Vasovagal syncope (VVS) has been diagnosed with increasing frequency in older patients since the head-up tilt-table test (HUT) was described over 2 decades ago. The incidence and prevalence of VVS in this age group remains unknown. Older individuals are more likely to display a dysautonomic hemodynamic pattern with a predominately hypotensive response during HUT. The positivity rates to passive and isoprotenerol-provoked HUT are reduced with age, but positivity rates for glyceryl-trinitrate-induced HUT are comparable with younger subjects. Few studies into treatment strategies have included older subjects. This is a review of the existing literature on the epidemiology, clinical characteristics, diagnostic tools, and treatment strategies for VVS in older patients, highlighting important areas for future research.

Epidemiology

The overall incidence of syncope in community-dwelling elders was reported as 6.2 per 1,000 person-years (6), with a sharp rise in incidence to 16.9 and 19.5 per 1,000 person-years for men and women older than age 80 years, respectively. Vasovagal syncope was diagnosed in 21.2% of all cases, and the cause remained unknown for 36.6%, but no age differential was available.

Vasovagal syncope in the elderly was assumed to be rare (7,8) until head-up tilt-table testing (HUT) was described by Kenny et al. (9) as a diagnostic tool for VVS. Positive HUTs have since been found with increasing frequency in the elderly with concomitantly higher rates of VVS diagnosed (10). In a retrospective study of 1,180 patients referred for evaluation of syncope in a specialist unit, VVS was diagnosed in 49% and 31% of subjects younger and older than 65 years, respectively (11,12). Any reported incidence or prevalence of VVS is likely to be an underestimate, as large numbers of cases of syncope remain unexplained owing to the lack of systematic evaluation of syncope in common clinical practice (5). A recent study into systematic evaluation of syncope of patients admitted to the emergency room diagnosed VVS in 190 (41%) of 465 patients (4), and the age distribution demonstrated 2 peaks at the ages of 20 to 29 years and older than 70 years (13).

The natural history of VVS in older people is also uncertain. In the younger population, syncopal symptoms tend to run a benign course and wane with maturity (14). There also appears to be no increase in mortality in subjects with neurally mediated syncope (6). However, there have been several case reports associating VVS with advanced malignancy and other terminal conditions (15–18). Kapoor et al. (8) observed that the mortality for patients age 60 years and older with noncardiovascular syncope or syncope of unknown cause was 5 times higher than for patients younger than the age of 60 years, while the mortality in the cardiovascular subgroup was similar for both age groups. The older age group was, however, more likely to have other comorbid illnesses. Multivariate analysis revealed that increasing age, congestive heart failure, and cardiovascular cause of syncope were risk factors for overall mortality and sudden death (8).

The actual incidence and prevalence of VVS in the elderly has not yet been established, but VVS is now being diagnosed with increasing frequency in this age group, suggesting a bimodal age distribution for this condition (12). Vasovagal syncope in the older population may not...
necessarily follow the benign course commonly observed in younger subjects (13).

Pathophysiology

The mechanisms underlying VVS remain poorly understood. The current wisdom suggests that orthostasis results in venous pooling and a reduction in venous return (19), although debate continues on this issue (20,21). It is believed that the vigorous contraction of the myocardium against an inadequately filled chamber then precipitates the Bezold-Jarisch reflex, which results in paradoxical hypotension and bradycardia (19). In younger patients, investigations using cardiac imaging, neurochemical assays, and electrophysiological analyses performed during HUT have found an increase in sympathetic nerve activity, serum epinephrine, and renin resulting in tachycardia and an initial rise in blood pressure in response to upright tilt (22). Before the onset of syncope, a sudden withdrawal in sympathetic drive evidenced by a reduction in sympathetic nerve activity (23), myocardial contractility (24), circulating norepinephrine, renin, and endothelin is observed (22). Increased cardiac vagal tone (25) and vasopressin levels (26) are observed after the onset of syncope. The mean age of subjects in the above studies was 42.5 years. Their generalizability to the older patient with VVS must, therefore, be open to question.

There are limited data on the pathophysiology of VVS specific to the elderly, though several age-related factors may predispose the older patient to VVS. Unlike younger adults, an overlap often occurs with orthostatic hypotension and carotid sinus hypersensitivity (27,28). The elderly are more likely to have coexisting medical conditions, including hypertension, and tend to be on more medications (8,29). Giese et al. (30) actually suggested that the elderly have greater arterial pressure “reserve” for the maintenance of consciousness, as the systolic blood pressure was not significantly different at tilt-induced syncope despite a significantly higher baseline systolic pressure, and older subjects also demonstrated longer time to tilt positivity (30).

Humoral responses to orthostasis do appear to differ with increasing age. Plasma renin activity declines with age, suggesting that blood pressure during orthostasis is maintained by sympathetic mechanisms rather than the renin-angiotensin system in the elderly (31). Vasovagal patients age >65 years possess higher baseline epinephrine levels but reduced epinephrine surge, but similar norepinephrine levels in response to tilt-table testing in comparison with patients age <35 years (32). Plasma catecholamines, however, do not accurately measure changes in sympathetic activity, as their levels are dependent on rate of release, clearance, and time delay of circulation.

Ruiz et al. (33) found that age was the single determinant of significantly lower low-frequency and high-frequency (HF)-heart rate variability (HRV) during supine rest and upright tilt (33). Low-frequency heart rate variability is an index of sympathetic activity whereas HF-HRV reflects parasympathetic activity. This study, therefore, suggests an overall blunting of autonomic response with age, supporting similar findings from earlier studies (34,35).

Brignole et al. (36) described 3 different patterns of responses to HUT. Younger subjects tended to exhibit the classical vasovagal response during which blood pressure and heart rate parameters remained constant before a catastrophic reduction in heart rate and/or blood pressure heralded the onset of symptoms. Older subjects tended to demonstrate a dysautonomic response, a more gradual drop in blood pressure from the initiation of upright tilt or administration of glyceryl trinitrate (GTN), which was associated with carotid sinus hypersensitivity (36). This finding was not observed by Kochiadakis et al. (37), who found similar responses in both age groups. Both studies as well as that of Kurbان et al. (38) found that younger subjects were more likely to have a bradycardic response, whereas older participants were more likely to have a hypotensive response (36–38).

The current knowledge about the pathophysiology of VVS is generated mainly from adolescents and young adults and cannot, therefore, be directly extrapolated to older people with the same condition. A simplistic view of the bimodal distribution of VVS prevalence would be that antianginals and antihypertensive agents cause the older-age peak, but it is more likely that VVS in the elderly is a more complex disorder, associated with other age-related changes in physiology, comorbid conditions, and drug therapy than its younger counterpart.

Clinical Features

The classical prodrome of pallor, sweating, nausea, abdominal discomfort, dizziness, or lightheadedness often accompanies VVS. In the elderly, however, this prodrome is more likely to be short or even nonexistent (28,39,40). The history of syncopal episodes in terms of length of time between symptom onset and presentation is also likely to be shorter (36). While injuries are common in older patients with carotid sinus hypersensitivity, another neurally mediated cause of syncope that often overlaps with VVS (41), there are no data on the risk of injury in older patients with VVS.

Vasovagal syncope can be precipitated by prolonged standing or sitting, hot environments, dehydration, systemic illness, emotional stress, fear, pain, venepuncture, and alcohol. Older people are more likely to be on prescription and over-the-counter medications. Chronic treatment with angiotensin-converting enzyme (ACE) inhibitors, long-acting nitrates, and calcium-channel blockers with or without...
concurrent diuretic therapy is associated with an increased susceptibility to a hypotensive response to HUT (42).

Carotid sinus hypersensitivity, a related neurally mediated disorder, has been associated with unexplained falls in the elderly (43). The elderly often experience amnesia for loss of consciousness in relation to carotid sinus hypersensitivity, rationalizing their falls to slips and trips (44). There has been 1 case report linking VVS to unexplained falls in an elderly patient (40).

Seizure-like episodes can occur during VVS, and these can be clinically indistinguishable from epileptic seizures. Two important studies have elegantly demonstrated positive responses to HUT with reproduction of convulsive responses in patients with treatment-resistant epilepsy (45,46). The mean ages of subjects in these studies were 29 and 38.9 years, respectively, and, hence, should be interpreted with caution with regard to older people.

In older individuals, periods of cerebral hypoperfusion during hypotension or bradycardia may threaten areas of poor cerebral circulation resulting in watershed infarcts, or apparent transient ischemic attacks (47). This relationship has been poorly described in the literature but may be a common occurrence in clinical practice (48,49). Ballard et al. (50) found that 77% of patients with Lewy body dementia and 57% of patients with Alzheimer’s disease had neurocardiovascular instability, the collective term for orthostatic hypotension, VVS, carotid sinus hypersensitivity, and related disorders. The degree of hypotensive response in subjects with carotid sinus hypersensitivity correlated with the severity of cerebral white matter hyperintensities on magnetic resonance imaging, which are associated with cognitive impairment (51).

Vasovagal syncope is associated with psychological distress and reduced quality of life (52–55). Older patients were not deliberately excluded from any of the studies in the preceding text, but the mean age of the subjects with VVS included, 334 patients in total, was 46 years. In the elderly, falls result in significant loss of confidence, fear of falling (56), loss of independence, and increased likelihood of subsequent institutionalization (57). There are no comparable data supporting such adverse psychological and social sequelae in older syncopal patients.

The majority of the information on the clinical characteristics of VVS in the elderly had to be extrapolated from studies involving mainly younger subjects with VVS or literature on related disorders in the elderly. There are currently no published studies looking directly at the presenting features, natural history, physical consequences, and psychological morbidity of VVS in the elderly.

Investigations

History can be misleading in the older patient with VVS due to a short or nonexistent prodrome (58) and the lack of collateral histories (27). Nonetheless, a detailed history (including an accurate medical history and drug history), physical examination, and surface electrocardiogram (ECG) remain the cornerstones of the evaluation of the older patient with suspected VVS.

Although it now seems that VVS is far more common than previously thought in old age, cardiac syncope increases sharply in incidence with age and is known to be associated with increased mortality (6,8). It is, therefore, important to first rule out cardiac causes of syncope in an older person presenting with a history of loss of consciousness. A previous history of heart disease predicts cardiac syncope with 95% sensitivity and 48% specificity, and its absence excludes a cardiac cause in 97% (59). It is also important to consider life-threatening acute illnesses such as pulmonary thromboembolism, gastrointestinal hemorrhage, and sepsis. Whereas neurological causes of loss of consciousness should be considered, investigations with brain computed tomography, carotid Doppler ultrasonography, and electroencephalograms have low yields and are only likely to be positive in patients with focal seizures or focal deficits on physical examination (60).

The history, physical examination, and surface ECG can be diagnostic in VVS (59). Where uncertainty remains, HUT is the diagnostic test of choice (9,61,62). It may also be useful to demonstrate the prodrome and diagnosis to the patients. During a HUT, the patient is tilted up to between 60° to 70° on a tilt-table with a footplate during continuous ECG and blood pressure monitoring, usually with no pharmacologic challenge initially (61,62). In the elderly, the sensitivity of drug-free passive HUT is relatively low (32% to 36%) (29,63) compared with 67% to 74% in all age groups (9,64).

If no symptoms are observed after 20 to 30 min, 400 μg of sublingual GTN can be administered as a provocation agent (the Italian protocol) (61,65), though passive tilt protocols of 30- to 45-min duration remain widely in use (62). Drug provocation with GTN produces a positivity rate (60% to 78%) comparable to younger age groups (66,67). Shortened nitrate-provoked HUT protocols with the administration of 400 to 800 μg of GTN immediately after upright-tilt, and a limited test duration of 15 to 25 min, have also been described (68,69). These protocols have not been formally evaluated in older patients but may be useful in patients who are unable to tolerate prolonged upright posture due to frailty or medical problems such as back pain and neurologic deficits.

Incremental infusion of isoproterenol from 1 to 3 μg/min during HUT increases the positive rate of tilt-testing by 28% to 33% in the elderly (10,63). Positive responses, however, diminish with age (10). Isoproterenol is also contraindicated in patients with ischemic heart disease, hypertension, left ventricular outflow tract obstruction, and aortic stenosis and has to be used with caution in the presence of dysrhythmias (62). Therefore, although nitrate-provoked tilt testing is well tolerated by the elderly (70), isoproterenol-provoked tilt testing is frequently relatively or
absolutely contraindicated in older subjects (71) and has more frequent adverse effects (28,69).

Alternative provocative agents studied include clomipramine, edrophonium, and isosorbide dinitrate (72–75). All the above agents have mainly been tested in younger subjects (mean age = 40.9 years), apart from edrophonium, which was tested in 2 studies involving patients up to the age of 94 years (mean age = 52 years), demonstrating equivalent positivity rates for isoproterenol and edrophonium administration (74,75).

The use of adenosine or its precursor, adenosine triphosphate (ATP), as a provocative agent for HUT is controversial (76). Adenosine and ATP in doses of up to 20 mg have been reported to contribute to the diagnosis of VVS, and its positivity rate increases with age (77). It remains uncertain whether a positive adenosine test indicates unmasking of VVS with cardioinhibition, sinus node disease, or a high-degree atrioventricular block (76,78). From 2 studies involving subjects with mean ages of 73.65 and 72.4 years (79,80), ATP may also be useful in determining the likely response to pacing intervention, though the putative underlying bradyarrhythmia remains obscure.

Nonpharmacologic provocation using lower body negative pressure has been described in subjects with a mean age of 39 years (81,82). Positivity rates were reported as 84% to 85% (81), but 23% of asymptomatic control subjects also demonstrated a positive response (82). This method is used occasionally in our laboratory and others (62), but there are no data on the utility of lower body negative pressure tilt in the elderly.

In summary, the elderly are more likely to require HUT testing to confirm the diagnosis of VVS due to the lack of typical features and shorter or nonexistent prodromes. The reproducibility of HUT in the elderly has been reported as 98% (83), which is at least comparable to the 65% to 85% reproducibility rate in younger subjects (84,85). Both unprovoked HUT and GTN-provoked HUT are safe in the elderly (86). The positivity rate of GTN-HUT in the elderly is comparable to that seen in younger subjects, but the positivity rates of passive HUT and isoproterenol-HUT decrease with increasing age.

**Treatment**

As in all patients with VVS, obtaining a diagnosis followed by reassurance and conservative advice is often adequate in older individuals. Patients should be advised to ensure adequate hydration and to avoid possible precipitants. They should also be instructed to be vigilant for the onset of prodromal symptoms and to initiate counter maneuvers immediately. Traditionally, patients were asked to lie down immediately with their feet propped up. Isometric handgrip, arm tensing, and leg crossing (87–89) have now been shown in a large randomized, controlled trial to reduce the recurrence of syncope in patients with VVS (90) (Table 1). This multicenter study did not include any patients older than age 70 years, and patients on the control arm were randomized to conventional treatment, not placebo. Older individuals may find it difficult to perform such maneuvers due to coexisting musculoskeletal and neurologic problems, but they remain useful adjuncts to other treatments.

Withdrawal of culprit medications should be considered. Discontinuation of chronic vasodilator therapy, which included ACE inhibitors, calcium-channel blockers, long-acting nitrates, and diuretics, resulted in a reduction in positive tilt response (42). However, over one-half of the subjects continued to have a positive response to either passive or GTN-induced HUT 2 weeks after discontinuation of vasodilator therapy compared with 85% of control subjects who continued to take their vasoactive medications (42).

Trials of preventive measures and pharmacologic agents have so far been disappointing. Elasticated compression hosiery is often tried but has only been formally tested in 3 patients with limited efficacy (91) and is often poorly tolerated by older people. Salt supplementation has been shown to be effective in small studies in younger adults (92) but cannot be recommended in the older age group due to the high prevalence of hypertension in this population.

Beta-adrenergic blockade was a widely used treatment in the past, but recent randomized controlled trials have shown limited efficacy with a potential for increased harm (93–95). The only multicenter, double-blind, randomized controlled trial (POST [Prevention Of Syncope Trial]) was published in 2006 (95). This trial involved 208 patients randomized to metoprolol or placebo. Subjects were then further stratified according to ages of ≥42 or <42 years, and the authors reported a weak trend to benefit in patients from the older age group. Previous small studies have suggested that responders to beta-blockers are older than nonresponders (96,97). Further randomized-controlled studies targeting older age groups may, therefore, be justified.

Fludrocortisone is now a commonly used treatment, despite there being no randomized controlled trial in adults. The only randomized placebo-controlled trial in a small number of children suggested that patients on the fludrocortisone arm had a significantly worse outcome than placebo (98). It is also poorly tolerated by older people, with a discontinuation rate of 33% due to hypokalaemia, hypertension, heart failure, edema, and depression (99). A randomized controlled trial on the treatment of VVS with fludrocortisone in adults is now underway (100).

Midodrine is a potent alpha-adrenergic receptor agonist, which stimulates peripheral vasoconstriction. It has demonstrated impressive results in several small randomized controlled trials (101–103). The main side-effects of supine systolic hypertension, urinary frequency, urgency, piloerection, worsening of angina, and cerebrovascular disease are frequently more troublesome in the elderly (104). Up to 25% of older subjects discontinued this drug within a year due to intolerance (104).
Several other drugs including serotonin selective reuptake inhibitors (105,106), disopyramide (107,108), etilefrine (109), theophylline (110), and scopolamine (111) have shown promising results in small studies conducted mainly in younger age groups. The few randomized placebo-controlled trials published subsequently have, however, demonstrated limited efficacy (106,112,113), with the exception of paroxetine (105). The only treatment assessed in the elderly specifically is enalapril (114), which was tested in a placebo-controlled trial involving 24 elderly subjects with symptom resolution in only 2 subjects in the placebo arm compared with symptom resolution in only 2 subjects in the enalapril arm (114). At present, the treatments noted in the preceding text cannot be recommended until they have been further evaluated in adequately powered randomized, placebo-controlled trials.

Tilt training or orthostatic training has been assessed in several small studies with encouraging results (115–119). Patients are exposed to orthostasis either as inpatients with increasing periods of upright tilt or at home by standing against a wall for varying periods of time. The 2 controlled trials so far (120,121), which randomized subjects to orthostatic training or conventional treatment, have demonstrated limited efficacy for orthostatic training. The mean age of subjects recruited to all the above studies was only 38.8 years. Their findings may not, therefore, apply to older people who may find standing against the wall for 15 to 40 min up to twice a day too physically challenging.

Several multicenter, randomized, controlled trials have investigated the use of a permanent pacemaker for the treatment of patients with cardioinhibitory VVS (122–126). The results are mixed with the 2 double-blind placebo-controlled studies demonstrating no efficacy for permanent pacemakers (124,126–128). This lack of efficacy could be influenced by the pacing modes used or the selection criteria for potential subjects. Recent small single-blind studies reported a significant reduction in symptom recurrence using a new contractility-driven DDDR pacing (129) and closed-loop stimulation compared with conventional DDI pacing (125). Further studies using either contractility-driven or closed-loop stimulation modes of cardiac pacing with more specific inclusion criteria are now required.

The treatment options for VVS remain limited, with disappointing results from the handful of large multicenter placebo-controlled trials published. With the exception of the pacemaker studies in which the mean ages of subjects ranged from 50 to 74 years (122–126), few of the studies published so far have included the elderly, the mean age of subjects in most studies not exceeding 45 years with only 1 study specific to the elderly (114). With increasing evidence of a divergence in the pathophysiol-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Treatment Options for VVS and Their Usefulness in the Younger and Older Populations</th>
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<tbody>
<tr>
<td><strong>Treatment Modalities</strong></td>
<td><strong>Younger Population</strong></td>
</tr>
<tr>
<td><strong>Physical counter maneuvers</strong></td>
<td>Reduction in median yearly symptom burden in 1 RCT</td>
</tr>
<tr>
<td><strong>Withdrawal of chronic vasodilator therapy</strong></td>
<td>No specific studies involving younger subjects</td>
</tr>
<tr>
<td><strong>Salt supplementation</strong></td>
<td>Significant increase in plasma volumes, increased orthostatic tolerance, and reduction in baroreflex sensitivity; mean age of participants in study = 41.2 ± 4.1 yrs</td>
</tr>
<tr>
<td><strong>Beta-adrenergic receptor blockade</strong></td>
<td>Limited efficacy in RCT (95)</td>
</tr>
<tr>
<td><strong>Fludrocortisone</strong></td>
<td>No published RCT; significant increase in symptom recurrence in 1 RCT involving children (98)</td>
</tr>
<tr>
<td><strong>Midodrine</strong></td>
<td>Effective in small RCTs (101,102)</td>
</tr>
<tr>
<td><strong>Serotonin selective reuptake inhibitors</strong></td>
<td>1 RCT suggesting paroxetine efficacious (105); 1 RCT demonstrating no benefit with fluoxetine (106); mean ages of participants in RCTs were 42 and 45 yrs</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>No published studies</td>
</tr>
<tr>
<td><strong>Disopyramide</strong></td>
<td>Effective in uncontrolled studies (107,108); small RCT of 22 patients suggested no benefit over 1 week (112)</td>
</tr>
<tr>
<td><strong>Scopolamine</strong></td>
<td>No reduction in tilt-induced syncpe in 1 RCT of 60 participants (113); mean age of participants in RCT was 32 ± 12 yrs</td>
</tr>
<tr>
<td><strong>Tilt training</strong></td>
<td>No benefit in small RCTs due to poor compliance (120,121); mean age of participants in studies was 38.8 yrs</td>
</tr>
<tr>
<td><strong>Permanent cardiac pacing</strong></td>
<td>Controversial evidence base; placebo-controlled studies show no benefit</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; RCT = randomized controlled trial; VVS = vasovagal syncope.
ogy underlying VVS in the elderly and younger subjects, more studies should be conducted specifically in older subjects in the future.

Conclusions

Vasovagal syncope is emerging as an increasingly important cause of syncope in older people. The disease pattern appears to differ from VVS in younger subjects, with a dysautonomic response more likely during diagnostic HUT and a higher proportion of hypotensive response in comparison with that seen in younger subjects. Head-up tilt-table testing is also more often required in the elderly due to the lack of prodromal symptoms. Current available strategies for treatment are limited. Further research on all aspects of this common disorder, from epidemiology to treatment strategies, is, therefore, imperative in this patient group.

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