The International Consortium on Ehlers-Danlos Syndromes & Related Disorders

In Association with The Ehlers-Danlos Society

Evaluation and Management of Autonomic Dysfunction in Ehlers-Danlos Syndrome

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Disclaimers

- “Off-label” uses of medications
- No financial conflicts of interest

Overview

- Autonomic nervous system (ANS) regulates all body processes that occur automatically, e.g. heart rate, blood pressure, breathing, digestion, body temperature, etc.
- ANS dysfunction is very common in Ehlers-Danlos and hypermobility spectrum disorder, and underlies many of their symptoms

- **Special Issue: The Ehlers-Danlos Syndromes: Reports from the International Consortium on the Ehlers-Danlos Syndromes**
- **March 2017,** Volume 175, Issue 1
- **Cardiovascular autonomic dysfunction in Ehlers-Danlos syndrome—Hypermobile type** (pages 168-174)
- Alan Hakim, Chris O'Callaghan, Inge De Wandele, Lauren Stiles, Alan Pocinki and Peter Rowe

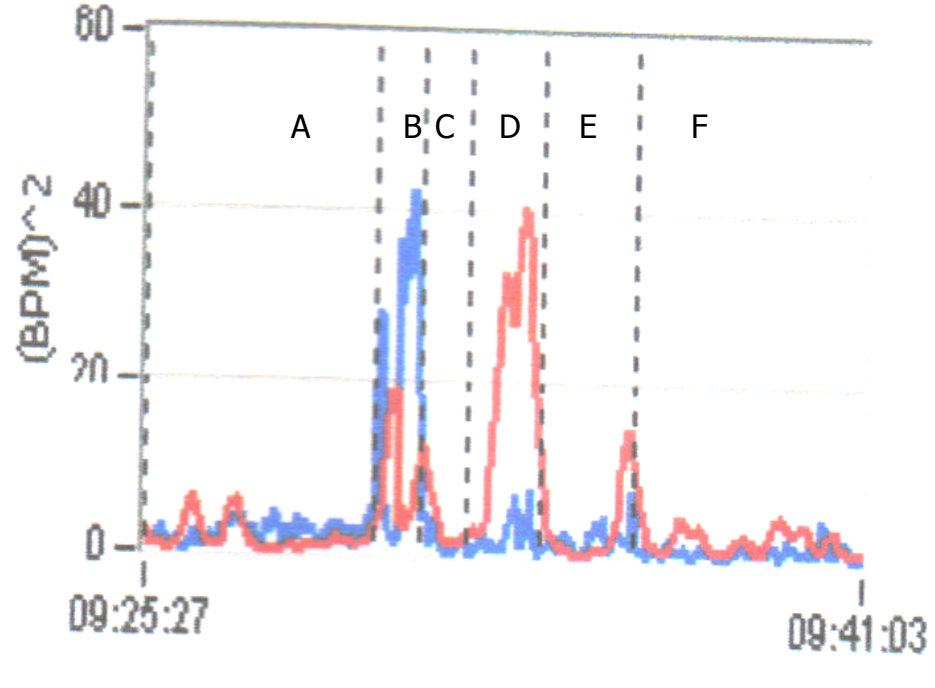
Basics of the ANS

- Sympathetic nervous system: “fight or flight,” the accelerator
- Parasympathetic nervous system: “rest and digest,” the brake
- The primary job of the ANS is to maintain stability and respond to stress appropriately

Autonomic Instability
"Failure to Modulate" Stress Responses

- Concept of adrenaline reserve
- Central paradox: the lower the reserves, the more exaggerated your stress response, so your body "overresponds" to minor stresses
- The overresponse often triggers an overcorrection, then an overresponse…

Sympathetic and Parasympathetic Activity with Autonomic Maneuvers



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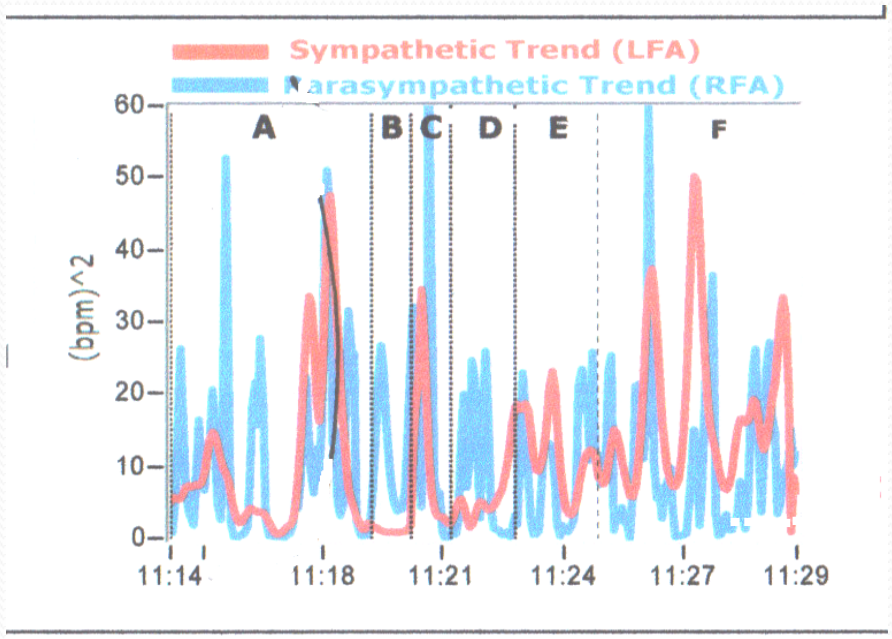

EDS with Dysautonomia

A=Baseline, B=Deep Breathing, C=Rest, D=Valsalva, E=Rest, F=Stand

ANX 3.0: ANS Test Results

Initial Baseline (Resting)

	Interpretation	VALUE	NORMAL RANGE
Mean Heart Rate	Elevated	91 bpm	60 – 100
Range Heart Rate (RangeHR; Max - Min)	Low	5 bpm	10 – 50
Sympathetic Modulation (LFa)	Low	0.23 bpm^2	0.5 – 10
Parasympathetic Modulation (RFa)	Low	0.12 bpm^2	0.5 – 10
Sympathovagal Balance (LFa/RFa)	Normal	1.91	0.4 – 3
Systolic Blood Pressure	High (Stage 1 Hypertension)	143 mmHg	90 – 120
Diastolic Blood Pressure		81 mmHg	80

Deep Breathing

	Interpretation ***	VALUE	FRF = 0.20 [OUT OF NORMAL RANGE (0.09 - 0.15)
Parasympathetic Response (RFa) Age and Baseline adjusted	Low	x3.83 bpm^2	x16.87 – x59.83
Range Heart Rate (RangeHR; Max - Min)	Low	7 bpm	15 – 50
Systolic Blood Pressure Expected: Decrease from Baseline	SYS Change: Borderline	140 mmHg	143
Diastolic Blood Pressure	DIA Change: Borderline	78 mmHg	81

Valsalva

	Interpretation	VALUE
Sympathetic Response (LFa) Age and Baseline adjusted	Borderline Low	x13.87 bpm^2 x19.10 – x67.71
Parasympathetic Response (RFa) Expected: <600% Increase from Baseline	Normal	0.46 bpm^2 0.85
Range Heart Rate (RangeHR; Max - Min)	Low	11 bpm 15 – 60
Systolic Blood Pressure Expected: Increase from Baseline	SYS Change: Borderline	147 mmHg 143
Diastolic Blood Pressure	DIA Change: Abnormal	71 mmHg 81

Stand

	Interpretation	VALUE
Mean Heart Rate Expected: >10% but <30 beats increase from Baseline	Normal	105 bpm 100.10 – 120.00
Range Heart Rate (RangeHR; Max - Min)	Normal	23 bpm 15 – 50
Sympathetic Response (LFa) Expected: 20% - 400% increase from Baseline	Low	0.05 bpm^2 0.28 – 1.15
Parasympathetic Response (RFa) Expected: Decrease from Baseline	Normal	0.05 bpm^2 0.12
Systolic Blood Pressure Expected: Up to 20 mmHg increase from Baseline	SYS Change: Low	122 mmHg 123 – 173
Diastolic Blood Pressure Expected: 10 mmHg decrease to 15 mmHg increase from Baseline	DIA Change: Normal	75 mmHg 71 – 96

ANX 3.0: ANS Test Results

Initial Baseline (Resting)

	Interpretation	VALUE (NORMAL RANGE)
Mean Heart Rate	Normal	61 bpm (60 – 100)
Range Heart Rate (RangeHR; Max - Min)	Normal	12 bpm (10 – 50)
Sympathetic Modulation (LFa)	Borderline Low	0.55 bpm^2 (0.5 – 10)
Parasympathetic Modulation (RFa)	Borderline Low	0.63 bpm^2 (0.5 – 10)
Sympathovagal Balance (LFa/RFa)	Low Normal	0.87 (0.4 – 3)
Systolic Blood Pressure	High (Stage 1 Hypertension)	146 mmHg (90 – 120)
Diastolic Blood Pressure		96 mmHg (80)

Deep Breathing

	Interpretation	VALUE
Parasympathetic Response (RFa) Age and Baseline adjusted	Normal	x25.52 bpm^2 (x22.17 – x78.61)
Range Heart Rate (RangeHR; Max - Min)	Normal	18 bpm (15 – 50)
Systolic Blood Pressure Expected: Decrease from Baseline	SYS Change: Borderline	132 mmHg (146)
Diastolic Blood Pressure	DIA Change: Normal	90 mmHg (96)

Valsalva

	Interpretation	VALUE
Sympathetic Response (LFa) Age and Baseline adjusted	Borderline Low	x16.29 bpm^2 (x24.71 – x87.61)
Parasympathetic Response (RFa) Expected: <600% Increase from Baseline	High	7.40 bpm^2 (4.42)
Range Heart Rate (RangeHR; Max - Min)	Normal	16 bpm (15 – 60)
Systolic Blood Pressure Expected: Increase from Baseline	SYS Change: Abnormal	118 mmHg (146)
Diastolic Blood Pressure	DIA Change: Abnormal	84 mmHg (96)

Stand

	Interpretation	VALUE
Mean Heart Rate Expected: >10% but <30 beats increase from Baseline	Normal	71 bpm (67.10 – 91.00)
Range Heart Rate (RangeHR; Max - Min)	Normal	21 bpm (15 – 50)
Sympathetic Response (LFa) Expected: 20% - 400% increase from Baseline	Borderline	0.63 bpm^2 (0.66 – 2.73)
Parasympathetic Response (RFa) Expected: Decrease from Baseline	Normal	0.38 bpm^2 (0.63)
Systolic Blood Pressure Expected: Up to 20 mmHg increase from Baseline	SYS Change: Borderline Low	127 mmHg (126 – 176)
Diastolic Blood Pressure Expected: 10 mmHg decrease to 15 mmHg increase from Baseline	DIA Change: Normal	100 mmHg (86 – 111)

Spectrum of Autonomic Symptoms

- Cardiovascular problems
  - Orthostatic intolerance
  - Temperature intolerance
  - Raynaud's
  - Migraine
- Digestive symptoms
- Urinary symptoms
- Respiratory symptoms
- Sleep problems

Cardiovascular Dysregulation

What We Know

- Literature applies primarily to heterogeneous group JHS / EDS-HT
- Symptomatic tachycardia and/or hypotension are observed.

[Rowe et al., 1999; Gazit et al., 2003; Hakim & Grahame, 2004; Mathias et al., 2011; Wallman et al., 2014; De Wandele et al., 2014].

- Symptoms can be highly debilitating

[Rowe et al., 1999, Hakim & Grahame, 2004; Mathias et al., 2011; De Wandele et al., 2014].

Cardiovascular Dysregulation
Causal Associations?

Mechanisms suggested include:

- Peripheral venous dilation and blood pooling
- Elevated circulating catecholamines
- Auto-immunity - auto-antibodies directed against baroreceptor
- Medications, e.g. tricyclics
- Histamine
- Brainstem / upper cervical cord impingement

Cardiovascular Dysregulation
Causal Associations – What Do We know?

Adrenergic states:

In EDS

- Gazit et al., [2003] identified evidence of alpha-adrenergic and beta-adrenergic hyper-responsiveness

In the general POTS population:

- Thieben et al. [2007] identified hyperadrenergic states in 29% of cases of POTS from a general cohort.
- Adrenergic and other neural autoantibodies found in a significant percentage of POTS patients.*

[Thieben et al., 2007; Li et al., 2014; Singer et al., 2014; Fedoroski et al., 2015].

Cardiovascular Dysregulation

Causal Associations – What Do We Know?

- In general populations – histamine induces hypotension and tachycardia. [Frieri et al., 2013].
- Mast cell activation identified in EDS-HT

  [Louisias et al., 2013; Cheung & Vadas, 2015].
- In general populations - Arnold Chiari malformation may trigger cardiovascular dysregulation. [Ireland et al., 1996].
- Association between Arnold Chiari and EDS-HT.

  [Milhorat et al., 2007]

Cardiovascular Dysregulation
Evaluation

- Thorough history and physical examination, considering
  - Broadly the causes
  - Specific potential causation in EDS
- Recognize that patients often have complex co-morbidities
- Recognize that there are many causes beyond EDS

Cardiovascular Dysregulation

Evaluation

Diagnostic Criteria / Tests :

- **POTS:** increase in HR of ≥ 30 bpm moving from recumbent to standing (or ≥ 40 bpm in 12-19 years of age); [in the absence of orthostatic hypotension (≥ 20 mm Hg drop].
- **OH:** sustained reduction ≥ 20 mmHg systolic or diastolic ≥ 10 mmHg within 3 minutes of standing or head-up tilt to at least 60˚ angle.
- **NMH**: orthostatic symptoms and ≥ 25 mm Hg drop in systolic BP during standing or tilt testing.
- **OI:** symptoms during 10 minutes of upright posture which improve upon lying down and do not meet the above criteria.

Cardiovascular Dysregulation
Evaluation

- Orthostatic signs normal in clinic, but suspicion high, Or,

  Signs present but non-pharmacologic treatments have not helped.
- Consider:
  - hematocrit, to rule out anemia
  - Electrocardiogram and/or Holter monitoring (to exclude other dysrhythmia)
  - Blood pressure monitoring, and
  - Echocardiogram* (screening for MVP and Aortic Root Disease)

Cardiovascular Dysregulation
Evaluation

- In some cases tilt-table testing might be helpful - more prolonged period than a standing test.
- In some cases more extensive evaluation by an expert Autonomic Unit might be required, and might include:
  - Thermoregulatory sweat test or QSART testing to detect autonomic neuropathy
  - Supine and upright plasma epinephrine and norepinephrine level tests,
  - 24-hour urine sample to assess sodium balance


VERTIGO CLINIC
WELCOME
JONNY HAWKINS

Cardiovascular Dysregulation

What We Know - Management

- Evidence for management in EDS-HT is lacking; there are no published clinical trials.
- There is some evidence from small cohort studies, case reports, and expert opinion. Confounding by imprecision in definitions and diagnostic methods.
- Pragmatic approach - guidance in EDS is based on expert opinion, but draws data published by international groups on management of dysautonomia per se

  [Grubb et al., 2006; Lahrmann et al., 2006; Sheldon et al., 2015].

Cardiovascular Dysregulation

Treatment

- Several treatments, used together, are likely to be needed.
- Education, advice and non-pharmacologic treatments should be offered first in all patients, including:
  - Avoid / Reducing exposure to triggering factors
  - Adjust / remove medications that might worsen symptoms
  - Maintaining good hydration and electrolyte balance
  - Reduce venous pooling with abdominal and lower limb compression garments
  - Graduated exercise program

Cardiovascular Dysregulation
Treatment

- For moderate-severe impairment of daily function, pharmacologic treatments include:

  [Grubb et al., 2006; Lahrmann et al., 2006; Sheldon et al, 2015]

  - Fludrocortisone
  - Midodrine
  - Ivabradine
  - Beta blockers. Lower doses tend to be better tolerated, but inter-individual variability.

Cardiovascular Dysregulation

Treatment

A long list of other pharmacologic treatments [Sheldon et al, 2015] include:

- Hormonal contraceptives can help OI symptoms in women. [Boehm et al., 1997].
- Pyridostigmine [Raj et al., 2005; Singer et al., 2006].
- Clonidine; useful for comorbid anxiety, pain [Robertson et al., 1983; Nahman-Averbuch et a., 2016].
- Serotonin or serotonin-norepinephrine reuptake inhibitors in some patients with OI; also for co-morbid pain, anxiety, or depression [Di Girolamo et al., 1999].

Cardiovascular Dysregulation
Treatment

- Methylphenidate [Grubb et al., 1996]
- Desmopressin
- Octreotide
- 1-2L of intravenous normal saline infused over 1-2 hour [Burklow et al., 1999; Takenaka et al., 2002], or other forms of sodium loading [Rosen and Cryper, 1992].
- Ruscus aculeatus (butcher's broom) [Altern, 2000].

Cardiovascular Dysregulation
Evaluation

- Thorough history and physical examination, considering
  - Broadly the causes
  - Specific potential causation in EDS
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Cardiovascular Dysregulation

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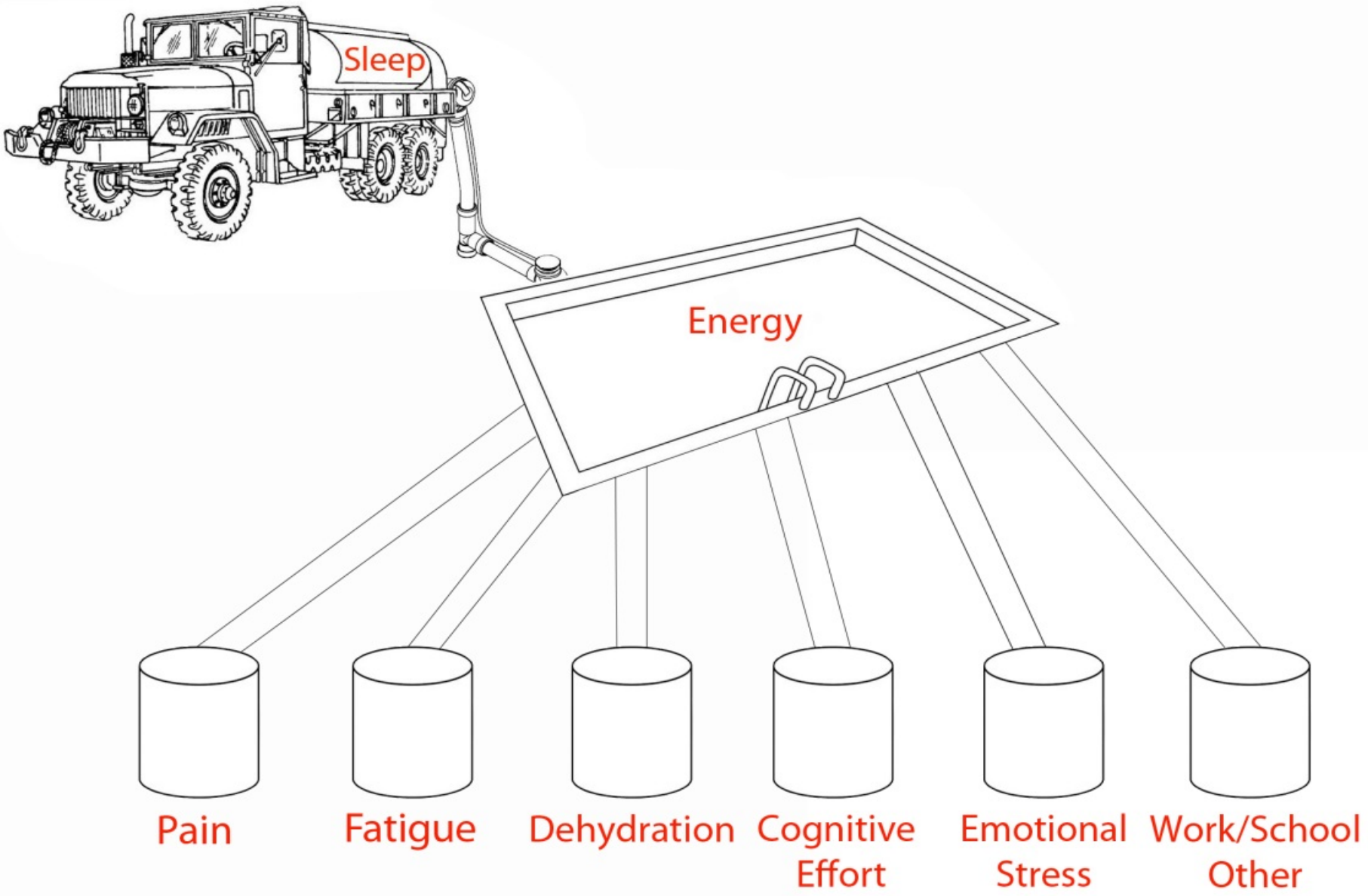

Sleep
Energy
Pain
Fatigue
Dehydration
Cognitive Effort
Emotional Stress
Work/School Other

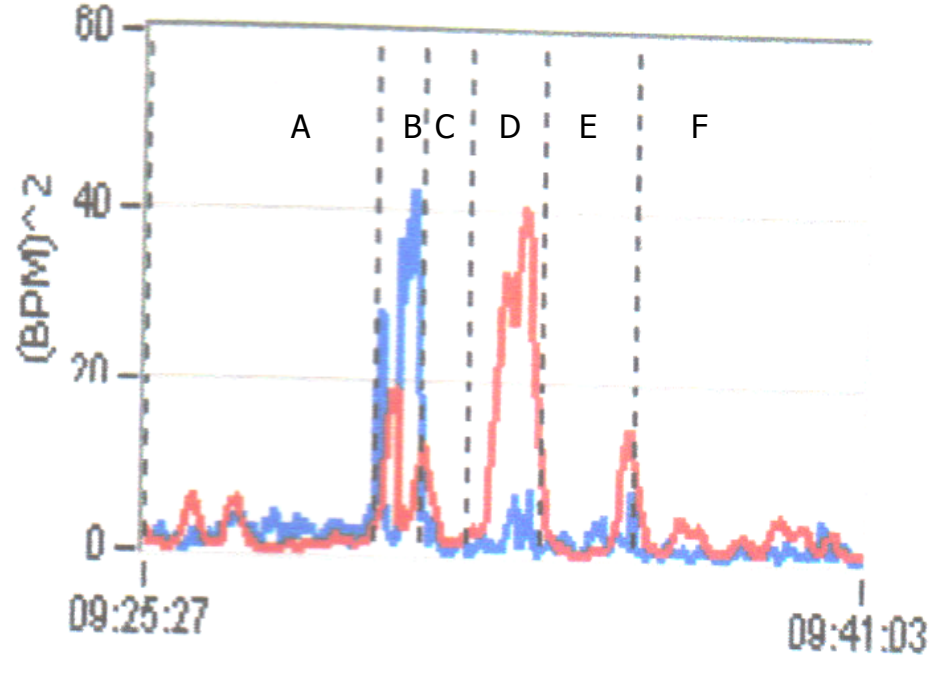
Summary

- Cardiovascular dysregulation is found in some patients with EDS-HT.
- Mechanisms exist that may explain in some cases the association with EDS-HT.
- The diagnosis is predominantly based upon taking a detailed history and examination for general causes and specific complications of EDS.
- Simple clinic room tests can provide support for the diagnosis and other tests may be useful to exclude other diseases that can present in a similar manner.
- Although pharmacological therapies may be required, non-drug treatments should always be considered first.

Summary

- Pharmacological therapy begins with minimizing or removing medications that are either ineffective or producing deleterious effects.
- Drug treatments include volume expansion, vasoconstriction, and modulators of autonomic tone.
- Prognosis remains uncertain [but most patients improve with treatment].
- Substantial epidemiological and therapeutics questions remain.

Sympathetic and Parasympathetic Activity with Autonomic Maneuvers



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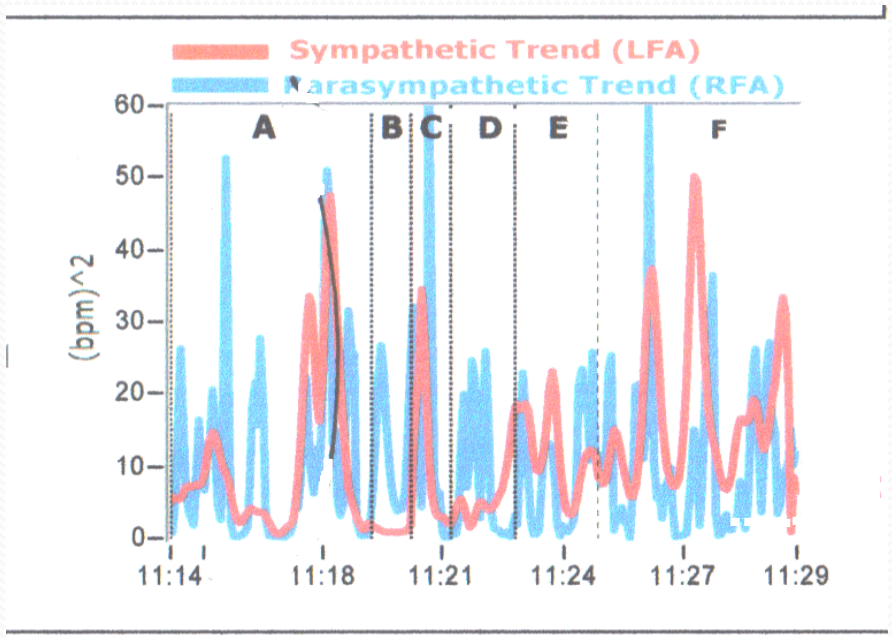

EDS with Dysautonomia

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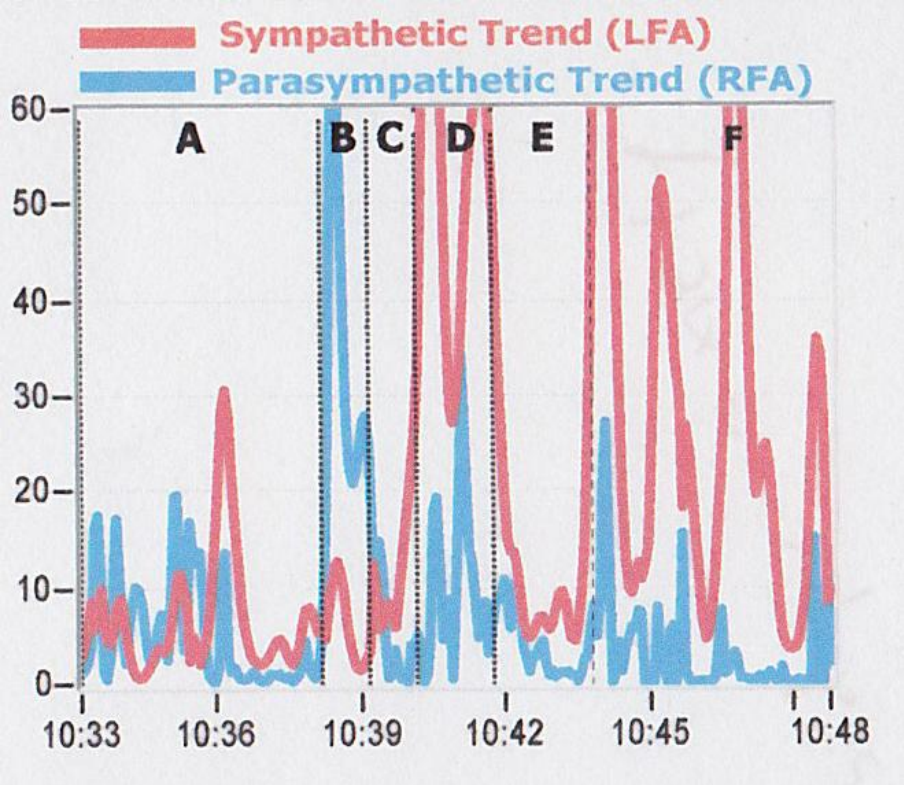
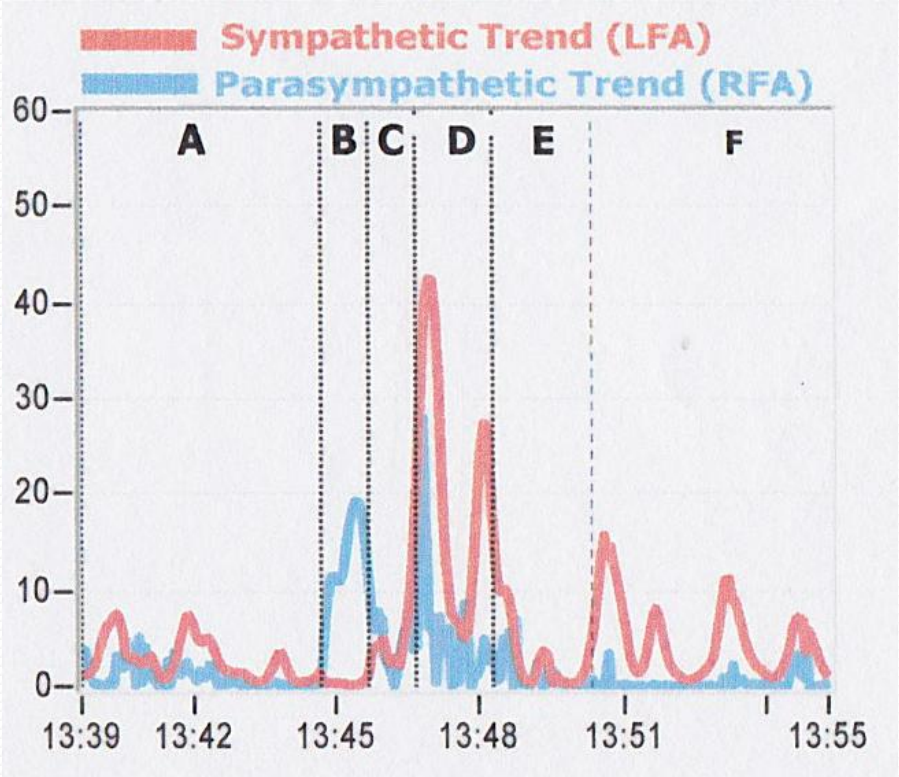
Sympathetic and Parasympathetic Activity Before and After Treatment

At Diagnosis



After 18 months of treatment



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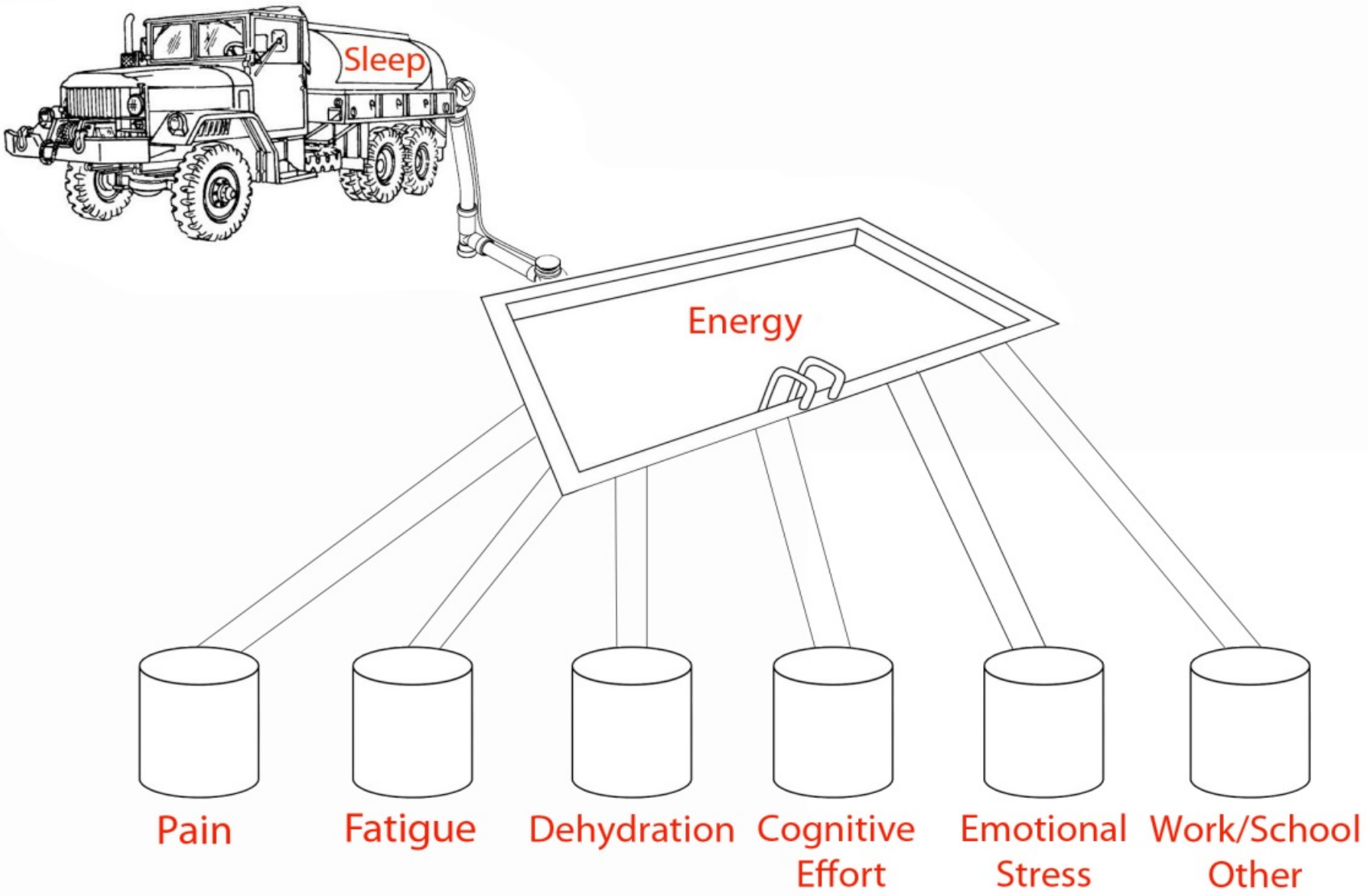
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Acknowledgements

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Dr. Peter Rowe and Dr. David Goldstein for encouraging me when others thought I was nuts

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