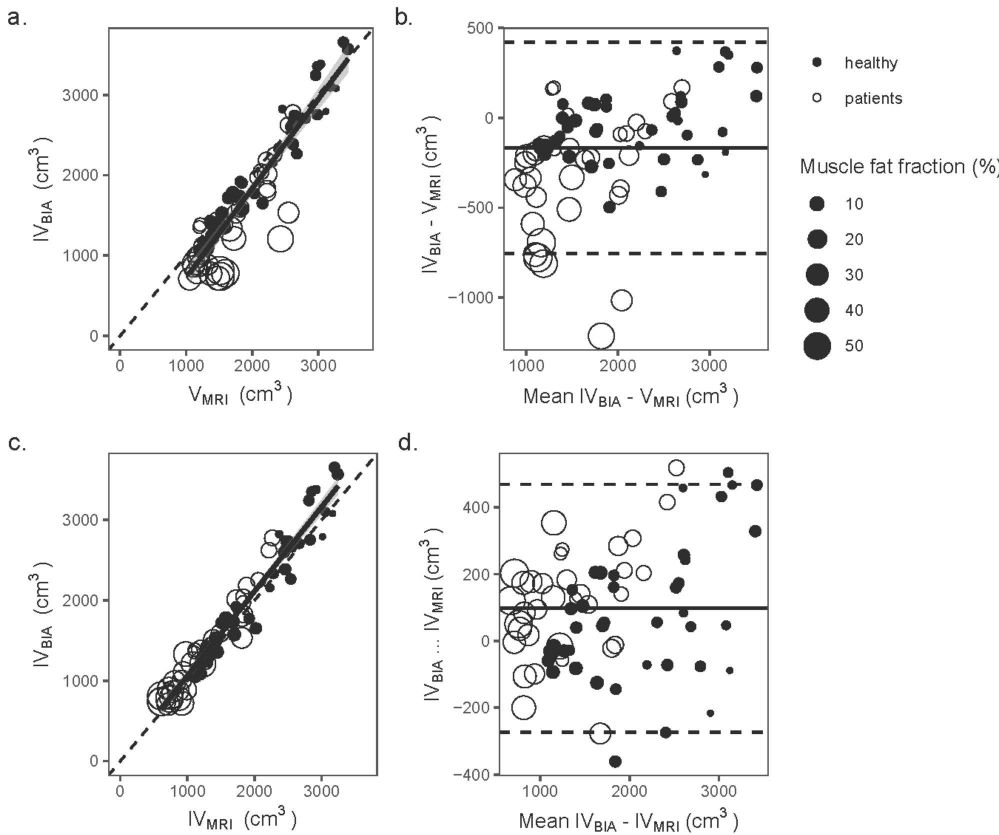
Ranged from 0.82 S/m at 50 kHz to 1.16 S/m at 350 kHz

Effect of location and frequency on ΔICSA



- Difference significantly <10 and >10 %
- Difference significantly larger ≥270 kHz

Agreement with MRI



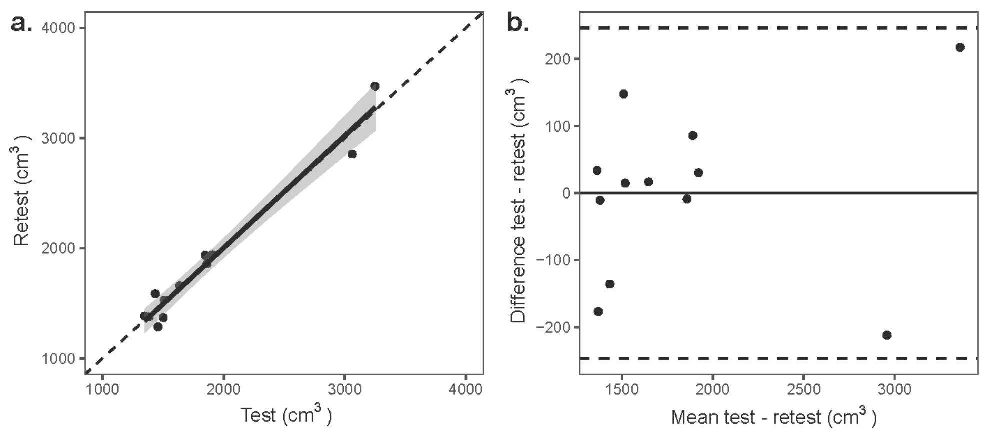
Bachasson et. al 2020, J Cachexia Sarcopenia Muscle PMID: 33377299

Agreement with MRI

Group	IV_{MRI} (cm^3)	IV_{BIA} (cm^3)	*P* value	DIM (cm^3) [95% CI]	SEM (cm^3) [95% CI]	SEM (%) [95% CI]	ICC [95% CI]
Healthy	2090 ± 683	2171 ± 773	<0.05	80 [14, 146]	145 [119, 187]	6.2 [5.1, 8.0]	0.95 [0.92, 0.97]
Patients[a]	1255 ± 494	1373 ± 570	<0.001	118 [59, 176]	118 [95, 156]	9.4 [7.6, 12.4]	0.93 [0.88, 0.96]

➔ Strong agreement of lean muscle volume estimates including in patients with severe muscle wasting and fatty degeneration

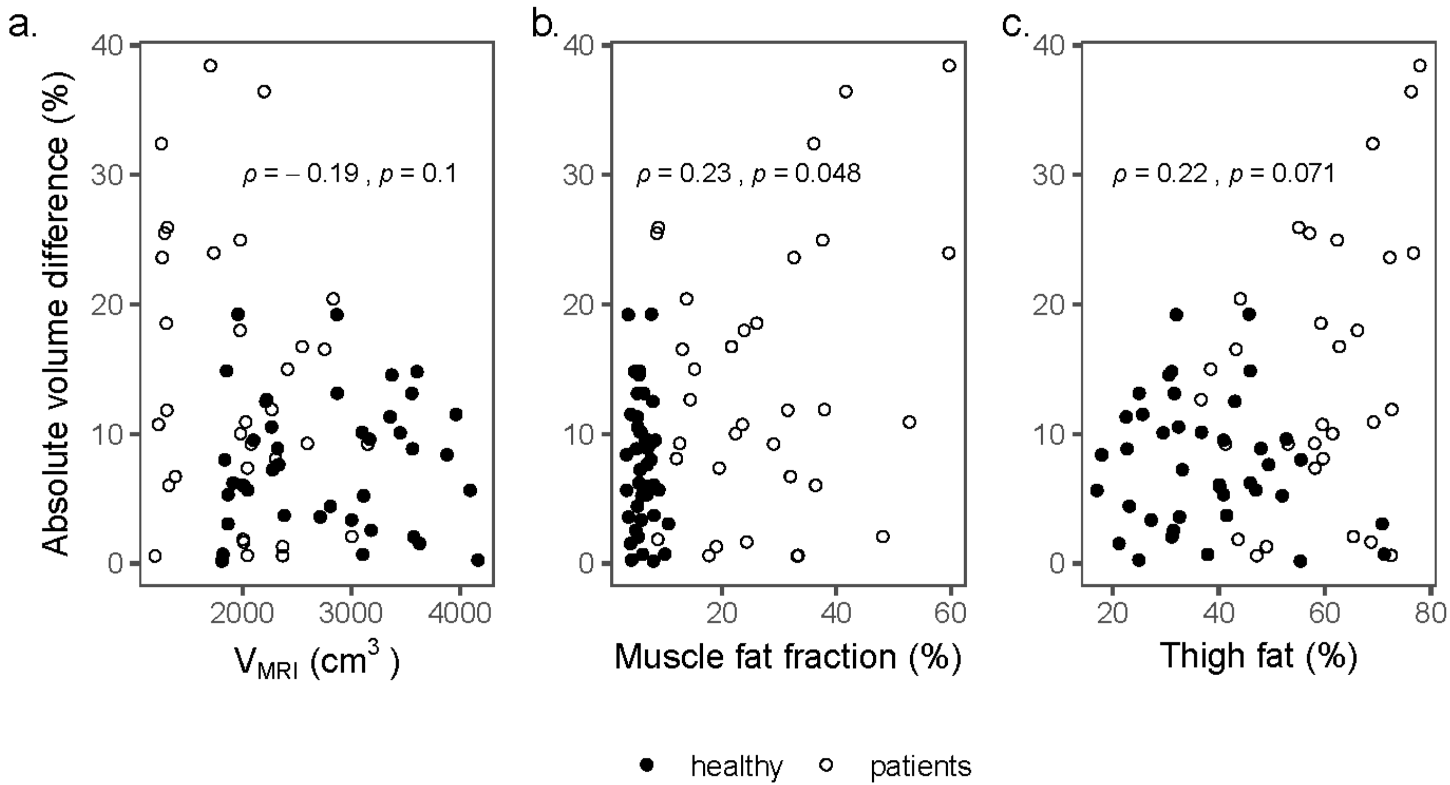
Reliability



	Location (%)	Day 1 (cm^3)	Day 2 (cm^3)	*P* value	DIM (cm^3) [95% CI]	SEM (cm^3) [95% CI]	SEM (%) [95% CI]	ICC [95% CI]
Frequency (kHz)								
50[a,b]	—	1853 ± 560	1809 ± 569	0.124	−44 [−102, 14]	65 [46, 110]	4.1 [2.9, 6.9]	0.98 [0.96, 0.99]
100[a,b]	—	1842 ± 599	1815 ± 616	0.369	−26 [−88, 36]	69 [49, 117]	3.9 [2.8, 6.6]	0.99 [0.97, 1.00]
150[a,b]	—	1850 ± 636	1848 ± 660	0.943	−3 [−81, 75]	87 [62, 147]	4.5 [3.2, 7.6]	0.98 [0.96, 0.99]
200[a]	—	1882 ± 681	1905 ± 709	0.629	22 [−77, 122]	111 [78, 188]	5.5 [3.9, 9.3]	0.98 [0.94, 0.99]
250[a]	—	1943 ± 743	1992 ± 786	0.449	49 [−88, 185]	152 [108, 258]	7.2 [5.1, 12.2]	0.96 [0.90, 0.99]
300[a]	—	2040 ± 839	2122 ± 924	0.401	83 [−126, 291]	232 [164, 393]	10.1 [7.5, 17.9]	0.93 [0.83, 0.98]
350	—	2176 ± 998	2322 ± 1189	0.377	146 [−203, 495]	389 [275, 660]	18.2 [12.1, 30.3]	0.88 [0.70, 0.95]
n electrodes								
All	−20 to 20	1852 ± 640	1852 ± 664	0.997	0 [−80, 79]	88 [62, 150]	4.6 [3.2, 7.8]	0.98 [0.95, 0.99]
5	−15 to 15	1391 ± 488	1386 ± 476	0.915	−5 [−124, 112]	132 [93, 224]	11.9 [8.3, 20.1]	0.93 [0.82, 0.97]
3[c]	−7 to 7	636 ± 214	678 ± 230	0.404	41 [−64, 147]	117 [83, 200]	20.8 [14.7, 35.3]	0.73 [0.40, 0.89]

- Acceptable reliability with 5-electrodes measurements

Confounding effects ?



Perspectives

➔ Promising approach for baseline assessment and monitoring of regional muscle volume

- Ability to capture changes in lean regional muscle volume ?
  - Muscle diseases
  - Chronic disorders
  - Aging
  - Rehabilitation and **training**
- Increasing our dataset for the computation of the conductivity constants in thigh and other regions
- Investigating disease-induced changed conductivity/relative permittivity
- Development of a user-friendly technological solution

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All participants that volunteered for participating in these experiments

Thank you for your attention

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