Testing for Problems Relating to Low Blood Pressure / Autonomic Dysfunction and Provision of Appropriate Advice

This paper is set out in four sections:

1. **Personal testimony regarding problems relating to low blood pressure / autonomic dysfunction, illustrating the need for testing to identify such problems and how this can be conducted;**
2. **Research illuminating patients' presentation;**
3. **Information on the Management and Treatment of Autonomic Dysfunction;**
4. **Capacity to distinguish patients from healthy controls and other patient groups on the basis of Testing for Orthostatic Intolerance.**

1. Personal Testimonies

I've been struck by how frequently and how cogently this has been mentioned since I started keeping an ear to the ground for problems relating to low blood pressure following the Cross Party Group on ME's enquiry to health boards on under-use of tilt tables in Scotland. Here are a few examples:

> **Firstly, an account of the experience of a 25% ME Group member with a physiotherapist who was unaware of the likelihood of orthostatic dysfunction in ME and how it is manifested. This had resulted in the provision of grossly inappropriate advice, to the detriment of the patient:**
>
> *The rehab physiotherapist who made a home visit was obviously unaware that severe ME patients can suffer orthostatic dysfunction. The physiotherapist requested that my son stand with legs straight, unsupported (and he thinks with eyes closed). A result of which was that he fell twice and was caught by the physiotherapist. Exhaustion and paralysis ensued. Significant deterioration followed several days later.*
>
> *The physiotherapist then cited that the lowest grade of exercise available was that my son should stand for a period twice a day unsupported with legs straight. His one attempt to do this had similar result as above.*

> **Secondly, the experience of a severely affected patient in the US. Her account is notable in that it highlights the need for care to be taken in tilt table testing, which must be conducted by someone who understands the need to constantly monitor the patient during the test. She also highlights some alternatives, which could perhaps be initiated by a general practitioner – blood pressure monitoring in the surgery following a suitable protocol and 24 hour remote monitoring. She also describes how neurally mediated hypotension/postural orthostatic tachycardia syndrome can feel like a panic attack – but isn't:**
>
> *Because I have NMH/POTS, I cannot stand in lines [queues] for long - it triggers the response (systolic plummets, pulse skyrockets). The feeling is scary - and it's supposed to be - your body is trying to scare you into sitting down. The experience is really one of panic if you don't know what's going on. Your heart is racing and your brain is shouting at you to get out of there and sit down. But the feeling of panic is natural - your body IS panicking, because you are about to lose the blood flow to your brain and then it WILL get you down, voluntarily or not.*
>
> *Once I went to a wheelchair, I had no problems with crowds or lines. But the genuine fear of falling, and the real possibility of passing out if I didn't sit down could easily have been misinterpreted as psychiatric anxiety, rather than the difficulty I had with my disease symptoms in crowded places. I keep track of my pulse if I start to feel weird standing - over 100 and I sit down wherever possible.*
>
> *I have to wonder how many patients have been misdiagnosed with panic disorder - or hysteria - when what was really happening was an NMH attack. And NMH/POTS (Rowe believes they are two sides to the same coin and I agree[1]) is not the same as orthostatic hypotension. In the latter you lose the blood flow when you stand up. NMH, in contrast, is somehow triggered after you have been standing for a bit of time. Fidgeting helps, too. /*

[1] Dr Peter Rowe is a US medic, based at Johns Hopkins University, who has specialized in this area. His work can be found at http://www.pediatricnetwork.org/medical/OI/johnshopkins.htm and relevant research papers of Dr Rowe's are referenced in the 'Canadian' paper (see below).

RE TESTING: Make sure that the person doing the tilt table tests understands NO talking, NO fidgeting, and barfing means you have to lie down. The person who ended up giving me the tilt table test was NOT sympathetic, left the room at one point, and allowed me to fidget and barf. I don't like tilt table tests - we've had people's hearts stop on them.

My specialist did the test in her office - she had me lie down for twenty minutes (I didn't know what she was up to - I thought I was just resting) - then she came in and had me sit up, took my blood pressure and pulse, and then asked me to stand, and not do anything else, and she waited until I suddenly said "I HAVE to sit down!" and she said - wait, let me take your blood pressure and pulse - and BINGO - there it was - pulse up 40 points, systolic down 40 points. NMH/POTS.

Then last year, another specialist had me use a 24-hour pulse and blood pressure monitor. I was standing in line to get a prescription filled when I felt an episode coming on - at which point normally I would have sat down, even if it had to be on the floor. But I stayed put until the cuff had gone off (squeezed my arm). So when the technician got the readout off it, I asked to see it - and there it was, systolic down 40 points and pulse up 40 points.

Thirdly, testimony from a patient from south of the border, who had NMH diagnosed via a tilt table test. Fortunately she had received appropriate advice re activity from her physiotherapist (in contrast to the young man in Scotland above). She emphasises that ignoring this advice and instead following what may well be the current 'establishment' advice on activity could have had very serious consequences for her:

In the first few years of my illness I would have been unable to walk for more than a few minutes without my systolic blood pressure dropping to 40, which could have killed me or seriously injured me.

It was two years before I had a tilt-table test and knew that Neurally Mediated Hypotension was causing my symptoms. That's when I learnt how dangerously low my blood pressure would go if I didn't sit/lie down when the light-headedness and blurred vision came on. I did do GET and my physiotherapist luckily had the opposite approach to Dr Clare Garada[2] and told me to stop when I got symptoms.

After my tilt-table test result came through my specialist stated my Neurally Mediated Hypotension was "potentially very dangerous".

In ME the severe potentially fatal blood pressure drop often happens after a person has been walking or standing for ten minutes or so. There are lots of people with ME out there who have undiagnosed NMH and have not had a tilt-table test (see Julia Newton's work.) You don't necessarily have to have low resting blood pressure to have NMH. You could have high resting blood pressure and have NMH. The problem is that when you remain standing the BP drops.

If a PWME frequently has lightheadedness, blurred vision, sweating or nausea whilst standing or walking then I believe they should be offered a tilt-table test.

As is mentioned in the Canadian Document, NMH may not show up in the standard office test where a doctor takes your blood pressure whilst sitting and then a couple of minutes later whilst standing. That will detect postural hypotension but usually not NMH. In ME the severe potentially fatal blood pressure drop often happens after a person with ME has been walking or standing for ten minutes or so.

Finally, a woman with an MSc qualification in the neuropsychology of ME offers some pointers to patients and emphasizes the need for appropriate medical education. She also addresses the misguided perspective that orthostatic intolerance in PwME may be about psychiatric anxiety/panic:

If you have evidence of autonomic dysfunction, as there is in ME, then it is clear that the psychiatric models of anxiety and panic disorder do not make much sense at all.

They assume 'normal' functioning of the autonomic nervous system. e.g. Clark's 1989 model of panic and generalised anxiety. Symptoms of panic and anxiety are assumed to be a catastrophic misinterpretation of physiological symptoms. CBT is good for these disorders..... can be very effective – if your autonomic nervous system is functioning..... /

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[2] The reference here is to a 'training video' produced by Kings College London, in which Dr Clare Garada, newly elected head of the Royal College of General practitioners, presents a role play with a 'patient' (played by Alicia Deale, lead author of one of the CBT studies).: CG: *"...even if you're absolutely exhausted I still want you to do your ten minute walk in the morning and the ten minute walk in the evening after work..."* AD (Patient): *'Is that going to be safe?'* CG: *"it will be safe - all the evidence that we've put together and all the research literature shows that is absolutely safe you will not do yourself any harm..."* [Available to view at http://www.veoh.com/]

If you are a doctor and ignore or are unfamiliar the work of Prof Newton in Newcastle and the work of docs like Dr Peter Julu at the B'Spear then the simple, easy answer is to blame the patient for 'being anxious' when in fact they are struggling like mad to function with wonky autonomic nervous system.....

I find that after teaching people about the sympathetic and parasympathetic nervous system, the relationship with this and how they feel and what are the symptoms in ME related to autonomic dysfunction then a lot of the anxiety reduces and patients can make more informed decisions about management of their condition - pacing makes a lot of sense for many reasons. I use Ellen Goudsmit's model. Relaxation, mindfulness and meditation does too. Whatever works, whatever floats the boat for the patient. …

The Canadian Guidelines book is a useful tool to go through with patients regarding the effects of autonomic dysfunction. Patients can readily identify with most of the symptoms of OI, NMH and POTS. It clearly helps to realise that they are not to blame for their symptoms.

Disequilibrium, balance problems and slow cognitive functioning can make negotiating the environment pretty tricky. …. We can experience panic and distress as a result of this as well as cognitive overload from light, noise, heat etc. It's a consequence of wonky biology and the patient is right to avoid distressing situations (standing still in line at the post office, supermarket), too much noise, heat/cold and to rest when needed. Overlooking biology and explaining this in terms of psychiatry alone is an insult to the patient and clearly unethical.

I do think that doctors and therapists do not understand the emotional limitations and disruption that will go on if people's autonomic nervous system is not working correctly. There is nothing really published about this important point. All CBT models have to be adapted for biomedical illnesses especially neurological ones. They cannot be used 'as is' with clients and therapists need to understand this.

2. Research Illuminating Clinical Presentation

A number of research articles have been published in this regard. Here are two examples:

- **a recent research study from Prof Julia Newton's team; and**
- **the research and clinical coverage on Orthostatic Intolerance from the Carruthers *et al.* diagnostic and treatment protocol.**

Impaired cardiovascular response to standing in Chronic Fatigue Syndrome

Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL; Eur J Clin Invest. 2010 May 20; Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK. Abstract from PubMed:

http://www.ncbi.nlm.nih.gov/pubmed/20497461

ABSTRACT:

Background Impaired skeletal muscle metabolism is recognized in chronic fatigue syndrome (CFS). This study examined the relationship between skeletal and cardiac muscle function and symptoms on standing in CFS using magnetic resonance spectroscopy (MRS) and impedance cardiography.

Materials and methods

- Phosphocreatine (PCr) / adenosine triphosphate (ATP) ratio by cardiac MRS, PCr / ADP and proton efflux by muscle MRS were performed in 12 CFS (Fukuda) and 8 controls.
- Head up tilt (HUT) and cardiac contractility (left ventricular work index, LVWI) (n = 64 CFS and matched controls) were found.
- Fatigue impact was accessed by Fatigue Impact Scale and orthostatic symptoms by Orthostatic Grading Scale (OGS).

Results

- Cardiac PCr / ATP correlated with measures of muscle bioenergetic function - half-time PCr recovery [kappa = -0.71, P = 0.005] and half-time ADP recovery [kappa = -0.60, P = 0.02] - suggesting that the muscle and cardiac bioenergetic function correlate in CFS.
- Four of 12 (33.3%) CFS patients had PCr /ATP values consistent with significant cardiac impairment.
- Those with impaired cardiac energy metabolism had significantly reduced maximal and initial proton efflux rates (P < 0.05). Cardiac PCr /ATP ratio correlated with myocardial contractility (LVWI) in response to standing (P = 0.03).
- On HUT, LVWI on standing was significantly higher in CFS (P = 0.05) with symptoms on standing (OGS) occurring in 61/64 (95%) (vs. 25/64 [39%] controls; P < 0.0001).
- OGS scores were significantly higher in those with abnormal LVWI responses to standing (P = 0.04), with the LVWI on standing correlating with OGS scores (r (2) = 0.1; P = 0.03).
- HUT was positive in 19 (32%). /

Conclusions

- Skeletal muscle and cardiac bioenergetic abnormalities associate in CFS.
- Cardiac bioenergetic metabolism associates with increase in cardiac contractility on standing.
- Haemodynamic assessment in CFS is well tolerated and safe with a high diagnostic yield comparable with unexplained syncope.

Autonomic Dysfunction Manifestations & Overview of Research

Carruthers, B. *et al.;* ***Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols*** Journal of Chronic Fatigue Syndrome, Vol. 11 (1) 2003

Diagnostic Criteria *Component 6: At Least **One** Symptom from **Two** of the Following Categories*:

a. *Autonomic Manifestations*: orthostatic intolerance – neurally-mediated hypotenstion (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea.

b. *Neuroendocrine Manifestations* ….

c. *Immune Manifestations* …

Signs and Symptoms [from Appendix 4] As the neurological, immune and endocrine systems are widely distributed, symptoms are numerous, multiform and of variable intensities. Many of the following symptoms are not present in everyone or at all times ...

Circulatory System

____ neurally mediated hypotension (NMH)
____ postural orthostatic tachycardia syndrome
____ delayed orthostatic hypotension
____ light-headedness
____ palpitations
____ fluid retention
____ extreme palor
____ bruising

Clinical Evaluation *Patient History*:

(includes) *Autonomic Nervous System & Cardiorespiratory System*: symptoms suggestive of orthostatic intolerance, neurally mediated hypotension, postural orthostatic tachycardia syndrome, delayed postural hypotension, palpitations, respiratory disturbances, vertigo, light-headedness, extreme pallor.

ME/CFS Symptoms: Description and Research Findings

Post-exertional Malaise and Fatigue [extract]

Research studies suggest that low circulating blood volume and blood pooling, orthostatic intolerance and cerebral hypoprofusion may play a role in both the fatigue and post-exertional malaise (153).

Cardiac/Circulatory Abnormalities and Neurally Mediated Hypotension (NMH)[extracts on NMH]

In 1995, researchers from Johns Hopkins University suggested that up to 95% of ME/CFS patients have neurally mediated hypotension, a condition in which blood pressure falls when it normally remains stable (196, 197). This has resulted in a research focus on orthostatic intolerance (198, 199, 200), particularly in the areas of low blood volume, (153, 201) abnormal sympathetic tone (202) and other autonomic nervous system dysfunctions.

When a healthy person stands up his/her pulse rate may or may not rise slightly, but after a short time the blood pressure and pulse rate stabilize. Orthostatic intolerance can be demonstrated by taking the blood pressure first when the patient is lying down and then after standing, but the drop in blood pressure is often delayed by more than ten minutes in ME/CFS (153, 203). Thus, the blood pressure of ME/CFS patients was relatively normal when prone, but they often exhibited orthostatic irregularities and aberrations when upright.

- Eleven of fifteen patients but none of the controls showed an excessive reduction in systolic and diastolic BP, excessive orthostatic tachycardia, and presyncopal symptoms after standing for 60 minutes or less (153).
- The destabilization of blood pressure may in part be due to the loss of beat-to-beat heart rate control (202).
- Another study (203) showed delayed orthostatic hypotension associated with reduced pedal vein compliance during norepinephrine infusion, implying impaired sympathetic innervation of foot veins. The orthostatic venous pooling was corrected by inflation of military antishock trousers (MAST) to 35 mm Hg suggesting excessive lower body venous pooling.
- In a tilt test study of adolescents, 25/26 ME/CFS patients experienced severe orthostatic symptoms compared to 4/13 controls and 18/26 simple faint patients (202).
- Hemodynamic instability in ME/CFS in response to postural challenge was also noted in a controlled study by Naschitz et al. (204).
- Abnormal autonomic control associated with sympathetic overactivity may present as neurally-mediated hypotension (198, 199).

Fatigue associated with low blood pressure and abnormal hemodynamic responses to upright postures can occur with or without faintness. *[… Further discussion of research findings:]*

- A low circulating erythrocyte volume, but not plasma volume, was identified in ME/CFS patients (the average was approximately 70% of normal but in some patients it was as low as 50% of normal) (153).
- In another small study of CFS patients by Streeten and Bell (201), 93.8% of the female patients were found to have significantly reduced red blood cell (RBC) mass, 52.6% of the patients had subnormal plasma volume, and 63.2% had below normal total blood volume. The blood vessels appear to be constricted and resist attempts to restore blood volume.
- This may be involved with the pathogenesis of ME/CFS and help account for the delayed hypotension and/or tachycardia caused by gravitational venous pooling (153).
- The reduction in circulating red blood cell mass may result in the decreased ability of the blood to carry oxygen and the reduced blood flow in the brain and thus, may contribute to the intolerance for standing and pathogenesis of ME/CFS patients (201).

REFERENCES:

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3. Management & Treatment

This section covers management and treatment, drawing on:

- **Coverage in the 'Canadian' paper (Carruthers *et al.* 2003);**
- **Link to ME Association material;**
- **Identification of a couple of newly emerging drug treatments.**

Clinical Guidance from the 'Canadian' protocol

Carruthers, B*. et al.* ***Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols*** Journal of Chronic Fatigue Syndrome, Vol. 11 (1) 2003

Those in charge of the GPS may wish to consider drawing on the following material, grounded as it is in the authors' extensive experience in the clinical care of patient with ME/CFS and their understanding of the breadth of relevant research on autonomic dysfunction.

> ***Dizziness/Orthostatic Intolerance:*** Simple instructions to avoid extension and quick rotation of the neck are often sufficient if dizziness is caused by proprioceptive disturbances in the neck. Instruct the patient to get up slowly while holding on to something, and avoid standing for long periods, especially in warm weather. Pumping legs intermittently and the use of support stockings can be helpful. Avoid large meals and dehydration.
>
> Neurally-mediated hypotension (NMH) and postural orthostatic tachycardia syndrome (POTS) can often initially be alleviated by lowering the head by lying down or bending forward and oral NaCl (up to 10-15 gm daily) with an adequate intake of water. High quality sea salt is best as it contains trace minerals but does not contain additives such as aluminum found in ordinary table salt. This effect is often temporary as the body adapts to the increased load of NaCl.

Pharmaceuticals for Orthostatic Intolerance, NMH and POTS

A *combination of therapies is suggested*:

Two placebo-controlled trials of fludrocortisones (125,126) showed no benefit over placebo. Although the 0.1 mg dose of fludrocortisone that was used in an 8 week trial (125) was insufficient to produce a positive effect, some panel members have found it useful in combination with other therapies. For example, start with increasing salt intake, add either a beta blocker such as atenolol, or an alpha 1 agonist such as midodrine. Consider fludrocortisone if the salt seemed to help for a while but then lost its effectiveness.

(125) Rowe PC, Calkins H, DeBusk K, McKenzie R, Anand R, Sharma C, *et al.* ***Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome.*** JAMA 2001 Jan 3;285(1):52-59.

(126) Peterson PK, Pheley A, Schroeppel J, *et al.* ***A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome.*** Arch Intern Med 1998;158:908-914.

It is possible to use all three approaches – volume expansion (salt or fludrocortisone), beta blockade (to increase the fill time of the heart), and alpha 1 agonist (to increase venous tone and reduce the orthostatic space that blood drops into while the patient is upright). If these approaches do not work, try paroxetine.

Note: before starting this therapy, NMH or POTS should be confirmed with a tilt-table test.

Drug	Dose	Effect/Comments	LE[3]
Fludrocortisone	0.05-0.2mg daily	Use in combination – see above. Increases sodium and water retention and may inhibit vasodilation. As it is a mineralocorticosteroid, be very careful to monitor the potassium levels. Use minimal effective dose. Side effects are extensions of its effects – excessive fluid retention, potassium loss and hypertension.	V
Midodrine	Start at 2.5mg tid, increasing to 5mg tid if tolerated	It is an alpha-adrenergic agonist. Side-effects include supine hypertension, palpitations, headache, bradycardia, pruritus, urinary retention. It can be used in conjunction with fludrocortisone since the mechanism of action differs.	V II for neuro-cardiogenic syncope[4]
Paroxetine	5-10mg daily qam, increasing to 20mg daily	A SSRI antidepressant. See pharmaceuticals for depression for general comments and precautions for SSRIs. More anticholinergic side effects than fluoxetine or sertraline. Commonly reported side effects include nausea, somnolence, sweating, tremor, asthenia, dizziness, dry mouth, insomnia, constipation, diarrhea, anorexia and male sexual dysfunction.	V II for refractory vasovagal syncope[5]
Pindolol	5mg bid, increasing to 10mg tid	A beta blocker used to increase ventricular filling, especially if tachycardia is a problem. Side effects include bronchospasm, bradycardia, aggravation of postural hyptension, insomnia, vivid dreams, fatigue, drowsiness, headache, diarrhea, constipation, nausea. *Observe beta blocker precautions.*	V
Atenolol	25mg daily, increasing to 100mg in a single daily dose	A beta blocker. Use to increase ventricular filling, especially if tachycardia is a problem. Use in combination with other therapies. Side effects include aggravation of orthostatic hypotension. Note: this and other beta blockers may be useful to correct POTS/NMH but may not help and may aggravate general symptoms of ME/CFS.	V; II for unexplained syncope & positive upright tilt table test results [6]

[3] ***Level of Evidence of Treatment*:** The level of evidence (LE) categories we have used are:

I. Large double blind randomized, control trials (RCT)s, or metaanalyses of smaller RCTs, clinically relevant outcomes;
II. Small RCTs, non-blinded RCTs, RCTs using valid surrogate markers
III. Non-randomized controlled studies, observational (cohort) studies, case-control studies, or cross-sectional studies
IV. Opinion of expert committees or respected authorities
V. Expert opinion

Ref: ***Level of evidence for clinical decisions: menopausal hormone therapy revisited.*** Therapeutic letter #30. Therapeutics Initiative, U.B.C., Dept of Pharm & Therapeutics, 2176 Health Sciences Mall, Vancouver, B.C., 1999 Jun/Jul; 30.

[4] Ref: Ward CR et al.. ***Mitodrine: a role in the management of neurocardiogenic syncope.*** Heart 1998;79:45-49.

[5] Ref: Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. ***Effects of paroxetine dydrocloride, a selective seratonin reuptake inhibitor, on refractory vasovagal syncope: a randomized double-blind, placebo-controlled study.*** J Amer Col Card 1999;33:1227-1230.

[6] Ref: Bhuripanyo K, Kangkajate C, Wansanit K, Kulchot B, Nademanee K, Chaithiraphan S. ***Randomized double-blind, placebo-controlled of oral atenolol in patients with unexplained syncope and positive upright tilt table results.*** Amer Heart J 1995; 130:1250-1253.

Vertigo			
Vertigo accompanied by nystagmus, nausea and/or vomiting and often associated with tinnitus and /or impaired hearing acuity requires an anti-nauseant but there is no good treatment.			
Drug	**Dose**	**Effect/Comments**	**LE**
Meclozine	25mg daily, increasing to 25mg tid	An antiemetic with antihistaminic and anticholin-ergic properties. Side-effects include drowsiness, dry mouth and fatigue.	V

MEA Management File

The ME Association has a new MEA Management File on "important clinical problem" of orthostatic intolerance and orthostatic hypotension. This is published in the latest edition of the MEA magazine (ME Essential Issue no 114; summer 2010, pages 6-8). Copies can also be obtained by ordering from the MEA website.

Ones To Watch? Some Emerging Treatments

I have heard from a patient who has just been prescribed Ivabradine for POTS by a cardiologist. She suggests that this may be a newly available treatment for POTS. See ***Symptom improvement in postural orthostatic tachycardia syndrome with the sinus node blocker ivabradine;*** Victoria Ewan, Michael Norton and Julia L. Newton

http://europace.oxfordjournals.org/content/9/12/1202.full

Another shares positive feedback regarding Droxidopa for NMH from a research study participant. It is not yet available in the UK. http://en.wikipedia.org/wiki/Droxidopa

4. Capacity of Tilt Table Testing to Distinguish people with 'CFS' from healthy controls and other patient groups

One of the questions addressed in the review carried out at the University of York in connection with the production of the 'NICE' guideline south of the border[7] was - ***Are there any substantiated or validated evaluations to support the diagnosis of CFS/ME in adults and children?***

Evaluation via tilt table testing emerged as having the strongest evidence. The relevant publications are:

Naschitz (2000) Thirty-two patients with CFS and 32 healthy controls were evaluated using the capnography head-up tilt test (CHUTT).

The authors concluded that the CHUTT may provide objective data to support a clinical diagnosis of CFS.

Reference: Naschitz JE, Rosner I, Rozenbaum M, Gaitini L, Bistritzki I, Zuckerman E, *et al.* ***The capnography head-up tilt test for evaluation of chronic fatigue syndrome***. *Semin Arthritis Rheum* 2000;30:79-86.

Rosner (2000) This study was carried out to seek precise parameters for detecting haemodynamic instability during a on postural challenge (tilt test) in CFS patients compared to FM patients and healthy controls.
Blood pressure and heart rate changes were converted into a linear discriminant score (DS) for each participant. DS values:
differed significantly between CFS and healthy patients ($p<0.0001$)
and between CFS and FM patients ($p<0.0001$)
but not between FM patients and healthy controls ($p=0.55$). /

The authors suggest that DS can reinforce a diagnosis of CFS by providing objective criteria for assessment.

Reference: Rosner I, Rozenbaum M, Naschitz JE, Sabo E, Yeshurun D. ***Dysautonomia in chronic fatigue syndrome vs. fibromyalgia.*** *Isr Med Assoc J* 2000;2 Suppl:23-4

[7] ***The diagnosis, treatment and management of chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME) in adults and children: work to support the NICE Guidelines'*** Anne-Marie Bagnall, Susaznne Hempel, Duncan Chambers, Vickie Orton, and Carol Forbes; Centre for Reviews and Dissemination, University of York, October 2005

Naschitz (2001) This paper described a haemodynamic instability score (HIS) measured during the head-up tilt test that can distinguish between CFS patients and healthy controls.

Participants were 25 CFS patients 30 fibromyalgia, 15 generalised anxiety disorder and 20 essential hypertension patients as well as 37 healthy controls. The mean HIS values of CFS patients were significantly different from mean values of healthy controls, fibromyalgia and essential hypertension patients but not from generalised anxiety patients.[8]

Reference: Naschitz JE, Sabo E, Naschitz S, Shaviv N, Rosner I, Rozenbaum M, *et al.* ***Hemodynamic instability in chronic fatigue syndrome: indices and diagnostic significance****. Semin Arthritis Rheum* 2001;31:199-208.

Naschitz (2002i) Patients with CFS (n=21), non-CFS fatigue (24), syncope of unknown cause (44) and healthy controls (21) underwent a head-up tilt test (HUTT). Abnormal reactions during the HUTT occurred in 79% of patients with CFS, 46% of those with syncope, 35% of those with non-CFS fatigue and 14% of healthy controls.

The authors concluded that a haemodynamic instability score HIS greater than -0.98 is an objective criterion to support a clinical diagnosis of CFS.

Reference: Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Madelain F, *et al.* ***Hemodynamics instability score in chronic fatigue syndrome and in non-chronic fatigue syndrome.*** *Semin Arthritis Rheum* 2002;32:141-48

Naschitz (2002ii) This study analysed numerous cardiovascular reactivity variables obtained during a head-up tilt test to predict CFS.

A discriminant Fractal & Recurrence Analysis-based score 'FRAS' based on analysis of heart rate and pulse transit time was derived. A cut-off of FRAS=0.22 achieved a sensitivity of 70% and a specificity of 88% when differentiating CFS patients from a control population consisting of healthy controls and patients with Familial Mediterranean Fever, psoriatic arthritis, syncope or generalised anxiety disorder.

Reference: Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Priselac RM, *et al.* ***Fractal analysis and recurrence quantification analysis of heart rate and pulse transit time for diagnosing chronic fatigue syndrome.*** *Clin Auton Res* 2002;12:264-72.

Naschitz (2003) This case-control study used the head-up tilt test with haemodynamic instability score (HIS) to differentiate 40 CFS patients from other patient groups and healthy controls.

A cut-off of >-0.98 showed a sensitivity of 90.3% and a specificity of 84.5%, potentially providing an objective criterion for the assessment of CFS. The HIS result was reproducible. The HIS can reinforce the clinician's diagnosis by providing objective criteria for the assessment of CFS.

Reference: Naschitz JE, Rosner I, Rozenbaum M, Naschitz S, Musafia-Priselac R, Shaviv N, *et al.* ***The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome.*** *QJM* 2003;96:133-42.

Yamamoto (2003) This study showed that the difference between baseline and after head-up tilt test (HUTT) in the fractal component of heart rate variability amplitude (DeltaAFR) differentiated between 24 female CFS patients and 22 healthy women.

The authors concluded that a decrease in aperiodic fractal component of heart rate variability in response to HUTT can be used to differentiate between CFS patients and healthy controls.

Reference: Yamamoto Y, LaManca JJ, Natelson BH. ***A measure of heart rate variability is sensitive to orthostatic challenge in women with chronic fatigue syndrome.*** *Exp Biol Med* 2003;228:167-74

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[8] The finding that this test did less well at distinguishing people with 'CFS' from people with 'generalised anxiety disorder' may be a reflection poor capacity of the clinical case definitions by which participants come to be classified as having these respective disorders in the first place rather than the capacity of this test of orthostatic intolerance to adequately separate these disorders. HB