The Newcastle protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders

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The Newcastle protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders

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Since their publication in 2000, the Newcastle protocols[1] on head-up tilt testing in the diagnosis of vasovagal syncope and related disorders have provided a succinct and practical guide for those setting up and managing syncope services incorporating the investigation and management of neurally mediated disorders. In the intervening seven years our protocols have changed in line with published evidence on new methodologies and management strategies and our own clinical experience (with more than 1000 new and 3000 review patients seen each year at our specialist syncope facility), so the time is ripe for a fresh approach. Much of this information is available in a number of important papers on syncope management[2–4] and pacing indications[5 6]; while comprehensive, these guidelines are also lengthy and inclusive of competing methodologies. They are therefore less accessible for those needing a more prescriptive and pragmatic view. The Newcastle protocols 2008 presented below provide such a view. Since these protocols reflect current clinical practice, an exhaustive review of the evidence base for the various methodologies presented will not be attempted—the reader should consult the more detailed papers referenced if this is required.[2–6] Similarly some prior knowledge of the subject matter is assumed, in particular the differentiation between syncope and non-syncopal loss of consciousness as well as the diagnostic process leading to head-up tilt table testing.[2 3] The protocols are designed for adults with syncope (defined as transient loss of consciousness with loss of postural tone and spontaneous and complete recovery), with no upper limit on age.

STYLE

The Newcastle protocols 2008 are intended to complement rather than reproduce the originals, so only new information will be presented, occasionally with a summarised version of the old to aid clarity. Still-valid detailed prior information will be referenced to the 2000 version.[1] The original protocols deliberately omitted reference to the management of the neurally mediated disorders, but a succinct and practical guide to treatment will also be presented below.

INDICATIONS FOR HEAD-UP TILT TABLE TESTING

These remain largely unchanged, though there is international consensus that the test is largely unnecessary for the majority of patients with vasovagal syncope. None the less, tilt testing is cheap, safe and well tolerated and has enormous clinical utility in the appropriate clinical circumstances. Given an appropriate and detailed clinical history, normal cardiovascular examination (or echocardiogram if available) and normal surface electrocardiogram (ECG), there is a very high probability that the individual will have neurally mediated syncope and can be managed with no further investigations.[2 3] Where the history is atypical or absent (for example, in those with cognitive impairment), where there is a driving or occupational imperative for a formal diagnosis, or where the patient has suffered injury, head-up tilt table testing should be considered.[1] Head-up tilt table testing may also occasionally be helpful in the investigation of unexplained drop attacks.[7] Other indications are unchanged.[1]

CONTRAINDICATIONS AND SAFETY MATTERS

Contraindications to head-up tilt table testing are few but include critical mitral stenosis and left ventricular outflow tract obstruction and severe proximal cerebral or coronary arterial disease.[1] The test remains remarkably safe at all ages,[8 9] though there are isolated reports of ventricular tachyarrhythmias[10 11] and myocardial infarction[12] during tilt testing. The majority of adverse events occur in the context of isoproterenol-provoked tilt.[10 12] Though without an evidence base, it is our practice to limit significant hypotension during tilt (arbitrarily defined as a fall in systolic blood pressure of >50% from baseline, or less than 90 mm Hg) to no more than three minutes in older more frail patients with known ischaemic heart or cerebrovascular disease. Consensus guidelines state that cardiopulmonary resuscitation equipment and expertise be immediately to hand[2 3]—given the safety profile of the test, this might legitimately be questioned, particularly for unprovoked and non-isoproterenol testing.

HEAD-UP TILT TEST METHODOLOGY

Patients are not required to fast and should continue suspected culprit medications on the day of testing. If suspected culprit medications are discontinued before testing, we prefer to gauge the clinical response before proceeding to tilt. The procedure should be explained to the patient, who remains supine for 10 minutes, or 20 minutes if cannulated. The 10-minute rest is a change from the previous protocols [1] and reflects our experience

with the shorter rest with no fall in positivity rates. Lower limb movements must be avoided to enhance the venous pooling needed to provoke the vasovagal episode.

Equipment, monitoring and environment

These are essentially unchanged. A footplate support-type tilt table capable of tilting upright to a calibrated angle of 70°,[1] and capable of rapid movements from upright to supine within 10 seconds is necessary, along with continuous ECG and blood pressure monitoring, which should be of the beat-to-beat variety. Since the original protocols were published, a number of devices for recording beat-to-beat blood pressure have come onto the market, including the TaskForce monitor (CN Systems, Graz, Austria) and Portapres and Finometer systems (Finapres Medical Systems, Amsterdam, The Netherlands). These have the advantage of providing derived cardiophysiological parameters including stroke volume, cardiac output, peripheral resistance and, in the case of TaskForce, heart rate variability and baroreflex sensitivity, though these have yet to find an accepted place in clinical practice. The test should take place in a quiet room, at a constant temperature avoiding excessive heat or cold to avoid autonomic stimulation. The test should be supervised by an individual (doctor, nurse or technician) trained in its conduct and capable of managing potential complications either alone or with previously identified immediately accessible support (for example, a cardiac arrest team).

Newcastle protocols 2008: overview and order of testing

Some of the major differences between the previous and current Newcastle protocols lie in the type, order and conduct of head-up tilt table testing as summarised in table 1, though all require the footplate support-type tilt bed and a 70° calibrated tilt angle. Previously, passive tilt testing was the first line tilt. This has been replaced by the 20/15 glyceryl trinitrate (GTN) tilt, the so-called "Italian protocol"[13] (table 1), now used widely because of the shorter time to tilt positivity.[13] If the patient has had a previous adverse reaction to nitrates or has suspected psychogenic syncope (where nitrate-induced false positivity may serve only to further confuse the issue), passive (unprovoked) tilt testing for 40 minutes remains the first-line tilt. If the 20/15 tilt is negative, and there is still need for a tilt diagnosis, the 20-minute 800 μg GTN tilt[14–16] ("front-loaded GTN head-up tilt"[16]) should be used, though with care regarding a higher propensity to false positivity.[16] The test is short, and has far fewer contraindications with superior tolerability in all age groups to isoproterenol provocation, the previous protocols' second-line tilt test.[1 13–16] While isoproterenol tilt testing has a far larger evidence base worldwide,[2 17] the complications mentioned above, its poor tolerability (particularly in the elderly),[15] side-effect profile and multiple absolute and relative contraindications (see original protocols[1]) make it a third-line choice in our practice. The previous isoproterenol protocol has been supplanted by a shorter test with equal clinical utility[18 19] (table 1). If the front-loaded GTN tilt is negative but a tilt diagnosis is still thought essential and isoproterenol is impracticable, the joint third line depending on local availability is lower body negative pressure (LBNP) tilt testing. The test has only been evaluated in a small number of patients[20] and, indeed, has never been validated in the older population. None the less, there is a role for LBNP tilt testing where either a diagnosis has not been achieved by conventional means or where isoproterenol cannot be used (see table 1 for details).

Though there has been interest in alternative pharmacological stimuli to provoke the vasovagal response during tilt testing, none has been widely validated or gained clinical acceptance. There has been increasing interest in the use of intravenous adenosine in the diagnosis of unexplained syncope, but the test is more likely to provide a proxy-indication for bradycardia pacing indications than neurally mediated syncope, and is best regarded as experimental.[2] For a more detailed discussion see Parry *et al*.[21]

Positivity criteria

The test is an imperfect one with no gold standard.[4] Hence adherence to the positivity criteria used in all validation studies is vital—namely, symptom reproduction (usually syncope) in tandem with the hypotension and/or bradycardia/asystole characteristic of the vasovagal response. Where haemodynamic changes occur in the absence of symptom reproduction (or vice versa), the test is deemed false positive.

NON-VASOVAGAL SYNCOPE RELATED DIAGNOSTIC USES OF THE HEAD-UP TILT TABLE

The use of the head-up tilt table in the differential diagnosis of convulsive syncope, postural orthostatic tachycardia syndrome (POTS),[22] orthostatic hypotension (OH)[23] and psychogenic and hyperventilation syncope have been previously described.[1] POTS and OH may be diagnosed with appropriate heart rate and blood pressure monitoring during 2 minutes of active standing, but tilt-aided diagnosis is mandatory for POTS diagnosis if the clinical suspicion is high and initial stand negative. Further advice on POTS investigation and management is readily available.[22] "Passive stand" during 3-minute tilt may be helpful where patients have difficulty with active standing.[23] Tilt protocols for POTS and OH are summarised in table 2.

CAROTID SINUS HYPERSENSITIVITY

The Newcastle protocols for the investigation of carotid sinus hypersensitivity have changed little since the originals were published with several important additions. In summary, carotid sinus massage may be indicated in cases of recurrent syncope or single episodes of high-risk syncope (for example, with injury, while driving, occupational imperative), particularly where there is a suggestive history (for example, head turning, shaving, etc) and in the absence of significant structural heart disease or ECG abnormality. The test may also be helpful in the diagnosis of drop attacks[7] and unexplained falls,[24] particularly where syncope is suspected from the individual or witness account. We now routinely consent patients for the procedure, given the remote but potentially devastating complication of stroke. The risk is approximately 1:1000,[25] but may be higher in those with concomitant cardiovascular and cerebrovascular co-morbidity. It is clearly important to provide a balanced view of this risk, with likely benefits from treatment counterbalancing the remote neurological risks.

During continuous ECG and blood pressure monitoring, the carotid sinus (maximal point of carotid pulsation between angle of mandible and superior border of thyroid cartilage) is massaged longitudinally and firmly for 5 seconds, right side then left, supine then repeated in the head-up tilt position.[26] Up to a third of diagnoses may be missed if the test is not repeated upright.[26] Test positivity is denoted by ⩾3 seconds asystole (cardioinhibitory subtype), a fall in systolic blood pressure of ⩾50 mm Hg (vasodepressor subtype) or both (mixed subtype),

Table 1 Head-up tilt testing protocols for the diagnosis of vasovagal syncope

Head-up tilt type	Maximal tilt duration	Protocol
20/15* "Italian protocol"[13]	35 minutes	20 minutes passive tilt, if positivity/discontinuation criteria not reached, 400 μg sublingual GTN administered while upright, continued for further 15 minutes
Front-loaded GTN[14 15]†	20 minutes	800-μg sublingual GTN administered supine, tilt for 20 minutes
Isoproterenol[18 19]	15 minutes	Intravenous isoproterenol 0.05 μg/kg/min (to maximum of 5 μg/min) administered for 5 minutes supine, then 10 minutes tilt. Discontinue if heart rate >180 bpm, BP>180/110 mm Hg, arrhythmia, chest pain, intolerable tremulousness, vomiting or other side effects
Lower body negative pressure[20]	30 minutes	10 minutes passive tilt, followed by 10 minutes 20 mm Hg suction, followed by 10 minutes 40 mm Hg suction

All tilts are at 70° using a footplate support-type tilt table, following 10 minutes supine rest (20 minutes post-cannulation for isoproterenol); tilt termination should be at maximal tilt duration, symptom reproduction with haemodynamic changes consistent with vasovagal syncope (see text) and/or side/adverse effects and/or patient request.
*Where psychogenic or hyperventilation syncope is suspected, 40-minute passive (non-medicated) tilt should be the sole tilt test.
†The front-loaded GTN head-up tilt may be used as first line where patients are unable to stand for the 35-minute 20/15 tilt.
BP, blood pressure; bpm, beats per minute; GTN, glyceryl trinitrate.

in tandem with symptom reproduction. This may be interpreted differently of course in those with no clear memory of the event. Some authorities recommend 10 seconds of massage, though this is not our current practice.[1 2]

Management of neurally mediated and related disorders

As with the diagnostic process, it can be difficult for the practising clinician to access succinct, evidence-based guidance on the management of the neurally mediated disorders. The following advice is intentionally not a slavish review of the literature, but reflects our evidence-based day-to-day practice. Sample references are provided for information.

1. Vasovagal syncope

(a) Immediate action to abort an attack

Tilt testing is particularly valuable in identifying prodromal symptoms (such as warmth, mild nausea or sweating, "feeling odd") not previously recognised by the sufferer as heralding a faint. Early action not only aborts attacks, but seems to shorten the duration of the profound post-event fatigue many sufferers experience. Patients should be instructed to perform the following manoeuvres at the very beginning of symptoms.

- *Sit*, on the floor with head between drawn-up knees
- *Squat*, on haunches if able
- *Lie*, supine elevating the legs as the preferred option.

The last is the most effective way of preventing syncope, with resumption of normotension from unrecordable blood pressures in seconds during tilt-induced faints. During these manoeuvres, and while upright for milder symptoms, physical counter-pressure manoeuvres should be attempted. There is now a good evidence base for these strategies,[27] which comprise isometric exercises designed to raise systolic blood pressure, including forearm tensing and hand clenching, leg crossing and muscle tensing, and elevating the heels to contract calf muscles (either when sitting or standing). These manoeuvres require a sustained contraction with regular breathing.

Table 2 Head-up tilt-aided diagnosis of postural orthostatic tachycardia syndrome and orthostatic hypotension

	Description
POTS[22]	Tilt for 10 minutes; positivity denoted by rise in heart rate of ⩾30 bpm and/or to ⩾120 bpm
OH[23]	Tilt for 3 minutes; positivity denoted by sustained fall in SBP ⩾20 mm Hg or DBP ⩾10 mm Hg

Tilts are at 70° using a foot-plate support-type tilt table, following 10 minutes supine rest
Test positivity assumes symptom reproduction, though sustained OH in the absence of symptoms may indicate dysautonomia, addisonism, etc, and require further investigation and management.
bpm, beats per minute; DBP, diastolic blood pressure; OH, orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome; SBP, systolic blood pressure.

(b) Longer-term preventive strategies

General measures: Reassurance regarding the benign nature of the condition and the absence of a "disease" is one of the most powerful methods of managing vasovagal syncope. Culprit medications (particularly antihypertensives, anti-anginals, psychoactive medications, α-blockers and vasodilators) should be rationalised and discontinued where possible; 24-hour ambulatory blood pressure monitoring may be helpful in less clearcut cases. Though there is no evidence base, our clinical experience is that dihydropyridine calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors seem less likely to be implicated in vasovagal syncope. Diuretic and nitrate users seem particularly prone to faints, though we see a very skewed population in our secondary and tertiary referral service. Situations provoking syncope should be avoided or managed with the manoeuvres suggested above, while compression hosiery (Grade II Duomed type rather than graduated elasticated stockings, below or above knee) may be helpful in selected cases. The patient support group STARS (Syncope Trust and Reflex Anoxic Seizures) provides useful information and links via its website www.stars.org.uk.

Adequate fluid intake: This strategy alone is highly successful in reducing the frequency of recurrent faints.[28] In recent years, since promoting this strategy vigorously, our clinic reviews for vasovagal syncope have plummeted. We advise approximately 1.0–2.0 litres (depending on body habitus, age and co-morbidities) of non-caffeinated fluids (preferably plain water) by lunchtime, then sufficient fluid intake to keep urine clear. Caffeinated drinks may be taken in moderation in addition.

Salt supplementation: See below under pharmacological management.

Cognitive behavioural therapy: Pilot work from our unit[29] has shown enormous benefit from cognitive behavioural therapy, with therapy being particularly useful in those with anxiety, depression and "fear of syncope".

Tilt training: Tilt training has recently been shown to be useful in some patients.[2 3 30] The original studies performed repeated tilt tests on sufferers to induce tolerance and prevent symptoms.[30] Initial studies were promising, but the evidence

base is scanty, while the technique requires considerable commitment from the patient. An ongoing placebo-controlled trial of home orthostatic training in our unit may help clarify these issues. Where attempted, patients should stand against a wall, with feet approximately 20 centimetres from the wall, surrounded by a "drop zone" of cushions, etc, for 40 minutes or until prodromal symptoms supervene, the duration decreasing over time as symptoms improve. This should be attempted daily and continued long term.

(c) Pharmacological management

The evidence base for drug treatment of vasovagal syncope is at best scanty and often contradictory.[2 3 31] Pharmacotherapy should be limited to the few patients with refractory symptoms following the above conservative measures, with attempted withdrawal of treatment a year after symptom control is achieved. Previously used treatments like β-blockers have now been shown to be of no use in adequately powered randomised studies,[32] while commonly used therapies like fludrocortisone have no current evidence base, though randomised studies are under way.[33] The following are used in our unit (for contra-indications (relative and absolute), interactions and side effects please see the relevant literature):

Fludrocortisone: 50 μg once daily for 1 week, if tolerated increasing to 100 μg once daily and reviewed after 1 month. The maximum dose is 300 μg once daily. Supine blood pressure monitoring and 4–6 monthly electrolyte monitoring are mandatory.

Midodrine[2 3 31]: This α-adrenoceptor agonist has no UK licence, but can be made available on a named patient basis. We routinely consent patients for this purpose, with counselling on expected side effects. Drug information sheets are provided for the patient and his/her general practitioner. The minimum dose is 2.5 mg twice daily, rising to a maximum of 15 mg three times daily in severe cases. The last dose should be given no later than 18.00 given the potential side effect of supine systolic hypertension. Some patients benefit from as-needed doses before situations known to precipitate events. Blood test (full blood count, urea and electrolytes, glucose, bone chemistry, liver and thyroid function tests) and supine blood pressure monitoring are vital 4–6 monthly. Combination therapy with these agents may be needed for some patients. If fludrocortisone and/or midodrine therapy are continued beyond a year, 24-hour ambulatory blood pressure monitoring should be undertaken to look for occult nocturnal hypertension.

Salt supplementation may be used in selected patients with no contraindications: the few studies available in small numbers of young patients[34] used 120 mmol of salt (as slow sodium, 12 tablets per day in divided doses) daily in patients with 24-hour urinary sodium estimations of <170 mmol/24 hour. In our experience patients are unlikely to tolerate more than 3–4 tablets twice daily because of nausea and vomiting. Blood pressure should be monitored closely, with discontinuation of salt therapy attempted after 1 year.

Paroxetine[35]: In isolated cases, paroxetine (starting at 10 mg once daily) may be useful in the management of refractory vasovagal syncope, though we limit its use to patients with concomitant anxiety and depressive features. Where this is the case, clinical psychological and/or psychiatric help are sought, and prescription made only after careful discussion of potential adverse effects.

(d) Permanent pacing

Evidence for the efficacy of permanent pacing in the management of vasovagal syncope is contradictory.[36] However, we refer a few patients for pacing per year with the so-called "malignant" vasovagal variant: unheralded, often injurious vasovagal syncope, with prolonged asystole on tilt testing, subsequently shown with either external or implantable ECG monitoring to have >3 seconds asystole during real-time syncope. Dual chamber pacing is mandatory, preferably DDI with hysteresis or a specifically designed algorithm for neurally mediated disorders (for example, rate drop response[37] (for example, Adapta DR, Medtronic Inc), closed loop stimulation[38] (for example, Cylos CLS, Biotronik)).

2. Carotid sinus syndrome

General measures per (1a) and (1b) above may be helpful. The treatment of choice for the cardioinhibitory and mixed subtypes is permanent pacing using the algorithms previously described.[39] Fludrocortisone may be helpful in vasodepressor carotid sinus syndrome,[40] though in our experience this is rarely the sole cause of syncope. Management is extensively reviewed elsewhere.[39]

3. Postural orthostatic tachycardia syndrome and orthostatic hypotension

Again, general measures frequently suffice, though beta-blockers can be helpful in POTS.[22] Fludrocortisone and midodrine may be of use in both disorders,[22 40] while there is a recent case report on treating POTS with ivabridine.[41] The acetylcholinesterase inhibitor pyridostigmine[42] and the norepinephrine precursor L-DOPS (L-threo-3,4-dihydroxyserine)[43] may be helpful in selected patients with neurogenic orthostatic hypotension, though experience is limited.

Competing interests: None.

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