Differential Effect of Variable Autonomic Modulation Stimulation Parameters on Autonomic Function

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INTRUDUCTION/GOAL

- Reduced heart rate variability (HRV) is associated with increased risk of cardiovascular morbidity and mortality.
- Transcutaneous stimulation of the auricular branch of the vagus nerve at the tragus of the ear has been used as a noninvasive form of autonomic modulation in cardiovascular diseases (Figure 1).
- Previous studies have shown that transcutaneous vagus nerve stimulation (tVNS) increases HRV and improves autonomic function, but the effect of variable stimulation parameters on autonomic function remains unclear.
- We examined the effect of variable stimulation parameters of tVNS on autonomic function.

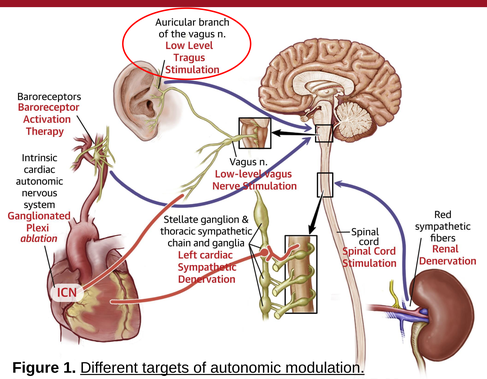

Figure 1. Different targets of autonomic modulation.
Modified from Stavrakis S. et al. JACC EP 2020;6:467-83

METHODS

- Healthy volunteers were recruited for this study.
- Each participant underwent autonomic function testing consisting of HRV during deep breathing and mental arithmetic stress test (MAST), with and without tVNS.
- During MAST, participants were instructed to count backwards from 500 by 7.
- Deep breathing was defined as repeatedly inhaling for five seconds and exhaling for five seconds.
- Participants were randomized to 4 groups of different stimulation parameters in a 2x2 fashion.
  - Frequency 5Hz and 20Hz; amplitude 1mA below discomfort threshold or 50% below discomfort threshold.
- tVNS was applied for 5 minutes for each session.
- HRV was analyzed in a blinded fashion using Kubios software.
- Results were compared with 2-way ANOVA, adjusted for multiple comparisons.

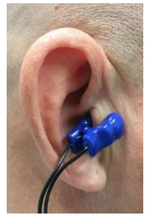

Figure 2. TENS unit ear clip on tragus. The ear clip was placed on the participant's right tragus with the anode facing away from the patient.

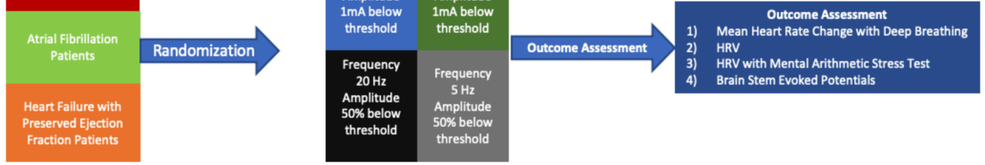

Figure 3: Schematic of study design. In this portion of the study, only healthy volunteers were selected. Participants were then randomized for frequency and amplitude settings. The first three outcomes in the figure were assessed.

RESULTS

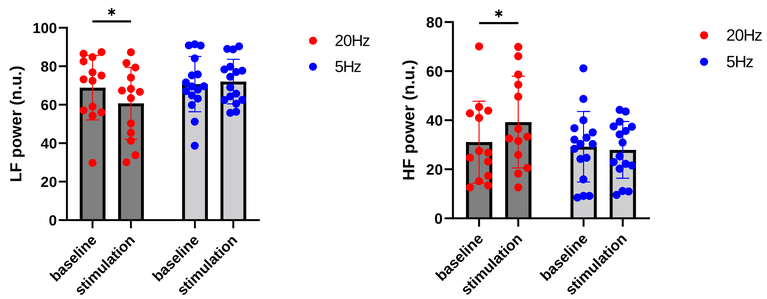

Figure 4: The effect of stimulation frequency on low-frequency power. 20Hz stimulation resulted in lower LF power when compared to baseline. 5Hz had no effect.

Figure 5: The effect of stimulation frequency on high-frequency power. 20Hz stimulation resulted in higher HF power when compared to baseline. 5Hz had no effect.

- Thirty participants were included
  - Mean age 39±14 years, 70% female.
- Stimulation amplitude:
  - 26±13 mA in the 1 mA below discomfort threshold
  - 14±7 mA in the 50% below discomfort threshold groups (p=0.001).
- 20Hz stimulation yielded a greater change in HRV parameters than 5Hz when compared to baseline during MAST, see figures 4-7.
- Low frequency: -8.1±2.8%, vs. 1.4±1.8%, p=0.01
- High frequency 8.2±3.7% vs. -1.3±1.8%, p=0.03
- SD2 of Poincare plot -7.9±2.9 ms vs. 4.2±3.1 ms, p=0.005
- Figures 8-11 show individual examples of RR spectrum and Poincare plots to depict difference between base and stimulation on one participant.
- No differences were observed between the two different amplitude groups.

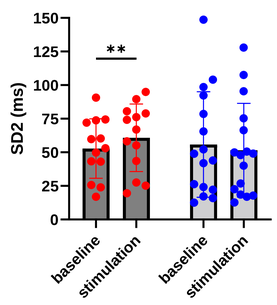

Figure 6: The effect of stimulation frequency on SD2. 20Hz stimulation resulted in slightly elevated SD2, whereas 5Hz had no effect.

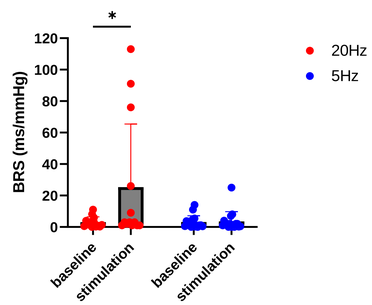

Figure 7: The effect of stimulation frequency on BRS. Stimulation at 20Hz resulted in a higher BRS than baseline, whereas 5Hz had no effect.

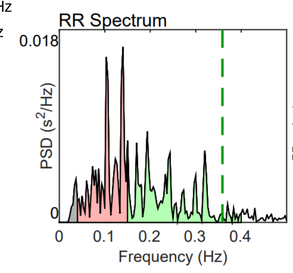

Figure 8: Frequency plot for breathing exercise at baseline. Frequency shows strong peaks at approximately 0.1Hz and 0.14Hz.

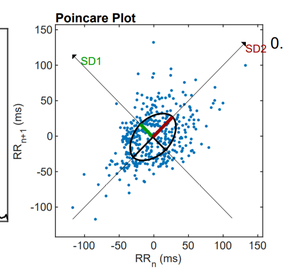

Figure 9: Poincare plot for breathing exercise at baseline. A tighter clustering can be observed.

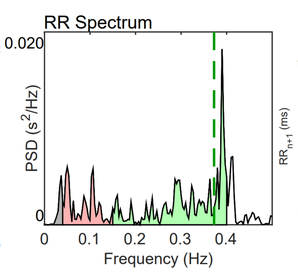

Figure 10: Frequency plot for breathing exercise with 20Hz stimulation. Frequency shows a strong peak at approximately 0.38Hz.

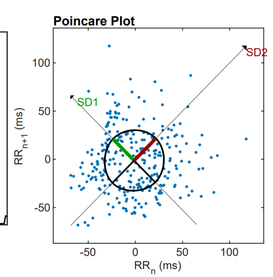

Figure 11: Poincare plot for breathing exercise with 20Hz stimulation. Less clustering can be observed.

CONCLUSION

- **Stimulation frequency may influence the acute effect of autonomic modulation on autonomic function parameters.**
- **These findings have implications for autonomic modulation study design.**
- **Further studies in disease states are warranted.**