Evaluation of Chronic Autonomic Symptoms in Gulf War Veterans with Unexplained Fatigue

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- Funded by VA Merit Review Clinical Science R & D
- Research approved by local IRB/R & D and conducted in VAMC-DC with compliance of stipulated human research regulations and VA policies regarding report or dissemination of research and non-research information.

Rationale

- GW veterans (7.7%) reported dizziness/imbalance. blurred vision, excessive fatigue, or tremor (Kang HK, et al. Illnesses among United States veterans of the Gulf War: a population-based survey of 30,000 veterans. J Occup Environ Med 2000; 42(5): 491-501
- Reported neurological symptoms are similar or identical to those from patients with diseases of autonomic nervous system
- Ill group (deployed) with post-exertion fatigue
- Control (deployed) without fatigue
- Objective of this study
- Autonomic parameters useful in treatment

Peripheral Autonomic Nervous System

- Afferent Pathways
- Efferent Components

  parasympathetic and sympathetic
- Neurotoxin may preferentially affect small nerve fiber
- Small fiber neuropathy vs Autonomic neuropathy
- Long delay in diagnosing autonomic system disorder:

  a) unclear nature course of acquired autonomic disorders

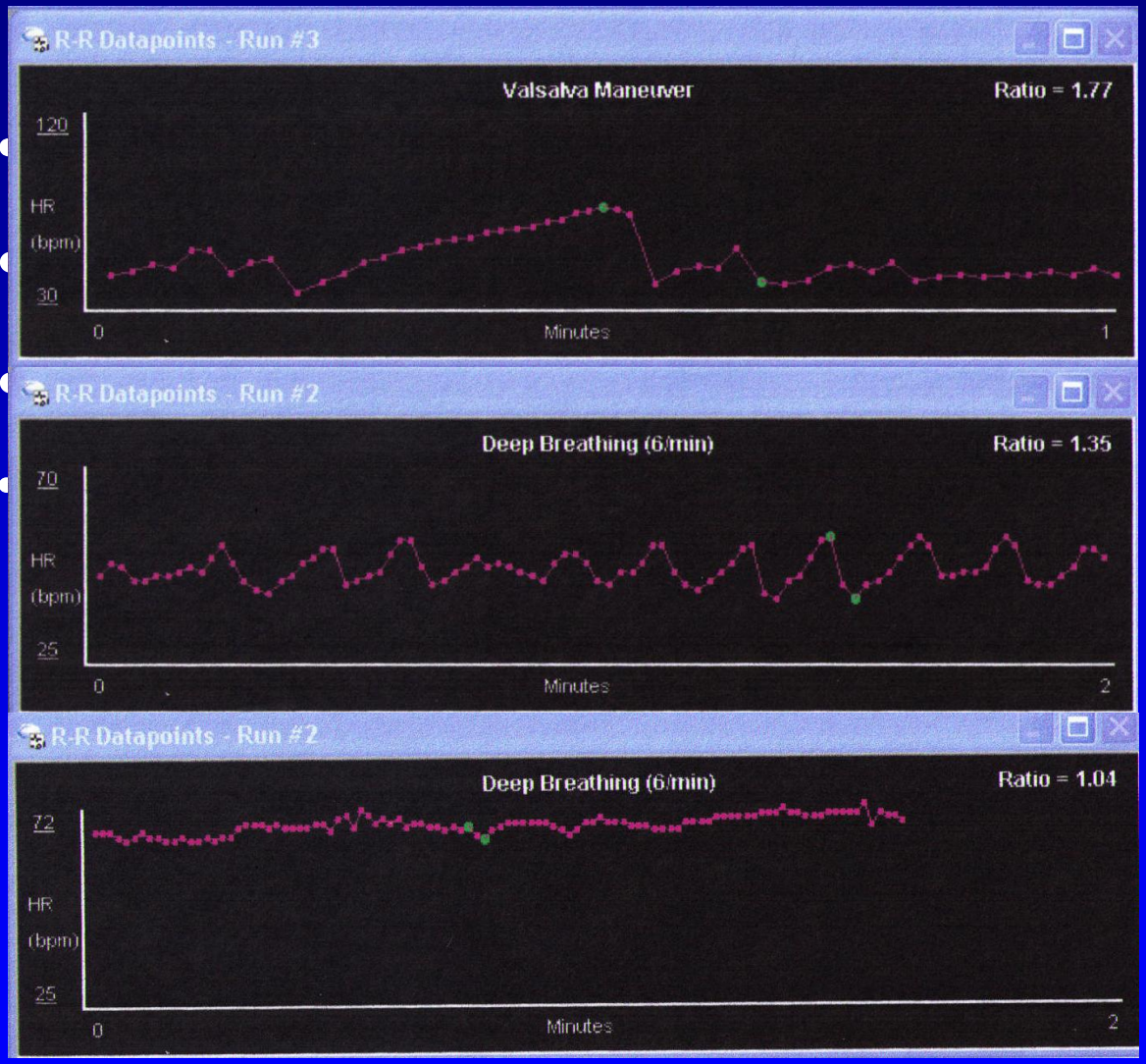
  b) lack of appropriate investigative team

Spectrum of Clinical Autonomic Disorders in Military Veterans at VAMC-DC

- Complex regional pain syndrome (CRPS)
- Central autonomic disorder
- Postural orthostatic tachycardia syndrome (POTS)
- Cardiac autonomic neuropathy
- Small fiber neuropathy
- Autoimmune Autonomic neuropathy

- Baroreflex Dysfunction
- Subset of IBS, CFS, Fibromyalgia, Multi-symptom Unexplained Illness, Chronic Pain Syndrome
- Post-traumatic disorders

Autonomic Testing in literatures about GW Research
Heart Rate Variability



Normal Valsalvar maneuver

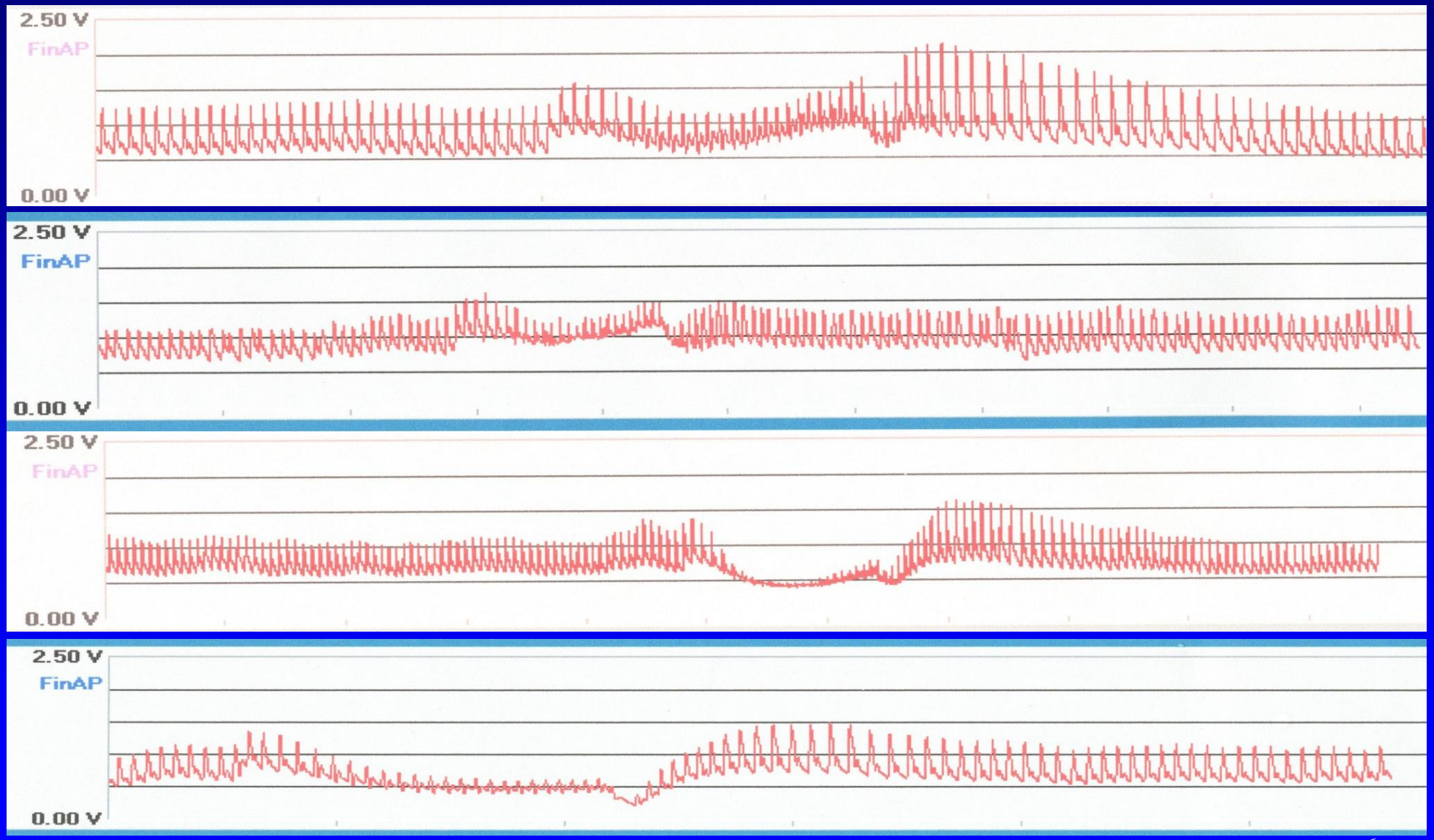
Normal HRV to deep breathing

High Resting Rate

Abnormal HRV to deep breathing

Screening tool for cardiovagal function, interpretation needs beat-to-beat BP measurement

Panel 1: normal; 2: β-blocker; 3: reduced PP; 4: α-blocker



"Valsalva ratio": why so low? What's the next to do?

Table 6 *Means ± SD of thermals and vibration perception thresholds according to neuromuscular symptoms at initial assessment*

Thermals and vibration perception thresholds	Gulf War-ill veterans	Gulf War-well veterans	Symptomatic Bosnia veterans	Symptomatic Era veterans
Hand				
Vibration thresholds	0.8 ± 0.6	0.6 ± 0.5	0.4 ± 0.3	0.5 ± 0.4
Cool sensory thresholds, °C	30.1 ± 0.9	30.3 ± 0.8	30.3 ± 0.8	30.2 ± 0.7
Warm sensory thresholds, °C	34.3 ± 1.3	34.1 ± 0.7	34.2 ± 0.8	34.1 ± 0.7
Cold-related pain thresholds, °C	7.2 ± 6.1	5.8 ± 5.2	7.1 ± 6.9	6.9 ± 6.6
Heat-related pain thresholds, °C	47.4 ± 6.8	47.3 ± 2.9	47.2 ± 3.9	46.3 ± 4.1
Sweating, g/m^2 h	10.4 ± 6.9	9.8 ± 6.3	10.3 ± 7.7	14.3 ± 8.3
Foot				
Vibration thresholds	4.8 ± 5.5	5.3 ± 6.1	2.4 ± 2.0	4.4 ± 3.9
Cool sensory thresholds, °C	26.5 ± 1.9	26.5 ± 1.9	26.5 ± 1.9	26.5 ± 1.9
Warm sensory thresholds, °C	39.1 ± 3.5	39.1 ± 3.5	39.1 ± 3.5	39.1 ± 3.5
Cold-related pain thresholds, °C	9.1 ± 8.1	10.1 ± 7.9	8.5 ± 8.4	9.5 ± 9.1
Heat-related pain thresholds, °C	48.4 ± 2.0	47.1 ± 2.0	47.8 ± 3.1	48.1 ± 2.5
Sweating, g/m^2 h	13.8 ± 10.1	14.9 ± 9.7	10.3 ± 6.5	18.1 ± 12.6
Cardiovascular reflexes				
Valsalva ratio	1.11 ± 0.25	1.23 ± 0.22	1.12 ± 0.16	1.24 ± 0.32
Standing ratio	1.21 ± 0.35	1.18 ± 0.30	1.31 ± 0.25	1.31 ± 0.32

Sharief MK, et al. Neurology, 2002;59:1518--1525

Table 1. Autonomic symptoms of study participants

Group	Ill (n=17)	Control (n=13)
age (years; range)	47.7 ± 1.3 (39-58)	47.8 ± 1.9 (40-64)
Sex distributions (M/F)	14/3	12/1
BMI (M ± SEM)	33.6 ± 2.1	28.8 ± 1.4
Night diarrhea	3	0
Sexual dysfunction	4	3
Syncope	4	1
Abdominal pain	6	2
Dry eye /dry mouth	6	1
Anxiety	8	1
Tremor	8	1
Dizziness	8	1
Blurred vision	11	1
Weakness	11	1
Excessive fatigue	17	0

Values are mean ± SEM. M/F: male/female.

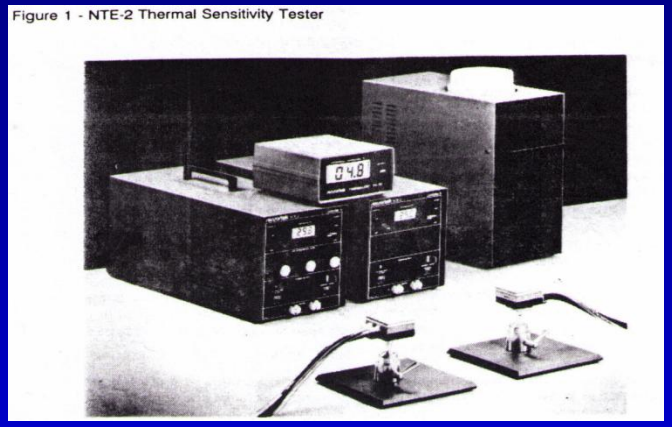
Table 2. The alteration of heart rate and blood pressure in standing, tilt table, deep breath and Valsalvar maneuver in ill (n=17) and control(n=13) groups.

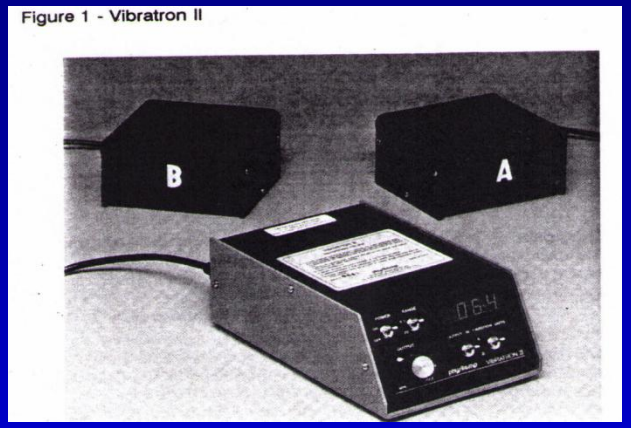
	Ill	Control	P Value
Supine systolic BP	128.4 ± 1.9	132.6 ± 2.2	0.299
Supine diastolic BP	76.8 ± 1.2	77.4 ± 1.7	0.780
Supine heart rate	78.9 ± 2.4 **	65.6 ± 2.8	<0.01
Standing systolic BP	125.7 ± 2.4	129.1 ± 2.3	0.189
Standing diastolic BP	79.8 ± 1.1	83.1 ± 2.3	0.629
Standing heart rate	93.1 ± 3.6 **	75.1 ± 3.5	<0.01
Maximum-minimum HR	15.2 ± 2.2	11.5 ± 2.2	0.236
Standing systolic BP fall	-5.5 ± 3.1	-5.6 ± 1.9	0.972
Standing diastolic BP increase	4.0 ± 1.2	5.8 ± 1.7	0.367
Tilt table headup systolic BP fall	10.4 ± 3.3 (n=16)	2.9 ± 4.4	0.179
Tilt table headup diastolic BP fall	10.9 ± 2.5 (n=16)	1.4 ± 3.8	0.843
Tilt table maximum HR	93.6 ± 3.1 * (n=16)	81.5 ± 4.6	<0.05
Tilt table HR increase	17.9 ± 2.4 (n=16)	17.7 ± 3.9	0.956
HRVdb Ratio	1.38 ± 0.04	1.33 ± 0.03	0.759
HRVvm Ratio	1.64 ± 0.03	1.84 ± 0.08	0.057

Test results expressed as mean ± SEM. HR: heart rate (beats/min). BP: blood pressure (mmHg).
* $p<0.05$, **$P < 0.01$.

Autonomic Testing in literatures about GW Research

- Quantitative Sensory Testing for Small Fiber Neuropathy



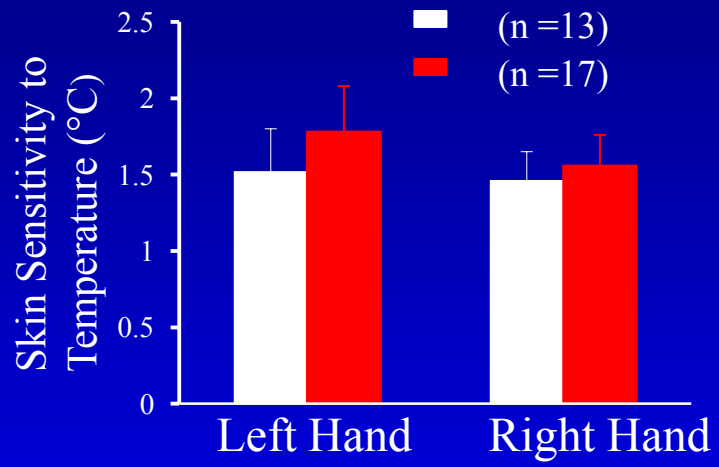


Comments on QST

- Nerve root or other pathology complicates the interpretation (Veterans with Low Back Pain)
- Sensitivity and specificity varies among Labs
- Less optimal in "positive symptoms"

Quantitative Sensory Testing (QST)

A



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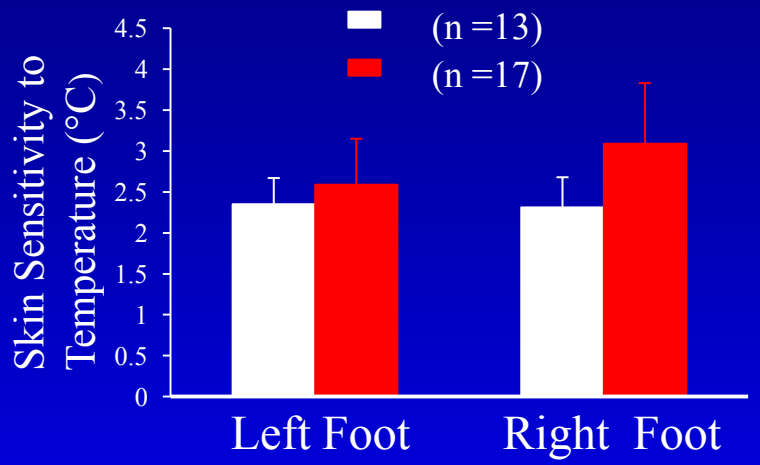

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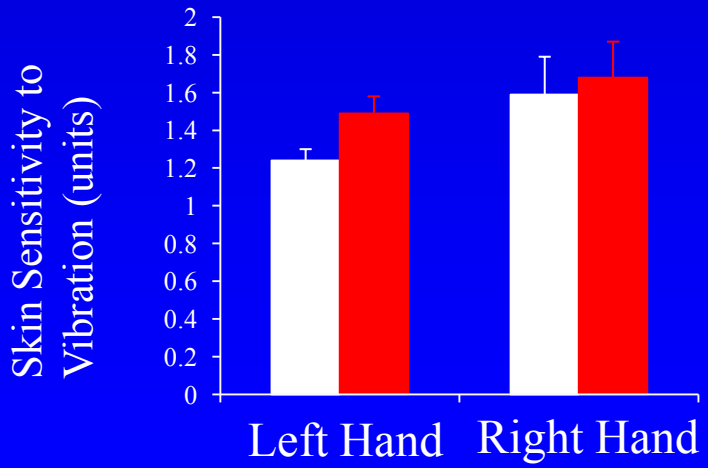

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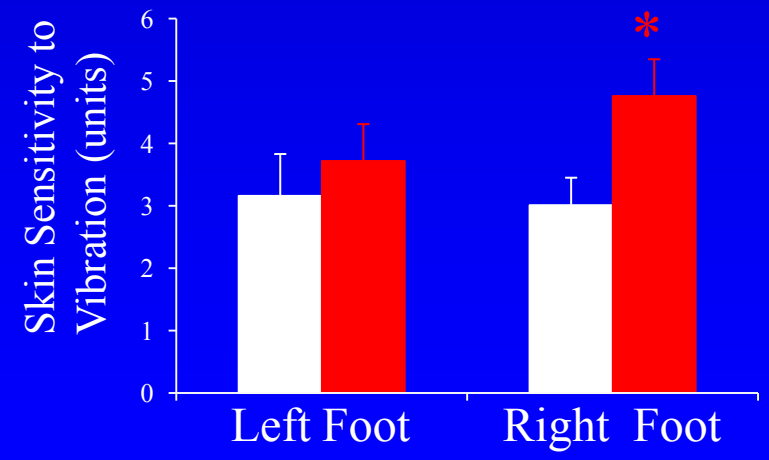


How do you interpret: more focal (compression) neuropathy in Control, more or less distal symmetrical sensory in this group?

Table 6 *Type of distal symmetric polyneuropathy diagnosed in deployed and non-deployed veterans and their spouses*

	Co-existing conditions included				Co-existing conditions excluded			
Type of neuropathy	Deployed, n = 1,061, %	Non-deployed, n = 1,128, %	*p* Value	OR (95% CI)	Deployed, n = 1,049, %	Non-deployed, n = 1,121, %	*p* Value	OR (95% CI)
Veterans*								
Sensory								
Physical examination	3.1	2.6	0.60	1.20 (0.61, 2.33)	2.2	2.3	0.88	0.94 (0.44, 2.03)
NCS	0.4	0.4	0.95	1.07 (0.15, 7.55)	0.4	0.3	0.76	1.41 (0.15, 13.03)
Either examination or NCS	3.5	3.0	0.61	1.18 (0.63, 2.23)	2.5	2.5	0.98	0.99 (0.48, 2.04)
Motor								
Physical examination	0.0	0.0	NA	NA	0.0	0.0	NA	NA
NCS	0.2	0.8	0.02	0.25 (0.07, 0.83)	0.2	0.8	0.04	0.26 (0.08, 0.92)
Either examination or NCS	0.2	0.8	0.02	0.25 (0.07, 0.83)	0.2	0.8	0.04	0.26 (0.08, 0.92)
Sensorimotor								
Physical examination	0.0	0.0	NA	NA	0.0	0.0	NA	NA
NCS	3.1	5.1	0.13	0.60 (0.31, 1.17)	2.5	3.7	0.32	0.67 (0.31, 1.47)
Either examination or NCS	3.1	5.1	0.13	0.60 (0.31, 1.17)	2.5	3.7	0.32	0.67 (0.31, 1.47)
Spouses†	Deployed, n = 484,%	Non-deployed, n = 533, %	*p* Value	OR (95% CI)	Deployed, n = 482, %	Non-deployed, n = 527, %	*p* Value	OR (95% CI)
Sensory‡	2.7	3.2	0.64	0.84 (0.31, 2.30)	2.3	2.1	0.83	1.10 (0.34, 3.50)
Motor	0.0	0.0	NA	NA	0.0	0.0	NA	NA
Sensorimotor	0.0	0.0	NA	NA	0.0	0.0	NA	NA

* Prevalences were generated in SUDAAN.
† Prevalences were generated in SAS.
‡ 99.3% CI.

NCS = nerve conduction study.

Davis, LE, et al. Neurology 2004;63(6):1070-1077

Neurological symptom score

Score 1 point for presence of a symptom

•***Symptoms of muscle weakness***

A. Bulbar

1. Extraocular _____
2. Facial _____
3. Tongue _____
4. Throat _____

B. Limbs

5. Shoulder girdle and upper arm _____
6. Hand _____
7. Glutei and thigh _____
8. Legs _____

•***Sensory disturbances***

A. Negative symptoms

9. Difficulty identifying objects in mouth _____
10. Difficulty identifying objects in hands _____
11. Unsteadiness in walking _____

B. Positive symptoms

12. "Numbness," "asleep feeling," like Novocain,"
" prickling," at any site _____
13. Pain burning, deep aching,
Render ness at any location _____

•***Autonomic symptoms***

14. Postural fainting _____
15. Impotence in male _____
16. Loss of urinary control _____
17. Night diarrhea _____

Dyck PJ. et al. Ann Neurol 8; 590-596, 1980

Total Neuropathy Score

Parameter	Score 0	1	2	3	4
Sensory symptoms	None	Symptoms limited To fingers or toes	symptoms limited to ankle or wrist	Symptoms extend to knee Or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require Help/assistance	Paralysis
Autonomic symptoms, n	0	1	2	3	4 or 5
Pin, sensibility	Normal	Reduced in fingers/Toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/ Knee
Vibration sensibility	Normal	Reduced in finger/ Toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/ Knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent Others reduced	All reflexes absent
Vibration sensation (QST vibration)	Normal to 125% ULN	126% to 150% ULN	151% to200 ULN	201 to 300% ULN	>300% ULN
Sural amplitude	Normal/reduced To <5% LLN	76 to 95% of LLN	51 to 75% of LLN	26 to 50% of LLN	0 to 25% of LLN
Personal amplitude	Normal/reduced To <5% LLN	76 to 95% of LLN	51 to 75% of LLN	26 to 50% of LLN	0 to 25% of LLN

QST = quantitative sensory test; ULN = upper limit of normal; LLN = lower limit of normal

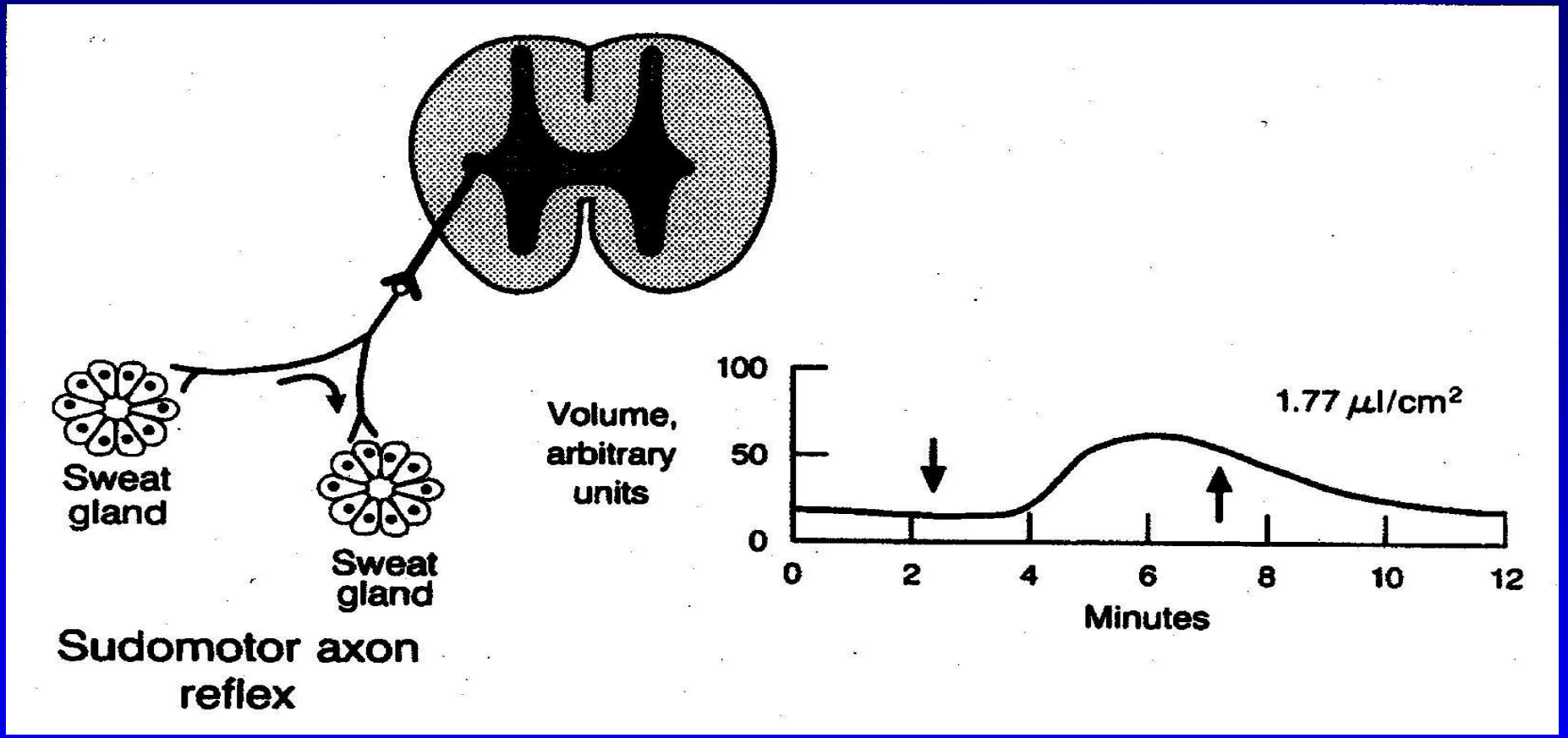
Total Neuropathy Score

- Initially designed for neurotoxin related neuropathy
- Useful outcome measures for length-dependant symmetrical polyneuropathy
- Components of sensory, motor, and autonomic symptoms
- Objective measurement based on large fiber data
- Diabetic Neuropathy (n=35)

	mild	moderate	severe	control
Mean	12	20	25	0.4
SD	5.2	4.9	7.4	0.5

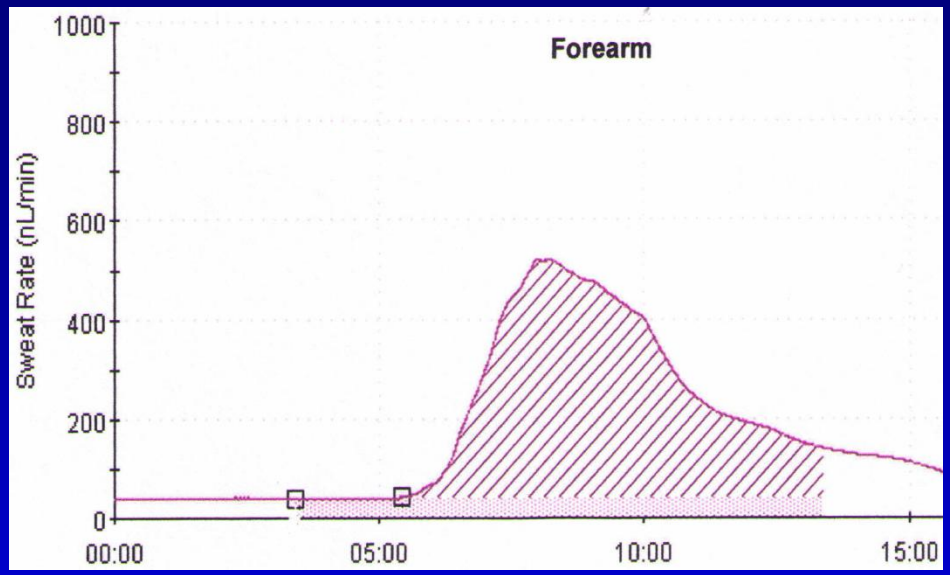
(*Cornblath, DR, et al. Neurology 1999;53:1660-4*)

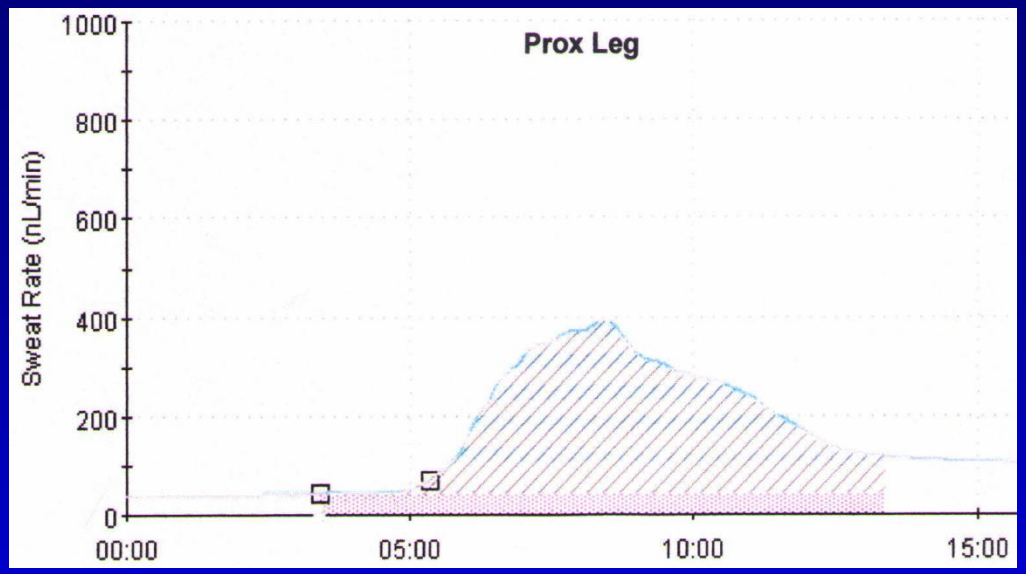
QSART Neural Pathway (P256, Clinical Neurophysiology)

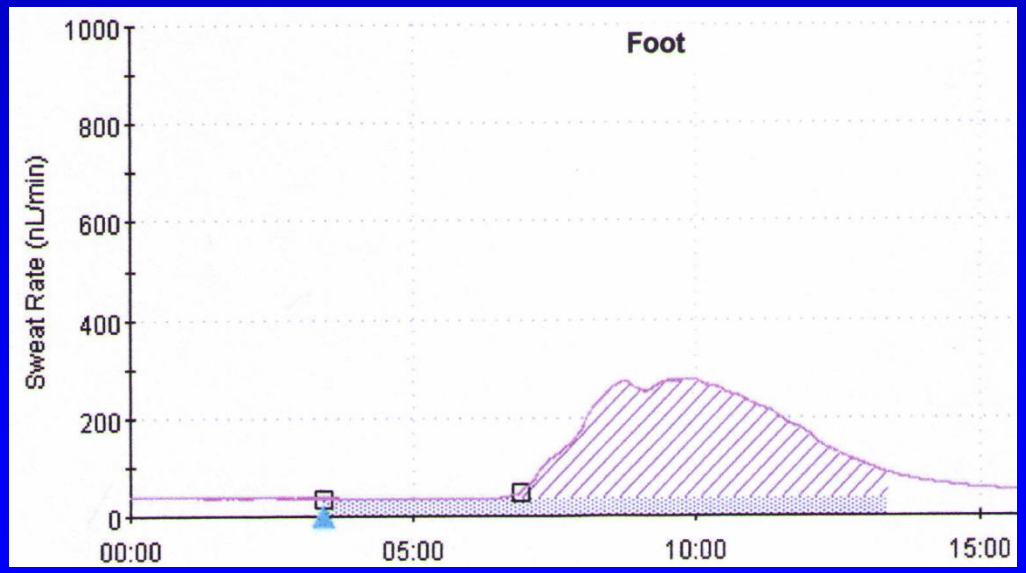


Our research method: Quantitative Sensory Axonal Reflex Testing
Clinical significance: correlated c somatic small nerve fiber on skin biopsy

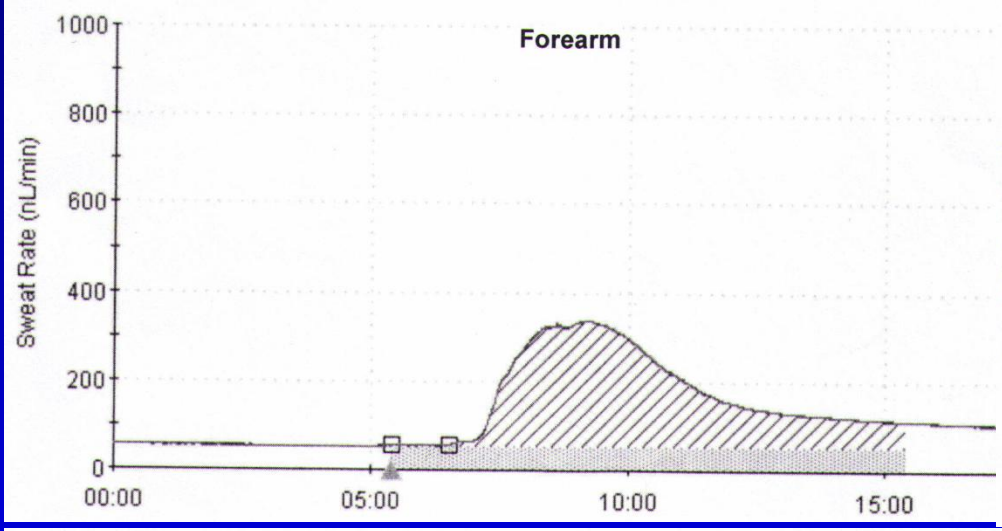
Normal Control

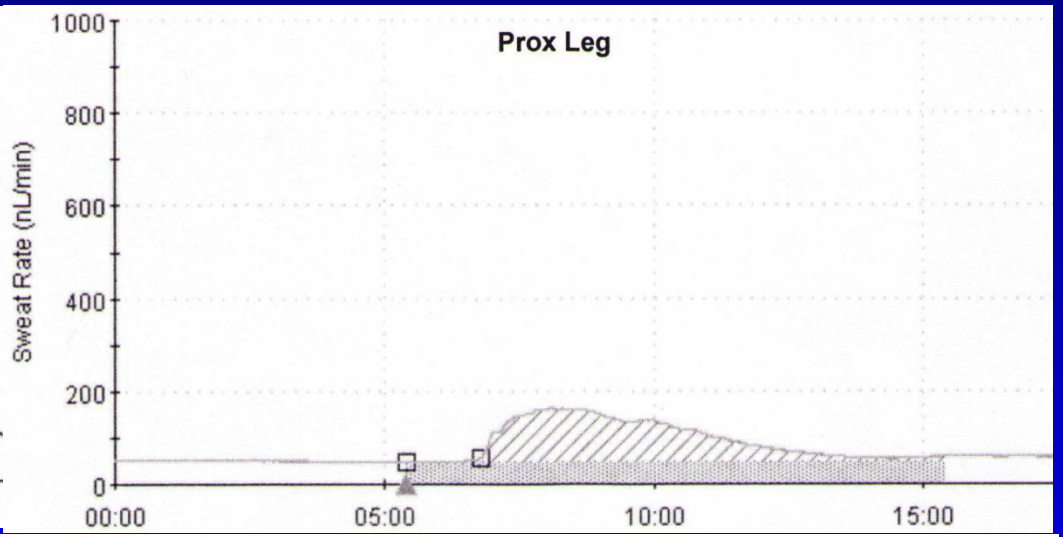


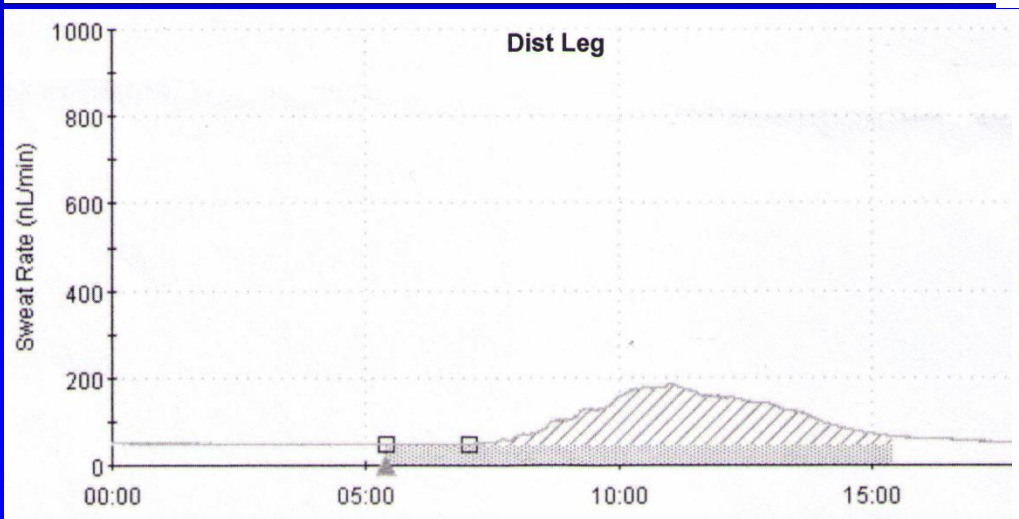




Sudomotor Impairment in Length-dependant small fiber Neuropathy







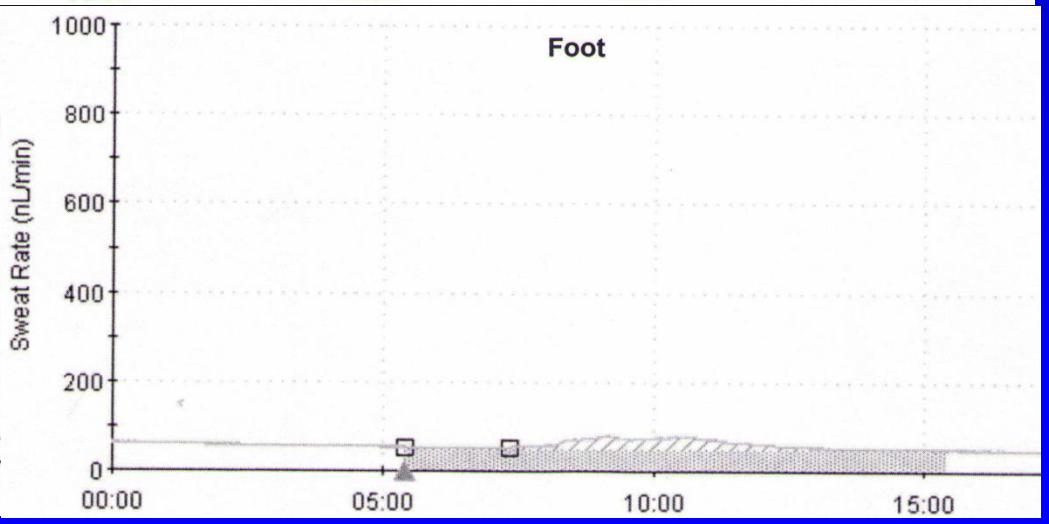
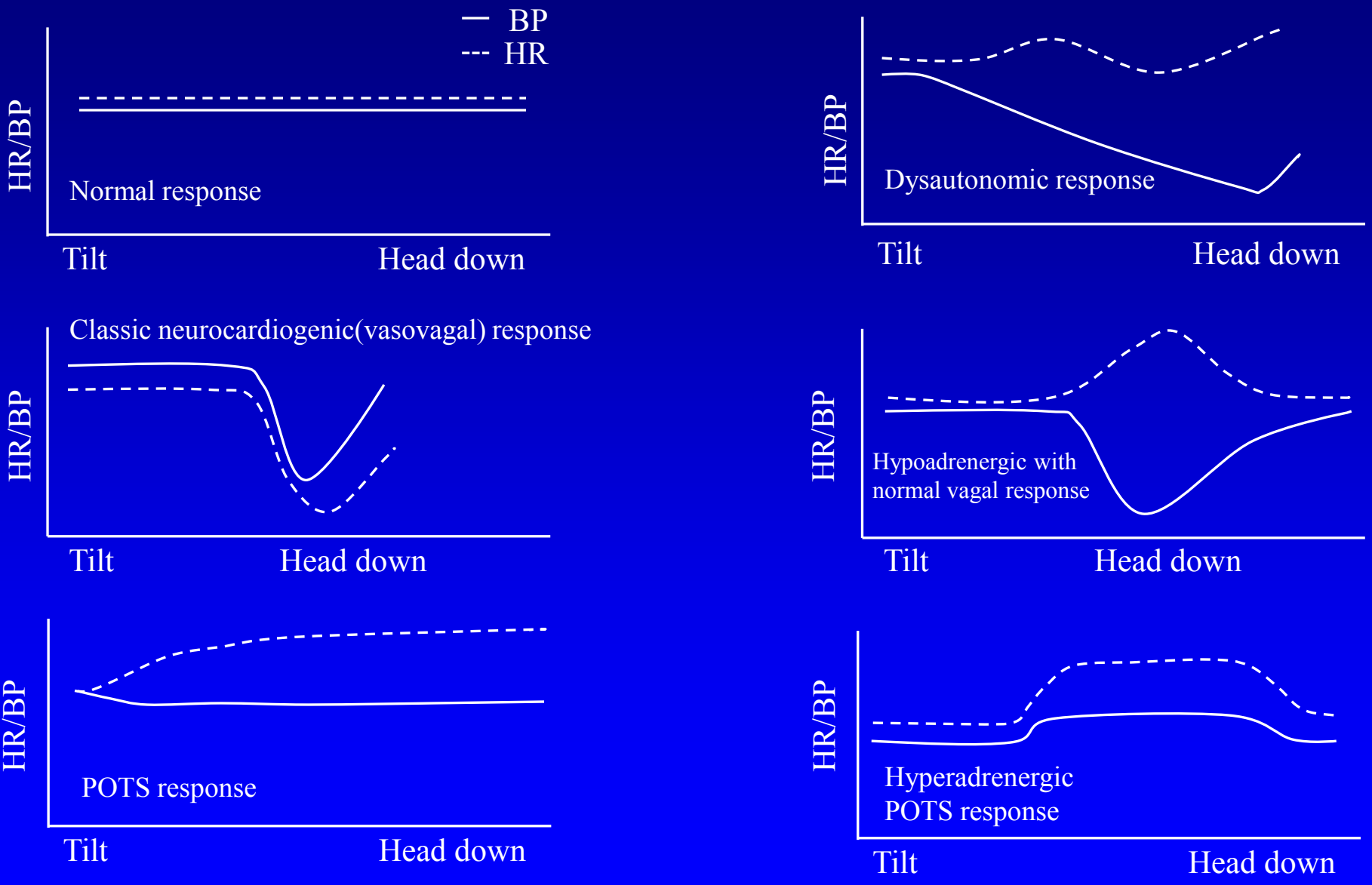


Table 4. Clinical Neuromuscular Disorders

Group	SFN	LFN	FN	Myopathy	NMT
Ill (n=17)	2	1	5	0	0
Control (n=13)	0	0	3	0	0

SFN: Small fiber neuropathy. LFN: Large fiber neuropathy.
FN: Focal neuropathy. NMT: Neuromuscular transmission disorder.

Autonomic Testing in Chronic Fatigue Research



Haemodynamic patterns during tilt table test

Compound Autonomic Severity Scales (CASS)

- Sudomotor Subscore (3 points)
  Quantitative Sudomotor Axonal Reflex Test
- Adrenergic Subscore (4 points)
  Valsavar Maneuvar or Tilt Table
- Cardiovagal Subscore (3 points)
  Heart Rate Variability

	Mean	SD
• Multisystem Atrophy (n=18):	8.5	(1.3)
Autonomic Neuropathy (n=20):	8.6	(1.2)
Parkinson disease (n=20):	1.5	(1.1)
Asymptomatic Peripheral Neuropathy (n=20)	1.7	(1.3)

(*Low PA. Mayo Clin Proc 1993;68:748-52*)

Composite Autonomic Severity Score (CASS)

Sudomotor Index

1. Single QSART site reduced, or Length-dependent pattern (distal sweat volume <1/3 of proximal value, or TST anhidrosis present but < 25%

2. Single QSART site <50% of lower limit, or TST anhidrosis 25-50%

3. Two or more QSART sites <50% of lower limit, or TST anhidrosis >50%

Adrenergic Index

1. Phase II_E reduction <40 >25 mm Hg MBP, or Reduced phase II_L, or
   Pulse pressure reduction to <50% of baseline
   Increased PRT (4 - 5 sec)
   Absent phase IV
2. Phase II_L absent or increased PRT (6 - 9 sec)
3. Absent phases II_L and IV and increased PRT (>10 sec)
4. 3 + OH (SBP reduction > 30 mm Hg; MBP > 20mm Hg)

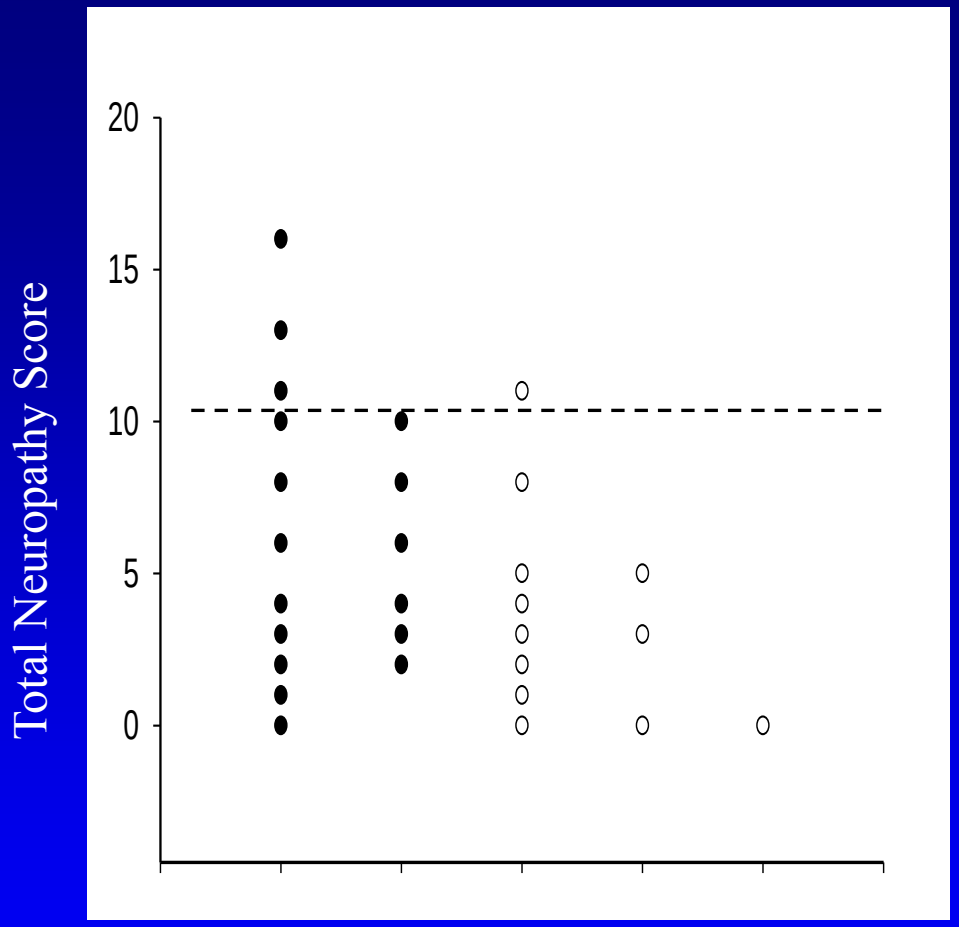
If the Valsalvar maneuver is *normal*, a score of 1 can be assigned if the following changes occur on *tilt up*:

a. Excessive oscillations in MBP (>20mmHg occupying at least 50% of the duration of tilt up)
b. Fall in pulse pressure >50%
c. Transient fall in SPB >20 mmHg with recovery (within 1 minute)
d. SBP reduction>20mmHg beyond 1 min
e. DBP reduction>10mmHg beyond 1 min
f. Overshoot >20mmHg following tilt back

Cardiovascular HR Index

1. HR_{DB} or VR reduced but >50% of minimum or reduced BRS_V
2. HR_{DB} or VR reduced to >50% of minimum or BRS_V (≤3 ms/mm Hg)
3. HR_{DB} or VR reduced to >50% of minimum and BRS_V (≤3 ms/mm Hg)

HRDB ,heart response to deep breathing; MBP, mean blood pressure; OH, orthostatic hypotension; PRT, pressure recovery time; QSART, quantitative sudomotor axon reflex test; SBP, systolic blood pressure; TST, thermoregulatory sweat test; VR, Valsalvar ratio.



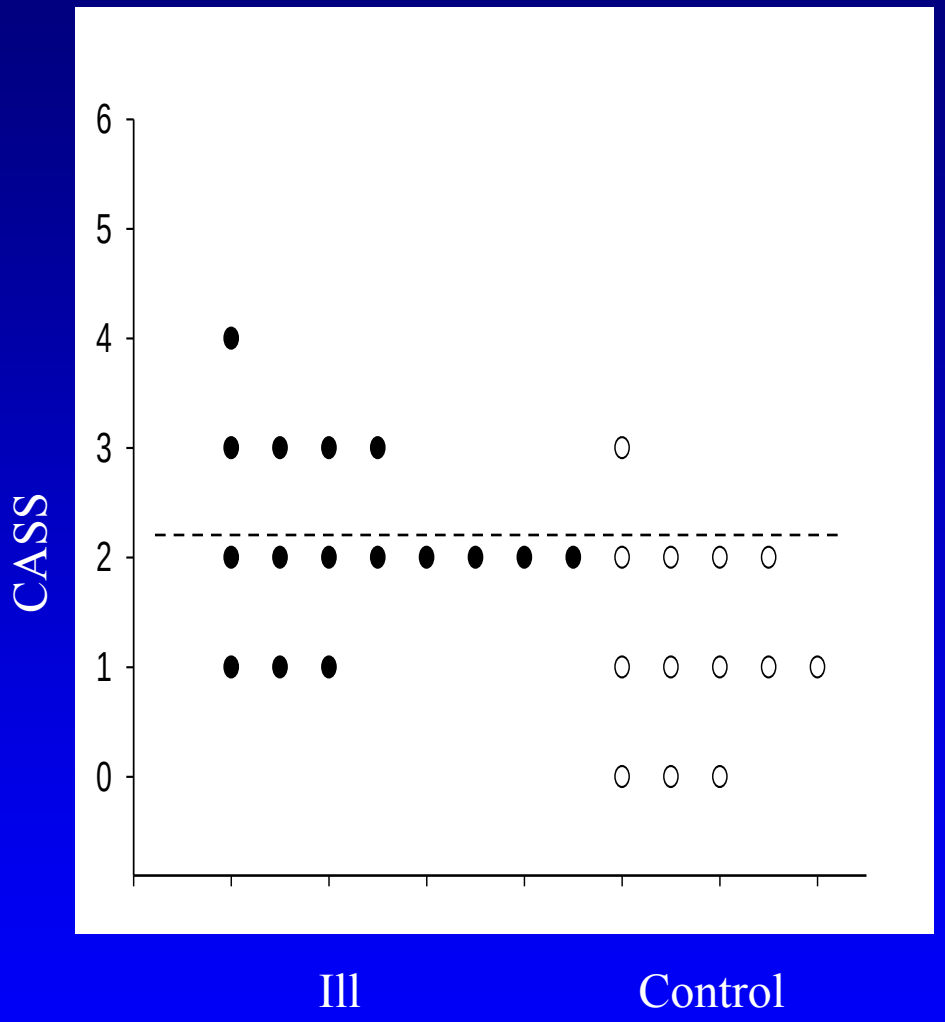


Fig. Total Neuropathy and CASS Score in Ill and Control groups

Table 3. TNS and CASS

	Ill (n = 17)		Control (n = 13)		P Value
	Mean/ ± SEM	95% CI	Mean/± SEM	95% CI	
SNAP (sensory)					
Amplitude (μV)	12.48 ± 1.91 (n = 15)	8.38—16.58	12.53 ± 2.46 (n = 9)	6.85—18.0	0.988
Latency (ms)	3.31 ± 0.12 (n = 12)	3.06—3.56	3.71 ± 0.19 (n = 9)	3.26— 4.17	0.073
CMAP (motor)					
Amplitude (mV)	4.45 ± 0.51 (n = 13)	3.34—5.55	6.13 ± 0.72 (n = 9)	4.48—7.79	0.061
Latency (ms)	4.79 ± 0.13 (n = 13)	4.51—5.07	4.79 ± 0.21(n = 9)	4.30—5.28	0.989
TNS	6.29 ±1.10	3.95—8.63	3.50 ± 0.98 (n = 12)	1.34—5.66	0.083
CASS	Median SD		Median SD		
Total	2.00	0.83 (n = 16)	1.00	0.92	0.011*
Sudomotor	1.00	0.75	1.00	0.63	0.069
Cardiovagal	0.50	0.62	0.00	0.50	0.482
Adrenergic	0.00	0.51	0.00	0.37	0.113

SNAP: sensory nerve action potential from sural sensory nerve.
CMAP: compound muscle action potential from peroneal nerve.
TNS: total neuropathy score. CASS: composite autonomic severity score.

Disorder Profiles

- Hx + PE + Neurophysiology/Autonomic function tests (n =30)
  Diagnosis depending on the definition
- Clinical autonomic disorders n = ?
- Small fiber dysfunction n = 4
- Autonomic neuropathy
  CASS=> 3 + Abnormal QSART n = 2
- Cardiac autonomic neuropathy n = ?
- POTS n = 2
- CRPS n = 1

- Metabolic disorders n = 7
- Cardiovascular disorder n = ?
- Autoimmune disorder n = 4

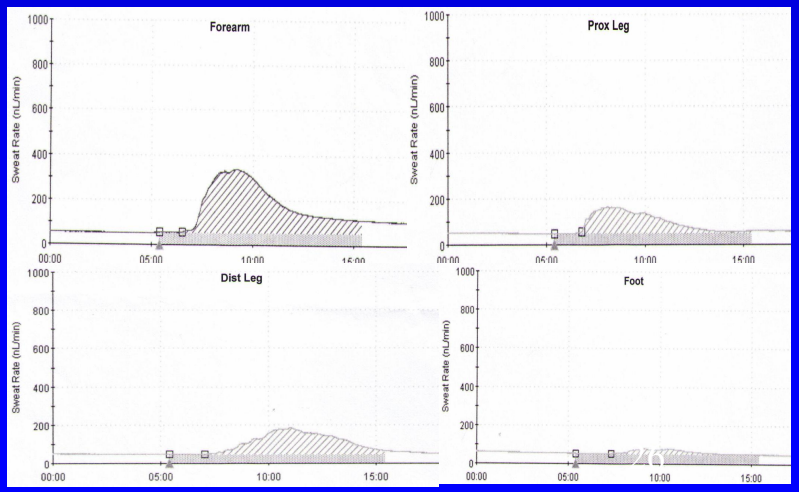
Case 1: Hydrocarbon Neuropathy

- Middle age Veteran (fuel technician) had exposure to JP 8 for a total estimated duration of 2 yrs. Evaluated for "PTSD" . NL Glucose. Negative SS-A/B, nAch-R Ab, ACE, infec panel, and immune panel.

- Normal Nerve Conduction Study
- Needle EMG: L S1 radiculopathy
- QST: Abnormal at feet

	Threshold (L/R)	
	Vibration	Thermal-Cold
Finger	1.6/1.4	1-2/1-2
Great Toe	8.6/3.1	6.0/3.0

- Total Neuropathy Score: 9
- Abnormal QSART



Case 2: Post-Vaccination POTS

- Young veteran had near syncope events with episodic "sinus tachycardia" 10 days after vaccination. Evaluated for "panic attack".

Panel A	BP	HR	*Panel B*	MinHR	Max	Ratio	(low cutoff)
Supine	108/72	45		HRdb 46	77	1.67	(> 1.20)
Standing	98/59	77					
Tilting (HU)				HRvm 44	84	1.91	(> 1.50)
3 min		98					

- NCS: Normal
- QST: Normal
- TNS: 4 (subjective autonomic symptoms)
- QSART: Mildly abnormal
- CASS: 5

Conclusion

- Self reported unexplained neurological symptoms can be confirmed on a battery of objective autonomic testing in selected GW veterans
- Objective parameters on autonomic testing may be useful in guiding the treatment of selected multi-symptom illnesses in an appropriate clinical context
- Ill group (deployed) defined in this study has impaired autonomic nervous system function by objective autonomic testing compared to Control (deployed)

- Special Thanks to both Veterans participating in the Study and Volunteer researchers
- Clinical content reflects PI and Co-PIs (FS, PZ, PK)'s opinions
- The research results are preliminary and hypothesis driven with small sample size of highly selected study participants. Alternative hypothesis and interpretation for these finding exist
- Cautious application of autonomic testing in individual cases requires an appropriate research or clinical context.