Standing up for ME

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Data, data everywhere and no one stops to think!
(With apologies for the adaptation to Samuel Taylor Coleridge and the line in The Ancient Mariner – 'Water, water, everywhere, Nor any drop to drink'.)

Myalgic encephalomyelitis (ME) does not receive a very good press. A recent example in a 'for' and 'against' argument in the *Daily Mail* (*Is the ME illness all in the mind?* 26 May 2003) had one correspondent stating: '*I don't believe ME exists; those who are genuinely ill and disabled possibly have something else wrong with them – the rest should get a life*'. A cruel comment – yet it has a ring of truth to it. While many claim to have the illness, they cannot prove it and the term ME is probably over-diagnosed, over-used and, for many people, over-bearing.

ME is not your conventional illness: it doesn't have diagnostic tests, it doesn't have treatment, and, most importantly, it has very few members of the 'caring professions' looking out for it. There are even arguments about the name. The term, ME, has largely been subsumed under the generic term chronic fatigue syndrome (CFS), which begged Simon Loblay, in the Medical Journal of Australia, to ask: '*Is CFS a recognisable disease entity with a unique pathophysiology, or is it a ragbag of common non-specific symptoms with many causes, mistakenly labelled as a syndrome?*' There is no straightforward answer; it depends who you ask. However, the 1998 statement by the then Chief Medical Officer, Sir Kenneth Calman, serves notice on the scale of the problem, '*I recognise that chronic fatigue syndrome is a real entity. It is distressing, debilitating, and affects a very large number of people. It poses a significant challenge to the medical profession*'. This led to a report (Department of Health, 2002), which concluded '*A programme of research on all aspects of CFS/ME is required. Government investment in research on CFS/ME should encompass health-services research, epidemiology, behavioural and social science, clinical research and trials, and basic science*'. In the context of that conclusion and in light of the recent MRC report on the illness (2003), it is prudent to ask what direction basic science research should take.

While the cause of CFS/ME remains to be elucidated, extensive literature exists on non-specific findings, including: the role of a variety of infectious agents; up-regulation of anti-viral pathways; immune abnormalities; disruption to the hypothalamic pituitary adrenal axis (HPA axis); neuropsychological impairments; dysfunction of the autonomic nervous system; oxidative stress; and lipid peroxidation. These have been recently reviewed (Afari and Buchwald, 2003), as has the role of cytokines and other immunological markers in the illness (Patarca-Montero *et al*., 2002). None of these biological findings, however, can possibly be afforded the status of a marker since they are not necessarily part of the major disease pathway. They are, then, no more than factors somehow involved in the

Title image. Tilt table testing can be used to assess orthostatic intolerance associated with CFS/ME.

process of illness. Looking at the literature as a whole, however, there are various strands of evidence suggesting that the vascular system in CFS/ME is compromised.

One of the key difficulties that CFS/ME patients face is standing (orthostasis), most especially standing still. Inability to remain standing because of subjective findings (symptoms) or objective findings (signs; such as hypotension) is designated 'orthostatic intolerance'. Many CFS/ME patients are unaware that something as simple as being upright can trigger a cluster of symptoms such as dizziness, altered vision, nausea, fatigue, neurocognitive difficulties, headache, sweating and pallor. Orthostatic intolerance is characteristic of so many of these patients that it could very well serve as a definable subset in its own right and might even be seen as diagnostic if the underlying mechanisms could be understood.

Orthostatic intolerance

Standing upright provokes major shifts of blood volume in the human body. Without compensatory mechanisms, the pooling of blood in the lower body and the position of the human head well above the heart would combine to produce unconsciousness in us all. In order to maintain blood pressure and consciousness, there are effective compensatory mechanisms (Table 1).

'Stand'-ardisation of tests

The optimum way of testing for orthostatic intolerance is to impose a controlled upright stress while recording cardiovascular responses. Standardisation is allowed by use of the head-up tilt table or the more research-oriented lower body negative pressure test. Passive upright tilt as shown in Figure 1 uses a head-up tilt (HUT) table with a footboard for support and typically employs angles between 60º and 70º.

While an angle of 90º would appear to make physiological sense, this can lead to false positives and lesser angles are more discriminatory. In a typical test, ECG, blood pressure and heart rate are monitored continuously for up to 45 minutes after a suitable rest period.

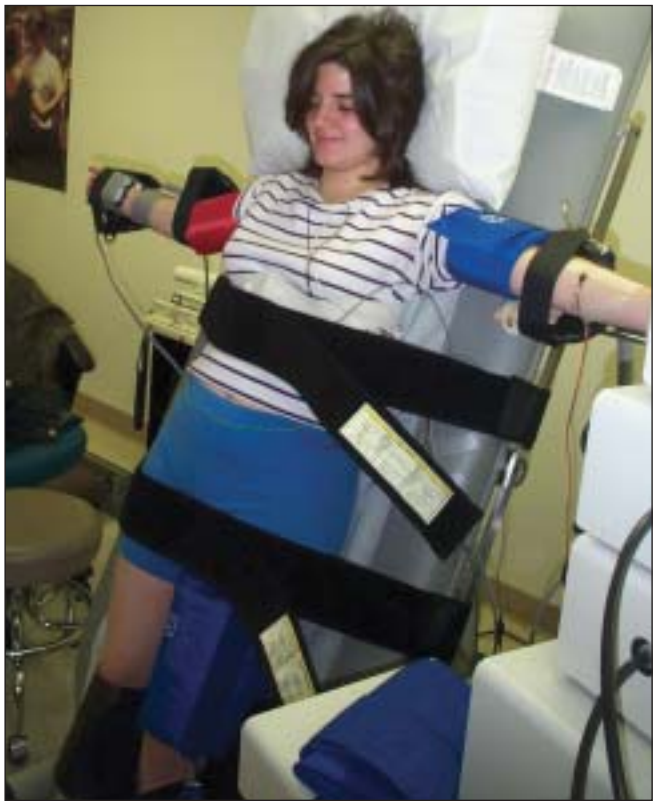

Figure 1. HUT testing. The subject here is tilted to 70º.

Tilt table testing was first employed as an orthostatic stressor in the 1940s. However, clinical testing was first performed in 1986 in the diagnosis of fainting (syncope). Therefore, cardiology results have been expressed as absence (negative test) or presence (positive test) of syncope and as the type of syncope if it occurs: thus, positive tests are often said to show slowing of the heartbeat alone (bradycardia; cardioinhibitory syncope), hypotension alone (vasodepressor syncope) or a mixed type, often referred to as vasovagal syncope.

Table 1. Compensating for standing up

Blood volume	If blood volume is inadequate then no amount of compensation can resolve the attendant changes in blood pressure and heart rate. Severe 'shock' leads to multi-system organ failure. Milder cases become apparent first when the subject is upright because of the additional effects of positional lower body blood pooling.
Physical forces (skeletal muscle pump)	The primary defence mechanism against gravitational pooling of blood in leg veins is the postural leg muscle, which propels blood back to the heart. A defective muscle pump is common in muscle atrophy associated with de-conditioning – astronauts, for example, develop leg muscle atrophy and refractory limb pooling after a period of exposure to the low gravity of space.
Long distance vascular control: autonomic nervous system	The second mechanism involves rapid vasoconstriction of arteries and arterioles in the extremities and in the gut. Such reflex mechanisms are mediated by high-pressure arterial baroreceptors located in the carotid sinus and aortic arch. Coronary receptors may play a role with lesser impact of cardiopulmonary receptors. Active venoconstriction also takes place in the gut, promoting venous emptying.
Long distance vascular control: humoral or neurohumoral effects	The third mechanism may be important in the protection of cerebral blood flow. It involves the renin-angiotensin-aldosterone system, adrenalin and vasopressin, and other neural mediators. It is important in the longer-term regulation of blood volume redistribution. There is speculation that catecholamines are also involved via ventricular mechanoreceptors and the dilation of skeletal muscle blood vessels.
Local vascular control (autacoids, inflammatory mediators, myogenic response)	Less well appreciated are contributions arising from local vasoactive responses produced by endothelial vasoactive products, metabolites, autacoids, local neurogenic mechanisms and neurogenic inflammation. These may contribute to myogenic, metabolic and venoarteriolar flow control.

Table 2. Various physiological responses to HUT (see Figure 2)

Normal	A modest tachycardia of 10 – 28 beats/min, possibly slight increase in diastolic BP, no change in systolic BP
Vasovagal Faint	Normal response for some minutes. Then, development of symptoms such as nausea, dizziness, feeling hot and sweaty accompanied by a slow, sometimes imperceptible fall in BP, associated with peripheral arterial vasodilatation (as distinct from normal neurogenic vasoconstriction) and followed by a precipitous fall in BP, occasionally accompanied by asystole. Vasovagal faint must be distinguished from the more serious but relatively rare cardogenic syncope associated with underlying cardiac pathology
Dysautonomia	This group contains patients with a variety of disorders of the autonomic nervous system, both primary and secondary forms, associated with diseases like diabetes and Parkinson's disease. In response to HUT there is a persistent fall in systolic/diastolic BP of greater than 20systolic/10diastolic mmHg within the first three minutes of the upright challenge and the appropriate response to hypotension – tachycardia – is often absent in such patients because of impaired baroreflex and vagal innervation. Such patients also have complications after a heavy meal and may even have supine hypertension.
POTS	Chronic orthostatic intolerance/Postural Tachycardia Syndrome (POTS) is the most widespread form of upright intolerance in adults and perhaps children. The key physiological change in response to HUT is a tachycardia – of more than 30 beats/min increase from supine within 10 minutes of orthostasis. Hypotension can occur later during orthostatic challenge. Patients with POTS have continuous disability and commonly have exercise intolerance in conjunction with other classical orthostatic symptoms like pallor, headaches, nausea, dizziness etc. There is rarely any history of actual fainting although they may faint under provocation (*e.g.*, prolonged tilt test). Specific tests on the autonomic nervous system are usually normal.

An alternative and more physiological way of looking at tilt results is shown in the diagrams in Figure 2 and explained in the text of Table 2.

Implications for CFS/ME

The first connections between CFS and orthostatic intolerance were made by Rowe and colleagues (1995). They noted similarities between CFS findings and patients with orthostatic intolerance. Initial data from CFS adolescents indicated the presence of POTS (private communication from Peter Rowe). Extended data collection from CFS adults indicated that a simple faint could be produced during upright tilt. The condition was designated 'neurally mediated hypotension' because referring physicians were reluctant to accept the fainting outcome since patients did not faint during daily life. Orthostatic intolerance was increased in CFS/ME patients but they rarely demonstrated low blood pressure nor were mechanisms of orthostasis necessarily due to neural mediation. Moreover, results were highly variable among diverse investigators largely due to the introduction of extra definitions for types of orthostatic intolerance and the various subpopulations of patients that fall within the heterogeneous CFS rubric. It was also largely because of the term 'neurally mediated hypotension' that abnormal tilt table testing was interpreted as evidence for autonomic dysfunction. This was an overly restrictive assumption (Table 1).

Nevertheless, the first foray into the orthostatic theory of CFS was fuelled by the restrictive assumption that orthostatic intolerance is a dysautonomic response. Extensive circulatory autonomic testing (Freeman and Komaroff, 1997 as one example) demonstrated that there was little wrong with autonomic regulation (with the exception of increased resting and upright heart rate in association with symptoms in somewhat more than 50% of adult patients). This suggests a likelihood of POTS in adult patients. And, to date, essentially all teenage patients with CFS/ME have POTS.

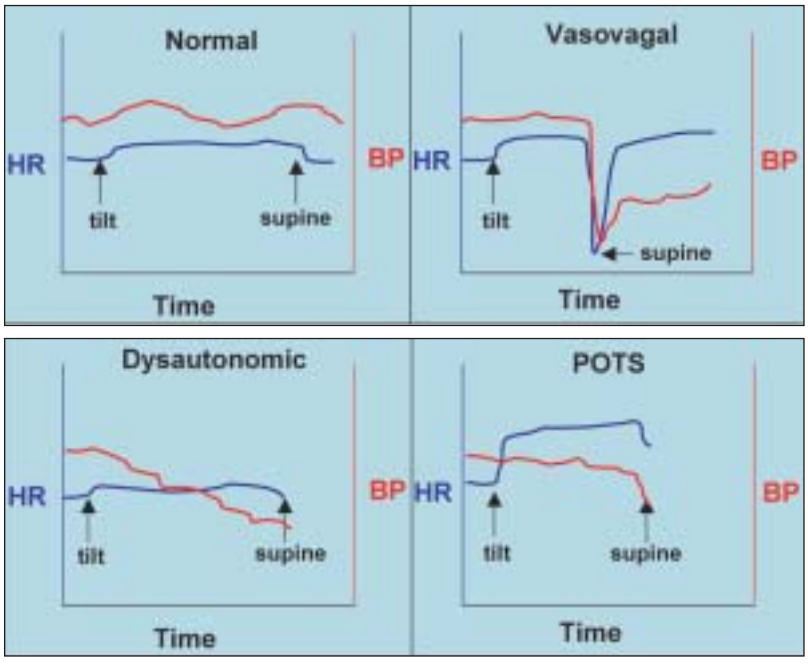

Figure 2. Various physiological responses to HUT (explained in Table 2).

It has been argued by some that orthostatic intolerance and POTS in CFS/ME is nothing more than cardiovascular deconditioning associated with bed rest. However, the majority of patients with CFS/ME are not bed bound and the most severe form of cardiovascular deconditioning, congestive heart failure, has no associated orthostatic intolerance. The orthostatic abnormalities associated with CFS/ ME have similarities to microgravity exposure and might better be designated as 'gravitational deconditioning'.

What causes orthostatic intolerance in CFS/ME?

If CFS/ME is not all autonomic dysfunction then what is it? A number of specific yet disparate mechanisms have evolved over time to explain orthostatic intolerance (Table 3). However, vascular dysfunction appears to be best supported by the available data.

CFS/ME patients with POTS often (but not always) display significant blue discoloration and sometimes swelling (pooling) of the legs,

Table 3.

Autonomic neuropathy that predominantly affects the lower extremities resulting in [alpha]1 adrenergic denervation hypersensitivity	$[Alpha]_1$-adrenergic control of venous filling in response to baroreflex stimulation during orthostasis is important only in the splanchnic circulations in human beings
Impaired innervation of the veins or in their response to sympathetic stimulation	Undetermined
Decreased $[beta]_1$-receptor sensitivity	This remains controversial
$[Alpha]_1$-receptor supersensitivity	$[Alpha]_1$-adrenergic effects may also alter venous filling indirectly through arterial vasoactivity
Altered venoconstriction	It is uncertain how important active venoconstriction is to the orthostatic response. Venous capacitance properties in POTS could be abnormal because of altered vascular structure, altered muscle tone, or both but preliminary data indicate unaltered venous distensibility
Increased capillary filtration	Blood pooling in POTS may result from a defect in arterial vasoconstriction which may be baroreflex sensitive in some cases and baroreflex insensitive in others. Increased venous filling and enhanced microvascular filtration during orthostasis results in pooling
Impaired Biomechanical Forces (Skeletal Muscle Pump)	The postural muscles of the lower extremities serve as "an accessory heart". Through rhythmic contraction these muscles serve to empty dependent venous structures thereby directly influencing cardiac venous return. They also increase the pressure gradient for forward flow. Increased blood flow with lower limb exercise would be impossible without this vital contribution
Abnormal blood vessel responses to various endothelial-dependent/ independent vasodilators	Nitric oxide (NO) is major endothelial independent vasodilator and there is evidence of an increased inducible expression of NO in CFS/ME. Alternatively acetylcholine is an endothelial dependent vasodilator and when this is added to blood vessels of patients with CFS/ME they respond in a supersensitive fashion

most especially on getting up in the morning (see Figure 3). This suggests that vascular abnormalities form the basis for many of the findings of CFS/ POTS and fitting well with our knowledge of compensatory mechanisms for orthostatic stress (Table 1). This has been termed the vascular hypothesis, which includes possible autonomic dysfunction as a subset.

Recent studies have focused on potential abnormalities of blood volume, neurovascular (including autonomic) function, local vascular function, and physical forces in producing or potentiating the findings of orthostatic intolerance in CFS/ME.

Blood volume may be decreased in certain subsets of CFS/ ME patients but, like so many CFS/ME-based hypotheses, there are disagreements about the reality and significance of this claim. Trials of blood expansion through erythropoietin, sometimes combined with a mineralocorticoid such as Florinef, are, however, currently under way.

On the one hand, investigations of peripheral vascular properties by Stewart, 2002 and by Freeman, 2002 have failed to demonstrate any important increase in lower limb distensibility (ability to distend) or compliance (physical property of yielding to pressure) in CFS/POTS. Indeed, they may show a decrease in vascular compliance related to smaller blood volumes. On the other hand, investigations of peripheral arterial resistance have shown both increased and decreased (and unchanged) leg blood flow in various CFS/ME/POTS subgroups. This is as it should be, since we are dealing here with a heterogeneous category of diseases rather than with a single disease entity.

Current thinking about both CFS/ME and POTS has emphasised the importance of disturbed blood flow physiology and some investigators have grouped patients by their patterns of altered blood flow and arterial resistance:

1. **A high blood flow**, low resistance group with normal limb capacitance is now denoted 'high flow POTS'. High flow patients have decreased resting peripheral resistance consistent with autonomic dysfunction. The prevailing theory is that they are 'neuropathic', meaning that they fit criteria for a long axon neuropathy with deficient norepinephrine (noradrenalin) release in the lower extremities and therefore ineffective postural vasoconstriction. Orthostatic tolerance is restored in response to phenylephrine infusion (Stewart *et al.*, 2002). Recent data demonstrate that increased microvascular filtration drives fluid collection in the lower extremities during orthostasis in these patients.
2. **A low blood flow**, high arterial resistance, high venous resistance, high venous pressure, low limb capacitance group is now denoted 'low flow POTS'. Some subjects show autonomic dysfunction in their internal organ vasculature while others in this group fail to respond

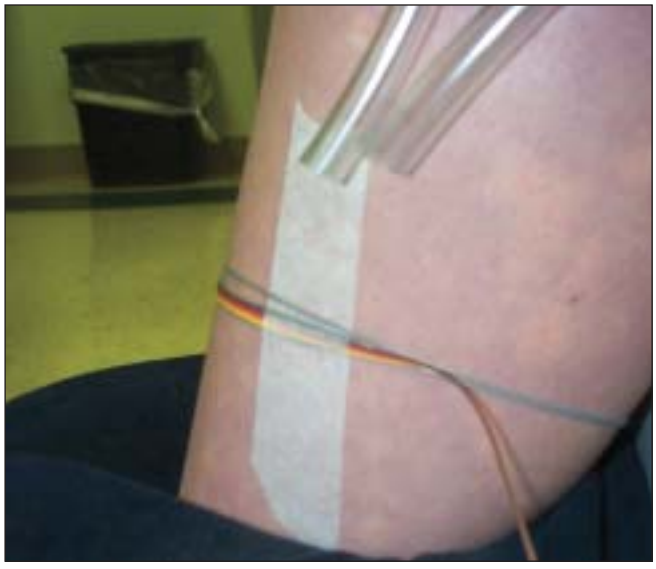

Figure 3. Example of CFS/ME/POTS patient with acrocyanosis/pooling in response to leg dependency.

adequately to phenylephrine infusion (Stewart *et al.*, 2002). Preliminary data using dye dilution methods suggests that blood volume may be low-normal in low flow POTS as reviewed by Streeten, 1999.

3. **A normal blood flow**, normal arterial resistance group with normal venous pressure, and normal limb capacitance is denoted 'normal flow POTS'. The normal flow group is associated with increased musculoskeletal flexibility, and preliminary evidence points towards enhanced pooling within the internal organs and pelvic regional circulations responding to alpha-1 adrenergic stimulation. Further discussion of these patients is beyond the scope of this article.

Similar arguments about defective vasoconstrictor reserve have been made regarding the physiology of vaso-vagal syncope (Bechir *et al.*, 2003).

The 'low flow POTS group' in CFS/ME

Stewart has concentrated on local blood flow regulation particularly in the microvasculature. Preliminary data indicate that reactive blood pooling, and local muscular and venoarteriolar responses are defective, implying that local regulatory endothelial systems may be abnormal. Spence, on the other hand, has examined endothelial integrity in CFS/ ME patients (reviewed in Spence *et al.*, 2004). CFS/ME patients are sensitive to the endothelium-dependent vasodilator ACh (see Figure 4) but not the endothelium-independent vasodilator NO. Such sensitivity is unusual if not unique and it is also clear that the sensitivity is specific to CFS/ME patients. It is not seen in other patient groups who are commonly classified under the CFS construct, like those with fibromyalgia whose endothelial responses to ACh are normal and, similarly, those with Gulf War Syndrome and farmers exposed to organo-phosphates when using sheep-dip preparations (references in Spence *et al.*, 2004).

What might be the reason for ACh sensitivity in CFS/ME patients? It could be caused by a reduced endothelial expression of the enzyme acetylcholinesterase (AChE) but alternative explanations are possible and these are outlined in Figure 5.

Under normal conditions the NO pathway will contribute most to vessel relaxation. Under pathological conditions, however, vasodilatation via the EDHF or phospholipase A2-activated prostacylcin pathways may be more dominant and investigation of the relative contributions of these acetylcholine-sensitive pathways is now urgently needed in CFS/ME patients.

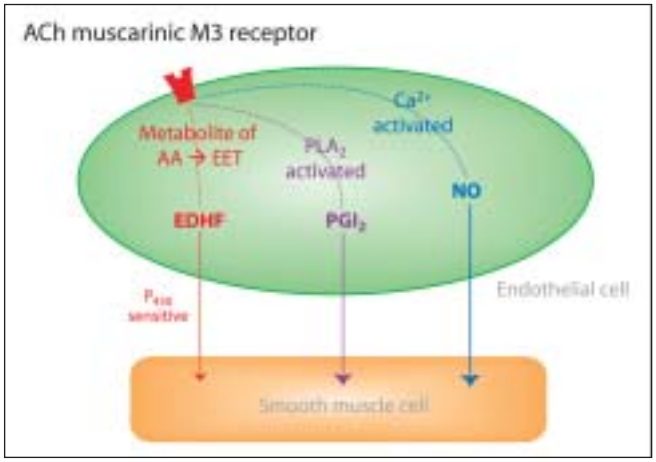

Figure 5. Potential endothelial-dependent vasodilator pathways via the ACh muscarinic M3 receptor.

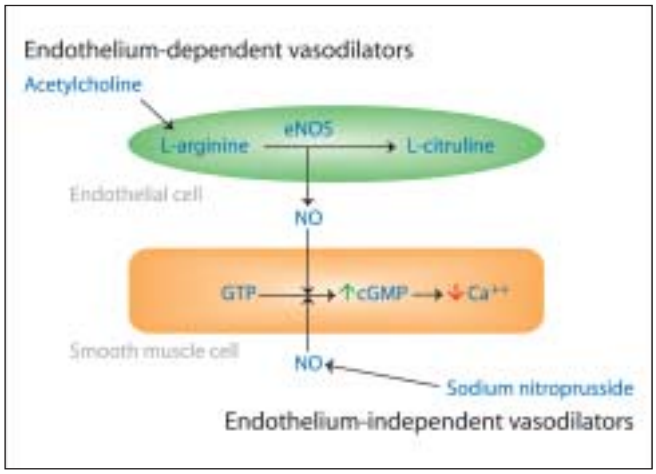

Figure 4. Acetylcholine is an endothelial-dependent vasodilator acting on a G-protein M3 receptor situated on the endothelial cell surface.

It should also be borne in mind that the onset of orthostatic symptoms in many CFS/ME patients is often predated by a viral infection. The involvement of inflammatory cytokines such as IL-1, IL-6 and tumour necrosis factor (TNFα), and NO needs to be considered. NO is an obvious candidate for generating orthostatic symptoms and since there is clearly a problem with local vasodilator and vaso-constrictor mechanisms in these patients, an imbalance between endothelial- and immunological-derived NO is an area worthy of further study. Of further interest are potential autoimmune mechanisms and the recent finding that circulating self-antibodies against the nicotinic receptor interfere with neurotransmission in patients with problems of the autonomic nervous system, including orthostatic intolerance.

Conclusion

There is, then, a significant body of evidence pointing to vascular dysfunction in the peripheral circulation of patients with CFS/ME and this is in addition to references of blood flow abnormalities within the central nervous system using SPECT imaging. Despite these data being widely available, the research interest in the illness is fragmented and this is largely due to problems of nomenclature surrounding CFS, which is a label that includes heterogeneous groups of patients with diverse symptoms. Many patients with CFS/ ME experience problems when upright but, as has already been made clear, the underlying biology of orthostasis in these patients takes several forms and it is vital that new biological research includes good patient selection and clinical assessment. Treatment is likely to become more specific and effective if, and when, the biology underlying a particular patient's problem is understood and quantified. Data, data everywhere and we need to stop and think.

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The web page of the CFS Association of patients of the US

www.nymc.edu/fhp/centers/syncope/index.htm
Julian Stewart's web page, including some very good material on orthostatic intolerance

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