Update on the theory and management of orthostatic intolerance and related syndromes in adolescents and children.

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Running Head: Orthostatic Intolerance

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ABSTRACT:

Orthostasis means standing upright. One speaks of "orthostatic intolerance" (OI) when signs, such as hypotension, and symptoms, such as lightheadedness, occur when upright and are relieved by recumbence. The experience of transient mild OI is part of daily life. “Initial orthostatic hypotension” on rapid standing is a normal form of OI. However, other people experience OI that seriously interfere with quality of life. These include episodic acute OI, in the form of postural vasovagal faint, and chronic OI, in the form of postural tachycardia syndrome. Less common is neurogenic orthostatic hypotension which is an aspect of autonomic failure. Normal orthostatic physiology and potential mechanisms for OI are discussed including forms of sympathetic hypofunction, forms of sympathetic hyperfunction, and OI that results from regional blood volume redistribution. General and specific treatment options are proposed.

Introduction. What is Orthostatic Intolerance?

The overall purpose of this review is to discuss orthostatic intolerance in young people, and how it relates to the autonomic nervous system. Orthostasis simply means "standing up". Thus "orthostatic intolerance" is defined by the inability to remain upright and is often erroneously designated "orthostasis". More specifically, orthostatic intolerance (OI) can be defined by the inability to remain upright relieved by recumbence [1].

OI is related to deviations from optimum regulation of heart rate, blood pressure, and cerebral blood flow that make remaining upright impossible. Environmental factors which promote OI (e.g. hot climate, dehydration) and the ubiquity of many forms of OI in the general population (simple faint, initial orthostatic hypotension) make some forms of orthostatic intolerance the result of over-taxed control systems, rather than disease *per se.* Thus, for example, any person can be made to suffer a simple faint given sufficient provocation [2]; therefore, should vasovagal syncope be regarded as an illness? The answer is perhaps yes if it importantly impairs the quality of life.

I will discuss sympathetic and parasympathetic contributions to mechanisms of orthostatic tolerance within a wider context of vascular control mechanisms that impact on the regulation of heart rate, blood pressure, and cerebral blood flow. Many of these modulate sympathetic activity. I will expand on the definition of orthostatic intolerance, then discuss orthostatic regulation as it pertains to the normal response to orthostasis and as it relates to sympathetic and parasympathetic activity. I will briefly review the measurement of OI in the laboratory and in real life, and then demonstrate how

problems with sympathetic adrenergic vasoconstriction produce distinct forms of OI along with approaches to treatment.

More on Orthostatic Tolerance and Intolerance

The inability to remain upright can be defined subjectively in terms of patient symptoms alone or more objectively by the combination of signs and medically associated symptoms. Typical signs and symptoms include loss of consciousness or less severe cognitive deficits such as lightheadedness and dizziness, as well as vertigo, pallor, visual difficulties or scotomata, fatigue, tachycardia, bradycardia, hypotension and sometimes hypertension, headache, weakness, abdominal pain and vomiting, palpitations, anxiety, diaphoresis, tremor, and exercise intolerance which is often delayed or may occur as part of a postural syndrome [3]. Among these, signs and symptoms referable to the central nervous system such as loss of consciousness, severe dizziness and cognitive difficulties are the most common reasons given for terminating an orthostatic stressor (upright posture) and seeking recumbence. Many of the remaining signs and symptoms are directly related to increased sympathoexcitation (e.g. pallor, hypertension, headache, palpitations, anxiety, diaphoresis, tremor), vagal withdrawal (e.g. tachycardia, abdominal pain and vomiting), or vagotonia (bradycardia during vasovagal syncope). The capability of assessing cerebral blood flow along with measurements of beat to beat heart rate and blood pressure facilitates the separation of spurious OI, or psychogenic syncope, from *bona fide* physiological impairments because reduced cerebral blood flow is a common feature in all forms of physiological OI but not in psychogenic syndromes. Representative reduced perfusion of the brain

[4,5] is shown in Figure 1 for two common forms of OI, vasovagal syncope (simple faint) and postural tachycardia syndrome (POTS). Cerebral blood flow may be related directly to hypotension [6,7], but not always [8,9]. Because cerebral blood flow (CBF) is autoregulated [10,11], CBF ought to remain stable within a range of cerebral perfusion pressures. However, impaired autoregulation results in decreased CBF which becomes directly dependent on perfusion pressure [4,5]. Thus, swings in blood pressure cause swings in CBF and any fall in BP contributes excessively to decreased CBF and impaired brain blood flow. That being said, virtually all people experience some degree of episodic mild OI during their lives, if only transiently during intercurrent illnesses or with dehydration[12]; occasional vasovagal syncope is extraordinarily common [13].

Normal Stressors and the Autonomic Regulatory Framework

I will now back up a bit to explain the phenomenology and physiology of orthostatic stress, AKA “orthostasis”. Standing upright and exercise comprise the most common physical stressors of daily life and “demand the full capabilities of the reflexes that govern cardiovascular function” [[14]] They therefore depend on intact arterial and venous vascular structure, intact vasomotor control, and sufficient blood volume and oxygen carrying capacity. However, foremost among compensatory mechanisms are the skeletal muscle pump and the respiratory-abdominal muscle pump [15,16]. These form the bases for a variety of physical orthostatic countermaneuvers which we will talk about later [17,18]. The compensatory responses to orthostasis are diverse and overlapping - thus mildly reduced blood volume or reduced vasoconstrictive capabilities are often well tolerated.

While neurohumoral vascular mediators have importance especially in a modulatory capacity, they are relatively slow to develop and therefore rarely directly determine initial responses to orthostatic stress [19]. Rapid cardiovascular adjustments depend on the autonomic nervous system (ANS), although the myogenic response [20] and local flow dependent mechanisms [21] may have a similar time course. Nevertheless, the ANS forms the framework for rapid circulatory adjustments resulting in changes in heart rate, arterial vasoconstriction, venoconstriction, adrenal secretion, renovascular adjustments and cardiac contractility in order to maintain blood pressure. Within the systemic circulation the parasympathetic nervous system via vagal nerve efferents contributes most to heart rate changes at rates less than the intrinsic rate [22], although recent work indicates strong vagal influences on sympathoexcitation [23]. In addition recent data suggest that parasympathetic ganglia have important effects on nitrergic (nitric oxide [NO] within nerves) vasodilation of the large cerebral arteries [24].

Rapid autonomic adjustments also depend on local environmental biochemistry produced by slower endocrine, and local regulatory mechanisms. These more slowly affect the vasculature in response to changes in posture. However, during more chronic changes they can modulate autonomic function and vascular tone. Thus, tonically altered nitric oxide and angiotensin-II act at central nervous system [25] and peripheral vascular [26] levels to alter the response to adrenergic vasoconstriction. While parasympathetic control of heart rate plays an important role in the beat to beat maintenance of blood pressure, the sympathetic nervous system and its primary vascular neurotransmitter norepinephrine [27], and co-transmitters neuropeptides Y and

ATP [26] are of paramount importance. Autonomic control of heart rate and blood pressure during orthostasis is provided by regulatory subsystems designated "baroreflexes" whose primary concern is the maintenance of BP under changing conditions. These are loosely grouped into arterial and cardiopulmonary baroreflexes, which interact with potent mechanoreceptor and chemoreceptor networks to maintain blood pressure during orthostasis.

Why do we need these control mechanisms? The Normal Orthostatic Response

Standing up decreases venous return to the heart and shifts a large fraction of central blood volume, in excess of 500 ml in the adult human, to the dependent body parts – i.e. those below the hemostatic indifference point located roughly at the diaphragm [28].

Initial Orthostatic Hypotension

There is an initial transient fall in blood pressure shortly after standing up shown in Figure 2. Initially blood is nearly instantly (at the speed of sound in the vasculature) redistributed by gravity from the central thoracic circulation to the dependent body parts: predominantly into the venous vasculature of the lower limbs and splanchnic circulation [29]. The decrease in BP is inversely related to initial vascular tone [30]; A delay of approximately 10-15 seconds, occurs before the onset of active compensatory responses. This initial response is denoted "initial orthostatic hypotension" [31], is complete within 30-60 seconds and blood pressure is restored, often while the typical adolescent balances precariously while holding onto furniture. Rarely fainting can occur, particularly if the child rapidly (say within 15 seconds) engages in exercise which further

dilates leg vasculature. Orthostatic countermaneuvers can avoid or remediate the condition [32,31]. This normal state of transient mechanical dysequilibrium is by far the most commonly experienced form of orthostatic intolerance [33] in the young and is normal. Sympathetic arterial tone contributes to resting vasoconstriction [34], is highly variable among individuals [35] and can alter the time to recovery across individuals.

Once hemodynamic stability is re-established blood volume is continuously reduced during continued non-active standing by microvascular filtration from plasma to interstitium [37]. While lymphatic activity and reabsorption of interstitial fluid helps to restore blood volume [38], this process is incomplete and an on-going reduction in blood volume and venous return occurs. This can be avoided by invoking the skeletal muscle pump by moving around, or by external mechanical compression through compression garments [39]. Since venous return equals cardiac output under steady conditions, there is a net reduction in central blood volume, stroke volume, cardiac output, and cerebral blood flow during quiet standing. Heart rate, total peripheral resistance (TPR), sympathetic nervous activity, vagal withdrawal and blood pressure increase (Figure 3). Diastolic BP increases more than systolic blood pressure and pulse pressure decreases coincident with reduced stroke volume.

The restoration of BP and partial restoration of systemic venous return during orthostasis is due in large measure to the reduced stretch and inactivation (unloading) of the inhibitory arterial baroreflexes. This results in vagal withdrawal, sympathetic vasoconstriction variable changes in myocardial sympathoexcitation [40], active venoconstriction within the splanchnic circulation [41], and passive venoconstriction of pooled blood within the splanchnic vasculature and legs by elastic recoil. Venous return

is thus partially corrected and central blood volume is partially but incompletely restored [42]. The cardiopulmonary baroreflexes are also unloaded when upright and potentiate the arterial reflexes[43]. Thus BP is restored and any reduction in BP normally occurs during initial orthostatic hypotension. Despite unchanged or even increased BP, increased sympathetic activity continues (Figure 3) which is thought to depend on arterial baroreflex resetting by cardiopulmonary reflexes [44]. This resolves the following paradox: diastolic blood pressure correlates best with sympathetic nerve activity in humans [45] and is increased at the level of the carotid sinus. Diastolic unloading and reduced stretch therefore does not occur while upright. Thus, the arterial baroreflex is not stimulated even while its effects on sympathetic activity are markedly increased. It turns out that baroreflex reflex curves are shifted to a higher HR and BP when upright as occurs during exercise [46],through the unloading of the cardiopulmonary receptors. This enables heart rate to remain increased via vagal withdrawal and promotes increased sympathetic nerve activity and vasoconstriction - the normal compensatory response to orthostasis [47].

Orthostatic Stress Test and Tools to Study OI

Orthostatic stress tests test orthostatic capability. The most physiologic test is standing in place without exercising. This allows some muscle pump activity which may mask defects in the ANS [48]. Therefore, clinicians sometimes use devices such as the motorized tilt table [49] which passively places the patient upright while restricting leg movement. Upright suspension has been used with often dramatic consequences[50].

Lower body suction or negative pressure (LBNP) which closely simulates hemorrhage can duplicate some findings of orthostasis even while remaining supine. Tilt + LBNP can produce fainting in everyone [2].

Instrumentation that measure BP, heart rate and cardiac rhythm, cardiac output (e.g. indicator dilution, inert gas rebreathing), regional blood flow (e.g. ultrasound, venous occlusion plethysmography, impedance plethysmography), and blood volume have all been bundled with clinical tilts. Recent conscious human studies of sympathetic control of orthostasis began in earnest with the use of microneurography to measure peripheral sympathetic nerve activity [45]. Other advanced techniques using norepinephrine sympathetic nerve spillover [51] to measure the effect of adrenergic vasoconstriction on local blood flow [52], and most recently to directly assess the integrity of norepinephrine synthesis and metabolic products by vascular biopsy [53,54] can be used to find the actual mechanism of OI in sufferers.

Orthostatic Hypotension.

Orthostatic hypotension (OH) is defined as a sustained reduction of systolic BP> 20 mmHg or diastolic BP>10 mmHg within 3 min of standing or head-up tilt to ≥60^{o} [55]. The requirement of a sustained reduction rules out IOH. This definition is recent [55] (2011) and was assembled by a consensus panel. Before that, there was no consistent definition of OH. Non-neurogenic OH can be caused by drugs, dehydration, blood loss, age and illnesses that secondarily cause acute or chronic hypovolemia. Neurogenic OH is identified with autonomic failure due to inadequate release of norepinephrine from

sympathetic vasomotor neurons leading to vasoconstrictor failure [55]. Neurogenic OH is rare in the young since most causes of autonomic failure are acquired with age either as a primary (e.g. pure autonomic failure, PAF) or secondary (diabetes) disease. Autonomic failure can be primary with pre-ganglionic, post-ganglionic, or both (e.g. Parkinson disease) forms of sympathetic dysfunction [56]; However, there exist congenital genetic variants such as Familial Dysautonomia (Riley-Day syndrome) [57] and the exquisitely rare dopamine beta hydroxylase deficiency (DBH deficiency) [58] Autonomic failure can be autoimmune [59] and may present with the post-infectious Guillain-Barre syndrome although autonomic dysfunction seems to have little effect on ultimate outcome [60]. Most commonly autonomic failure is acquired as a secondary aspect of systemic disease such as diabetes [6]. Sympathetic cardiac denervation is a central aspect of Parkinson's disease [61] and may be found in other forms of autonomic failure. Cardiac parasympathetic innervation is also often defective resulting in a steady fall in BP with little reflex tachycardia during orthostatic challenge as shown in Figure 4.

Supportive care and treatment of the underlying illness are essential. Thus, in the case of DBH deficiency, Droxidopa, which by-passes the missing enzyme can provide definitive remediation. It may also be the drug of choice for most neurogenic OH since it can provide norepinephrine production through alternative pathways. Supportive therapy focuses on decreasing symptomatic orthostatic hypotension and syncope. Such therapy would include physical countermaneuvers including compression garments, and dietary changes (increased salt, rapid water drinking). Supportive drug therapy often

aims to increase blood volume by promoting salt and water retention (fludrocortisone) or by increasing red blood cell mass (recombinant erythropoietin). Defects in erythropoietin may occur as part of the denervation in autonomic failure [62]. Short acting pressor drugs such as midodrine or drugs that enhance autonomic activity (atomoxetine, yohimbine, pyridostigmine) are also used [63,56].

Rapid water ingestion of approximately 16 ounces deserves special mention. Studies in adults have demonstrated that intake of water free of solute can increase blood pressure and improve sympathetic vasoconstriction after a sufficient time has elapsed for the water to reach the small intestine, say 20 minutes [64]. The palliative effect of water encompasses all OI including OH, POTS and vasovagal syncope [65] and can be successfully used to prevent blood phobic vasovagal syncope. Effects last for several hours. The mechanism is dependent on osmolarity and may depend on TRPV4 C-fiber receptors within the portal system [66]. This is a very important, simple and effective palliation that is not often considered by clinicians.

Common Variants of Orthostatic Intolerance the postural tachycardia syndrome (POTS) also known as Chronic Orthostatic Intolerance and Reflex Postural Vasovagal Syncope

POTS

POTS is defined by day-to-day symptoms of OI associated with excessive upright tachycardia but not with hypotension [67,9] (Figure 5). Excessive tachycardia in adults is defined by an upright increase in HR exceeding 30bpm or to a heart rate exceeding 120bpm. Recall that the normal HR response to orthostasis is an increase in HR while

the autonomic failure patient often has no significant increase in HR when upright. Larger heart rate increments are observed in the young with POTS [68] which is important to know in avoiding over diagnosis. Symptoms must be concurrent with the excessive tachycardia. No symptoms, no POTS. Tachycardia and concurrent symptoms are very often observed during extremely prolonged orthostatic testing which are therefore to be avoided if the specific diagnosis of POTS is to be made. POTS has often been divided into subgroups designated "neuropathic POTS", in which it is assumed that partial sympathetic denervation or adrenergic hypoactivity is present, and "hyperadrenergic POTS", in which upright adrenergic overactivity dominates the picture.

Neuropathic POTS

As originally described, neuropathic POTS is caused by decreased sympathetic adrenergic vasoconstriction in the lower limbs, associated with reduced leg norepinephrine spillover [69] and reduced vasoconstriction of the lower extremities [70]. There is often increased blood flow ("high flow") in the lower extremities even while supine. Another neuropathic variant has normal lower extremity hemodynamics ("normal flow") but decreased regional sympathetic adrenergic vasoconstriction in the splanchnic circulation [71]. Neuropathic POTS can represent an autoimmune autonomic neuropathy [59]. Thus when upright, neuropathic POTS patients have greater than normal redistribution of blood to the dependent vasculature causing baroreflex mediated tachycardia and vasoconstriction. The cardiac baroreflex response is also blunted in POTS [72]. Central hypovolemia can also result in hyperpnea and hypocapnia in nearly 50% of patients [73] through a baroreflex mediated mechanism [74].

Therapy for neuropathic POTS includes general supportive measures such as physical countermaneuvers, increased salt and water intake and exercise (see below). Pharmacotherapy has focused on improving sympathetic vasoconstriction which unfortunately uses medications with widespread systemic effects. Midodrine, an alpha-1 adrenergic agonist, can be helpful and has few side effects apart from piloerection [75]. Droxidopa is in trials outside the USA and has great expectations. Mestinon (pyridostigmine) [76] an acetylcholinesterase inhibitor, alone or in combination with midodrine, can be very helpful through its potentiation of cholinergic ganglionic nerve activity and through its muscarinic effects.

Hyperadrenergic POTS

The tachycardia of hyperadrenergic POTS is caused by increased pre-synaptic or post-synaptic adrenergic potentiation. This might include central sympathetic activity and increased sympathetic nerve activity. Increased supine sympathetic activity has been reported [67], but not universally [77]. To date my laboratory has only observed increased upright muscle sympathetic activity in POTS. One cause of hyperadrenergic POTS is increased synaptic norepinephrine. The norepinephrine transporter deficiency heterozygote [78] is the prime example of this mechanism but has been found as an autosomal mutation in only one pedigree. Less extensive, possibly epigenetic NET deficiency has also been demonstrated recently and may have a wider prevalence[53] . Alternative considerations of mechanism include modulation of the adrenergic synapse through enhanced norepinephrine synthesis and release, and enhanced post-synaptic affinity which may be modulated by local and humoral transmitters. Thus, for example,

the reciprocal actions of nitric oxide (NO) and angiotensin-II respectively reduce and enhance adrenergic activity. The role for NO as an inhibitory neurotransmitter is now well-known [79]. Nitrergic NO released from nerves having parasympathetic activity act at pre-synaptic and post-synaptic sites to decrease adrenergic transduction [80], the process by which a sympathetic nerve impulse causes vascular smooth muscle contraction. This includes reduction of the release and binding of norepinephrine from the neurovascular synapse [81], interference with post-synaptic neurotransmission [82], chemical denaturing of norepinephrine [83], and down-regulation of adrenergic receptors [84]. Conversely, studies of sympathoexcitation show that angiotensin-II act through AT1 receptors to increase production of reactive oxygen and nitrogen species (ROS) within the brain at presynaptic sympathetic neurons [85], and act in the periphery where they produce pre and post-synaptic augmentation of sympathetic transduction, and upregulation of adrenergic receptors [84]. In addition, the release and binding of norepinephrine is facilitated [81], as are the effects of norepinephrine. This depends critically on the formation of ROS [86] which also decrease NO [87], often uncoupling nitric oxide synthase [88]. This mechanism occurs in a variant of "hyperadrenergic POTS" associated with tachycardia, pallor, vasoconstriction ("low flow") and absolute hypovolemia even while supine [89]. NO, plasma renin, and serum aldosterone are decreased [90], while plasma angiotensin-II [91] is increased by a defect in ACE-2 [92].

Beta blockers have been used in forms of hyperadrenergic POTS with variable success [93,94] .Innovative treatment with ARB’s and Droxidopa are under investigation. Exercise has always been a mainstay of rehabilitation in these patients. Recent work

indicates that gravitational deconditioning (e.g. bedrest) is a frequent concomitant of the illness and that a graded exercise program can be very effective in improving overall patient well-being [94].

Postural Syncope (Vasovagal Syncope, Acute OI, Simple Faint)

Syncope (fainting) is defined as "complete loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery" [95,96]. Approximately 40% of people will faint during their lives; half of these presenting during adolescence. The peak age for first faint is 15 years old [98]. Most syncope is caused by systemic hypotension and reduced cerebral blood flow. It is possible that a cerebrovascular accident could present in similar fashion [99] although never reported in pediatrics. Syncope can be caused by orthostatic hypotension which we have already discussed. OH is easily ruled out by a 3 minute standing test (Figure 4). Syncope is divided among cardiovascular syncope, frequently arrhythmic or structural cardiopulmonary disease, and reflex or neurally mediated syncope. Cardiovascular syncope has a poor prognosis unless specifically treated. Reflex syncope has an excellent prognosis [100]. Postural syncope and emotional or phobic syncope comprise vasovagal syncope (VVS) [95], the largest subgroup within the reflex syncope category. Regional or system-wide loss of vasoconstriction is an element in all vasovagal syncope, at least as a terminal event; it may not always be due to loss of sympathetic nerve activity as discussed below. Postural syncope is acute orthostatic intolerance wherein loss of consciousness is often preceded by a prodrome of OI symptoms, particularly lightheadedness, nausea, sweating, weakness and blurred

vision. Traditionally, postural syncope was believed to be due to reflexes from a hypercontractile underfilled heart analogous to the Bezold-Jarisch reflex [101]. Evidence to the contrary has accrued: such stimulus would be short lived because of baroreceptor would unloading [102]; very few afferent nerves were excited in the original experiments by Oberg and Thoren in the moribund hemorrhaged cat [103]; VVS can occur in a ventricular denervated transplant recipient [104]; and the heart is neither empty nor hypercontractile prior to syncope [105]. As yet we do not completely understand the pathophysiology of simple faint [106].

In the most common variant of postural faint occurring in young patients, postural faint comprises 3 stages (Figure 6) which strongly resemble the circulatory changes found during hemorrhage [107]. After initial orthostatic hypotension and restoration of circulatory homeostasis, BP stabilizes while HR increases in Stage 1. BP stability distinguishes postural faint from true OH. BP often exhibits rhythmic fluctuations during this stage referred to as “Mayer waves” [108] with an approximate 10 second period (0.1Hz). Similar periodicity is shared by fluctuations in heart rate, sympathetic nerve activity and peripheral resistance. The fluctuations are the closed loop time for sympathetic baroreflex response – i.e. the time it takes for detection and compensation for BP changes [109]. Oscillations are accentuated during central blood volume reductions such as occur during orthostasis. During this stage TPR increases to sustain BP in the face of a reduced cardiac output (Figure 3).

During Stage 2 BP slowly declines as the baroreflex increases HR further. The decrease in BP is most often related to decreased cardiac output [110] even though

sympathetic activity [111] and peripheral arterial resistance [112] are sustained. Thereafter, resistance and pressure oscillations decrease despite sustained sympathoexcitation. Hyperpnea and hypocapnia occurs at this stage in most patients [113]. In some patients Stage 2 is abbreviated. This is especially true for patients with convulsive syncope (Figure 7) in whom episodes occur abruptly in association with asystole. Convulsive or asystolic syncope (Figure 7) is distinguished from epilepsy by decreased EEG activity in the former and by nearly immediate resolution of opisthotonic posturing by recumbence. Despite appearances, Asystolic faints are not cardiogenic but reflex mediated and are a relatively uncommon form of simple vasovagal fainting that may also be found in phobic fainting.

Several mechanisms have been proposed for vasovagal syncope in some patients. Patients with decreased resting BP can have reduced tyrosine hydroxylase and NE synthesis. A group of normotensive patients can have excess NET [114]. A selective deficit of splanchnic vasoconstriction and venoconstriction has also been demonstrated [71]. Prodromal OI symptoms begin during the second stage and clinicians might therefore entertain a diagnosis of POTS in the laboratory setting. Clinical history offers the best way to distinguish patients with acute episodic faints with long periods free of symptoms (postural syncope) from POTS, in which symptoms are chronically present; Indeed, the prodrome of simple faint and the signs and symptoms of POTS are similar because they may have similar initial pathophysiology – excessive reduction in central blood volume resulting in reflex tachycardia [70,71,115]. Postural fainters corresponding to pale and vasoconstricted hyperadrenergic POTS patients are not observed in

practice. For the most part, in our experience, POTS patients have day-to-day symptoms but do not faint, while syncope patients have episodic faints but not daily symptoms. This distinction has become less clear with time: thus, some chronic OI (POTS) patients faint, and some episodic fainters also have underlying daily symptoms of OI. However, fainting of POTS patients in laboratory must be viewed cautiously and cannot, by itself, be regarded as proof of real-world fainting. A “real-world” clinical history compatible with fainting is compulsory.

In the last stage, Stage 3, CBF, BP and HR rapidly fall in that order, seemingly defying BP – CBF causality [116]. Similar effects are often seen in nonlinear systems of all kinds whenever a sufficiently strong external signal entrains linked signals. Thus, recent work shows that both cardiovagal and sympathetic baroreflex efferent arms are impaired prior to fainting, and Mayer waves disappear. Similarly cerebral autoregulation becomes impaired with entrainment of CBF, BP and HR by an extrinsic signal which may be hyperpneic respiration [4,117]. Why baroreflex integrity is lost is not yet known. But this results in abnormal BP-HR and BP-MSNA functional relationships such that HR, BP, and sympathetic nerve activity all decrease resulting in bradycardia, hypotension and sympathetic silence [118]. The faint is associated with marked systemic vasodilation while CBF falls with declining BP. Recent work challenges the necessity of sympathetic silence as the precipitant of the final hypotension [119]. While vasodilation always occurs, the sympathetic baroreflex can fail with or without sympathetic silence because of a loss of the functional relationship between blood pressure and sympathetic activation. Loss of functional connections between BP and

sympathetic nerve activity, but not heart rate occurs in patients with vasodepressor syncope where vasodilation without bradycardia occurs. While there is a loss of the sympathetic efferent baroreflex causing progressive loss of compensatory vasoconstriction, the cardiovagal baroreflex remains intact.

POTS and postural syncope are both associated with hyperpneic hyperventilation [113,8,73]. Hyperpnea and resultant hypocapnia precede unconsciousness in virtually every vasovagal syncope patient. Hypotension and bradycardia might be explained by the pulmonary stretch reflex unfettered by compensatory baroreflex effects [117,120]. The cause of hyperpnea is unclear but may relate to the ventilatory efferent arm of the arterial baroreflex [74]. Similar findings of hyperpnea are found in approximately 50% of POTS patients with central hypovolemia who do not faint.

First time postural noncardiogenic fainting with no sequelae probably requires no treatment. The first time fainter rarely knows what is happening to him. Once suitably apprised, countermeasures can be employed. These include avoidance of precipitants and physical countermaneuvers; the most effective countermaneuvers are lying down with legs up or squatting. Both propel blood from the lower body below the diaphragm back into the central circulation. Other countermaneuvers include those that enhance the skeletal muscle pump (e.g. leg crossing) or activate the exercise pressor reflex (isometric hand grip) [15,39,17]. Generally enhanced salt and water intake is encouraged and has shown some efficacy in small studies employing very large amounts of salt loading [121]. Rapid water ingestion offers an effective palliative effect.

Thus, once syncope patients have staved off the faint with physical maneuvers, they are counseled to consume 16 ounces of water before attempting to stand up. In older patients confounding use of antihypertensives or diuretics need to be considered. Pharmacotherapy (atenelol or fludrocortisone) has not been shown to be more effective than placebo in younger patients in large multicenter studies [122]. Reports of exquisite sensitivity to midodrine are found in Chinese children [123] but are not uniformly born out in other populations [124]. Other pharmacologic strategies tested in small studies include SSRI's including paroxetine which showed efficacy in a 68 patient double blind randomized study of a select patient subset [125]. Asystolic faints have recently been shown to improve with pacemaker insertion [126]. Work into the fundamental molecular physiology of fainting is on-going in our laboratory and in others. Our hope is to determine specific therapy based upon specific pathophysiology.

We have only considered well-known forms of orthostatic intolerance. It is entirely likely that there are other forms that are not well described will emerge.

Expert Commentary

Orthostatic intolerance (OI) is very common. Except for forms of autonomic failure with true neurogenic orthostatic hypotension or postural fainting while in harms way (accidents) OI is not life threatening. Autonomic regulation is usually abnormal or maladaptive in disorders of orthostatic tolerance and often relate to suboptimal sympathetic adrenergic function. Mild OI, especially initial orthostatic intolerance, is universal and rarely harmful. Other forms of OI can seriously impact on quality of life.

True neurogenic orthostatic hypotension, which can signal the presence of potential life threatening autonomic failure, has only recently been unequivocally defined by consensus and simple testing devised. Postural vasovagal faint and postural tachycardia syndrome are two well-described common forms of orthostatic intolerance. The ability of simple non-pharmaceutical measures of physical countermaneuvers and rapid water ingestion to aid in improving OI must be emphasized.

Five-year view

The mechanisms of chronic and acute orthostatic intolerance are incompletely understood. This even includes simple postural faint which had been treated for years by practitioners with drugs with placebo effects only. Placebo therapy might be helpful if unorthodox. Treatments are therefore often non-specific. However, several investigations hold promise for specific therapy targeting specific mechanisms of orthostatic intolerance.

Key Issues

- Orthostasis means standing up.
- Orthostatic intolerance (OI) is defined by signs and symptoms that make remaining upright impossible and improve when lying down
- Initial Orthostatic Intolerance is a normal, common, short lived form of OI in the young. It is the most common form of OI in the young.
- Physical Countermeasures and rapid water ingestion can improve most forms of OI

- With the exception of neurogenic orthostatic hypotension, OI can even be “normal” in the sense that anyone can be made to faint with sufficient provocation, and fainting occurs in 40% of people). Normalcy is not the issue. Rather OI becomes a problem when it interferes with the quality of life.

Treatment

Orthostatic Syndrome	Defect/Pathophysiology	Treatment
Initial Orthostatic Hypotension	None/Rapid redistribution of blood to dependent body	Physical Countermaneuvers: sit down, isometric exercise (exercise pressor reflex) Rare medication
Neurogenic Orthostatic Hypotension (OH)	Systemically defective or absent adrenergic vasoconstriction. Autonomic Failure Frequent parasympathetic dysfunction	Physical Countermaneuvers:lie down, sit down, squat, clench buttocks, leg crossing, support garment. Droxidopa, salt and water loading, fludrocortisone, midodrine, atomoxetine + yohimbine. If secondary (e.g. diabetes) treat underlying disorder. Rapid water ingestion palliation
Non-neurogenic OH	Loss of blood volume, vasodilator drugs	Correct problem
Neuropathic POTS	Loss of regional vasoconstrictive ability	Physical Countermaneuvers Droxidopa, midodrine, mestinon Exercise Rapid water ingestion palliation
Hyperadrenergic POTS	Adrenergic Potentiation	Physical Countermaneuvers Beta Blockers, AT1RB (ARB), ivabradine? fludrocortisone, Exercise
Postural Vasovagal Syncope	? Loss of regional vasoconstrictive ability ?Acute reversible baroreflex dysfunction	Physical Countermaneuvers Salt and Water Acute Water Ingestion SSRI. Midodrine Rapid water ingestion palliation Pacemaker for Asystolic vasovagal faint

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Figure Legends

Figure 1 shows arterial pressure (AP) in upper panels and cerebral blood flow velocity (CBFv) measured by transcranial Doppler ultrasound in lower panels. The left panels show data from a vasovagal syncope patient while right sided panels show data from a POTS patient. AP and CBFv are initially stable then decrease gradually and finally abruptly decrease by >50% with loss of consciousness in the syncope patient. The POTS patient has no decrease in AP but has a >20% reduction in CBF throughout tilt.

Figure 2 shows initial orthostatic hypotension (IOH). Arterial blood pressure is shown during a standing test. The blood pressure begins to decrease immediately upon standing, reaching its nadir in about 15 seconds and recovers spontaneously. The inter-beat interval is quite decreased when hypotensive corresponding to an increased HR.

Figure 3. The left panel shows from top to bottom: arterial pressure (AP), muscle sympathetic nerve activity (MSNA) from the peroneal nerve, heart rate, and cardiac output (CO). The right panel shows from top to bottom: total peripheral vascular resistance (TPR), cerebral blood flow velocity (CBFv) by transcranial Doppler ultrasound, stroke volume (SV), and a vagal index calculated from the respiratory sinus arrhythmia component of the frequency spectrum of heart rate variability. The subject is a representative healthy volunteer. During upright tilt, systolic, diastolic and mean arterial pressures increase slightly while pulse pressure is decreased with a decrease in SV by approximately 40%. HR increases so that CO is only decreased by 20% because of the increase in heart rate. Cerebral blood flow decreases by 5-10%. Both TPR and

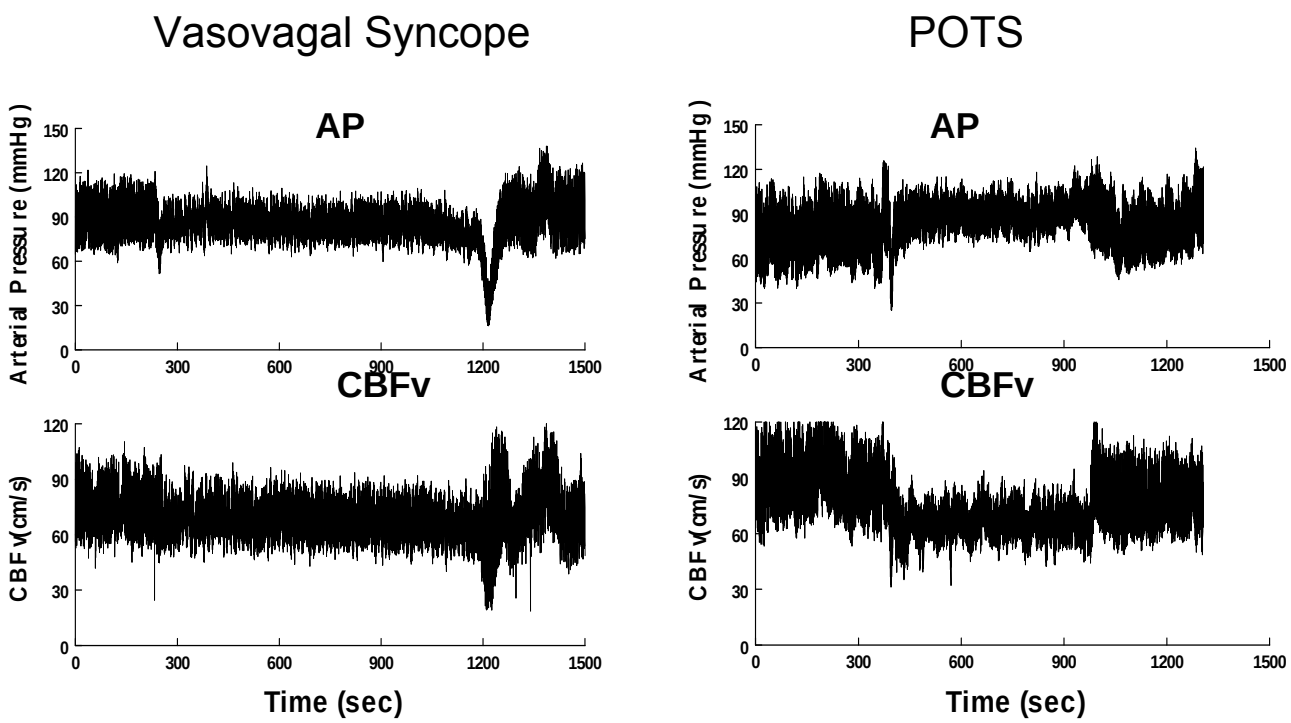
MSNA increase while the vagal index decreases, reflecting respectively sympathetic activation and parasympathetic withdrawal.

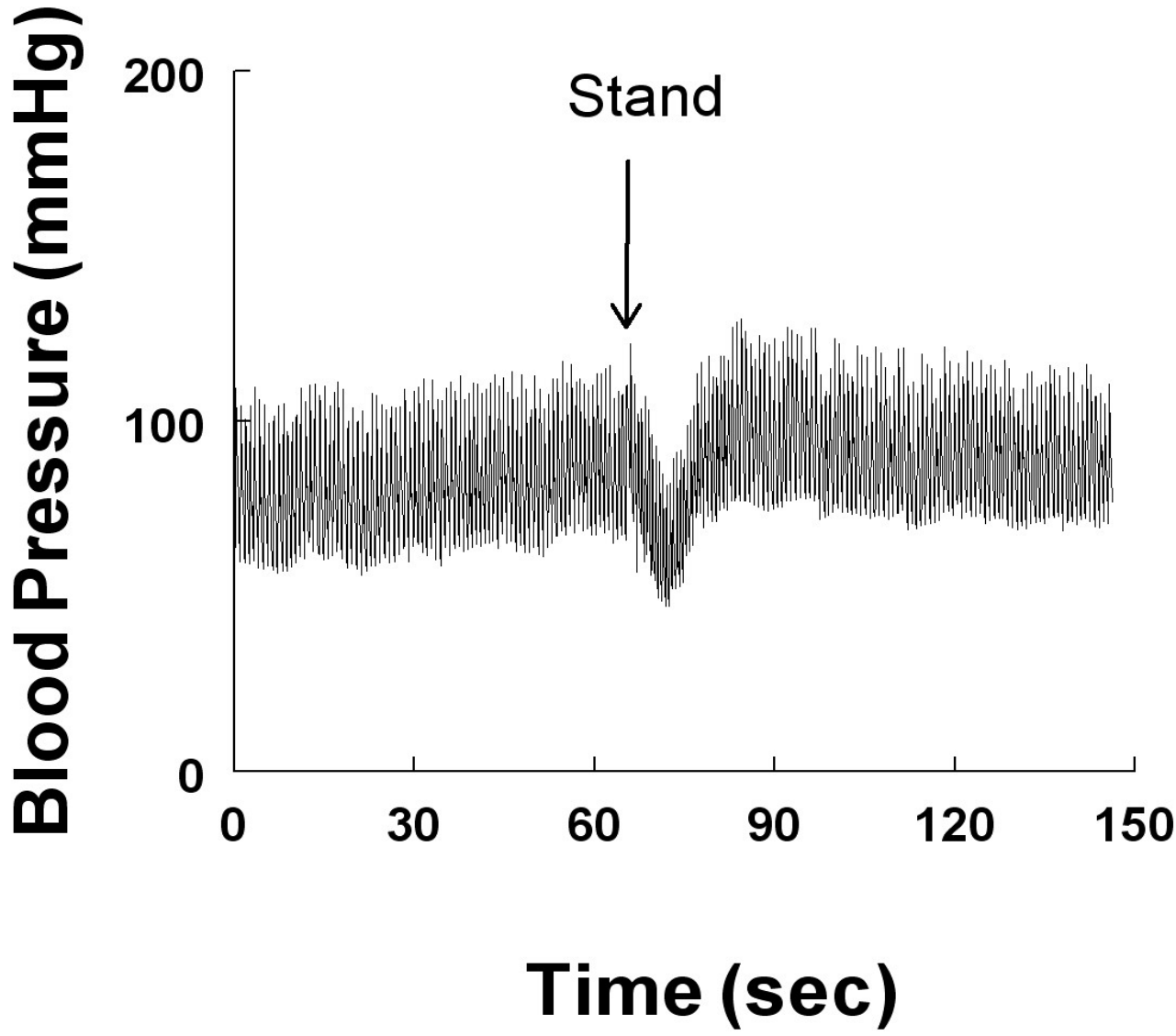
Figure 4 Neurogenic OH is demonstrated. Arterial blood pressure in the upper panel declines steadily during upright stance while HR is only slightly increased.

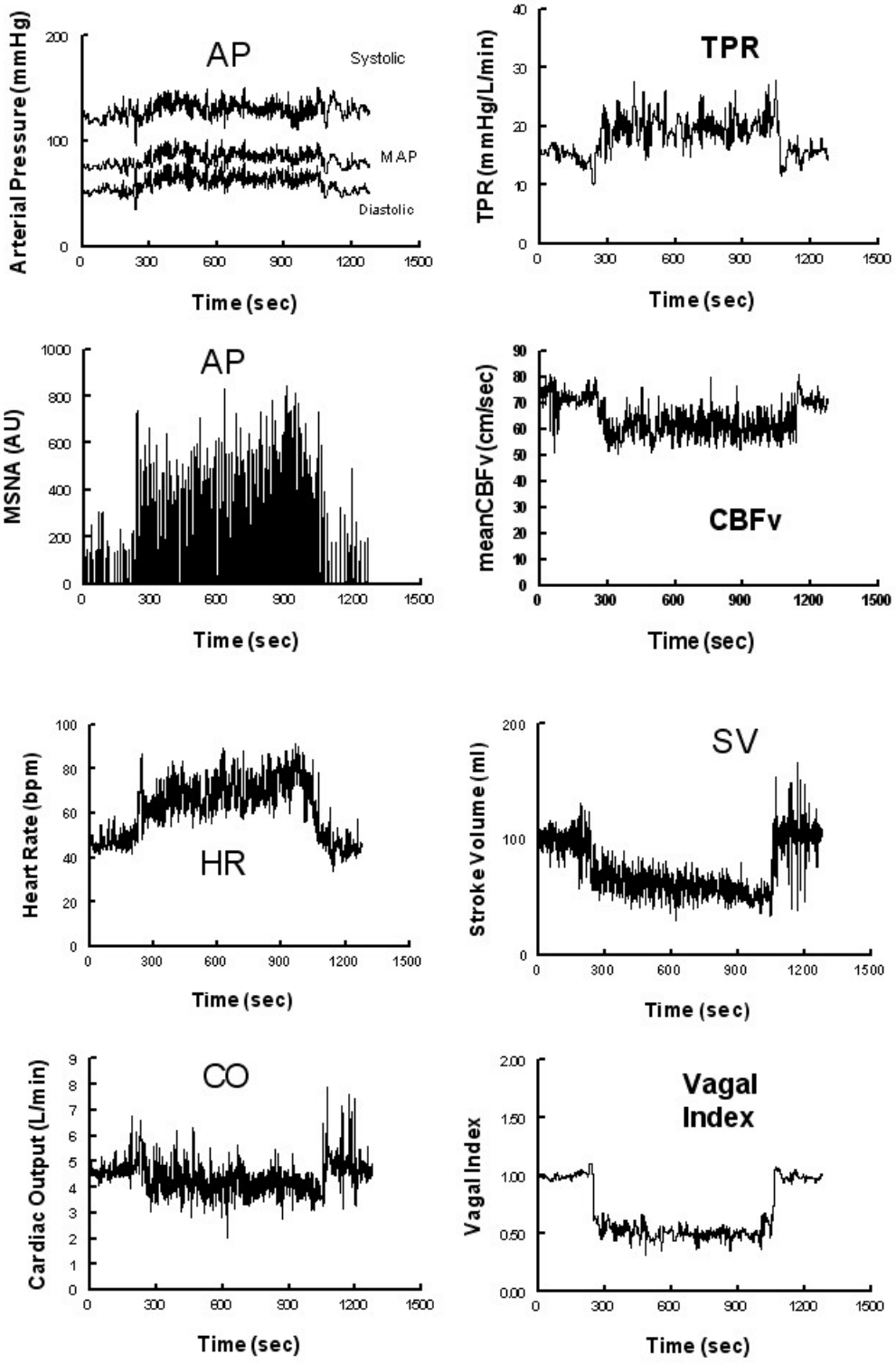
Figure 5 shows representative heart rate (HR) in the upper panel and mean arterial pressure (MAP) in the lower panel during upright tilt in a POTS patient. HR increases while MAP is stable throughout tilt in POTS.

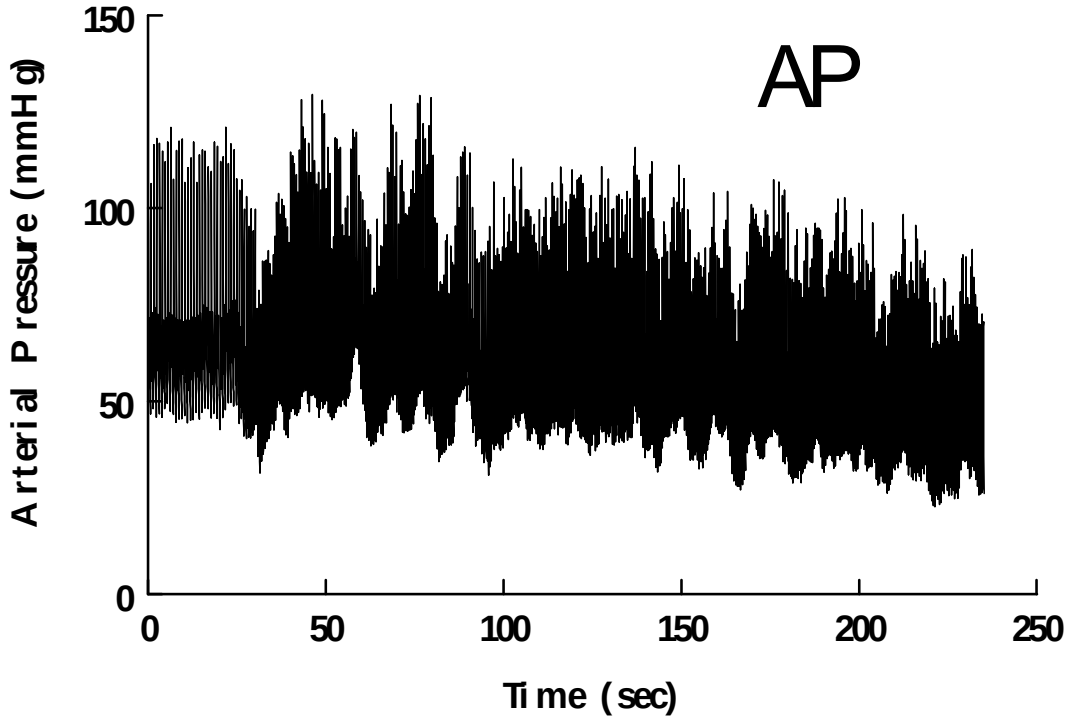
Figure 6 shows representative heart rate (HR) in the upper panel and mean arterial pressure (MAP) in the lower panel during upright tilt for a postural syncope patient. Changes during tilt occur over three stages: during the first stage, following initial hypotension MAP stabilizes at a slightly higher than resting pressure while HR increases. During the second stage MAP begins to fall gradually while HR continues to increase. Note that the increment in HR from supine to upright fulfills tachycardia criteria for POTS. During the third stage MAP and then HR fall abruptly and rapidly as loss of consciousness supervenes.

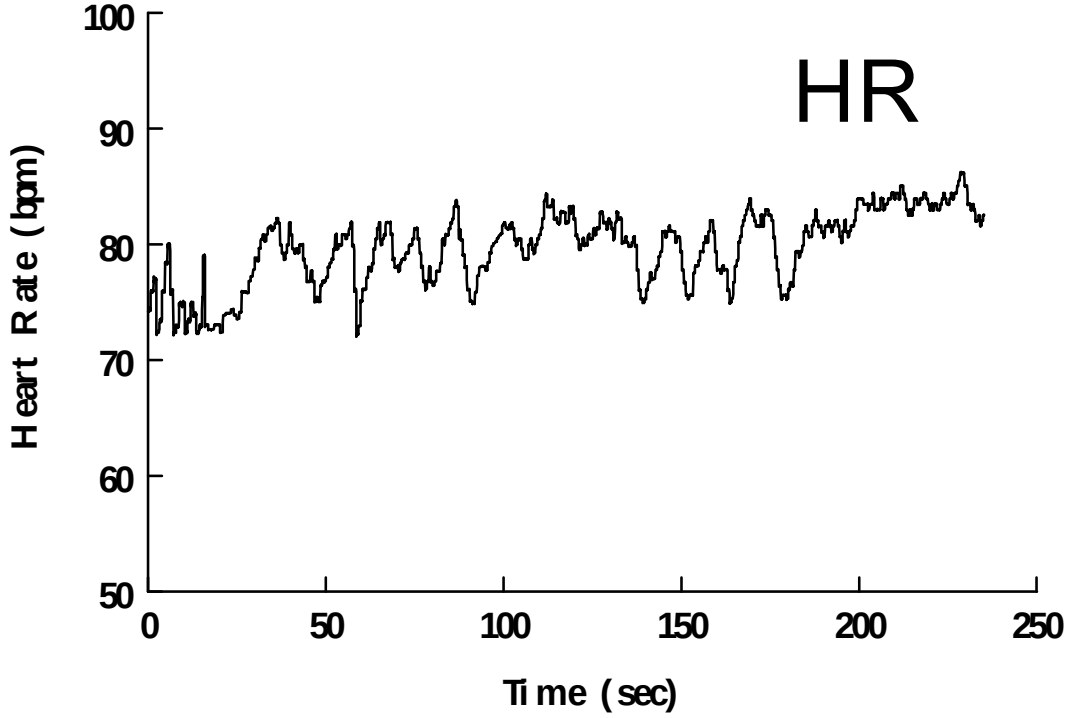
Figure 7 shows an asystolic faint. This is episodic, relatively infrequent and unrelated to intrinsic sinus node disease. Asystolic faints are associated with opisthotonic posturing and have been sometimes referred to as “convulsive syncope”.

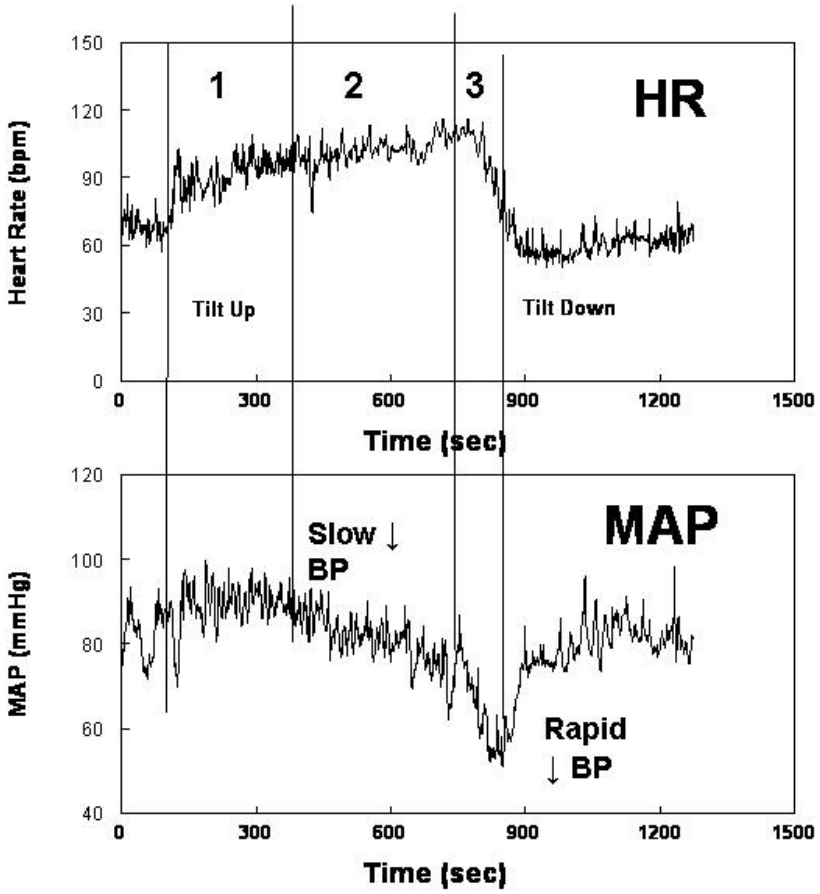

Vasovagal Syncope
POTS
AP
CBFv
Arterial Pressure (mmHg)
CBFv(cm/s)
Time (sec)
0
30
60
90
120
150
300
600
900
1200
1500

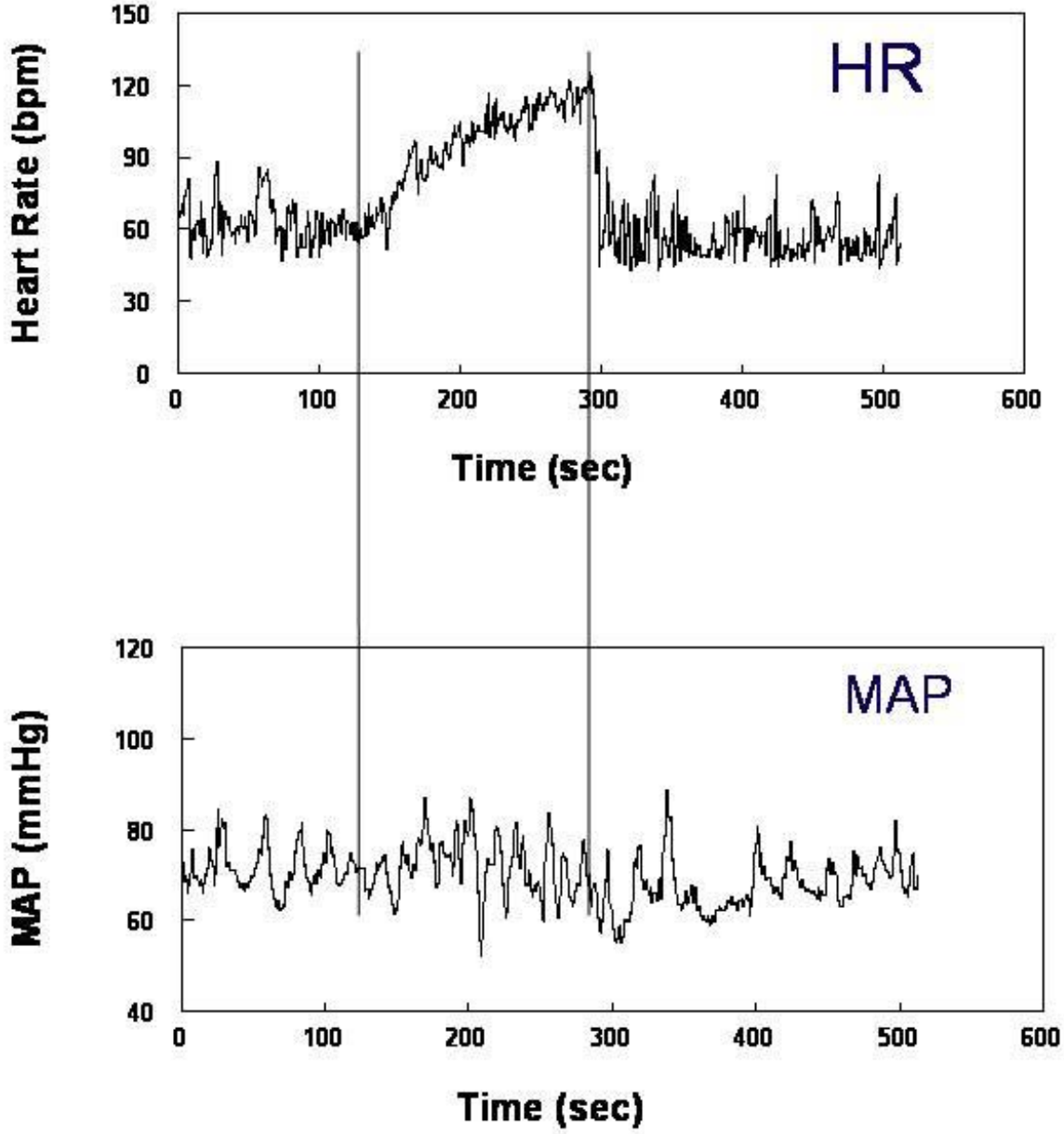

Blood Pressure (mmHg)
200
100
0
Stand
0
30
60
90
120
150
Time (sec)

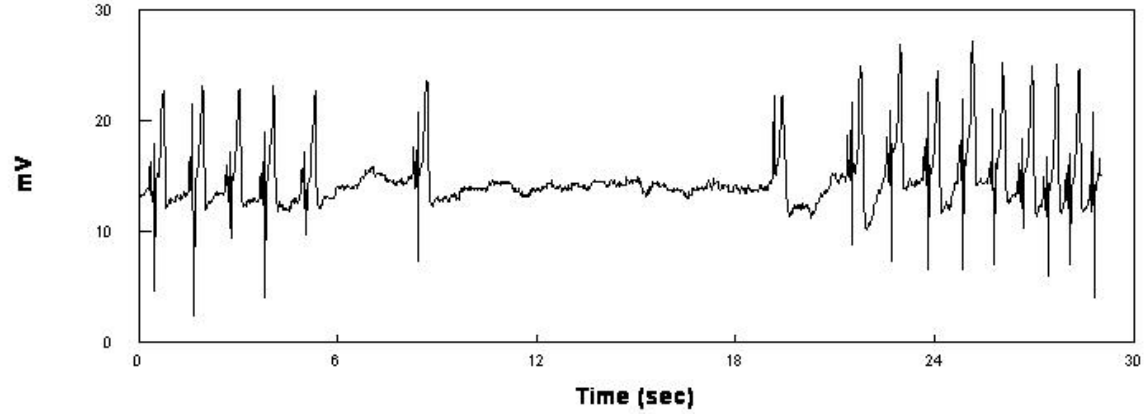

AP
Systolic
MAP
Diastolic
Arterial Pressure (mmHg)
Time (sec)
TPR
TPR (mmHg/L/min)
Time (sec)
AP
MSNA (AU)
Time (sec)
meanCBFv (cm/sec)
CBFv
Time (sec)
HR
Heart Rate (bpm)
Time (sec)
SV
Stroke Volume (ml)
Time (sec)
CO
Cardiac Output (L/min)
Time (sec)
Vagal Index
Vagal Index
Time (sec)

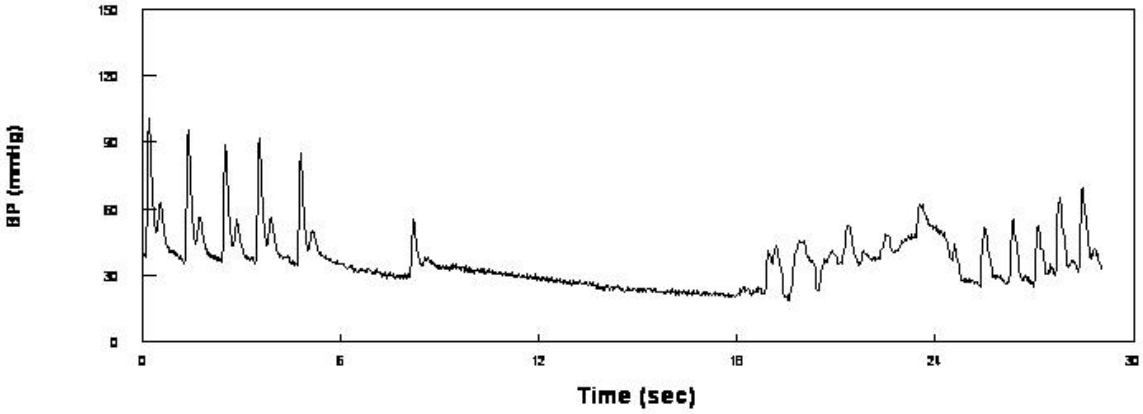

AP
Arterial Pressure (mmHg)
150
100
50
0
0
50
100
150
200
250
Time (sec)


HR
Heart Rate (bpm)
100
90
80
70
60
50
0
50
100
150
200
250
Time (sec)


Heart Rate (bpm)
150
120
90
60
30
0
1
2
3
HR
Tilt Up
Tilt Down
0
300
600
900
1200
1500
Time (sec)
MAP (mmHg)
120
100
80
60
40
Slow ↓ BP
MAP
Rapid ↓ BP
0
300
600
900
1200
1500
Time (sec)


HR
Heart Rate (bpm)
150
120
90
60
30
0
0
100
200
300
400
500
600
Time (sec)
MAP
MAP (mmHg)
120
100
80
60
40
0
100
200
300
400
500
600
Time (sec)


mV
30
20
10
0
0
6
12
18
24
30
Time (sec)


BP (mmHg)
Time (sec)