UNIWERSYTET MIKOŁAJA KOPERNIKA W TORUNIU
Wydział Nauk o Zdrowiu
Collegium Medicum w Bydgoszczy

UNIVERSITAS MEDICA VARSOVIENSIS 1809 SALUTI PUBLICAE

Autonomic Dysfunction in ME/CFS

Pawel Zalewski
Joanna Slomko
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Marcin Kozuchowski
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CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

ME/CFS Conference 2023

Understand, Diagnose, Treat

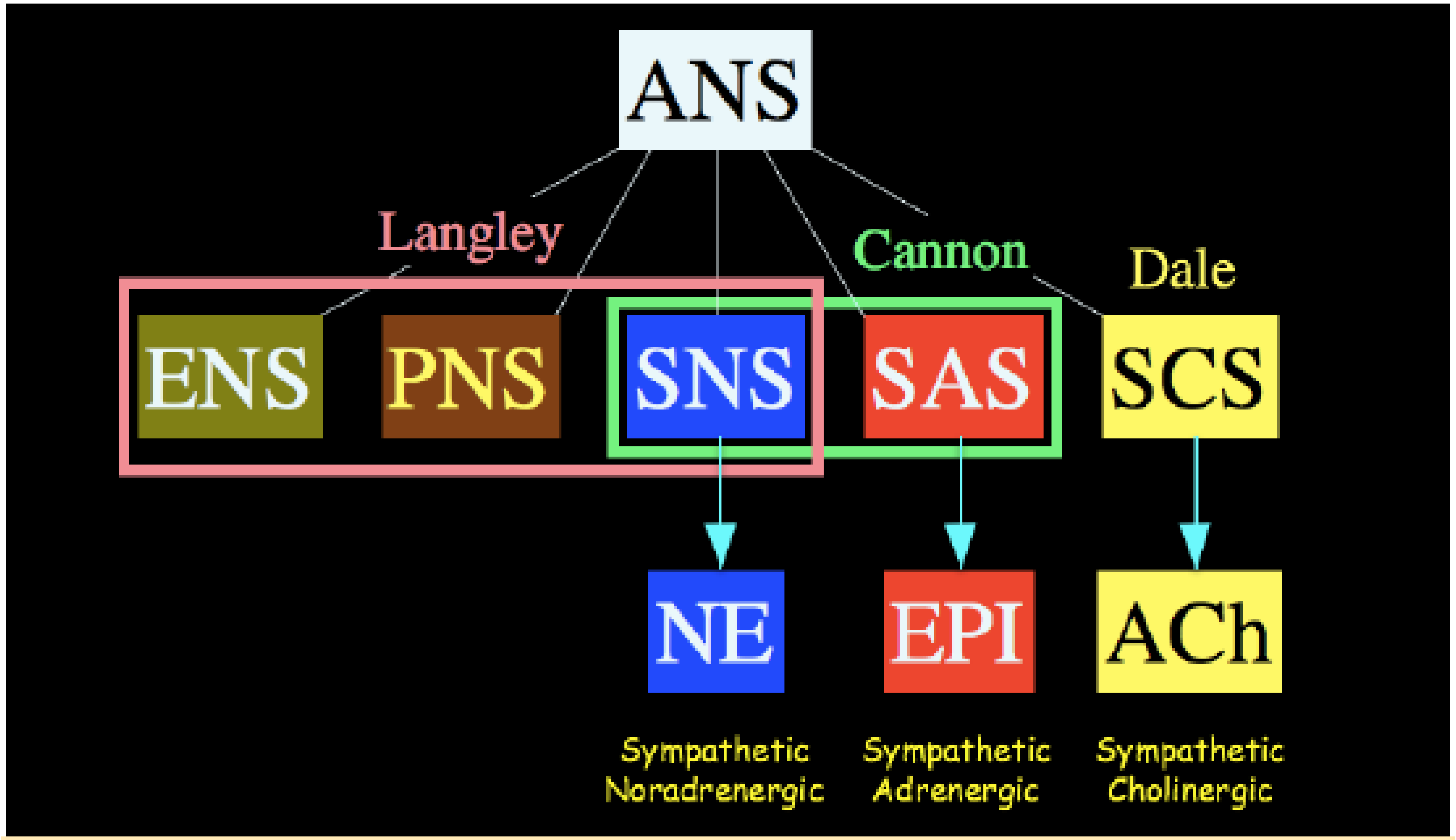
2nd International Meeting of the CFC – Charité Fatigue Center

11 May, 9 am – 12 May 2023, 2 pm (CET)

Hybrid event (on-site and online)

Charité Fatigue Center (CFC)
Institute of Medical Immunology

Division of ANS

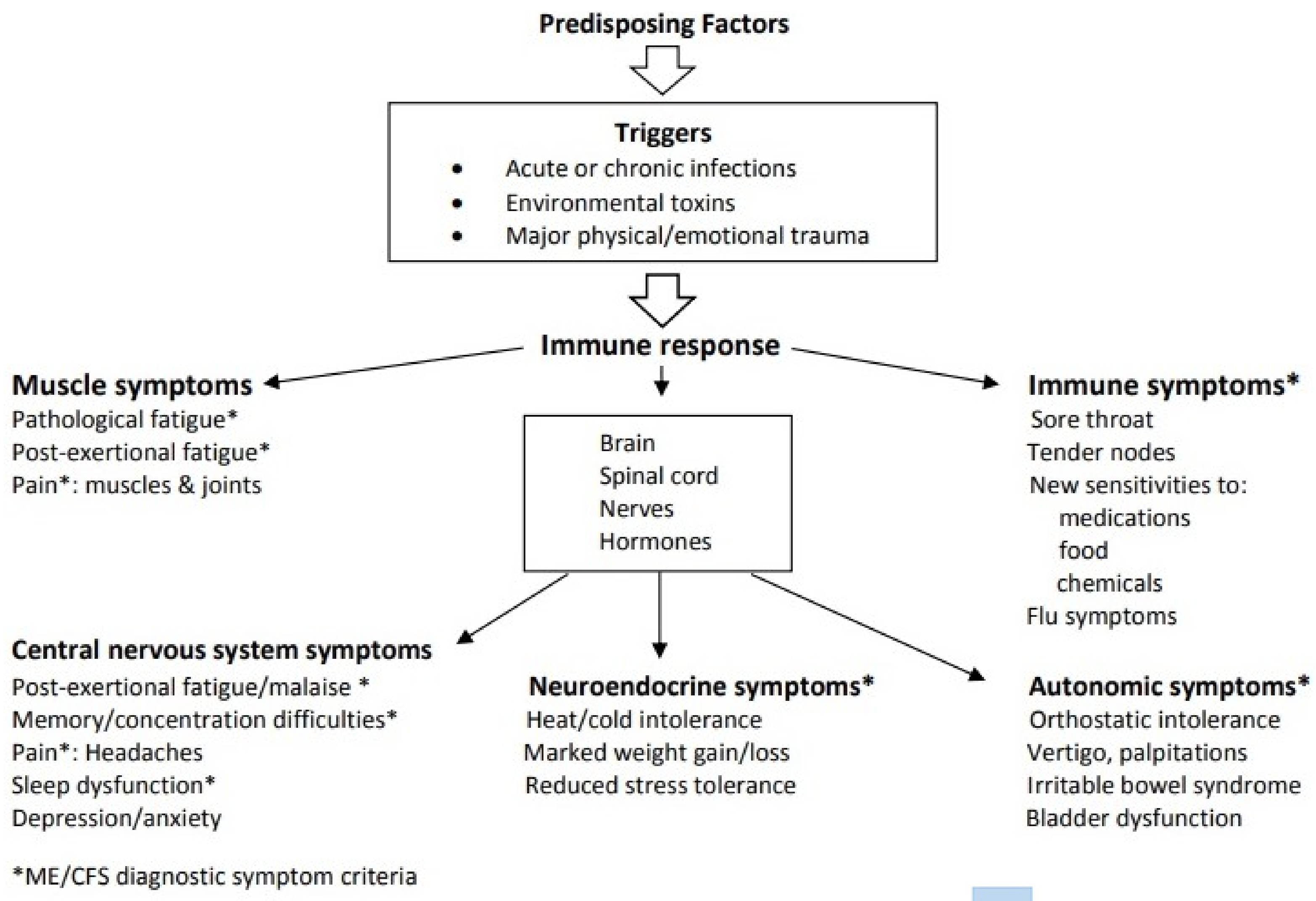


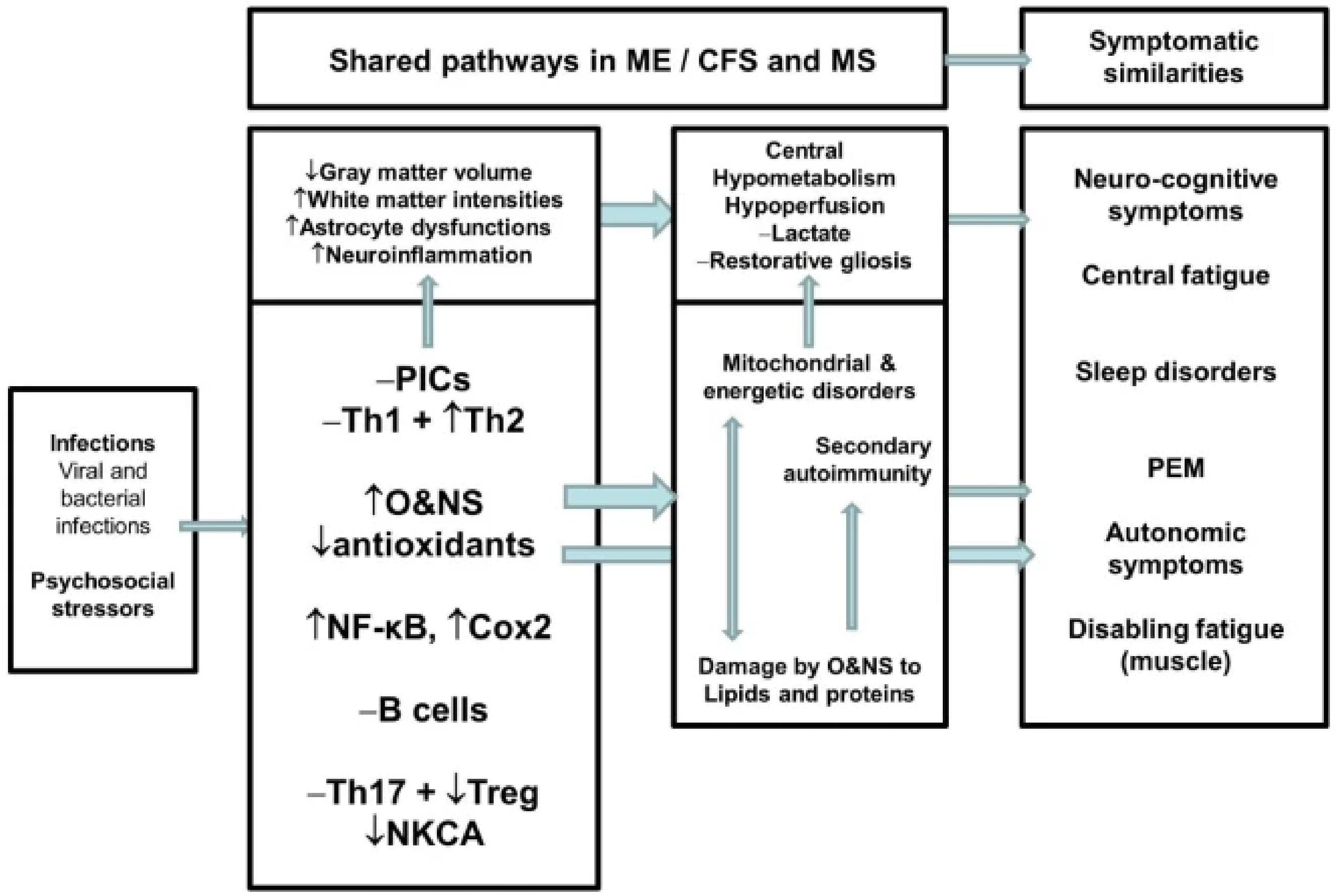
The parasympathetic nervous system regulates "vegetative" body functions—things you do at night or behind closed doors.

It was long thought that the sympathetic nervous system is an "emergency system" and is inactive during day to day life. Actually, this system is always active and participates in many automatic reactions that occur continually, such as tightening of blood vessels in the muscles when you stand up, keeping your glucose level within bounds if you skip a meal, and sweating when you are exposed to a warm environment.

David S. Goldstein, MD PhD, Principles of Autonimic Medicine v. 3.0

Dysautnomias in ME/CFS

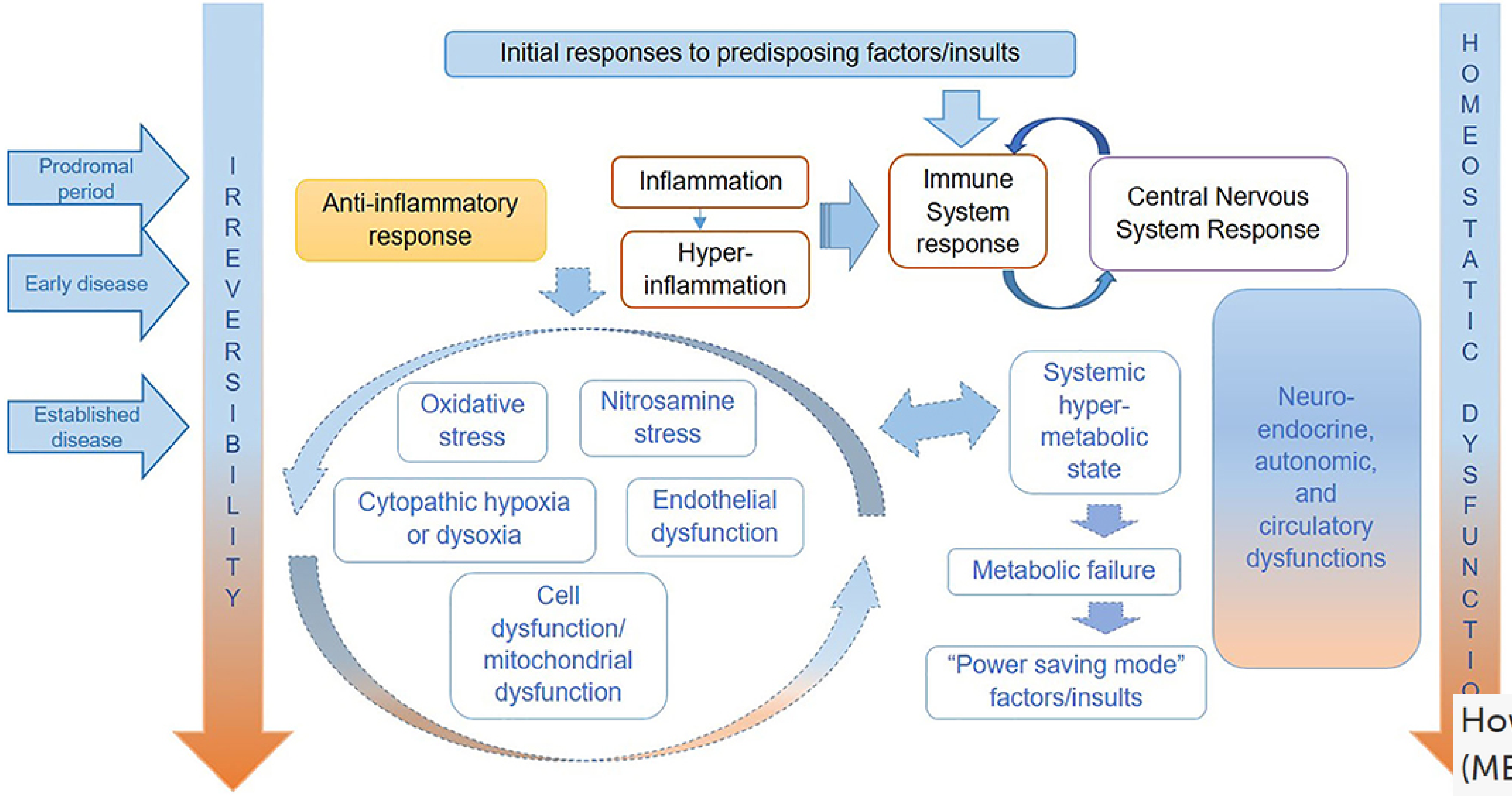




Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics

Gerwyn Morris[1,2*] and Michael Maes[2,3]

International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis IACFS/ME



How Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Progresses: The Natural History of ME/CFS

Luis Nacul[1,2], Shennae O'Boyle[1*], Luigi Palla[3,4], Flavio E. Nacul[5], Kathleen Mudie[1], Caroline C. Kingdon[1], Jacqueline M. Cliff[6], Taane G. Clark[6], Hazel M. Dockrell[6] and Eliana M. Lacerda[1]

Symtoms & Signs of Dysautonomia in ME/CFS

- **inability to stand, sit up, or maintain an upright position (orthostatic intolerance)**
- **dizziness or light headedness, fainting or near fainting (syncope)**
- headache (a sense of intracranial pressure)
- **weakness, exercise intolerance**
- **palpitations, with or without cardiac arrhythmias**
- shortness of breath, respiratory irregularities, air hunger
- chest discomfort or pain, including costochondritis with localised tenderness
- **abdominal pain, nausea, irritable bowel syndrome (IBS)**
- **impaired bladder control, urinary frequency**
- abnormal temperature regulation, flushing, sweating, cold extremities
- visual disturbances, including blurred vision
- **cognitive impairment**
- difficulty swallowing (dysphagia)
- visible and internal tremors
- sexual dysfunction

Sympathetic Noradrenergic System Failure

Orthostatic intolerance & hypotension
Fatigue
Heat intolerance & hypotension
Exercise intolerance

Sympathetic Noradrenergic System Hyperactivity

Pallor
Tendency to high blood pressure
Sweating
Trembling
Bristling hair

Symtoms & Signs of Dysautonomias

Parasympathetic System Failure

Dry mouth
Constipation
Dry eyes
Urinary retention
Slow gastrointestinal transit

Parasympathetic System Hyperactivity

Increased salivation
Tendency to slow pulse rate or heart block
Nausea & vomiting
Increased stomach acid secretion
Fatigue and exercise intolerance

Symtoms & Signs of Dysautonomias

ANS assessment

Clinical Autonomic Research
https://doi.org/10.1007/s10286-019-00615-x

LETTER TO THE EDITOR

Autonomic dysfunction in myalgic encephalomyelitis and chronic fatigue syndrome: comparing self-report and objective measures

Jane Kemp[1] · Madison Sunnquist[1] · Leonard A. Jason[1] · Julia L. Newton[2]

- **EFFECTORS**
- **NEUROTRANSMITTERS, IMMUNOLOGY**
- **SELF-REPORTS**
- **VALIDATED QUESTIONNAIRES (ASP, COMPASS-31)**

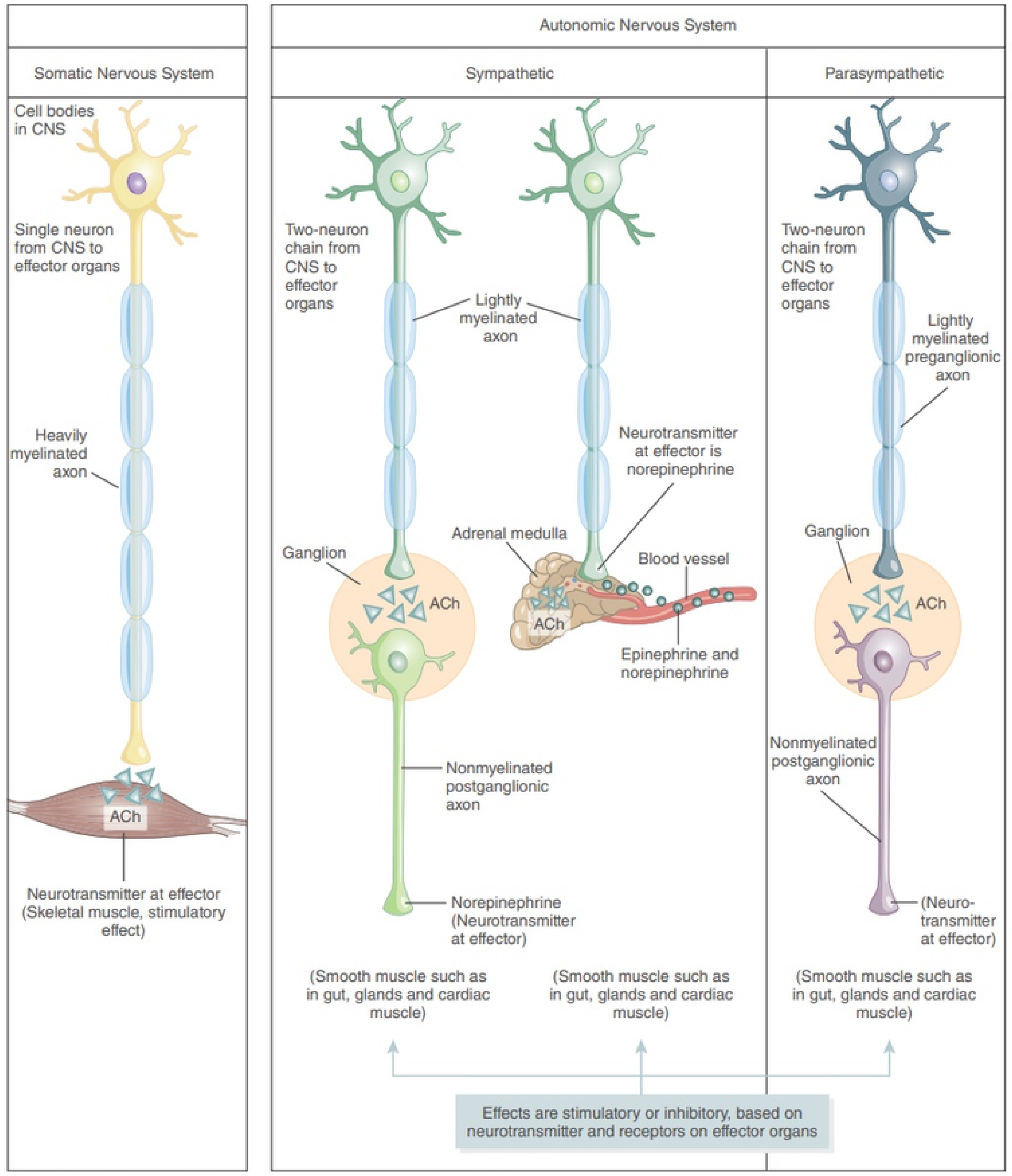
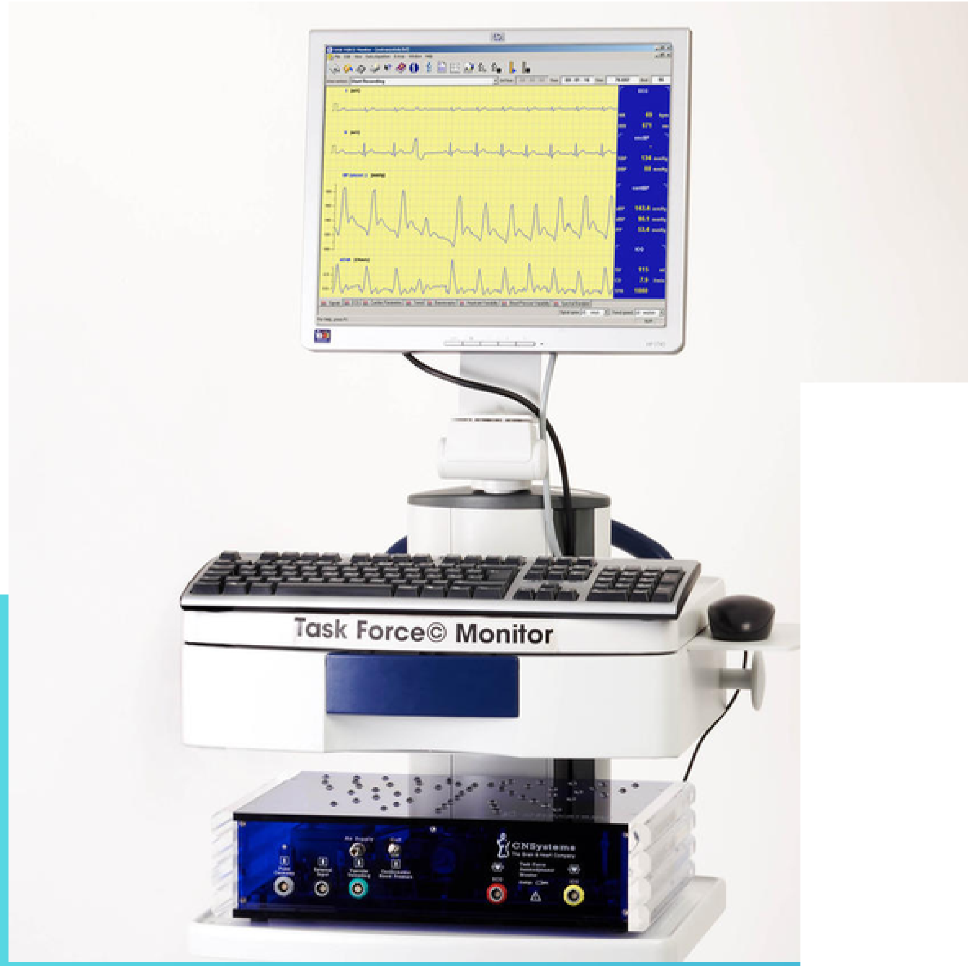
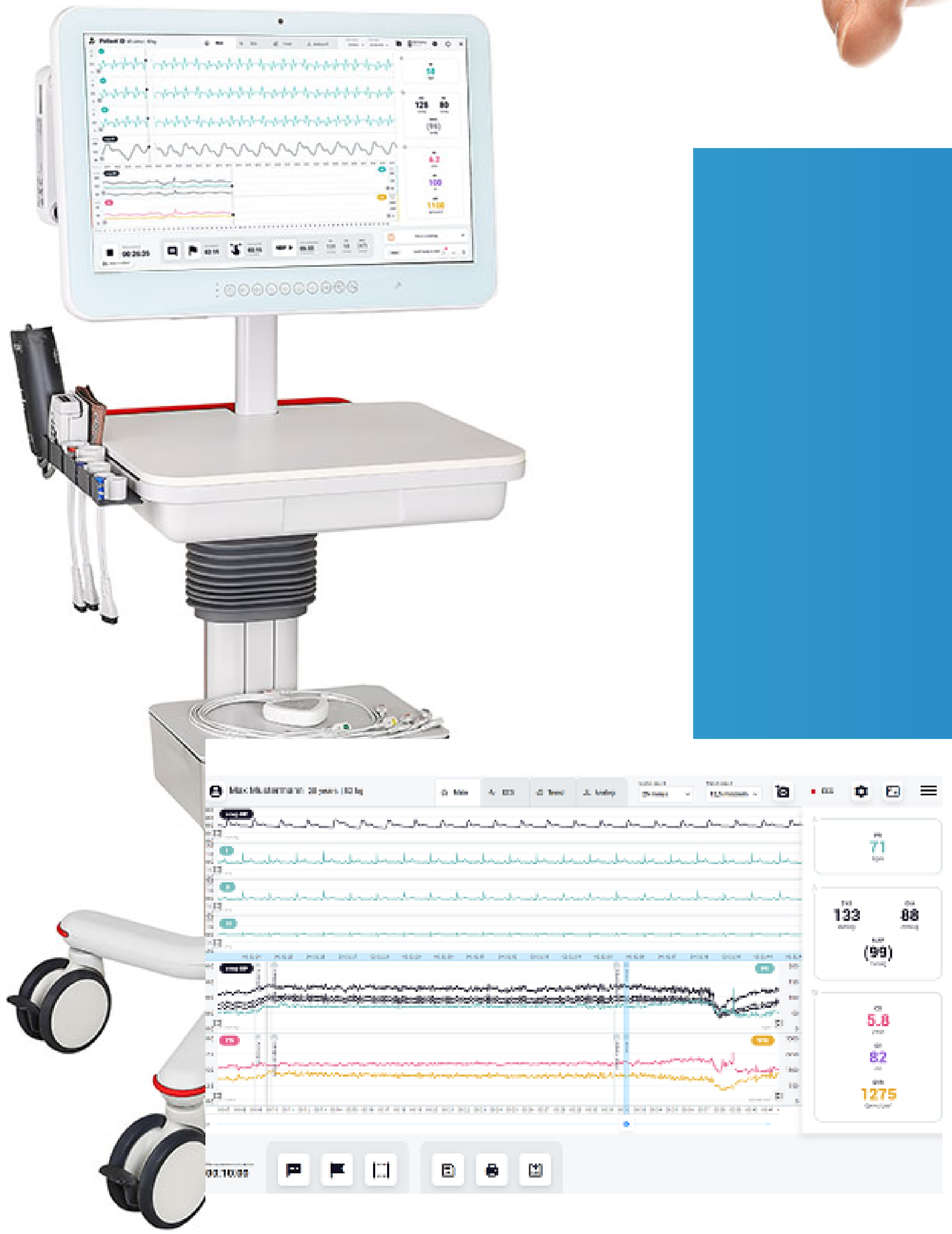
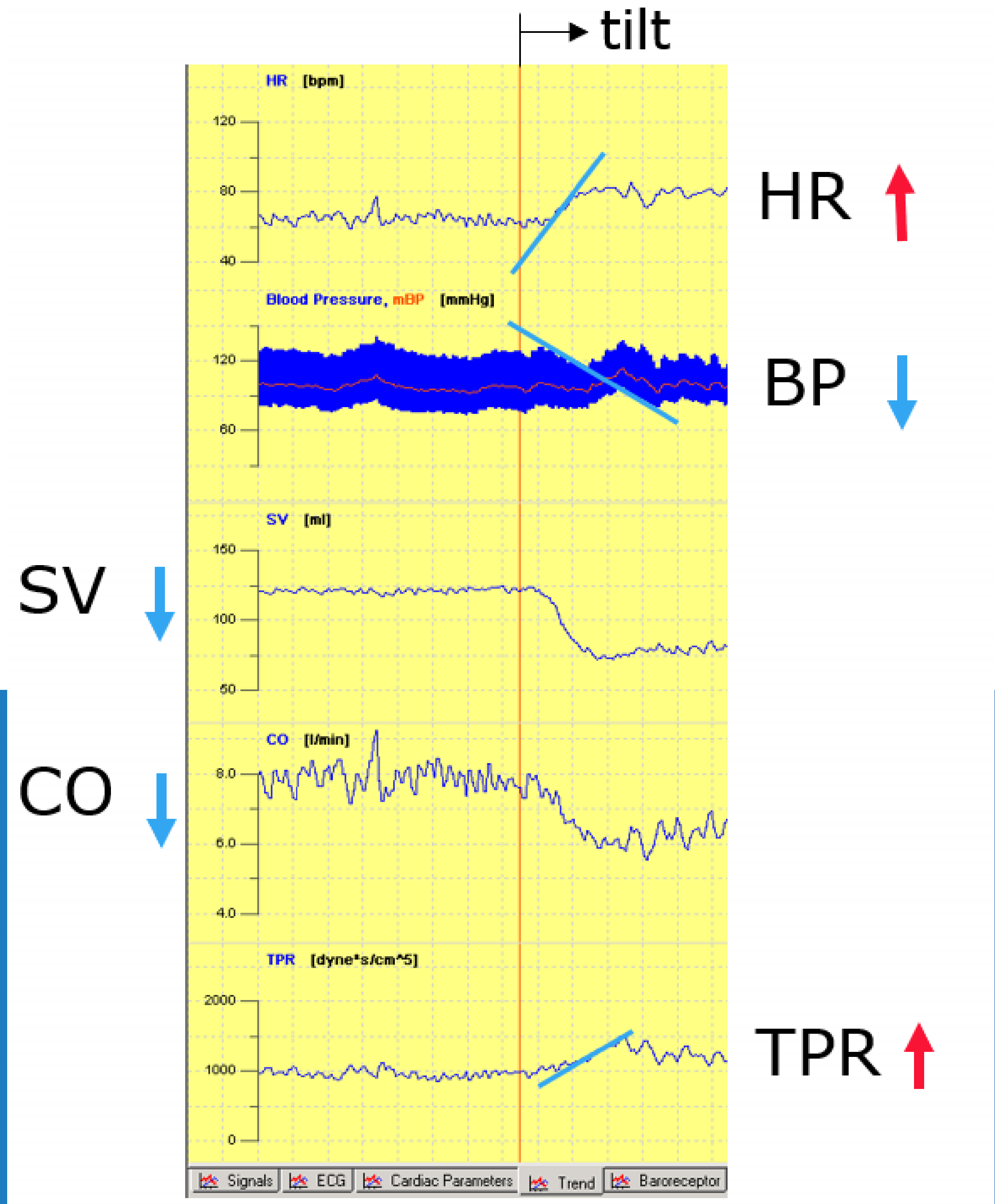


FIGURE Comparison of motor neurons in the somatic and autonomic nervous systems.

ANS assessment



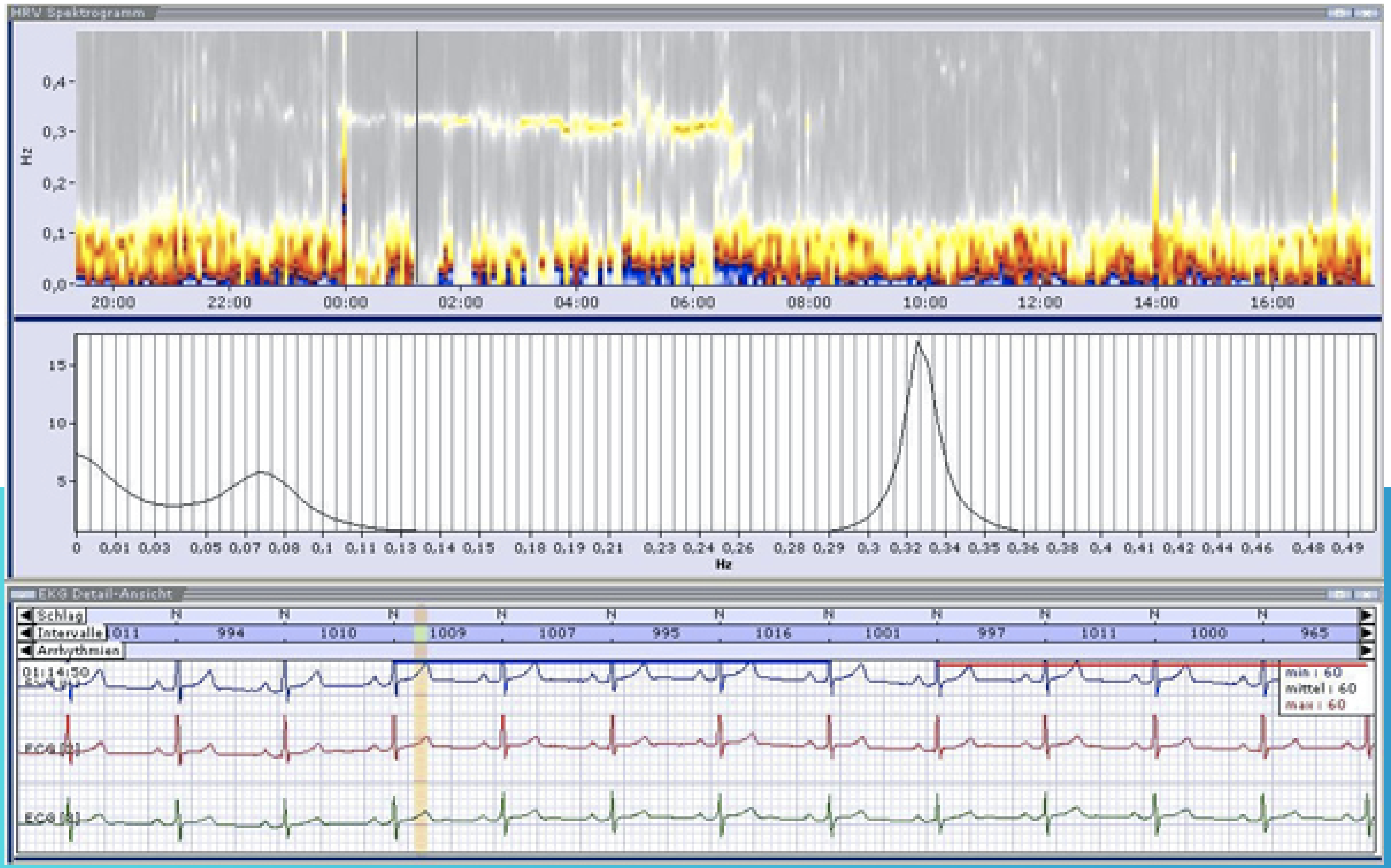


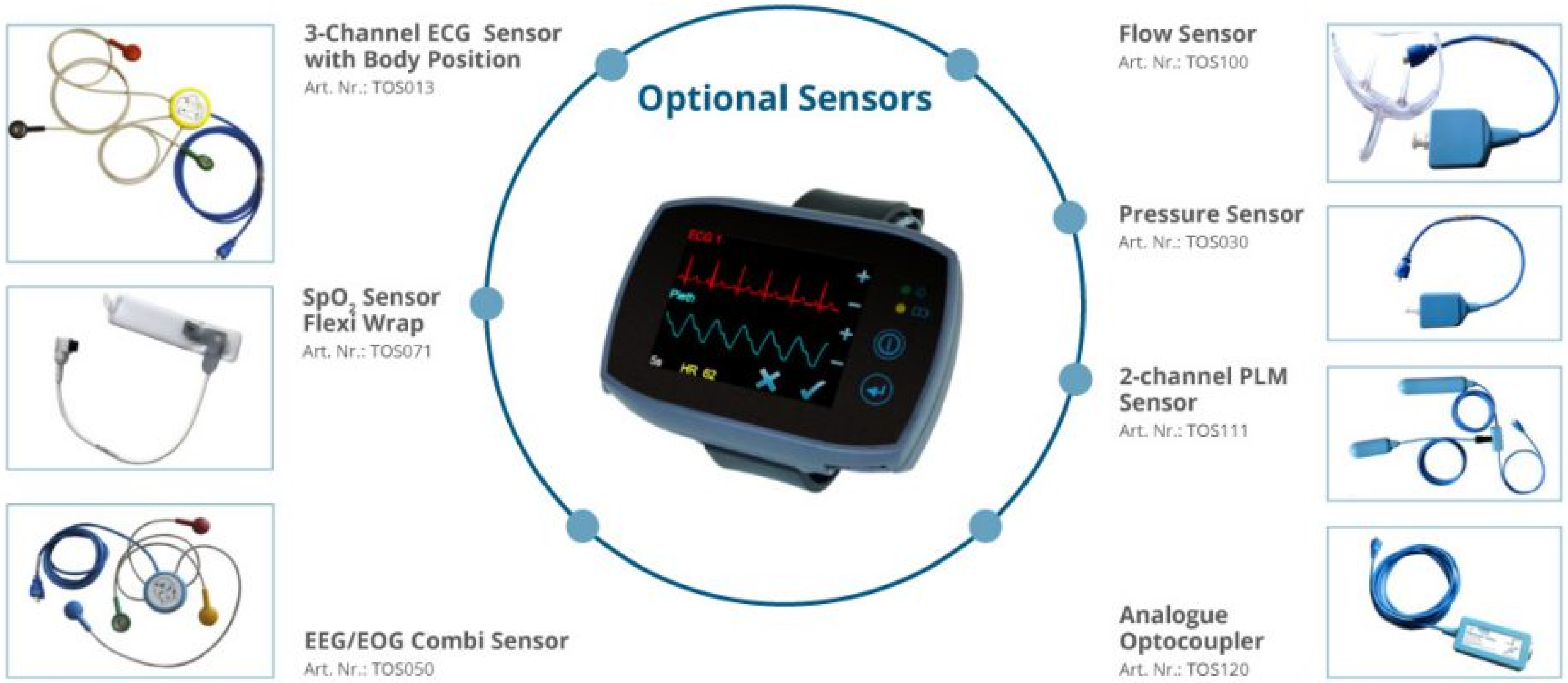


The Task Force® CARDIO* software delivers synchronized patient signals:

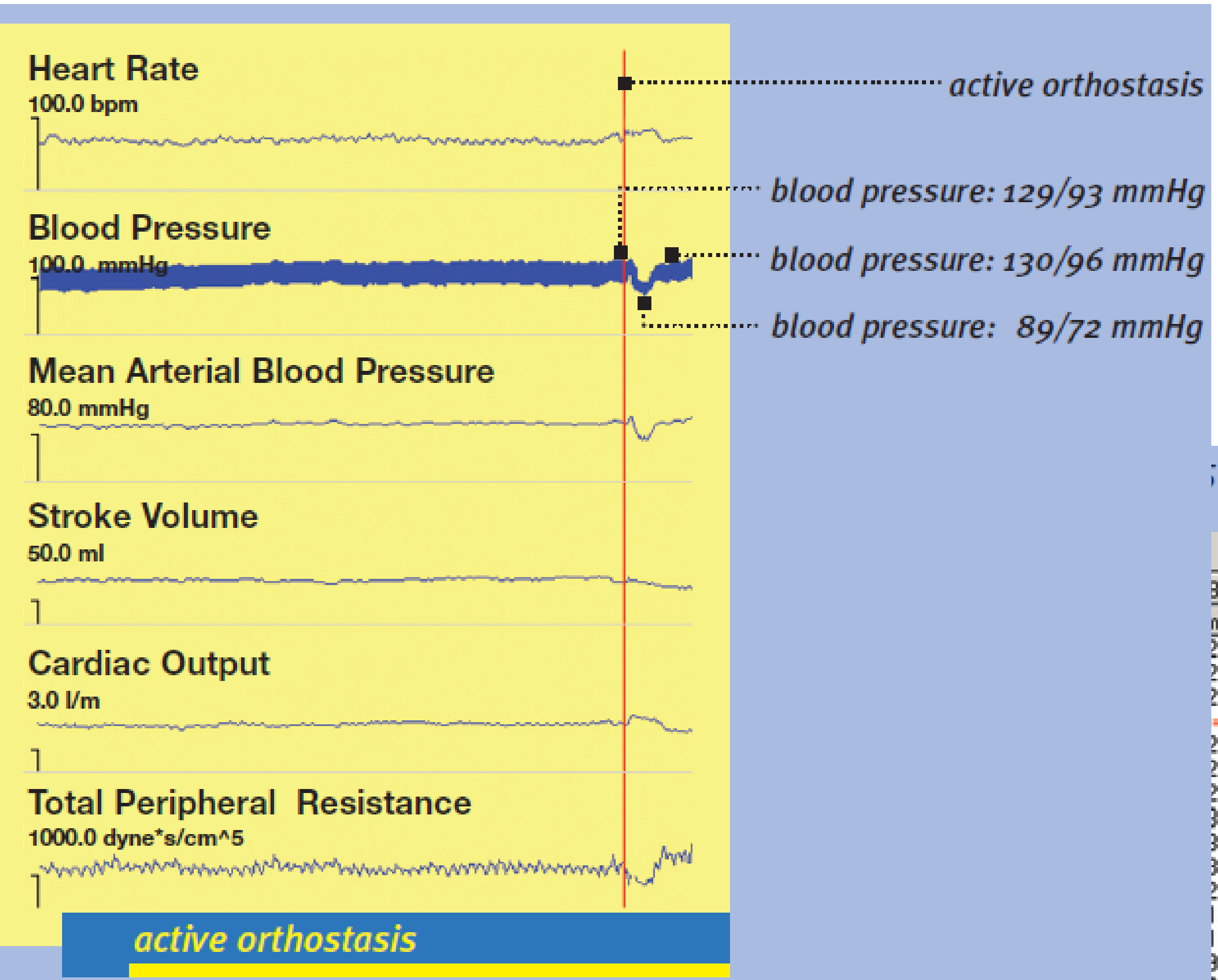
- Finger blood pressure: CNAP® waveform, SYS, DIA, MAP, Pulserate, Inter-Beat-Interval (available for post processing)
- Upper arm NBP: SYS, DIA, MAP
- Advanced hemodynamics (CNAP® HD): SV, SI, CO, CI, SVR, SVRI
- 12-channel wireless ECG

ANS assessment





ANS assessment

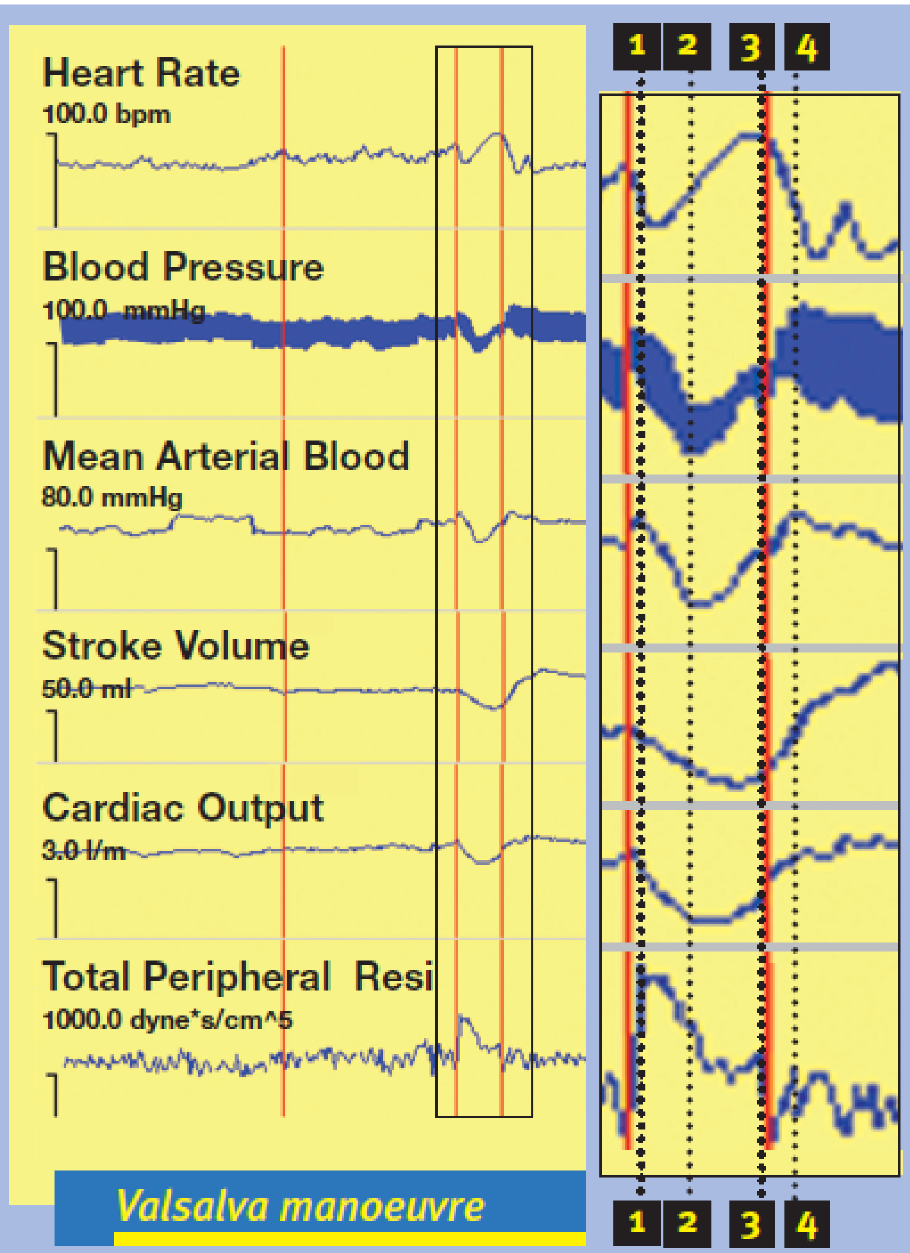


30:15 ratio : $\frac{898}{712} = 1,26$

The female patient is 30 years old and the result lies within the normal range for her age.

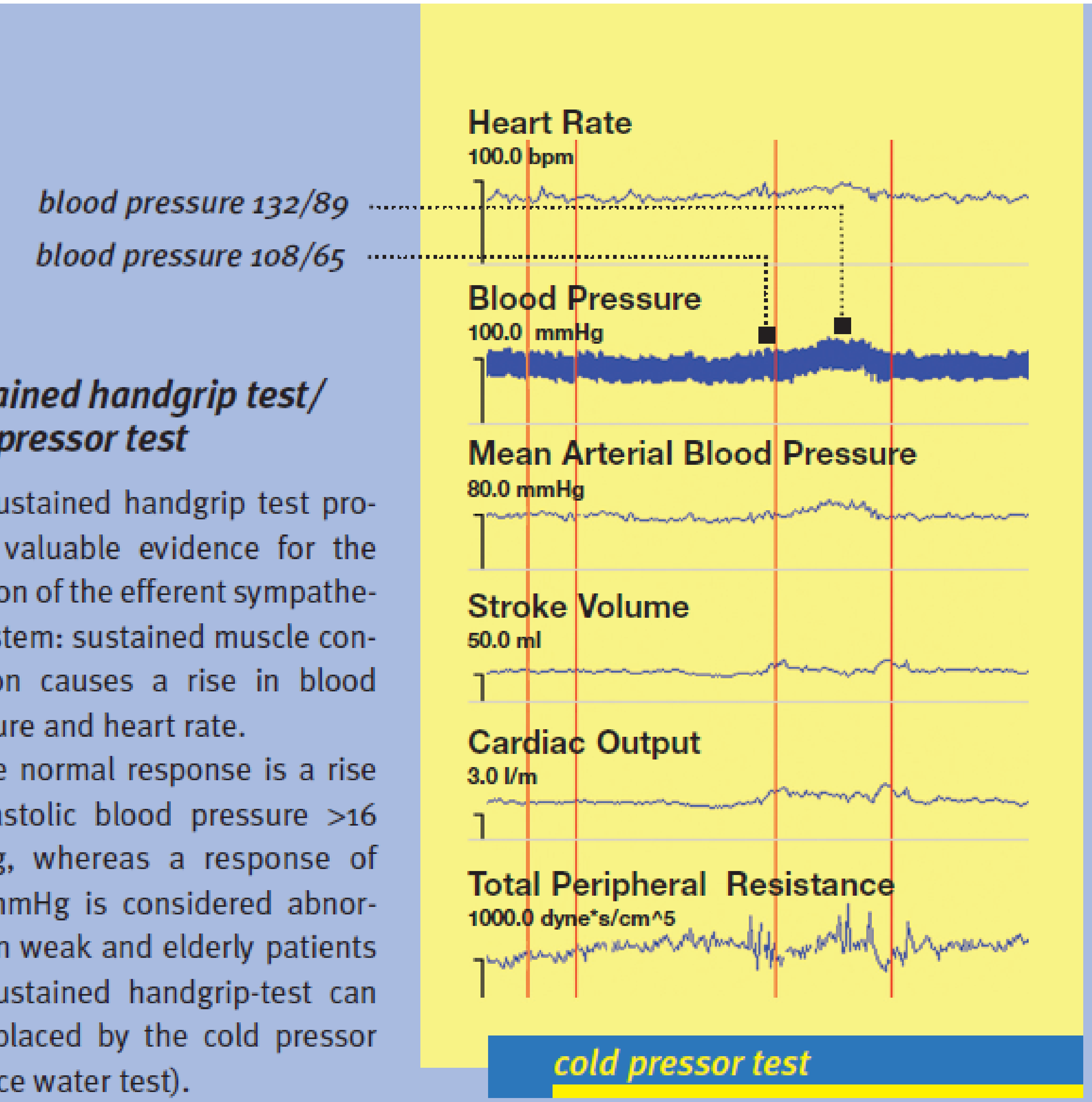
783	691.59	09:54:24.22	779	721	83.2	89.6
784	692.31	09:54:24.94	780	730	82.2	105.7
785	693.04	09:54:25.67	781	732	82.0	89.5
786	693.77	09:54:26.40	782	726	82.6	91.0
787	694.50	09:54:27.13	783	[illegible]	81.8	97.6
788	695.23	09:54:27.86	784	712	84.3	108.8
789	695.94	09:54:28.57	785	715	84.0	109.3
790	696.66	09:54:29.29	786	721	83.2	113.5
791	697.38	09:54:30.01	787	731	82.0	118.0
792	698.11	09:54:30.74	788	750	80.0	119.8
793	698.86	09:54:31.49	789	779	77.1	121.4
794	699.64	09:54:32.27	790	844	71.1	122.4
795	700.48	09:54:33.11	791	[illegible]	68.9	123.5
796	701.35	09:54:33.98	792	898	66.8	123.7
797	702.25	09:54:34.88	793	[illegible]	69.1	122.4
798	703.12	09:54:35.75	794	882	68.0	121.9
799	704.00	09:54:36.63	795	887	67.6	123.0
800	704.89	09:54:37.52	796	870	69.0	128.3
801	705.76	09:54:38.39	797	837	71.7	132.9
802	706.59	09:54:39.22	798	858	70.0	129.7
803	707.45	09:54:40.08	799	846	70.9	130.3
804	708.30	09:54:40.93	800	836	71.7	130.3
805	709.13	09:54:41.76	801	822	73.0	124.9
806	709.96	09:54:42.59	802	834	72.0	126.0
807	710.79	09:54:43.42	803	843	71.2	125.9

active orthostasis



	Phase 1	Phase 2 (early)	Phase 2 (late)	Phase 3	Phase 4
Normal blood pressure reaction	transient rise in blood pressure	clear decrease in blood pressure	recovery in blood pressure	short-term decrease in blood pressure	exaggerated increase in blood pressure
Para-sympathetic disturbance	normal reaction	reduced decrease in blood pressure	normal reaction	normal reaction	normal reaction
Slight sympathetic disturbance	normal reaction	highly developed decrease in blood pressure	reduced or no recovery in blood pressure	normal reaction	slight reduction in the increase in blood pressure
Moderate sympathetic disturbance	normal reaction	highly developed decrease in blood pressure	significant reduction in the increase in blood pressure	normal reaction	highly developed decrease in blood pressure
Severe sympathetic disturbance	normal reaction	extremely developed decrease in blood pressure	no recovery in blood pressure	normal reaction	no recovery in blood pressure

ANS assessment



Sustained handgrip test/ cold pressor test

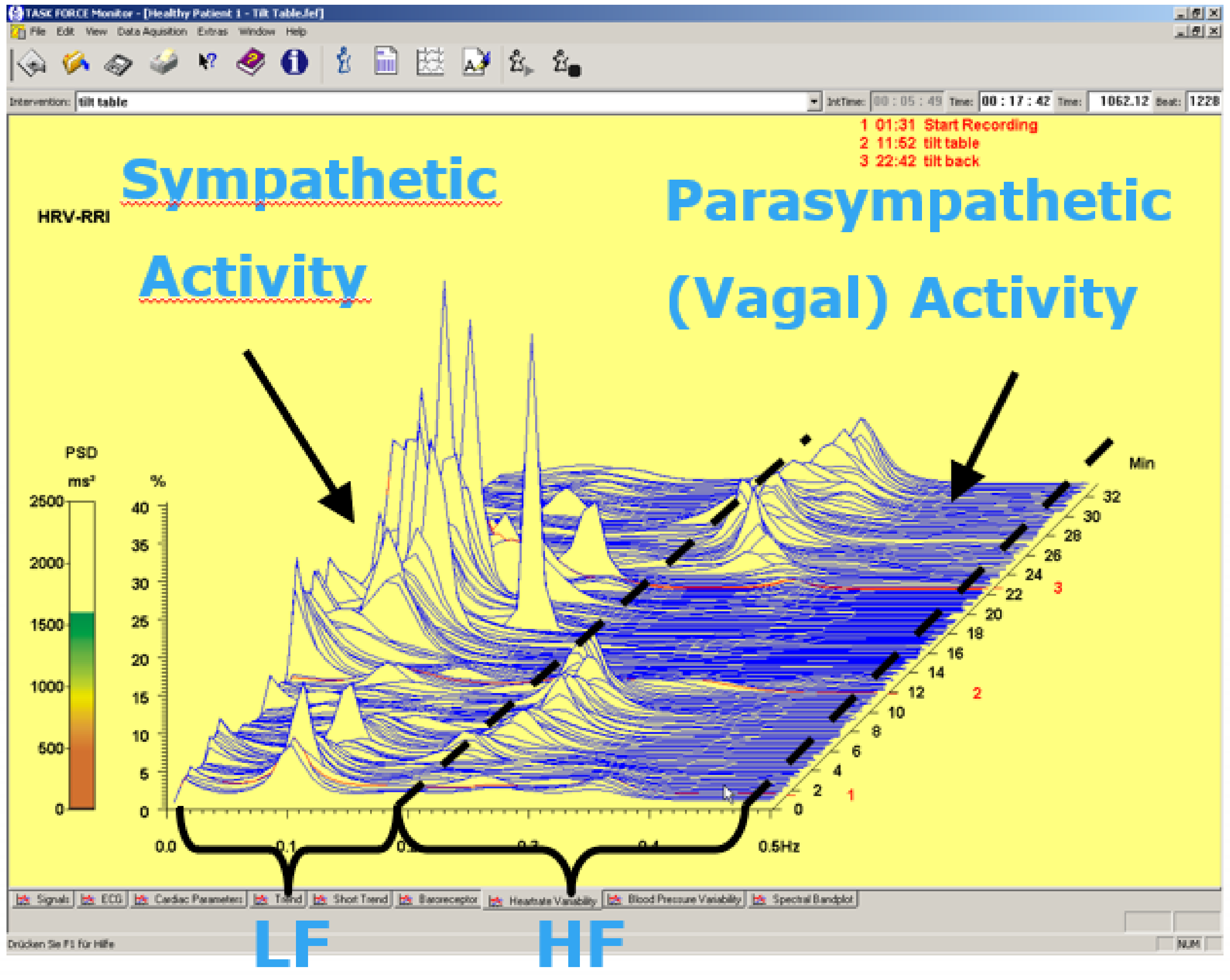
The sustained handgrip test provides valuable evidence for the function of the efferent sympathetic system: sustained muscle contraction causes a rise in blood pressure and heart rate.

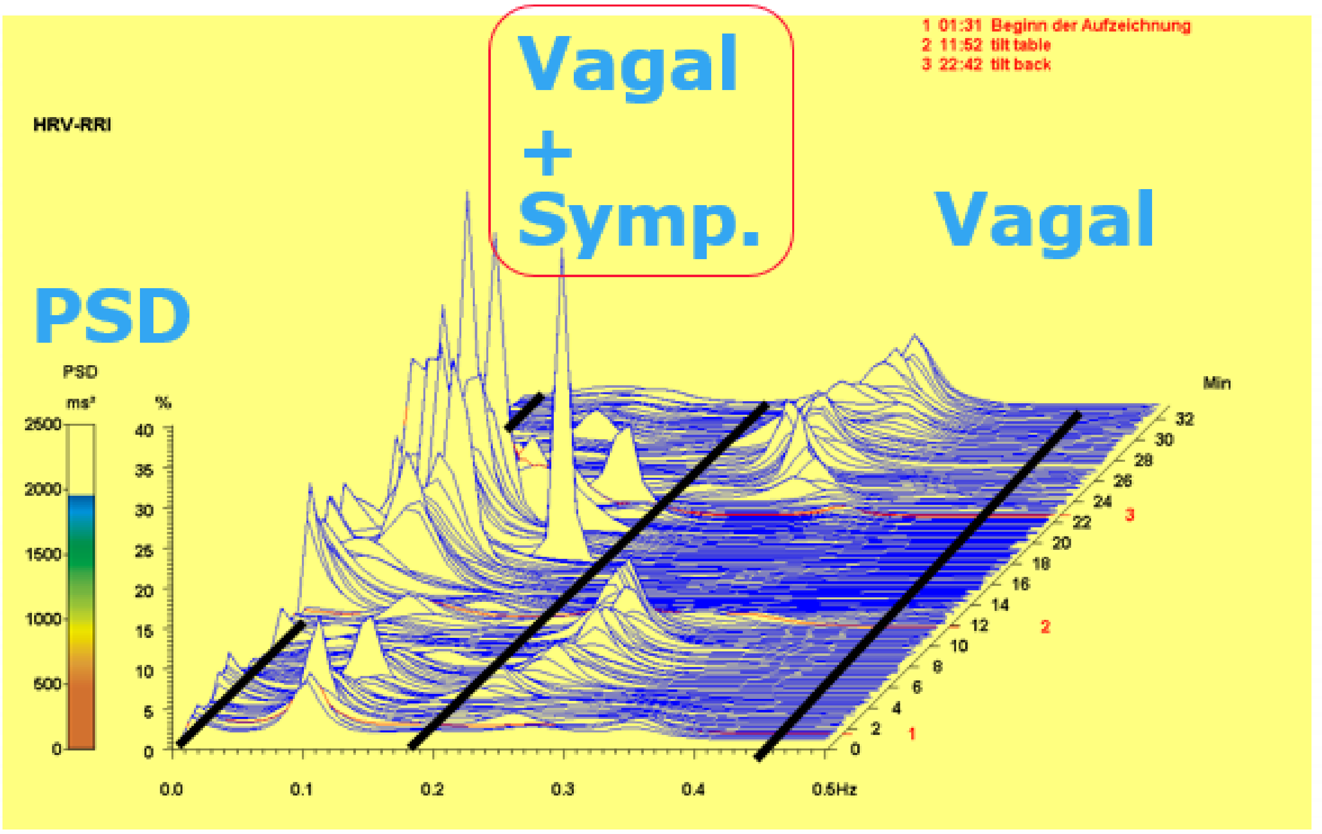
The normal response is a rise of diastolic blood pressure >16 mmHg, whereas a response of <10 mmHg is considered abnormal. In weak and elderly patients the sustained handgrip-test can be replaced by the cold pressor test (ice water test).

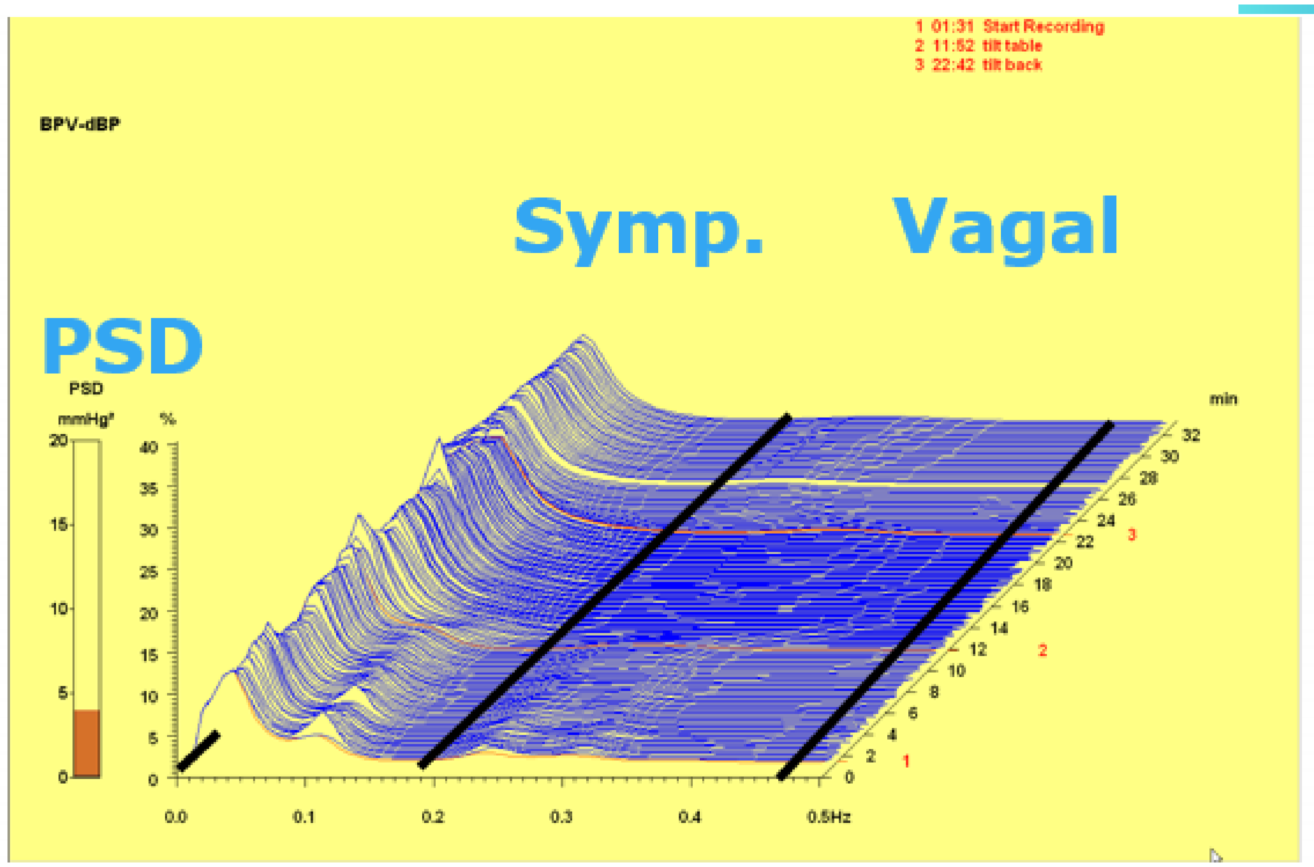
Hand grip strength and fatigability: correlation with clinical parameters and diagnostic suitability in ME/CFS

Bianka Jäkel[1], Claudia Kedor[1], Patricia Grabowski[1,2], Kirsten Wittke[1], Silvia Thiel[1], Nadja Scherbakov[3,4,5], Wolfram Doehner[3,4,5], Carmen Scheibenbogen[1,4] and Helma Freitag[1*]

Valsalva, Active Standing, Tilt-table testing
HRV, BPV and CBF







Sympathetic Modulation	Parasympathetic Modulation
LF-RRI [ms^2]	HF-RRI [ms^2]
LFnu-RRI [%]	HFnu-RRI [%]
LF-sBP [mmHg^2]	HF-sBP [mmHg^2]
LFnu-sBP [%]	HFnu-sBP [%]
LF-dBP [mmHg^2]	HF-dBP [mmHg^2]
LFnu-dBP [%]	HFnu-dBP [%]

BPV displays pure sympathetic component !

Valsalva, Active Standing, Tilt-table testing HRV, BPV and CBF

- ANS dysfunction presenting as increased sympathetic hyperactivity may contribute to fatigue severity in individuals with ME/CFS
- The differences in HR parameters identified by the meta-analysis indicate that ME/CFS patients have altered autonomic cardiac regulation when compared to healthy controls
- Objectively measured abnormalities of blood pressure variability in CFS and that these abnormalities have the potential to be a bedside diagnostic tool
- Cerebral blood flow in ME/CFS patients remains abnormal 5 min post-tilt test
- Post cerebral blood flow abnormalities are most severe in more severely diseased ME/CFS patients.

Randomized Trial

Cerebral Blood Flow and Heart Rate Variability in Chronic Fatigue Syndrome: A Randomized Cross-Over Study

Anneleen Malfliet, PT, MSc[1,2,12], Roselien Pas, PT, MSc[1,2], Raf Brouns, MD, PhD[4,5], ...n, MD[6], Samar M. Hatem, MD, PhD[2,7-9], Mira Meeus, PT, PhD[1,10,11], ...ns, PT, PhD[1-3], Robbert-Jan van Hooff, MD, PhD[4,5], and Jo Nijs, PT, PhD[1-3]

ELSEVIER
Journal of Psychosomatic Research
Volume 93, February 2017, Pages 6-13

Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: An exploratory pilot study

Petra Windthorst [a 1], Nazar Mazurak [a 1], Marvin Kuske [a], Arno Hipp [b], Katrin E. Giel [a], Paul Enck [a], Andreas Nieß [b], Stephan Zipfel [a], Martin Teufel [a]

https://doi.org/10.1186/s12967-019-02184-z
Journal of Translational Medicine
RESEARCH Open Access

Reduced heart rate variability predicts fatigue severity in individuals with chronic fatigue syndrome/myalgic encephalomyelitis

Rosa María Escorihuela[1*†], Lluís Capdevila[2], Juan Ramos Castro[3], María Cleofé Zaragozà[4], Sara Maurel[5], ...

Contents lists available at ScienceDirect
ELSEVIER
Clinical Neurophysiology Practice
journal homepage: www.elsevier.com/locate/cnp

Research paper

Cerebral blood flow remains reduced after tilt testing in myalgic encephalomyelitis/chronic fatigue syndrome patients

C. (Linda) M.C. van Campen [a,*], Peter C. Rowe [b], Frans C. Visser [a]

Medicine
Systematic Review and Meta-Analysis
OPEN

Evidence of altered cardiac autonomic regulation in myalgic encephalomyelitis/chronic fatigue syndrome

A systematic review and meta-analysis

QJM

Impaired blood pressure variability in chronic fatigue syndrome—a potential biomarker

J. FRITH[1,2], P. ZALEWSKI[3], J. J. KLAWE[3], J. PAIRMAN[1,2], A. BITNER[3], M. TAFIL-KLAWE[4] and J. L. NEWTON[1,2]

Valsalva, Active Standing, Tilt-table testing HRV, BPV and CBF

- There are different interrelation between hormones of the HPA axis, the SAM system, and the thyroid system in CFS patients and healthy controls, and an association between hormone control characteristics and important clinical variables in the CFS group.
- The CFS group was in a state of dysautonomia due to autonomic overstimulation, with an elevated baseline heart rate. The CFS group was considered to be in a state of impaired autonomic homeostasis, with an increased likelihood that overstimulation would induce a pathological vagal reflex and the Reilly phenomenon would develop.
- Combination of whole body cryotherapy with static stretching exercises reduces fatigue and improves functioning of the autonomic nervous system in CFS patients.

South African Journal of Physiotherapy
ISSN: (Online) 2410-8219, (Print) 0379-6175
AOSIS
Page 1 of 7 Original Research

The effects of warm water immersion on blood pressure, heart rate and heart rate variability in people with chronic fatigue syndrome

The Journal of Child Psychology and Psychiatry
ACAMH The Association for Child and Adolescent Mental Health
Journal of Child Psychology and Psychiatry **:* (2017), pp **–** doi:10.1111/jcpp.12711

Stress vulnerability in adolescents with chronic fatigue syndrome: experimental study investigating heart rate variability and skin conductance responses

Katharine A. Rimes, Kate Lievesley, and Trudie Chalder

Autonomic Nervous System Regulation Effects of Epipharyngeal Abrasive Therapy for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Associated With Chronic Epipharyngitis

Ito Hirobumi [1]

Kujawski et al. Journal of Translational Medicine (2022) 20:273
https://doi.org/10.1186/s12967-022-03460-1
Journal of Translational Medicine
RESEARCH Open Access

Combination of whole body cryotherapy with static stretching exercises reduces fatigue and improves functioning of the autonomic nervous system in Chronic Fatigue Syndrome

Sławomir Kujawski[1*], Joanna Słomko[1], Beata R. Godlewska[2], Agnieszka Cudnoch-Jędrzejewska[3], Modra Murovska[4], Julia L. Newton[5], Łukasz Sokołowski[1] and Paweł Zalewski[1,3]

Sympathetic innervation and HRV

Liver volume is lower and associates with resting and dynamic blood pressure variability in chronic fatigue syndrome

Pawel Zalewski, Andreas Finkelmeyer, James Frith, Laura Maclachlan, Andrew Blamire & Julia L. Newton

Table 1. Relationship between liver volume corrected for body surface area and symptom burden, hemodynamic measures and vascular volume.

		r	P	r^2	95% CI
Symptoms	FIS	0.07	0.7	0.005	−0.2 ; 0.4
	Compass 31 Total	−0.07	0.6	0.005	−0.3 ; 0.2
Hemodynamics	DBP	0.18	0.2	0.03	−0.1 ; 0.4
	HR	0.05	0.7	0.003	−0.2 ; 0.3
	MBP	0.18	0.19	0.03	−0.1 ; 0.4
	SBP	0.2	0.13	0.04	−0.1 : 0.4
Diastolic blood pressure variability	HFnu	0.09	0.5	0.008	−0.2 ; 0.3
	LF/HF	0.08	0.55	0.007	−0.3 ; 0.2
	LFnu	−0.36	0.008*	0.13	−0.6 ; −0.1
	PSD	0.10	0.5	0.009	−0.2 ; 0.4
Systolic blood pressure (SBP) variability	HFnu	0.13	0.35	0.02	−0.1 ; 0.4
	LF/HF	−0.18	0.19	0.03	−0.4 ; 0.1
	LFnu	−0.4	0.0032*	0.2	−0.6 ; −0.1
	PSD	0.05	0.7	0.003	−0.2 ; 0.3
Impedance measures	Acceleration cardiac index	−0.33	0.01*	0.11	−0.6 ; −0.1
	Cardiac Index	−0.2	0.15	0.04	−0.5 ; 0.1
	Stroke Index	−0.2	0.13	0.04	−0.5 ; 0.1
	Total peripheral resistance index	0.3	0.018*	0.10	0.1 ; 0.5
	Thoracic fluid content	−0.36	0.008*	0.13	−0.6 ; −0.1
	Baroreflex sensitivity	−0.3	0.03*	0.084	−0.5 ; −0.01
	Return to baseline SBP	0.4	0.005*	0.14	0.1 ; 0.6
	RR15	0.35	0.01*	0.12	0.1 ; 0.6
	Red cell volume	0.3	0.05*	0.07	0.003 ; 0.5
	Plasma Volume	0.3	0.04*	0.08	0.01 ; 0.5

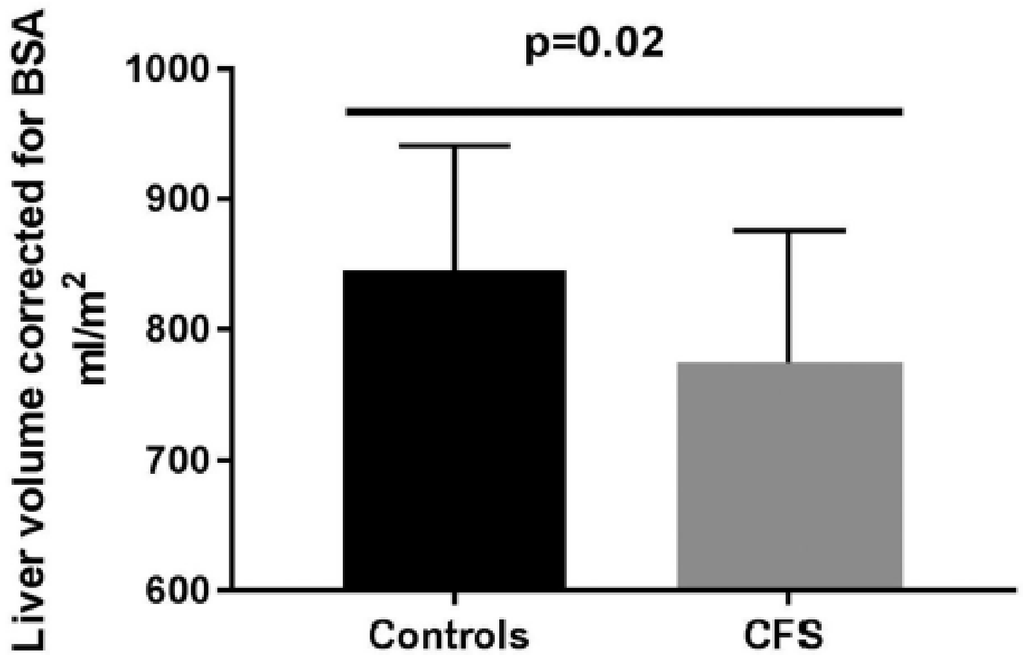


Figure 3. Liver volume corrected for body surface area is significantly reduced in CFS ($N = 44$) compared to controls ($N = 10$) matched group wise for age, sex and activity.

Cardiac sympathetic innervation associates with autonomic dysfunction in chronic fatigue syndrome – a pilot study

George Petrides, Pawel Zalewski, David McCulloch, Laura Maclachlan, Andreas Finkelmeyer, Tim Hodgson, Andrew Blamire & Julia L. Newton

CFS subjects demonstrate disturbed myocardial adrenergic innervation and adrenergic innervation defects.

POTENTIAL PHENOTYPES of ME/CFS

Are current chronic fatigue syndrome criteria diagnosing different disease phenotypes?

Laura Maclachlan[1¤], Stuart Watson[2,3], Peter Gallagher[2], Andreas Finkelmeyer[2], Leonard A. Jason[4], Madison Sunnquist[4], Julia L. Newton[1,5]*

Extended B cell phenotype in patients with myalgic encephalomyelitis/chronic fatigue syndrome: a cross-sectional study

F. Mensah, A. Bansal, S. Berkovitz, A. Sharma, V. Reddy, M. J. Leandro, G. Cambridge

Clinical Heterogeneity in ME/CFS. A Way to Understand Long-COVID19 Fatigue

Iñigo Murga[1*], Larraitz Aranburu[2], Pascual A. Gargiulo[3], Juan Carlos Gómez Esteban[1,4] and José-Vicente Lafuente[1,4]

Deep phenotyping of myalgic encephalomyelitis/chronic fatigue syndrome in Japanese population

Toshimori Kitami, Sanae Fukuda, Tamotsu Kato, Kouzi Yamaguti, Yasuhito Nakatomi, Emi Yamano, Yosky Kataoka, Kei Mizuno, Yuuri Tsuboi, Yasushi Kogo, Harukazu Suzuki, Masayoshi Itoh, Masaki Suimye

Chronic fatigue syndrome (CFS/ME) symptom-based phenotypes and 1-year treatment outcomes in two clinical cohorts of adult patients in the UK and The Netherlands

Simon M. Collin[a], Jon Heron[a], Stephanie Nikolaus[b], Hans Knoop[b], Esther Crawley[a]

Phenotypic characteristics of peripheral immune cells of Myalgic encephalomyelitis/chronic fatigue syndrome via transmission electron microscopy: A pilot study

Fereshteh Jahanbani[1©]*, Rajan D. Maynard[1©], Justin Cyril Sing[2], Shaghayegh Jahanbani[3], John J. Perrino[4], Damek V. Spacek[5], Ronald W. Davis[6], Michael P. Snyder[1]*

Association of T and NK Cell Phenotype With the Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Rivas JL[1], Palencia T[1], Fernández G[2], García M[1]

Journal of
Clinical Medicine

MDPI

Article

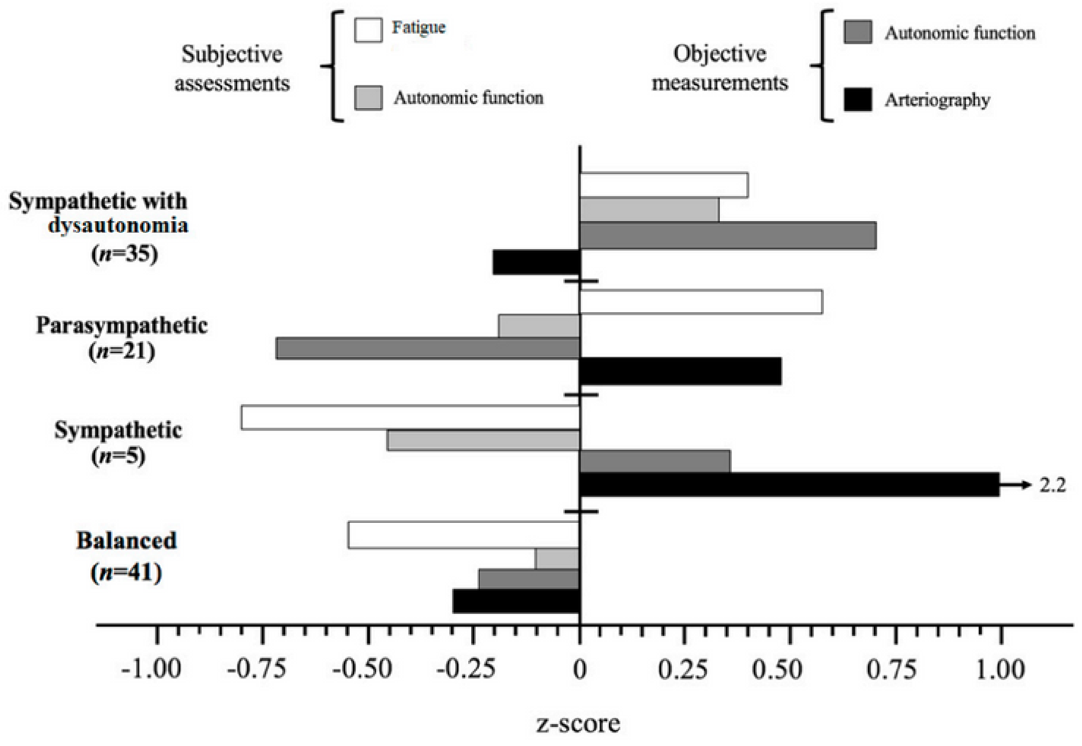
Autonomic Phenotypes in Chronic Fatigue Syndrome (CFS) Are Associated with Illness Severity: A Cluster Analysis

Joanna Słomko [1,*], Fernando Estévez-López [2], Sławomir Kujawski [1], Monika Zawadka-Kunikowska [1], Małgorzata Tafil-Klawe [3], Jacek J. Klawe [1], Karl J. Morten [4], Justyna Szrajda [1], Modra Murovska [5], Julia L. Newton [6] and Paweł Zalewski [1] on behalf of the European Network on ME/CFS (EUROMENE)

In this study we set out to define the characteristics of autonomic subgroups of patients with Chronic Fatigue Syndrome (CFS).

It was hypothesized that fatigue severity was different in relation to autonomic function in patients with CFS.

Factor	Cronbach's α	Scales/Measurements
Fatigue	0.86	Chalder Fatigue Scale, mental domain (CFQ), Fatigue Severity Scale and Fatigue Impact Scale
Subjective autonomic function	0.73	Chalder Fatigue Scale—physical domain (CFQ), Epworth Sleepiness Scale (ESS), Orthostatic Grading Scale (OGS, total score), orthostatic intolerance (COMPASS), secretomotor (COMPASS), gastrointestinal (COMPASS) and pupilomotor (COMPASS)
Objective autonomic function	0.68	LFnu-RRI, LFnu-dBP and LFnu-sBP (all, Task Force Monitor—TFM, CNS Systems, Gratz, Austria)
Arterial stiffness	0.76	Aortic pulse wave velocity (PWVaortic), augmentation index (Aixaortic) and central blood pressure (SBPaortic); (all, Arteriograph, TensioMed Budapest, Hungary)



Participants

131 participants:
29 excluded (did not meet the Fukuda criteria, n = 9, had an underlying psychiatric illness, n = 13, had another diagnosis or fatigue was not the primary complain, n = 7).
Of the total group with CFS (n = 102), 64.7% were female, mean age was 38.1±8.0 years and years since first episode of fatigue 4.5 ± 4.1 years.

Tools

Chalder Fatigue Scale,
Fatigue Impact Scale,
Fatigue Severity Scale,
Epworth Sleepiness Scales,
self-reported Composite Autonomic Symptom Scale;
Task Force Monitor (CNS Systems)
Arteriograph (TensioMed Kft.)

Factors

fatigue,
subjective autonomic dysfunction,
objective autonomic dysfunction,
arterial stiffness

Profiles

sympathetic symptoms with dysautonomia (34%),
sympathetic alone (5%),
parasympathetic (21%)
sympathovagal balance (40%)

Differences in factors between subgroups, n = 102.

Factors #	Post-hoc Differences Testing	F (3, 98)	*p*
Fatigue	Parasympathetic, Sympathetic with dysautonomia > Balanced, Sympathetic	32.57	<0.001
Subjective autonomic function	Sympathetic with dysautonomia > Balanced, Parasympathetic, Sympathetic	6.40	0.001
Objective autonomic function	Sympathetic with dysautonomia, Sympathetic > Balanced > Parasympathetic	33.57	<0.001
Arteriography	Sympathetic > Parasympathetic > Sympathetic with dysautonomia, Balanced	30.63	<0.001

Post-hoc differences were tested by Student-Newman-Keuls.

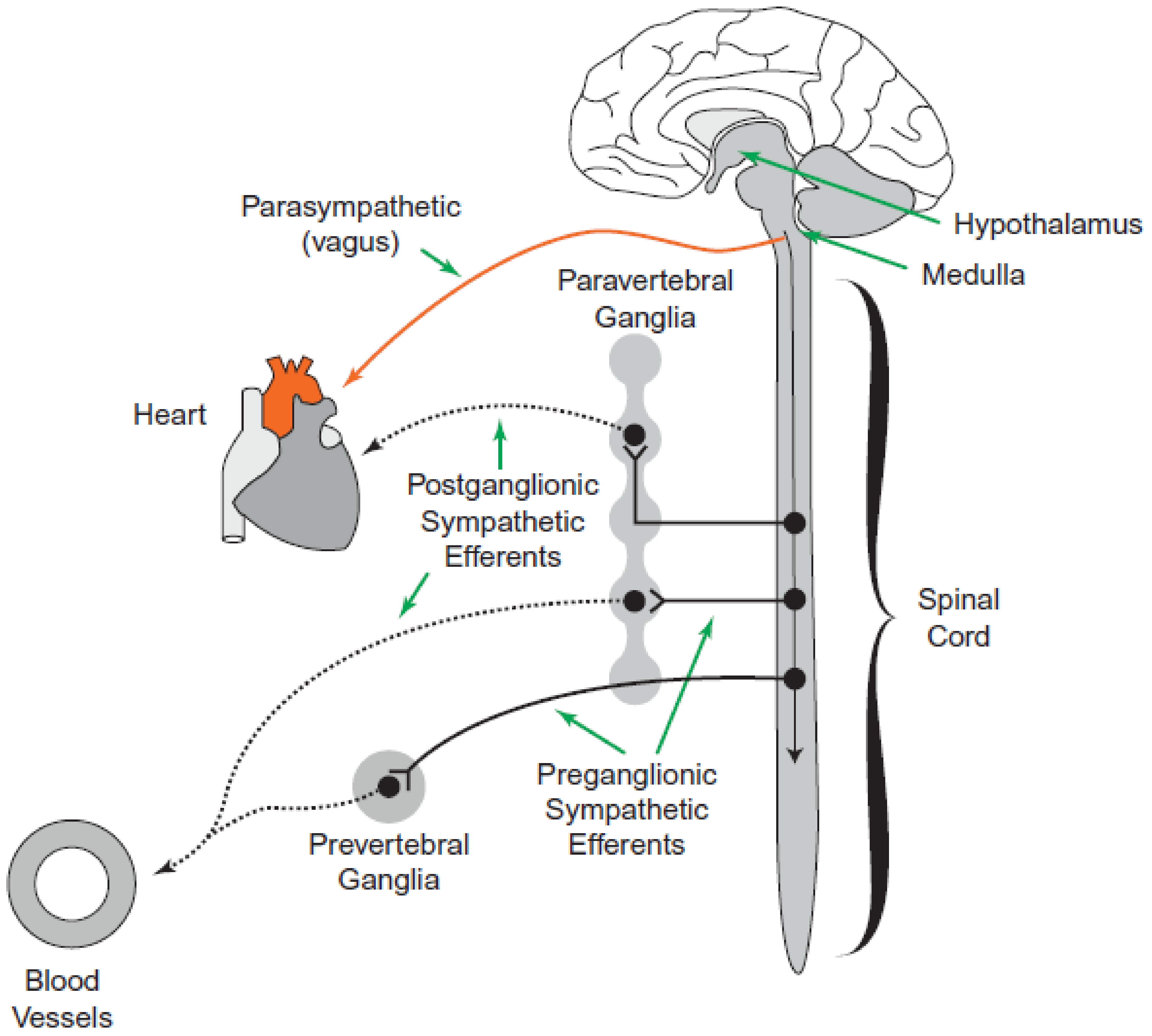
The sympathetic with dysautonomia subtype was distinguished by more frequent postexertional malaise than other subtypes, more severe disease expressed by high value of fatigue scales, most frequently reported greater subjective autonomic symptoms with sympathetic over-modulation and the lowest quality of life;

Patients characterized by the **parasympathetic** profile were at higher risk of fatigue;

Patients in the **sympathetic** subtype were the oldest, at lower risk of fatigue, reported the least subjective autonomic symptoms with sympathetic over-modulation and had the highest value of arterial stiffness;

Patients in the **balance** subtype were the youngest, at lower risk of fatigue, in sympathovagal balance, had the highest quality of life and had the lowest value of arterial stiffness.

Thank you



Parasympathetic
(vagus)
Hypothalamus
Medulla
Paravertebral
Ganglia
Heart
Postganglionic
Sympathetic
Efferents
Spinal
Cord
Preganglionic
Sympathetic
Efferents
Prevertebral
Ganglia
Blood
Vessels