First Congress

International Society of Diamagnetic Therapy

“Vagus nerve stimulation”

13th – 14th September 2024
Magna Graecia University - Catanzaro

Dr. biol. hum. Stephanie Otto
Dr. sc. hum. Marc N. Jarczok

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Cervical vagus nerve stimulation using CTU mega-20

A pioneering study

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Framework from identification to implementation

Need Identification

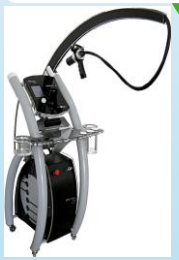
- Vagus nerve inhibition

Gap Analysis

- Analysing standard treatment options

CTU mega-20

- Identification of new treatment options
- Vagus stimulation

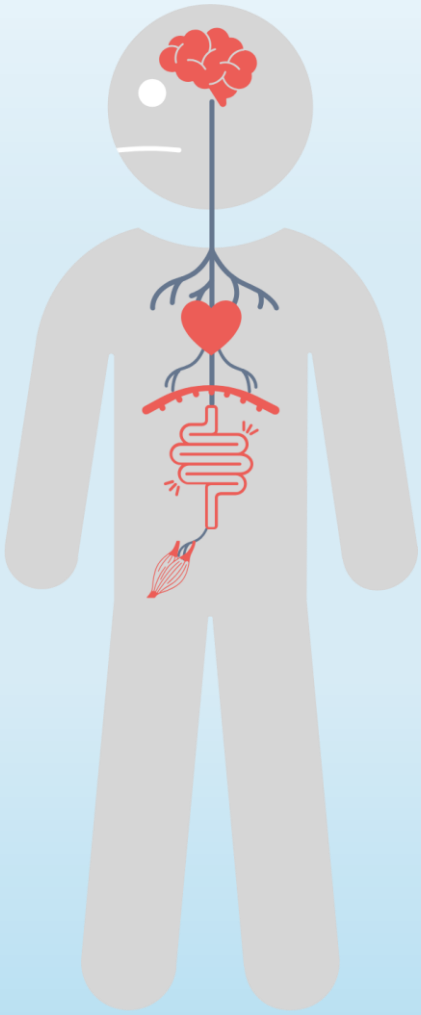


Evaluation

- Confirmatory study (healthy)
- Clinical study (cancer)

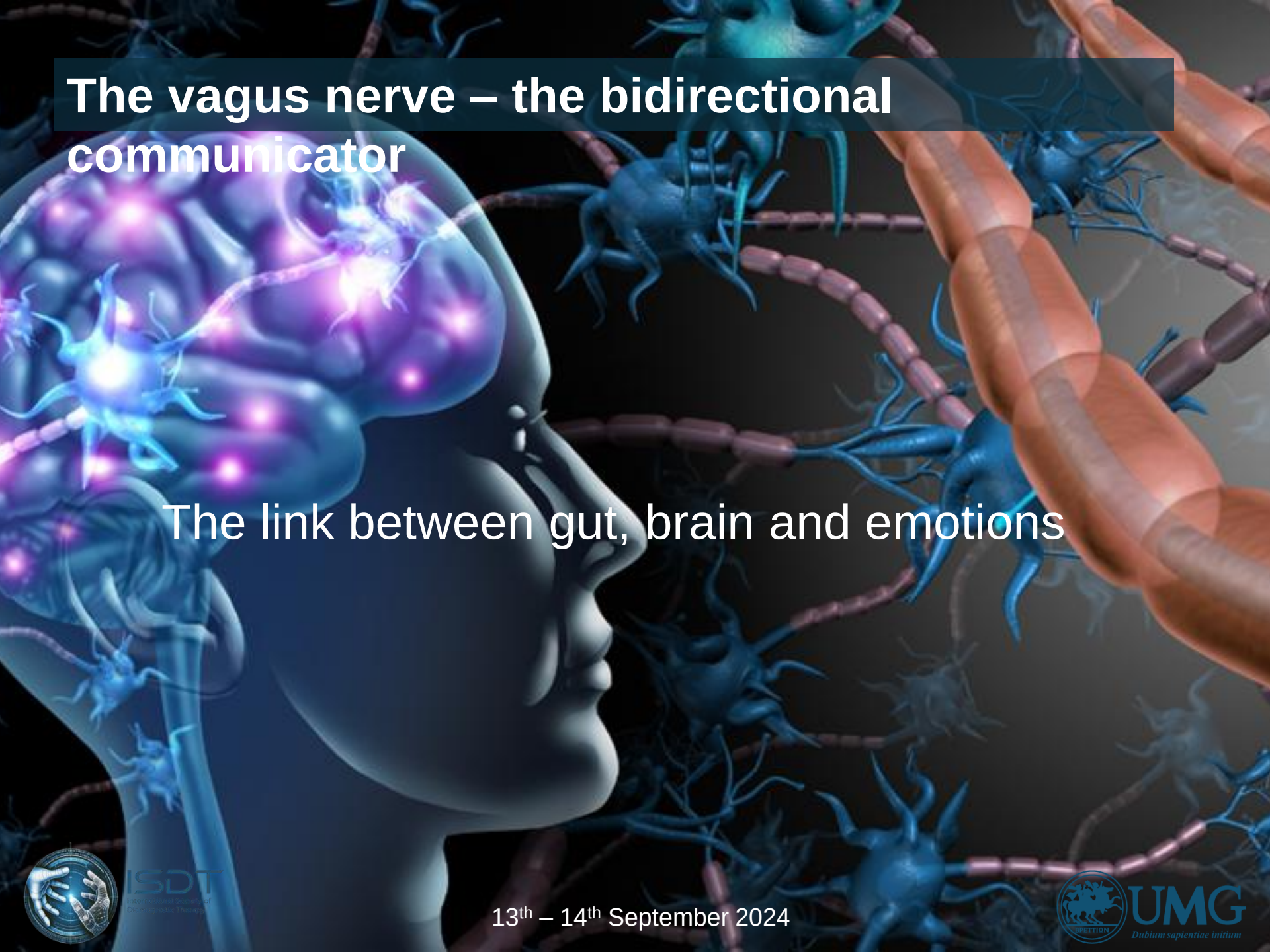
Key functions of the ANS

- ✓ Stress response
- ✓ Heart rate and blood pressure
- ✓ Digestion
- ✓ Respiratory function
- ✓ Body temperature regulation
- ✓ Pain



The Vagus Nerve

The vagus nerve – the bidirectional communicator



The link between gut, brain and emotions

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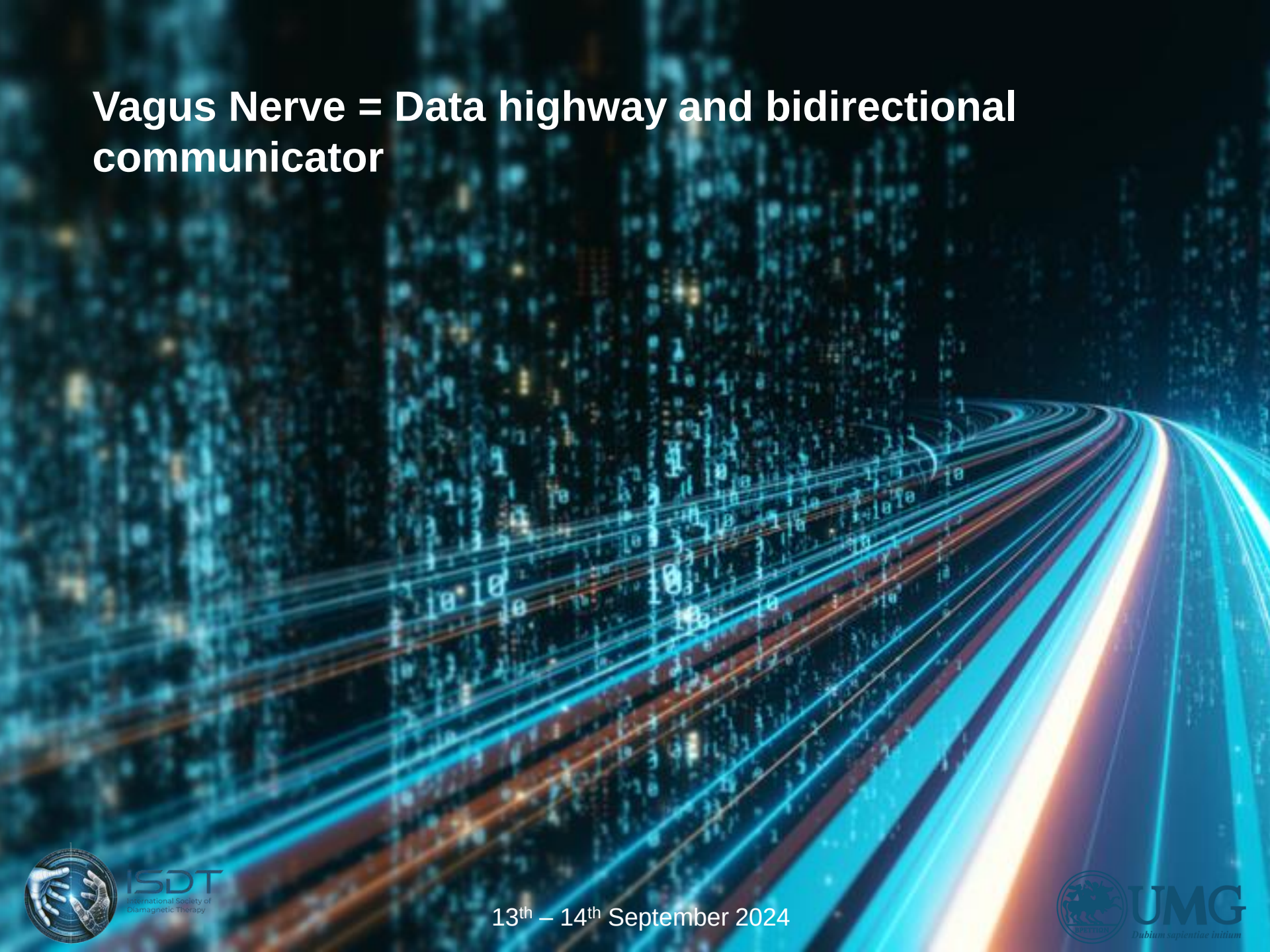
Vagus Nerve = Data highway and bidirectional communicator



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Vagus Nerve = Data highway and bidirectional communicator

- Sends electrical messages back and forth between the brain and the body
- Plays a key role in:
  - communicating changes in fascia to the brain
  - the processing of pain
- By stimulating it, we can target both, the brainstem and brain circuits, where pain is processed and controlled

Potential of VNS in cancer

- Oxidative stress reduction
- Inhibiting inflammation by:
  - regulating the hypothalamic–pituitary–axis (HPA) and release of corticosteroid by adrenal gland (afferent pathways)
  - cholinergic anti-inflammatory pathway (CAP) (efferent pathways)
  - suppression of the NF-kB pathway
  - stimulation of tumor-infiltrating lymphocytes
- Inhibition of sympathetic activity (decreased plasma level of TNF-α)
- Severity of chemotherapy induced peripheral neuropathy (CiPN) reduced
- Improvement of cancer-related fatigue, lymphopenia, and QoL

Abdullahi A et al. Cancer Med. 2023 Sep;12(18):19081-19090. doi: 10.1002/cam4.6466. Epub 2023 Aug 17. PMID: 37587897; PMCID: PMC10557911.

The Role of the Vagus Nerve in Cancer Prognosis: A Systematic and a Comprehensive Review.

Stimulation of the vagus nerve has therapeutic potential in oncology.

As the vagus nerve regulates HR, its stimulation results in an increased HRV and indirectly vital prognosis.

Indeed, the vagus nerve can inhibit oxidative stress, inflammation and excessive orthosympathetic activity.

De Couck M, Caers R, Spiegel D, Gidron Y. J Oncol. 2018 Jul 2;2018:1236787. doi: 10.1155/2018/1236787.

Increased yin-deficient symptoms and aggravated autonomic nervous system function in patients with metastatic cancer.

HRV in patients with metastatic cancer was lower than in patients without metastasis, and an increased HRV correlates with a better vital prognosis of cancer patients, while a high resting heart rate has been shown to be predictive of cancer mortality.

Lin SC, Chen MF. J Altern Complement Med. 2010 Oct;16(10):1059-63. doi: 10.1089/acm.2009.0487. Epub 2010 Sep 28.

Gidron Y et al. (2018) examined the relationship between a new vagal neuroimmunomodulation (NIM) index and survival in fatal cancers. https://doi.org/10.1155/2018/4874193

Case report: 68 ys, CMML (07/20), post allo HSCT (06/22), CR (12/22), COVID-19 (02/2020)

- Emergency presentation: progressive gait instability, tingling paresthesia (left foot) for 5 days, pain, fall event, blurred vision, dizziness
- aGvHD intestine/skin

  -> prednisolone (2022/06), 0,5 mg/kg body weight
- Reactivated cGvHD (intestine, liver)

  -> PDN 1 mg/kg, Ruxolitinib (2023/02)
- Paraparesis of the legs, PDN + CsA + HD-Ig + Rituximab

  cGvHD of CNS? Or chronic muscle GVHD?

Vagus nerve stimulation by cupping, breathing, eye movement, vibration,…

Post Neurological rehabilitation

… one year later

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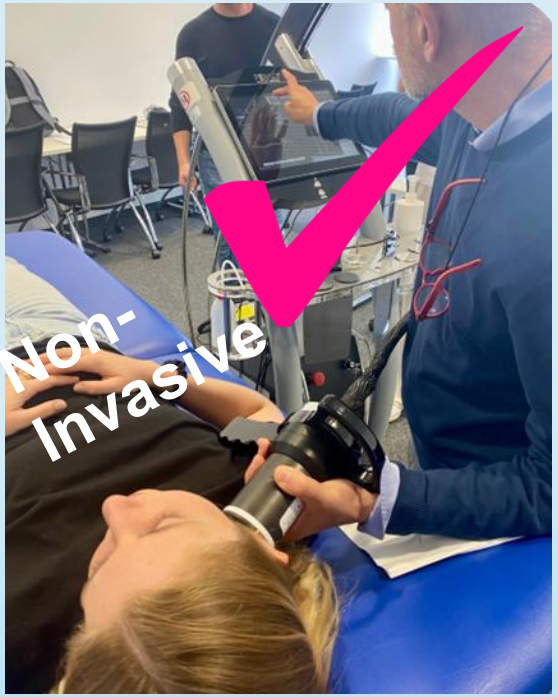
Bioelectronic Medicine: From Preclinical Studies on the Inflammatory Reflex to New Approaches in Disease Diagnosis and Treatment

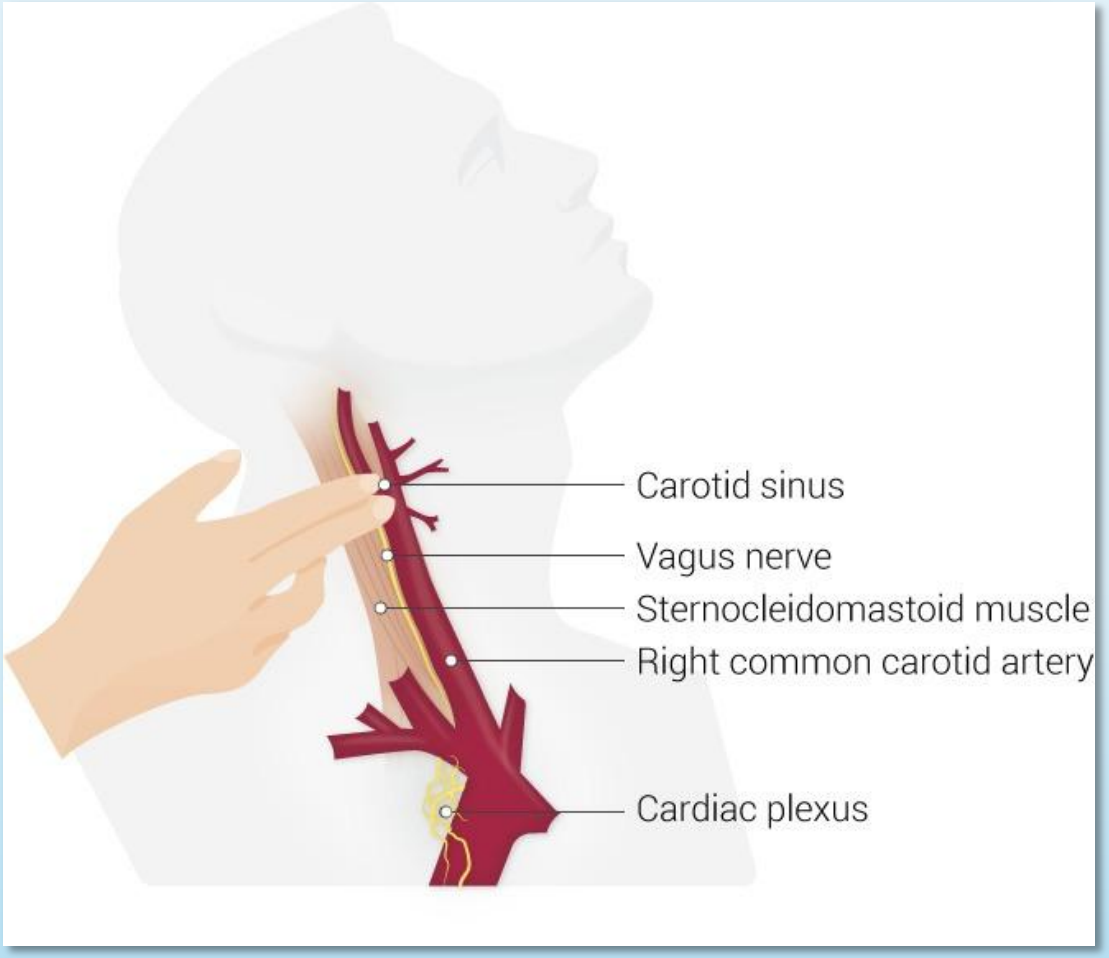
Electric rechargeable neurostimulation device

Diamagnetic VNS: dmVNS

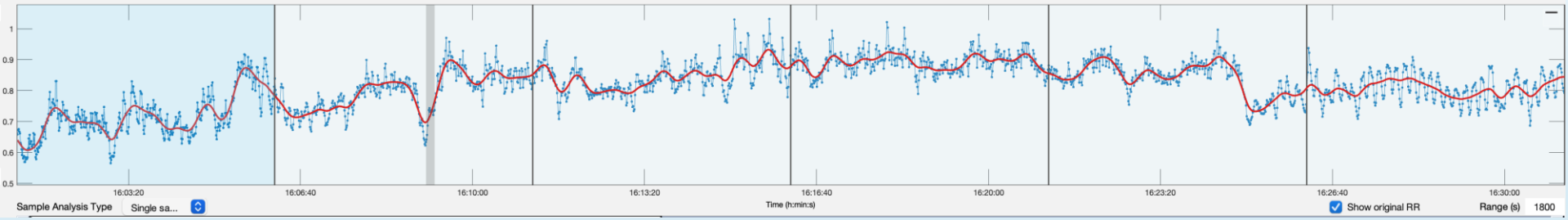


Reijmen E et al. Immunol Lett. 2018 Oct;202:38-43. doi: 10.1016/j.imlet.2018.07.006. Epub 2018 Aug 2. PMID: 30077536.

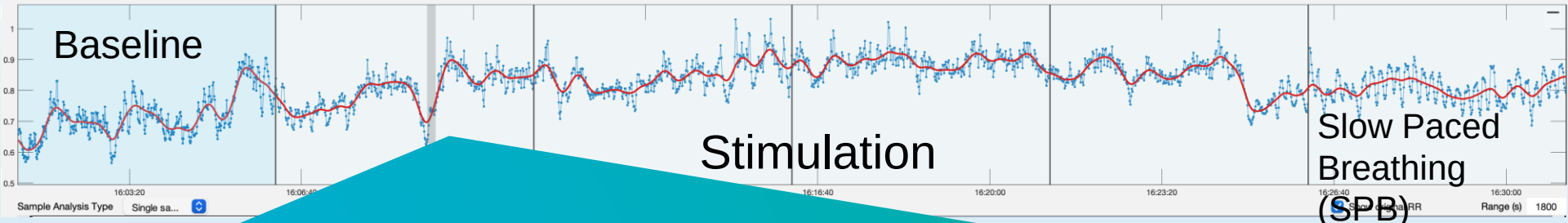
Vagus nerve stimulation with CTU mega-20 to balance SNS and PNS

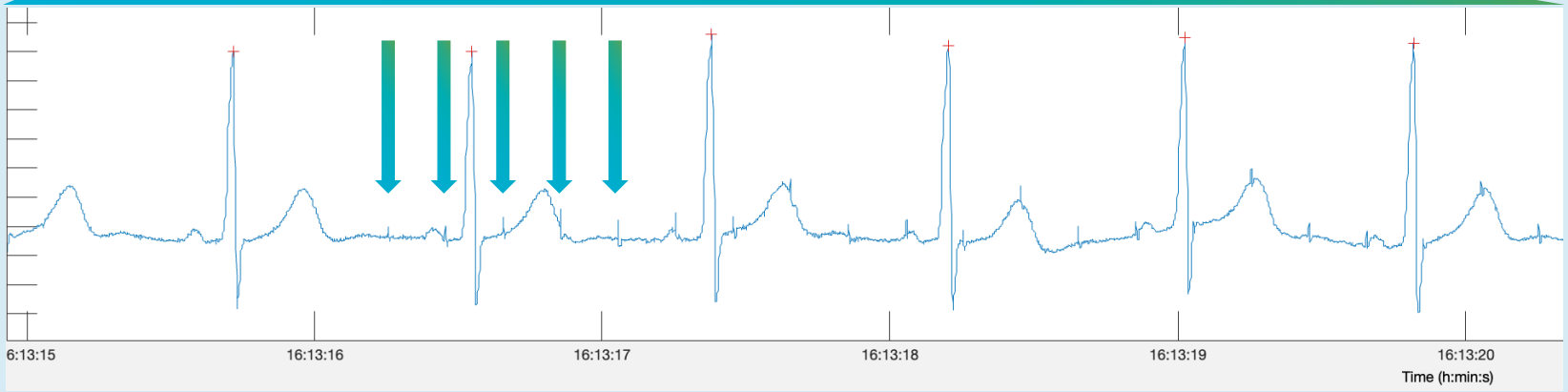


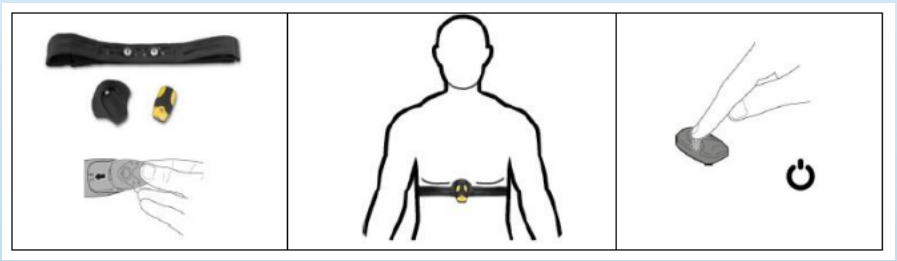
orldwide first attempt right side Cervical VNS using CTU mega-2



Vagus nerve stimulation with CTU mega-20







Kubios HRV Premium Scientific Software 3.5.0

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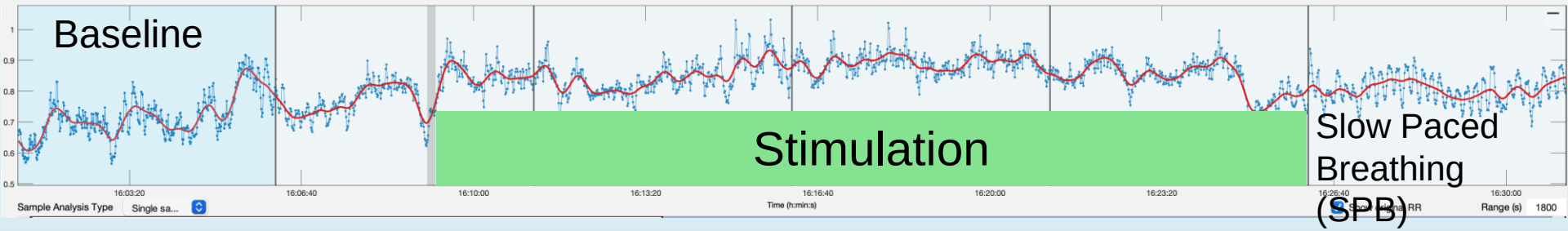
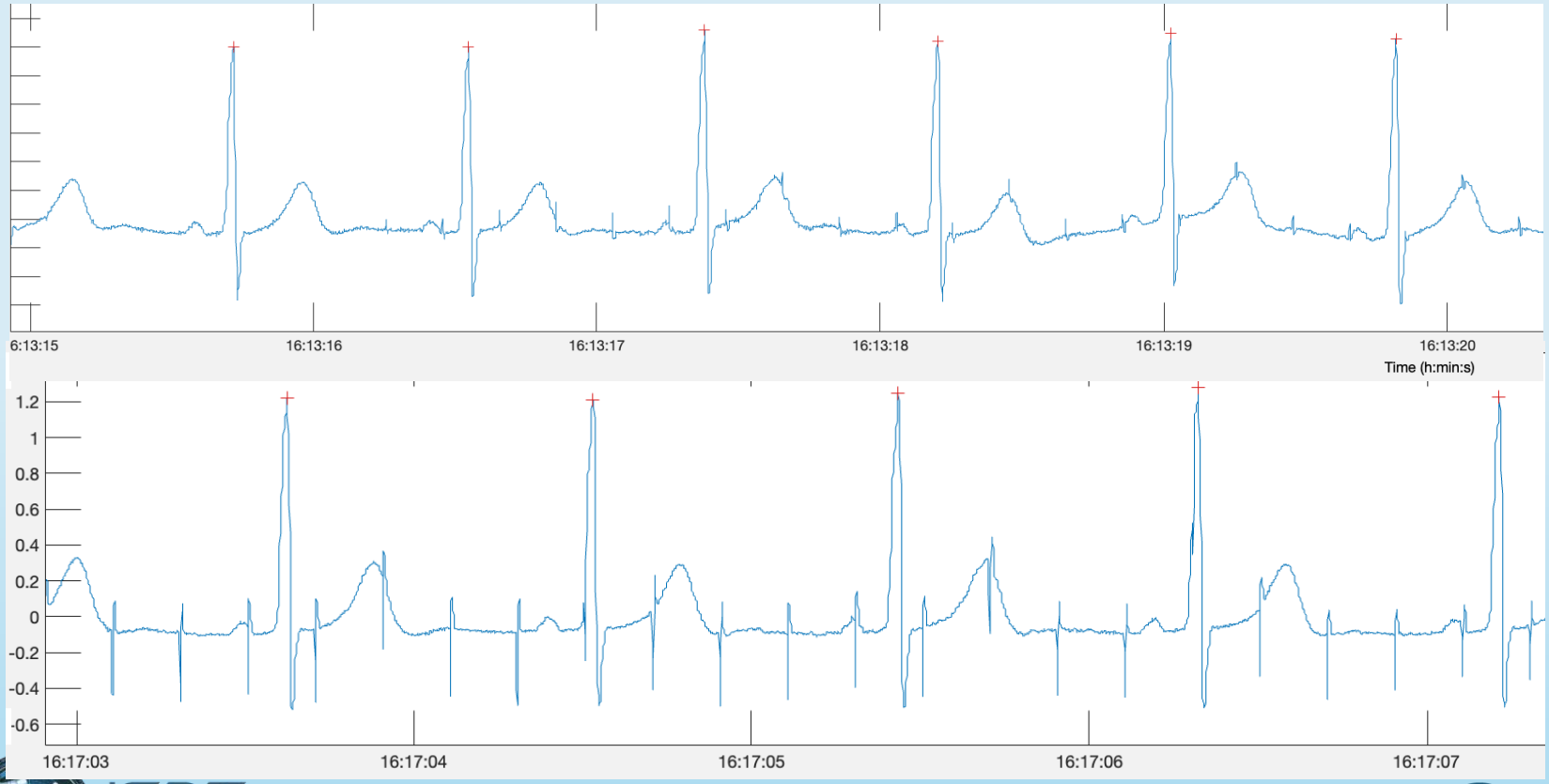
Vagus nerve stimulation with CTU mega-20





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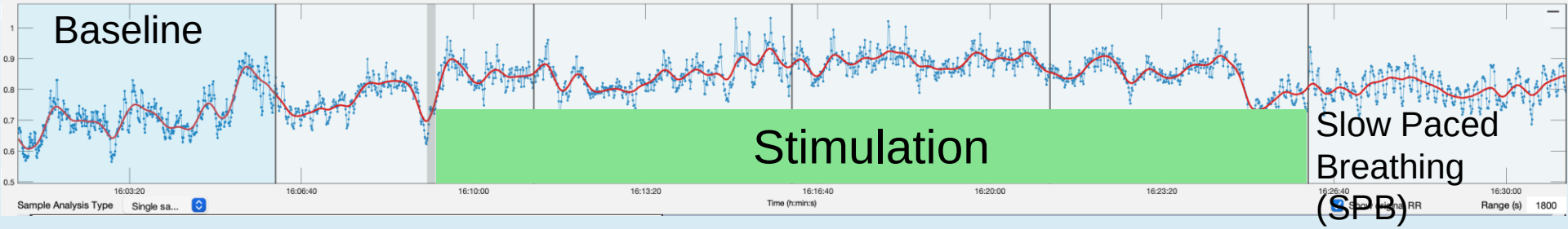
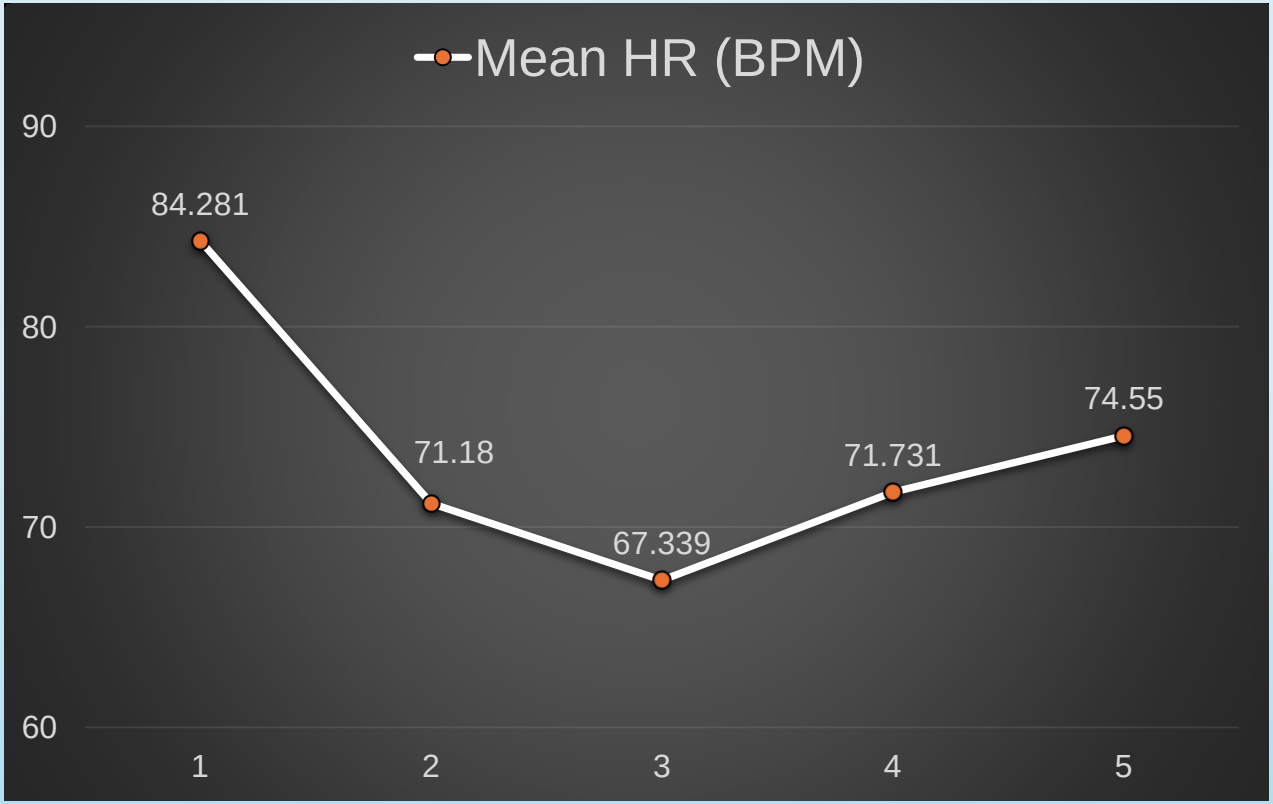
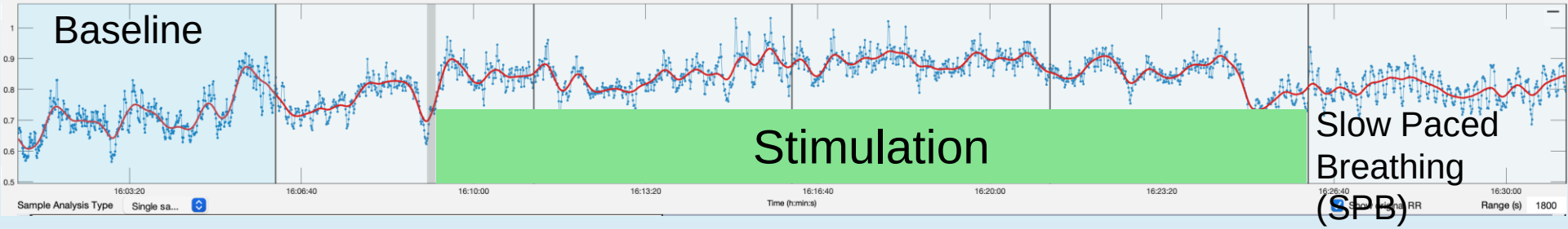
Vagus nerve stimulation with CTU mega-20

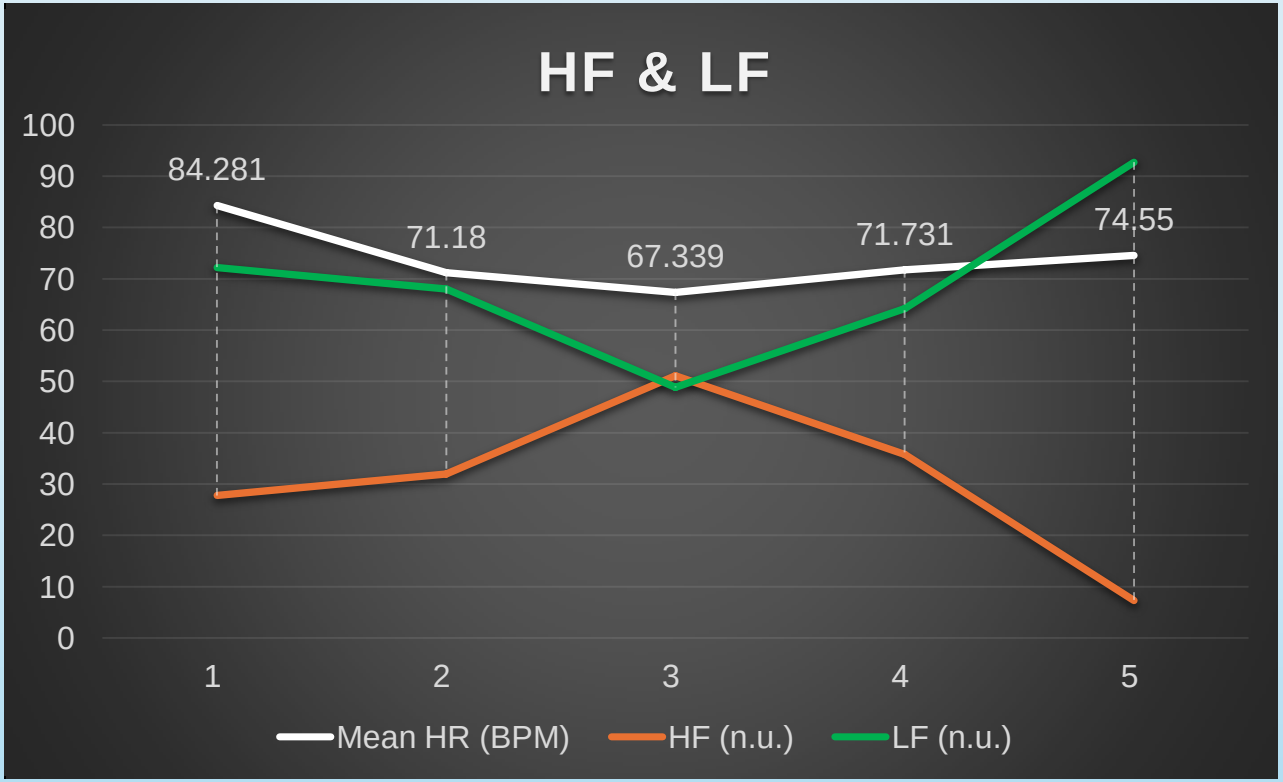


Right side stimulation using different settings, each 5 minute
With 2-minute pause

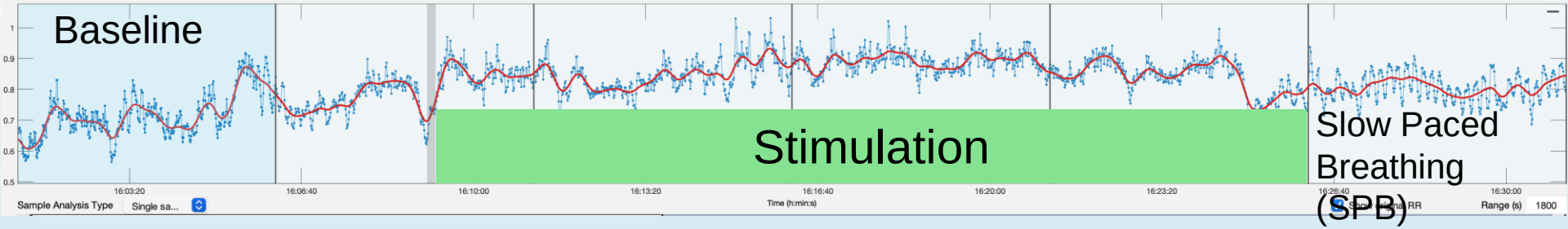


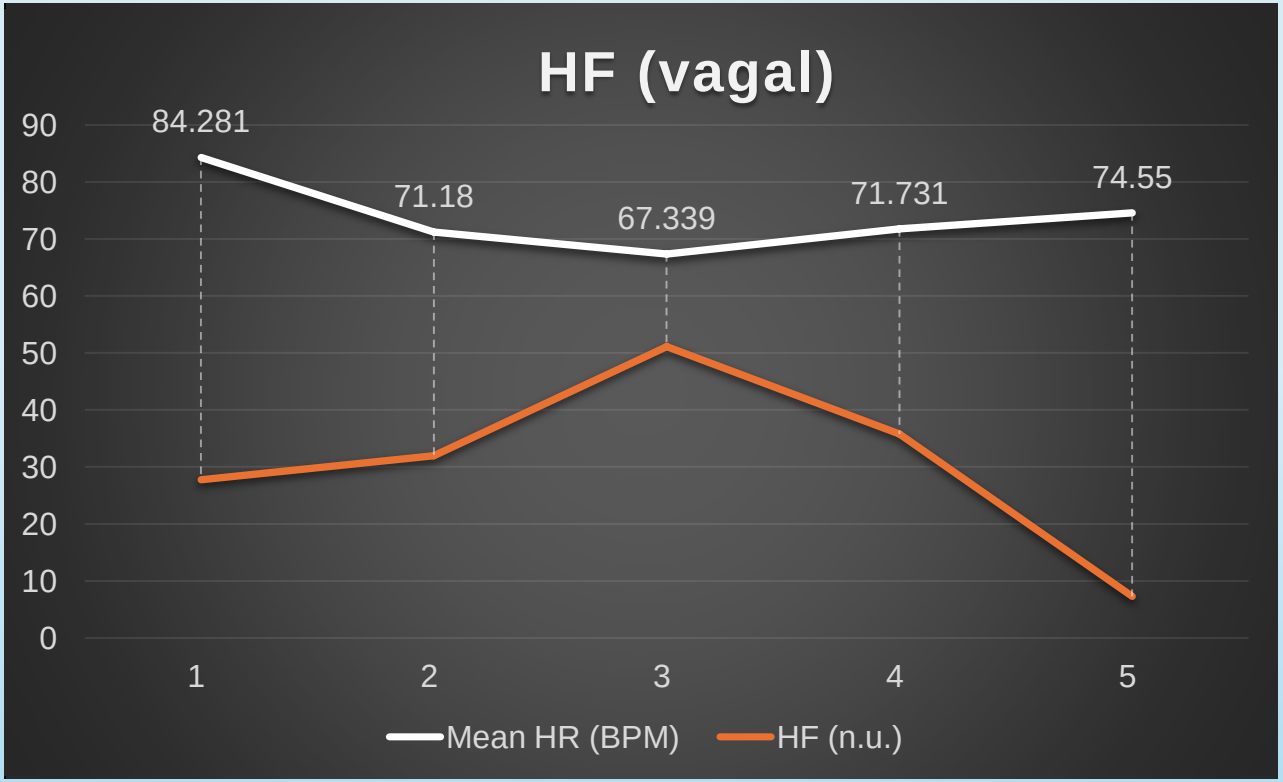
Vagus nerve stimulation with CTU mega-20





Vagus nerve stimulation with CTU mega-20

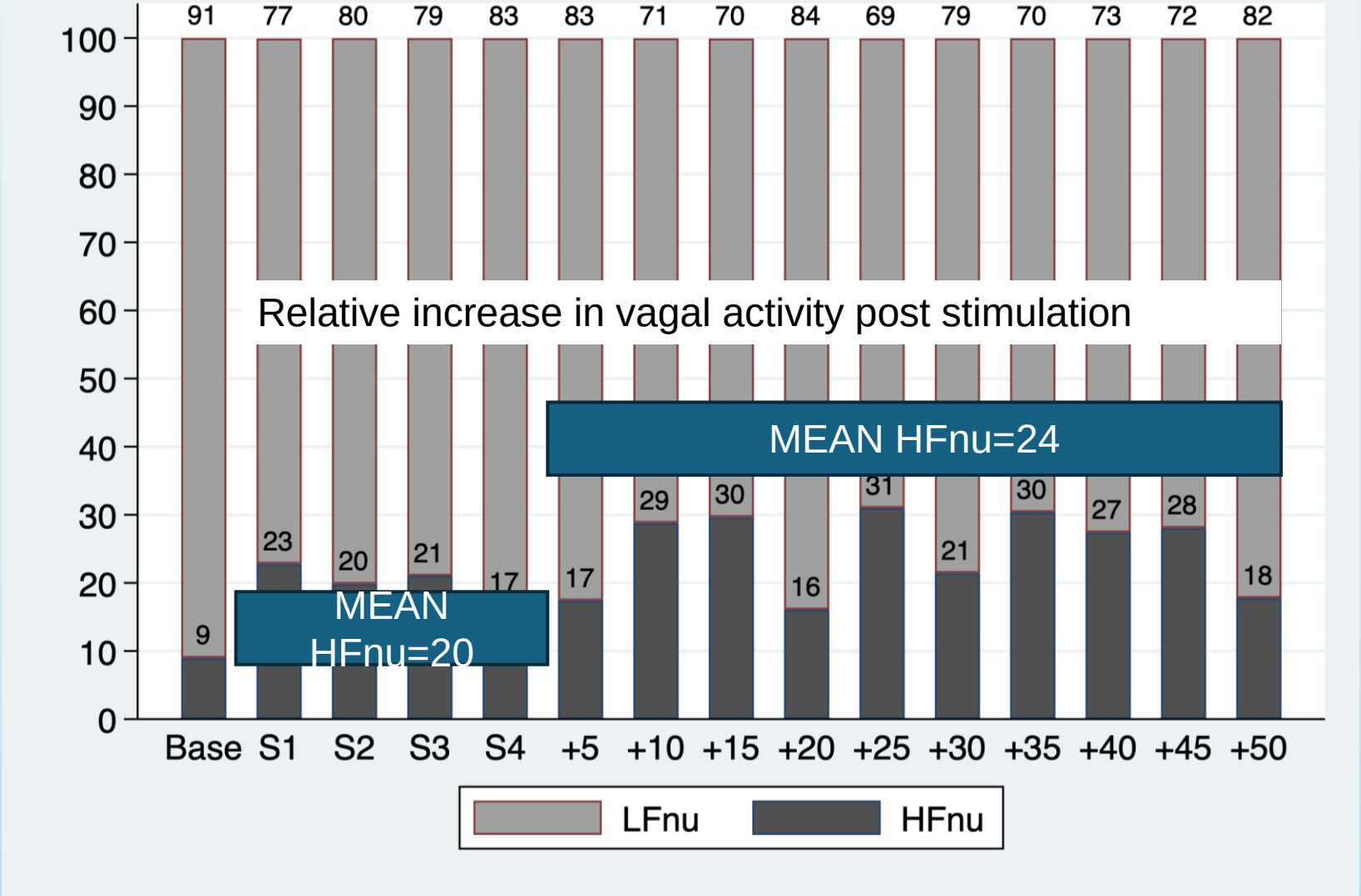




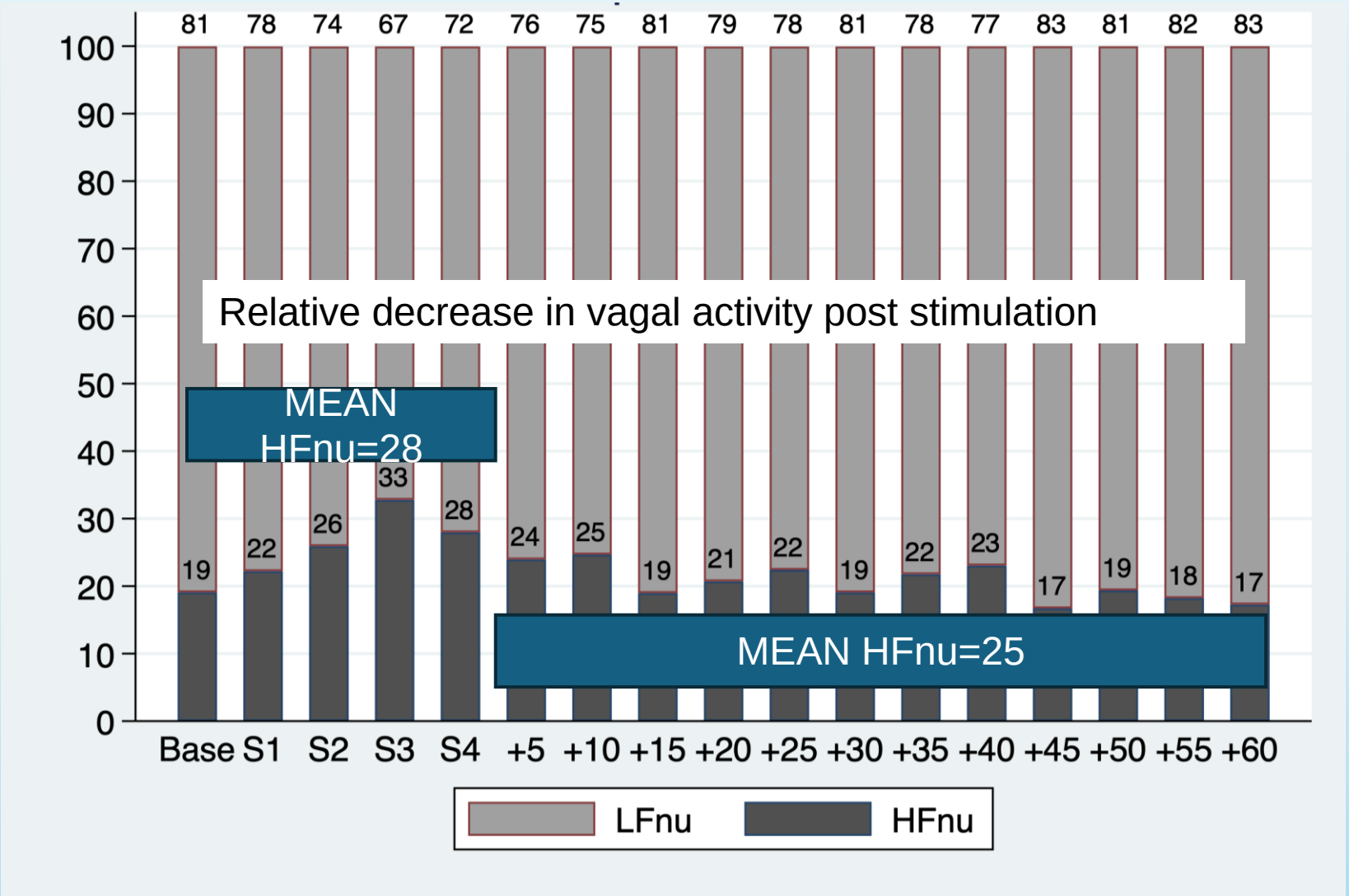
Question:
Do we achieve efferent effects / peripheral effects with CTU mega-20 vagus nerve stimulation?

Answer:
Yes, representative organ of the heart, peripheral physiological changes visible through stimulation in healthy individuals (exploratory)

Experimental testing II (Male 43)



Experimental testing II (Female 57)



Question:
Will we observe lasting effects after 20 minutes of stimulation using Right side 90/40

Answer:
Inconclusive results, need more experimental testing with more males and females.

Next steps:
Confirmatory study, in healthy subjects (crossover randomized in Sham and mVNS) 30 participants.
Add on: Changes in immune cells / activity (see upcoming slides)

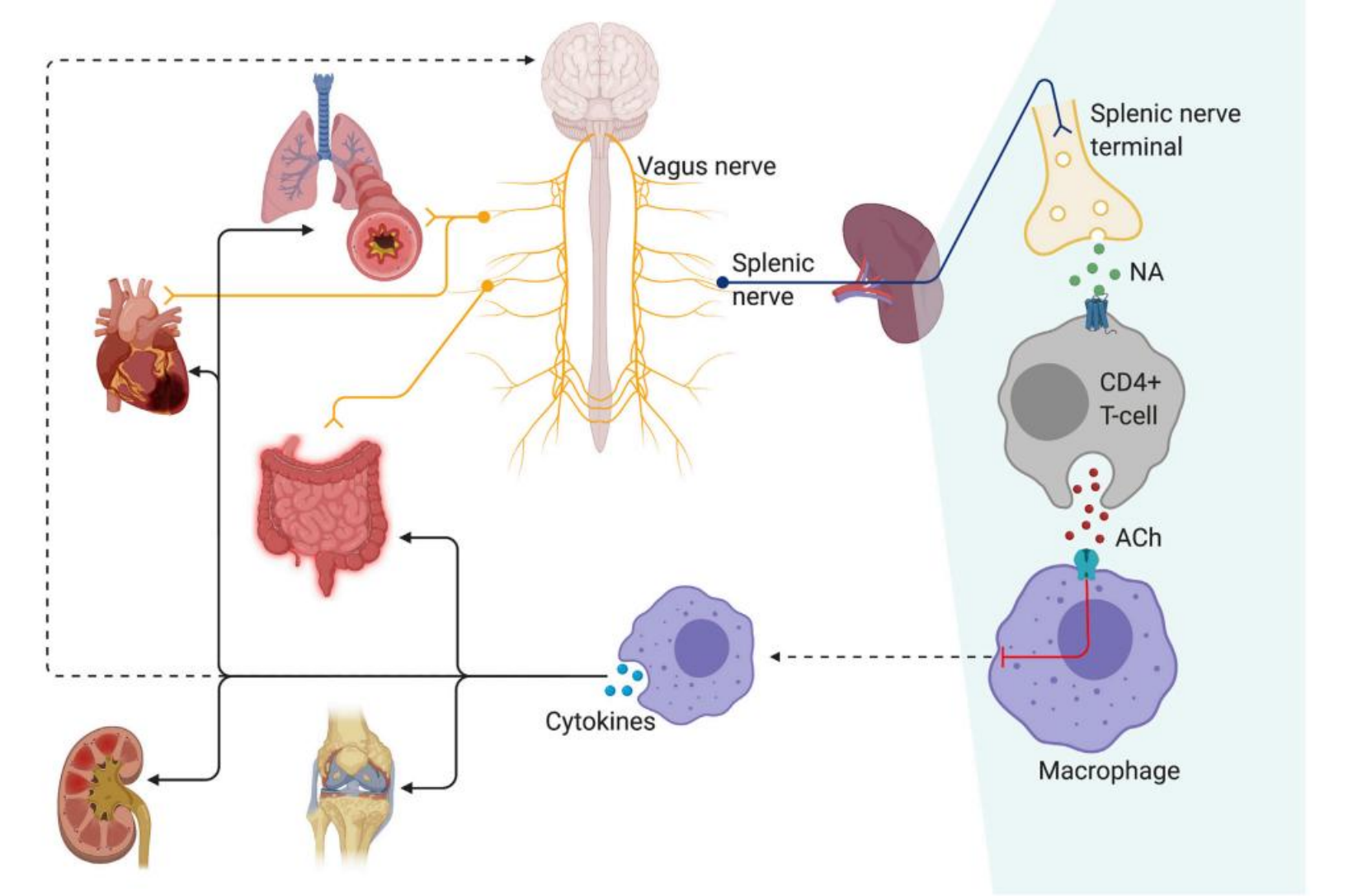
Open Questions

- Why do we see a decrease in absolute power during stimulation, but a relative shift towards HF (our aim)
- During SPB in the BeatCOVID study, we observe an overall increase in absolute values, mostly due to an increase in LF (as expected under SPB). Relatively, we also see a decrease in HF (as expected under SPB).
- The Area of stimulation is rather large, and as of now, more “power” and deeper stimulation seem to have more “success” in changes. It is unclear if , anatomically spoken, it is possible to get a nerve stimulated when magnetic waves are hitting the “wire” / axione, not the beginning or end where the terminals are (synapses).
- So, yes, we see changes in HRV under stimulation, but we do not know right now how this is exactly happening

Next question:

Does stimulation of the vagus nerve via *CTU mega 20* modulate immune cell function (T-cells) in the spleen?

Cholinergic anti-inflammatory pathway



Kelly MJ et al. Cell Rep Med. 2022 Jul 19;3(7):100696. doi: 10.1016/j.xcrm.2022.100696

Derivation:

- The efferent signals generated in the vagus nerve are transmitted via the celiac ganglion to the spleen to acetylcholine-producing (ChAT+) T cells.
- This acetylcholine, released under the control of the vagus nerve, mediated by catecholamine release from the splenic nerve, interacts with α7nAChR on macrophages and other immune cells.
- Acetylcholine decreases cytokine production by macrophages in a manner dependent on the nicotinic acetylcholine receptor α7 subunit (α7nAChR).
- The efferent signals generated in the vagus nerve are transmitted to acetylcholine-producing (ChAT+) T cells via the celiac ganglion to the spleen.
- Acetylcholine attenuates cytokine production by macrophages depending on the nicotinic acetylcholine receptor subunit a7 (a7nAChR).

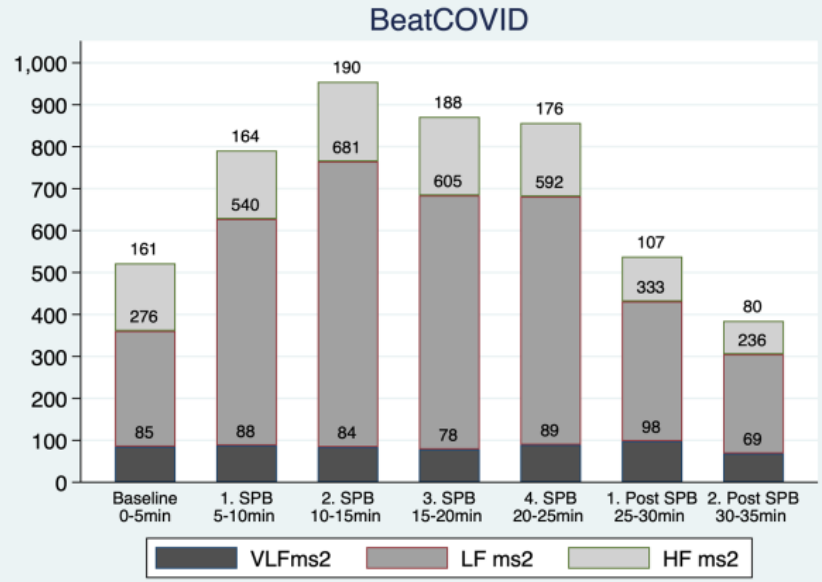
Verification:

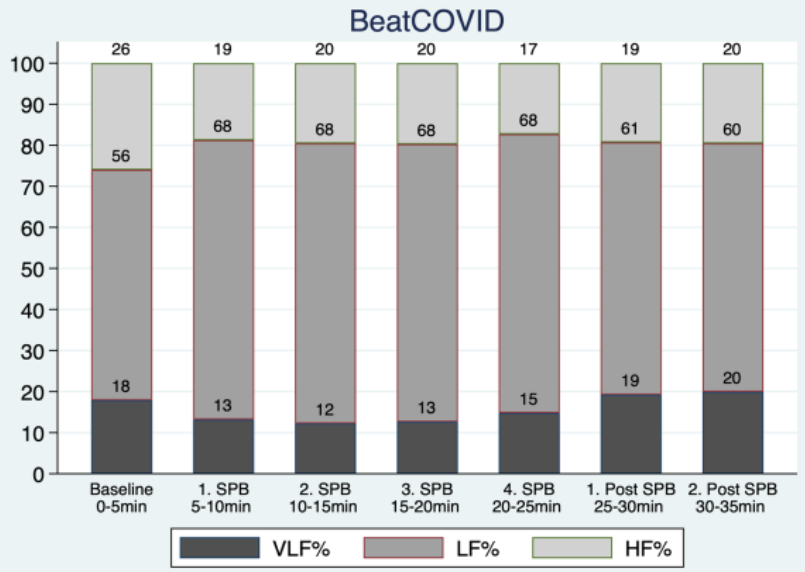
- Cell collection and further processing (extraction of pronounced increase in the number of peripheral blood mononuclear cells (PBMCs) and plasma interleukin 6 (IL-6) TNFα and CRP concentrations) by TA before & after stimulation, time points 0, +20 (directly after stimulation) +30 +60 +90 + 120 +150 (7 MTPs).
- Number of subjects 20 (no patients)
- Stimulation of PBMCs with ConA or LPS to recognize the functionality of PBMCs after stimulation …

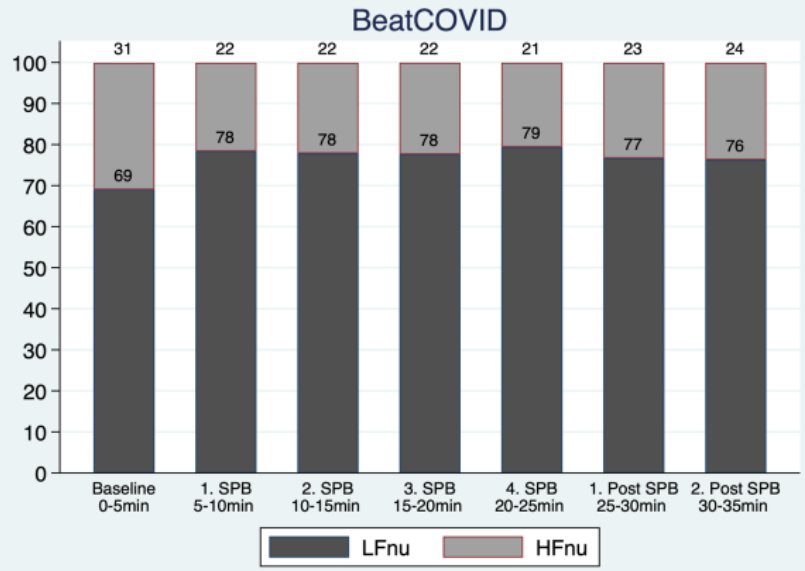
- Single-center randomized controlled clinical trial with enrolment of 46 patients hospitalized with confirmed severe acute respiratory syndrome (SARS-CoV-2) infection and moderate COVID-19 pneumonia (primary diagnosis)
- Intervention: 3 x 20min SPB
- Linear mixed model including group-by-time interaction revealed a significantly lower trajectory of IL-6 in the intervention group (effect size Cohens f2 = 0.11, LR-test p=.040) in the intention-to-treat sample, confirmed by per-protocol analysis (f2 = 0.15, LR-test p=.022)
- These effects were on top to treatment as usual and individual medication.

Balint EM, Grüner B, Haase S, Kaw-Geppert M, Thayer JF, Gündel H and **Jarczok MN** (2022) A randomized clinical trial to stimulate the cholinergic anti-inflammatory pathway in patients with moderate COVID-19-pneumonia using a slow-paced breathing technique. Front. Immunol. 13:928979. doi: 10.3389/fimmu.2022.928979

Can dmVNS achieve similar effects in cancer patients?







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Additional information

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