POTS Iperadrenergica vs Non-Iperadrenergica: differenze in profili autonomici, sintomi ortostatici e rispettive risposte alla stimolazione transcutanea cronica delle afferenze vagali.

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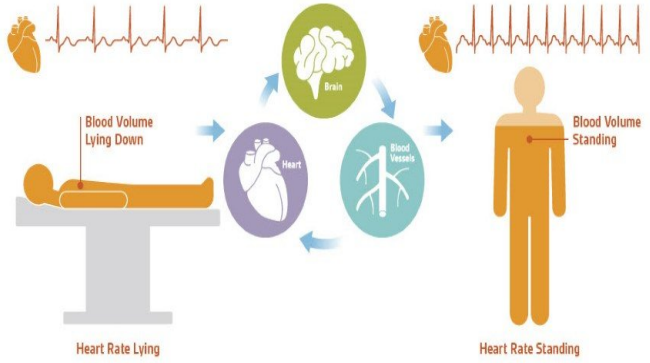
Postural Orthostatic Tachycardia Syndrome (POTS)

- Postural Orthostatic Tachycardia (POTS) is a syndrome of orthostatic intolerance characterized by excessive increase in heart rate upon standing (≥ 30bpm) without concomitant orthostatic hypotension (Furlan *et al., 1998*)



- The orthostatic tachycardia is often accompanied by symptoms (dizziness, fatigue, heart palpitations) which diminish quality of life and working ability (Dipaola *et al.*, 2020) (Barbic *et al.*, 2020)

Transcutaneous Vagus Nerve Stimulation (tVNS)

Non-invasive, inexpensive, safe method of neural stimulation to increase vagus nerve activation

Effects of tVNS on the ANS:

- Decrease in mean HR
- Increase in parameters of HRV reflecting cardiac vagal modulation
- Decrease in muscle sympathetic nerve activity (MSNA)

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Study Aims

We have previously shown that tVNS enhanced cardiac vagal modulation, reduced muscle sympathetic nerve activity and improved dysautonomia symptoms in Hyperadrenergic POTS, a subtype that exhibits centrally-derived **sympathetic overactivity** and **reduced cardiac vagal modulation** (Shiffer *et al.,* 2021)

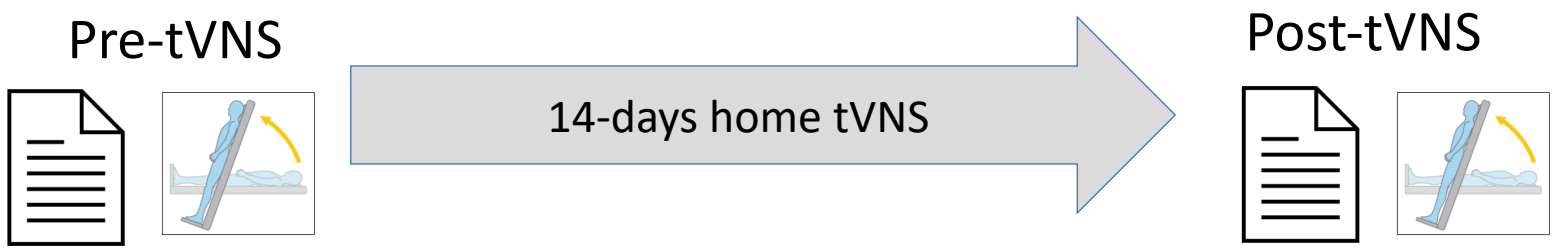
In this study the aims were to:

- Characterize Hyperadrenergic versus Non-Hyperadrenergic POTS patients based on baseline autonomic profile and symptoms
- Compare their responses to tVNS treatment by analyzing the changes in autonomic profiles and symptoms

Methods – Protocol, N=58

HF_{RR} < 200 ms^2
Hyperadrenergic
(n=25, 23 Female)

HF_{RR} > 200 ms^2
Non Hyperadrenergic
(n=33, 27 Female)



- Cardiovascular autonomic profile was assessed by ECG, non-invasive beat-to-beat arterial blood pressure and respiratory activity recordings, on which power spectrum analysis techniques were used.

Low frequency, LF_{RR} (≈0.1 Hz) / **High frequency, HF_{RR} ratio**→ index of cardiac sympatho-vagal modulation
High frequency, HF_{RR} (≈0.25 Hz) → index of cardiac vagal modulation

- Muscle sympathetic nerve activity (MSNA) by **microneurogaphy.**
Signals were continuously recorded in supine position and during a passive, stepwise head-up tilt, up to 75°.

Dysautonomia symptoms were assessed using **COMPASS-31**
Investigates 6 different domains orthostatic intolerance, vasomotor, secretomotor, gastrointestinal genitourinary, pupillomotor.

Results – Baseline Autonomic Profile

	SUPINE		HEAD-UP-TILT	
	Hyper	Non-Hyper	Hyper	Non-Hyper
HR, bpm	81.8 ± 3	69.8 ± 1.5*	122.9 ± 3.9	110.3 ± 3
SAP, mmHg	118.2 ± 2.6	112.3 ± 2.2	127.2 ± 5.7	117 ± 2.8
DAP, mmHg	73.1 ± 2.1	64.4 ± 1.2*	77.5 ± 2.9	72.3 ± 1.9
RESP, cycles/min	16.7 ± 0.9	16.2 ± 0.6	19.9 ± 1.2	18.7 ± 0.9
ET_{CO2}, mmHg	26.4 ± 0.7	25.8 ± 0.7	21.8 ± 0.9	22.2 ± 0.8
MSNA, bursts/min	31.5 ± 2.8	24.2 ± 2.2*	41.1 ± 3.5	32.0 ± 2.1
MSNA, bursts/100 beats	37 ± 3.6	34.2 ± 2.8	33 ± 2.7	29.2 ± 2
NE, pg/ml	349.7 ± 47.2	299.3 ± 26.4	708 ± 64.4	570.5 ± 43.1
E, pg/ml	23.9 ± 3.2	27.2 ± 3.8	61.4 ± 7.6	59.4 ± 8.3
RR variance, ms^2	892.1 ± 113.3	2705.1 ± 292.8*	348.3 ± 61.9	825.6 ± 135.5*
LF_{RR}, ms^2	261.1 ± 47.5	774.9 ± 100.5*	159.7 ± 32.9	394.7 ± 95.6*
LF_{RR}, nu	63.7 ± 3.4	47.2 ± 3.1*	84.7 ± 2.7	80.3 ± 2.1
HF_{RR}, ms^2	109.7 ± 12.6	1045.6 ± 214.4*	13.6 ± 3.9	79.7 ± 21.7*
HF_{RR}, nu	35.1 ± 3.5	51 ± 3.1*	7.1 ± 1	15.6 ± 2.1*
LF/HF	2.7 ± 0.3	1.2 ± 0.1*	17.4 ± 2.4	10.4 ± 1.6*
SAP variance, $mmHg^2$	10.4 ± 1.2	18.3 ± 6.3	31.6 ± 4.4	39.5 ± 5.7
LF_{SAP}, $mmHg^2$	3.5 ± 0.7	2.7 ± 0.7	23.8 ± 4	19.4 ± 3.6
αLF, ms/mmHg	12.4 ± 2	25.8 ± 3*	2.5 ± 0.3	5.1 ± 0.6*

*P<0.05 Hyper vs. NonHyper

Hyperadrenergic POTS

Higher HR*

Higher MSNA*

Higher LF/HF*

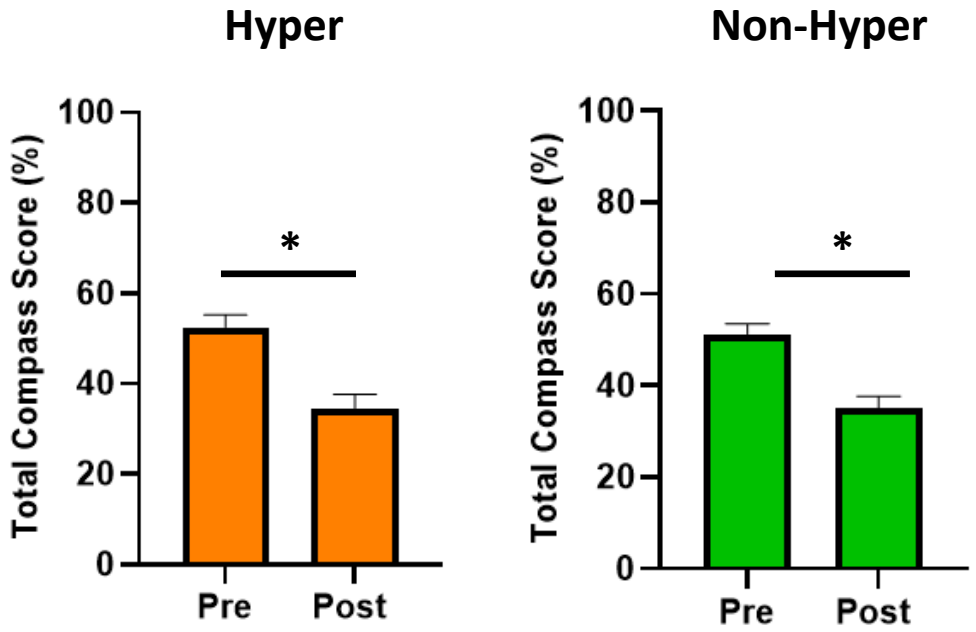
Results- changes induced by tVNS in supine and during tilt

Supine	Hyper		Non-hyper	
	Pre-tVNS	Post-tVNS	Pre-tVNS	Post-tVNS
MSNA, bursts/min	31.5 ± 2.8*	20.0 ± 1.7†	24.2 ± 2.2	19.8 ± 1.3
MSNA, bursts/100b	37 ± 3.6	24.4 ± 2.1†	34.2 ± 2.8	27.6 ± 1.9
NE, pg/ml	349.7 ± 47.2	296.5 ± 30.2	299.3 ± 26.4	300.7 ± 29.1
E, pg/ml	23.9 ± 3.2	21.3 ± 3	27.2 ± 3.8	21.7 ± 1.8
RR variance, ms²	892.1 ± 113.3*	1035.1 ± 119.1	2705.1 ± 292.8	2538.6 ± 464.9*
LF_{RR}, ms²	261.1 ± 47.5*	287.4 ± 34.5	774.9 ± 100.5	723.9 ± 100.9*
LF_{RR}, nu	63.7 ± 3.4*	56.8 ± 3.9	47.2 ± 3.1	51.1 ± 3.6
HF_{RR}, ms²	109.7 ± 12.6	168.1 ± 22.2†	1045.6 ± 214.4	1099.3 ± 406.8
HF_{RR}, nu	35.1 ± 3.5*	39.2 ± 3.8	51 ± 3.1	47.7 ± 3.6
LF/HF	2.6 ± 0.4*	1.8 ± 0.2†	1.2 ± 0.1	1.4 ± 0.2
SAP variance, mmHg²	10.4 ± 1.2	13.2 ± 3	18.3 ± 6.3	16.9 ± 3.9
LF_{SAP}, mmHg²	3.5 ± 0.7	2.9 ± 0.7	2.7 ± 0.7	2.4 ± 0.4
αLF, ms/mmHg	12.4 ± 2*	12.1 ± 1.4	25.8 ± 3	19.7 ± 2.1*
HR, bpm	81.8 ± 3*	78.8 ± 2.3	69.8 ± 1.5	69.6 ± 1.8*
SAP, mmHg	118.2 ± 2.6	117.2 ± 3.1	112.3 ± 2.2	110 ± 2*
DAP, mmHg	73.1 ± 2.1*	70.7 ± 2.1	64.4 ± 1.2	62.6 ± 1.1*
RESP, cycles/min	16.7 ± 0.9	18.8 ± 0.9	16.2 ± 0.6	17.2 ± 1
ET_{CO2}, mmHg	26.4 ± 0.7	26.4 ± 0.7	25.8 ± 0.7	25.2 ± 0.7

TILT	Hyper		Non-hyper	
	Pre-tVNS	Post-tVNS	Pre-tVNS	Post-tVNS
MSNA, bursts/min	41.1 ± 3.5	24.9 ± 1.9†	32.0 ± 2.1	25.4 ± 2.1†
MSNA, bursts/100b	33 ± 2.7	21.7 ± 1.8†	29.2 ± 2	25.2 ± 2.2
NE, pg/ml	708 ± 64.4	575.5 ± 56.3	570.5 ± 43.1	517.7 ± 42.3
E, pg/ml	61.4 ± 7.6	51.7 ± 6.2	59.4 ± 8.3	45.7 ± 4.4
RR variance, ms²	348.3 ± 61.9*	458.1 ± 104.8	825.6 ± 135.5	800.3 ± 125*
LF_{RR}, ms²	159.7 ± 32.9*	246.7 ± 80.5	394.7 ± 95.6	420.3 ± 82.5
LF_{RR}, nu	84.7 ± 2.7	82 ± 3.5	80.3 ± 2.1	82.2 ± 2.7
HF_{RR}, ms²	13.6 ± 3.9*	32.3 ± 11.4	79.7 ± 21.7	69.6 ± 19.3
HF_{RR}, nu	7.1 ± 1*	11.6 ± 1.9†	15.6 ± 2.1	13.9 ± 2.6
LF/HF	17.4 ± 2.4*	16.7 ± 3.2	10.4 ± 1.6	15 ± 2.5
SAP variance, mmHg²	31.6 ± 4.4	27.5 ± 2.7	39.5 ± 5.7	39.5 ± 8.2
LF_{SAP}, mmHg²	23.8 ± 4	18.3 ± 2.2	19.4 ± 3.6	21.9 ± 4.7
αLF, ms/mmHg	2.5 ± 0.3*	3.1 ± 0.4	5.1 ± 0.6	4.6 ± 0.4*
HR, bpm	122.9 ± 3.9*	118 ± 4.1	110.3 ± 3	108.2 ± 3.7
SAP, mmHg	127.2 ± 5.7	122.8 ± 4.1	117 ± 2.8	113.1 ± 2.2*
DAP, mmHg	77.5 ± 2.9	77.3 ± 2.8	72.3 ± 1.9	67.8 ± 2*
RESP, cycles/min	19.9 ± 1.2	20.9 ± 1.1	18.7 ± 0.9	19.5 ± 1
ET_{CO2}, mmHg	21.8 ± 0.9	23.2 ± 0.9	22.2 ± 0.8	20.9 ± 0.6*

*P<0.05 Hyper vs Non-Hyper. †P<0.05 Post-tVNS vs Pre-tVNS.

Results – Symptoms



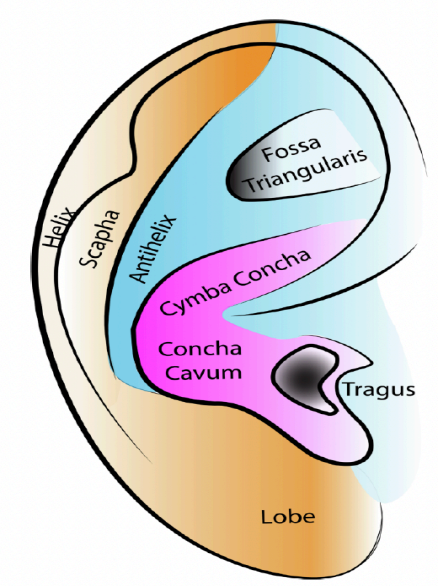
Data expressed as mean ± SEM. **P*<0.05 Hyper vs Non-Hyper.

- Both populations reported similar symptom severity at baseline and both reported similar levels of improvement after tVNS

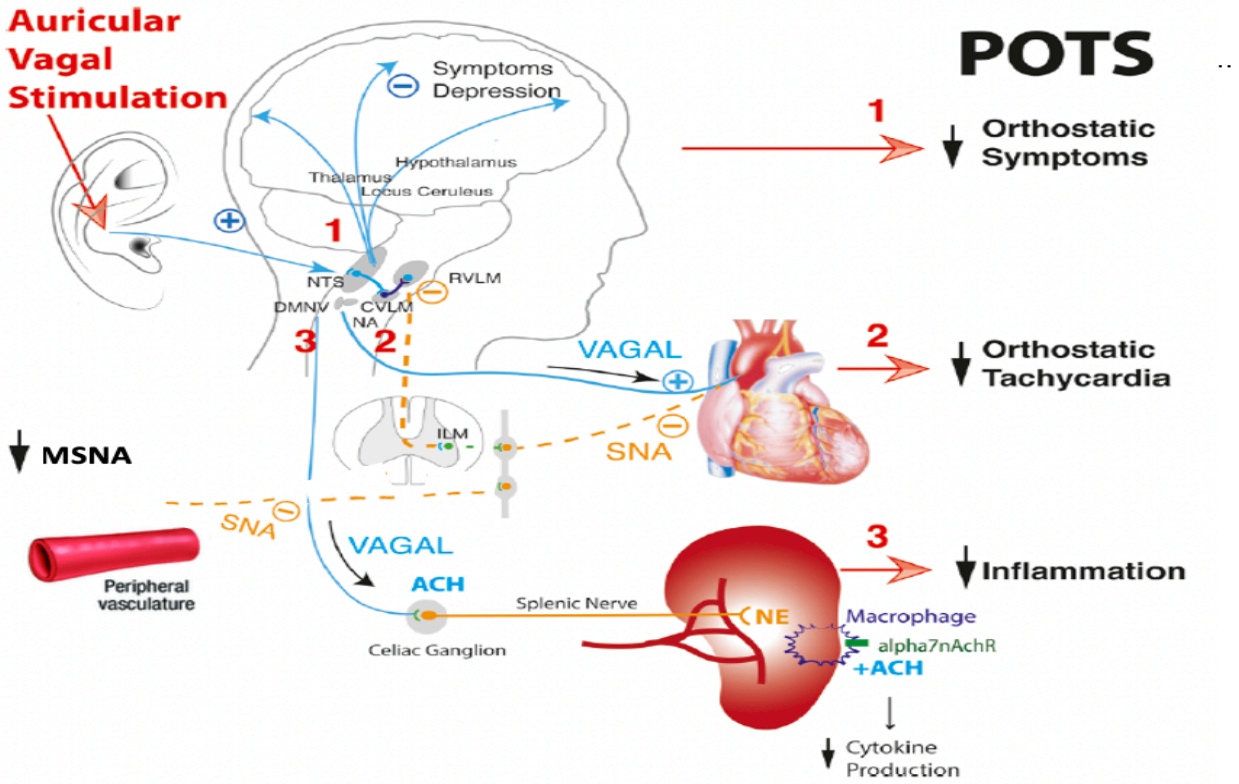
Conclusions

- Hyperadrenergic and NonHyperadrenergic POTS are characterized by significantly different baseline autonomic profiles yet report similar symptom severity
- tVNS induces varied changes in the autonomic profiles of these populations, yet they again report similar levels of symptom improvement
- Response to transcutaneous Vagus Nerve Stimulation may be independent of underlying autonomic profile and could be an effective treatment for a variety of POTS patients.

tVNS mechanism of action



Auricular branch of the Vagus nerve



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Thank you for your attention!

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