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CLINICAL RESEARCH

Age-related tilt test responses in patients with suspected reflex syncope

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Aims Tilt testing (TT) is recognized to be a valuable contribution to the diagnosis and the pathophysiology of vasovagal syncope (VVS). This study aimed to assess the influence of age on TT responses by examination of a large patient cohort.

Methods and results Retrospective data from three experienced European Syncope Units were merged to include 5236 patients investigated for suspected VVS by the Italian TT protocol. Tilt testing-positivity rates and haemodynamics were analysed across age-decade subgroups. Of 5236 investigated patients, 3129 (60%) had a positive TT. Cardioinhibitory responses accounted for 16.5% of positive tests and were more common in younger patients, decreasing from the age of 50–59 years. Vasodepressor (VD) responses accounted for 24.4% of positive tests and prevailed in older patients, starting from the age of 50–59. Mixed responses (59.1% of cases) declined slightly with increasing age. Overall, TT positivity showed a similar age-related trend ($P = 0.0001$) and was significantly related to baseline systolic blood pressure ($P < 0.001$). Tilt testing was positive during passive phase in 18% and during nitroglycerine (TNG)-potentiated phase in 82% of cases. Positivity rate of passive phase declined with age ($P = 0.001$), whereas positivity rate during TNG remained quite stable. The prevalence of cardioinhibitory and VD responses was similar during passive and TNG-potentiated TT, when age-adjusted.

Conclusions Age significantly impacts the haemodynamic pattern of TT responses, starting from the age of 50. Conversely, TT phase—passive or TNG-potentiated—does not significantly influence the type of response, when age-adjusted. Vagal hyperactivity dominates in younger patients, older patients show tendency to vasodepression.

Keywords Syncope • Tilt testing • Cardioinhibition • Vasodepression • Ageing

Introduction

Tilt testing (TT) represents a cornerstone in the diagnostic work-up of syncope, allowing clinicians to assess patients' susceptibility to reflex syncope and to understand the underlying pathophysiology.[1] Reflex syncope manifests different haemodynamic features, including vasodepression, cardioinhibition, and a combination of the two which implies different therapeutic approaches.

Previous small observational studies suggest that responses to TT, both positivity rates[2,3] and haemodynamic patterns of response,[4–8] may be influenced by age. Yet, these studies did not allow a detailed age-stratified analysis of TT responses. A large study[9] investigated TT results in different age groups using two different tilt protocols (Westminster and isoprenaline protocol) and confirmed a significant impact of age on passive TT-positivity rate. Data on nitroglycerine (TNG)-potentiated TT, which is recommended by the current

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What's new?

- In specialized syncope units, the number of patients referred for tilt testing (TT) increases with age. Owing to the different clinical presentation of reflex syncope in older vs. younger people (atypical vs. typical forms), the diagnosis becomes more challenging as age increases, which confers on TT a prominent role in the diagnostic work-up of older patients.
- With advancing age, TT-positivity rate decreases during the passive phase, whereas it remains stable during nitroglycerine-potentiated phase.
- Age influences the haemodynamic pattern of TT response, with a breakpoint at 50 years, where the cardioinhibitory component of reflex syncope starts declining and the vasodepressor component progressively increases.
- The proportion of cardioinhibitory and vasodepressor response is similar during passive and nitroglycerine-potentiated TT, at any age decade.

European syncope guidelines, are lacking. As TT responses may guide therapy, knowledge of age-related differences is relevant to intervention strategies for syncope prevention.

This study analysed a large patient sample with suspected reflex syncope divided into age-decades, aiming to assess age influence on the haemodynamic type of TT response and to compare positive responses during passive and TNG-potentiated TT ('Italian Protocol').

Methods

We merged and retrospectively analysed data from patients referred to the Syncope Units of Florence and Lavagna, Italy, and Malmö, Sweden, in the period 2003–19. The study population included all patients consecutively undergoing TT for suspected reflex syncope. Suspected reflex syncope was defined as clinical features consistent with reflex syncope and a negative or inconclusive workup for cardiac syncope and other causes of non-syncopal transient loss of consciousness, in accordance with European guidelines.[1] Therefore, patients with established diagnosis of vasovagal syncope or cardiac syncope were excluded, as well as those diagnosed with orthostatic hypotension or orthostatic intolerance without syncope. The study population was divided into age subgroups corresponding to age decades (10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80–89 years). Tilt testing-positivity rates and haemodynamic patterns of response were then analysed by age decades.

All centres participating in the study applied the same TT protocol, namely the 'Italian protocol',[10] which consists of a 20-min passive phase at a tilt-angle of 60°, followed by a 15-min sublingual TNG phase (400 μg), if no syncope occurred during the passive phase. At the time of the test, TT responses were classified according to the New VASIS classification.[11] Positive TT was defined as the reproduction of spontaneous symptoms accompanied by the characteristic vasovagal pattern of hypotension and bradycardia. Indeed, as presyncope symptoms may develop before heart rate decreases resulting in asystole, TT early interruption, before complete loss of consciousness, may lead to underdiagnosing of CI responses. For the purpose of the present study, we used a simplified VASIS classification that is similar to the classification of responses proposed by the 2018 ESC guidelines[12]: cardioinhibitory (CI) response was defined as syncope occurring in presence of a ventricular pause of >3 s; mixed response was defined as syncope occurring in the presence of bradycardia and hypotension; vasodepressor (VD) response was defined as syncope occurring during hypotension with no or slight heart rate decrease (<10 b.p.m.). More in detail:

- VASIS 2B (asystole >3 s) corresponded to CI form (asystolic response).
- VASIS 2A and VASIS I corresponded to Mixed form (hypotension plus bradycardia).
- VASIS 3 and Exception 1 and 2 corresponded to VD form.

The diagnosis was accordingly re-assigned for each patient.

The regional ethical review board in Lund, Sweden approved the study protocol (reference no 82/2008). All study participants gave written informed consent.

Statistical analysis

Categorical data were expressed as proportions. Multivariable regression analysis was used to correlate TT-positivity rates with age (as continuous variable), gender and baseline systolic blood pressure (BP) (also continuous variable). χ^2 test for independence was used for comparison of type of response during passive and TNG phases of TT. Statistical significance was set at *P*-value <0.05. The statistical software IBM SPSS Statistics version 26 (SPSS Inc., Chicago, IL, USA) was applied.

Results

Overall, TT was performed in 5236 patients with suspected reflex syncope (mean age 60 ± 22 years, 44.9% males, mean baseline systolic BP values 128 ± 18 mmHg). The number of patients undergoing TT increased with advancing age (*Figure 1*).

Tilt testing was positive in 3129 patients (60%) and negative in 2107 (40%): 59.1% of all tilt-positive patients showed a mixed response, 16.5% a CI response and 24.4% a VD response (*Table 1*).

Tilt testing-positivity rate decreased with advancing age ($P = 0.0001$) (*Figure 2*) but was independent of gender ($P = 0.19$) (*Figure 3*). The prevalence of CI responses was higher in younger patients, while VD responses prevailed in older groups. The prevalence of VD responses progressively increased across decades starting from age 50 to 59, while prevalence of CI responses showed an

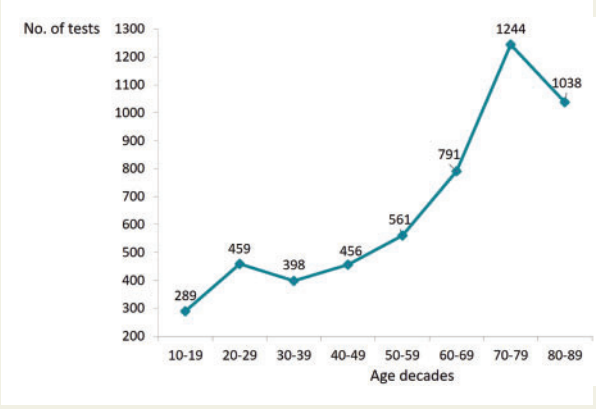

Figure 1 Number of patients undergoing tilt testing by age decades.

Table 1 TT-positivity rates and risk factors by age decades

Age-groups	Study population	Tilt-positive patients, *n* (%)			Mixed, *n* (%)	CI, *n* (%)	VD, *n* (%)	SBP values (mmHg), mean ± SD	Hypertension (%)
		Total	Males	Females					
10–19	289	203 (70)	67/103 (65)	136/186 (73)	135 (47)	53 (18)	15 (5)	114.1 ± 12.8	3
20–29	459	290 (63)	94/137 (69)	196/322 (61)	178 (39)	76 (17)	36 (8)	119.2 ± 13.3	3
30–39	398	230 (58)	86/153 (56)	144/245 (59)	137 (36)	67 (17)	26 (7)	121.3 ± 14.4	6
40–49	456	266 (58)	114/190 (60)	152/266 (57)	150 (33)	84 (18)	32 (7)	123.8 ± 15.0	14
50–59	561	352 (63)	176/268 (66)	176/293 (60)	227 (40)	62 (11)	63 (11)	127.6 ± 17.1	27
60–69	791	484 (61)	251/410 (61)	233/381 (61)	306 (39)	61 (8)	117 (15)	131.9 ± 18.2	38
70–79	1244	714 (57)	376/642 (59)	338/602 (56)	413 (33)	78 (6)	223 (18)	133.0 ± 18.4	45
80–89	1038	590 (57)	264/448 (59)	326/590 (55)	303 (29)	35 (3)	252 (24)	132.6 ± 19.2	51
Total	5236	3129 (60)	1428/2351 (61)	1701/2885 (59)	1849 (35)	516 (10)	764 (15)	128.2 ± 18.1	1655 (32)

CI, cardioinhibitory response; SBP, systolic blood pressure; SD, standard deviation; TT, tilt testing; VD, vasodepressor response.

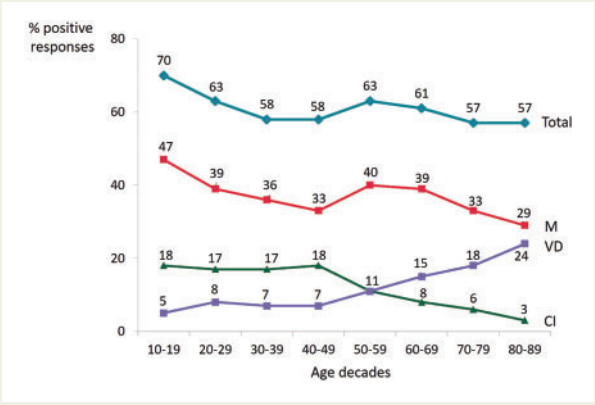

Figure 2 Tilt testing-positivity rates and prevalence of different haemodynamic responses across age decades. The prevalence of VD responses progressively increased across decades starting from age 50 to 59, while prevalence of CI responses showed an opposite trend. CI, cardioinhibitory; M, mixed; VD, vasodepressor.

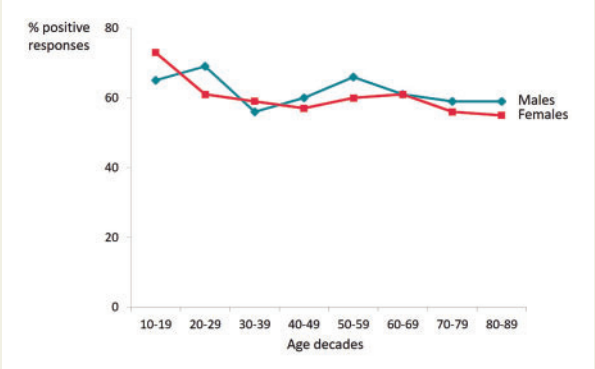

Figure 3 Tilt testing-positivity rates by age decades and gender.

opposite trend. The prevalence of mixed responses tended to decrease with advancing age, except for a slight increase around the age of 50 (*Figure 2*).

Baseline systolic BP values increased with advancing age and were significantly related to TT positivity ($P < 0.001$). At multivariable analysis, in patients with VD response, positivity rate was related to increasing age ($P = 0.0001$) and to low baseline systolic BP values ($P = 0.0008$). Conversely, in patients with a CI response, positivity rate was inversely related to age ($P = 0.0001$) but was unrelated to baseline systolic BP values. In patients with mixed response, positivity rate was inversely related to age ($P = 0.0001$) and, to a less extent, to low baseline systolic BP values ($P = 0.04$).

Tilt testing was positive during the passive phase in 560 patients (18%) and during TNG phase in 2541 (82%). While positivity rates during the TNG phase remained quite stable over increasing age decades, positivity rates during the passive phase progressively decreased with advancing age ($P = 0.001$) (*Figure 4*).

The prevalence of different haemodynamic types of response varied similarly across age decades in the positive passive group and in the positive TNG group (*Figure 5*).

Discussion

Our data from a large sample of 5236 patients undergoing TT for suspected reflex syncope provide evidence that age significantly impacts the positivity and haemodynamic pattern of tilt-test responses. At the age of 50 years, the VD response starts prevailing over the cardioinhibitory response, whereas the mixed response proportion remains stable. The positivity rate declines from teenage until the age of 30–40 years. Conversely, tilt-test phase—passive or TNG-potentiated—does not significantly influence the type of response, when age-adjusted.

Although the rates of VD and CI responses remained stable up to the age of 50 years, they showed opposite trends in older age subgroups, consisting of a progressive increase of VD responses and a decrease of CI responses with advancing age (*Figure 2*). Logistic

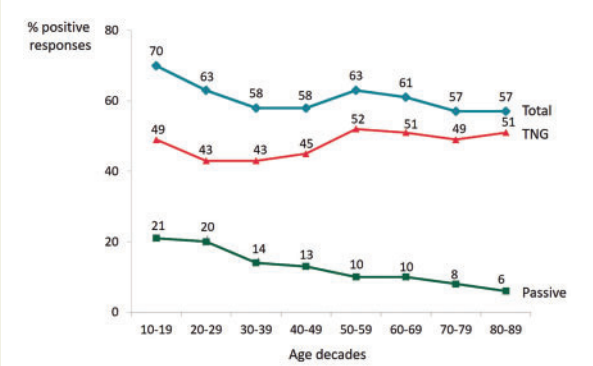

Figure 4 Rates of TT-positive responses in passive vs. nitroglycerine-potentiated TT phase across age decades. While positivity rates during the TNG phase remained quite stable over increasing age decades, positivity rates during the passive phase progressively decreased with advancing age ($P = 0.001$). TNG, nitroglycerine; TT, tilt testing.

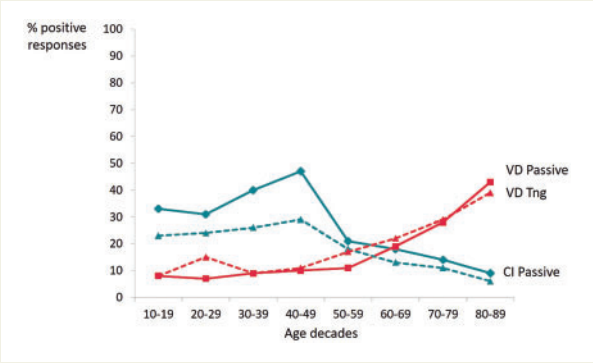

Figure 5 Prevalence of CI and VD responses in passive vs. nitroglycerine-potentiated TT phase across age decades. There was a statistically significant relationship between passive and TNG phase across all age decades (χ^2 test for independence, $P = 0.008$). CI, cardioinhibitory; TNG, nitroglycerine; VD, vasodepressor.

regression confirmed a significant effect of age on the haemodynamic pattern of response. We may thus suppose that the CI component of reflex syncope recedes around age 50, with VD becoming prevalent (*Figure 2*). This age-related gradient is consistent with that previously described in smaller samples[2,5–7] and is likely to be attributable to cardiovascular autonomic ageing. Indeed, ageing is accompanied by decreased baroreceptor sensitivity,[13] reduced cardiac responsiveness to beta-adrenergic stimulation[14] and decreased vagal efferent cardiac outflow.[7,8,15–17] Therefore, younger patients have greater heart rate changes, suggesting greater range of cardiac autonomic responses, while older patients show reduced cardiac responses to stress.[6] The age-related decline in vagal drive to the heart[7,8,15,16] is especially relevant in explaining why younger individuals are more prone to develop CI TT-induced reflex syncope, in contrast to older populations. In addition, the haemodynamic trigger for CI response is blunted in older patients due to restricted cardiac filling. Vascular alpha-adrenergic desensitization also occurs with ageing,[16] allowing greater vasodilatation in vascular beds, notably splanchnic, which may further promote vasodepression. Finally, hypotensive medications and comorbidities should be taken into consideration as factors potentially contributing to vasodepression at old age. Indeed, autonomic dysfunction secondary to comorbidities such as Parkinson disease, diabetes, and renal impairment, may overlap with cardiovascular autonomic ageing, thus further exacerbating tendency to VD responses. As concerns hypotensive medications, they may predispose to vasodepression, especially if patients are intensively treated,[18,19] or use pharmacological agents interfering with autonomic compensatory responses, e.g. vasodilators (nitrates and alpha-blockers) or diuretics.[20]

A previous study by Baron *et al.*[9] including 1219 participants did not demonstrate any influence of age on the haemodynamic pattern of response. This discrepancy may be related to the different age distribution of the study populations. Indeed, older patients were more represented in our sample (59% vs. 29%), which may have facilitated identification of their predisposition to vasodepression.

Contrary to the common opinion that TNG-potentiated TT promotes VD responses, whereas passive TT promotes CI responses,[4,5] we have shown that the prevalence of CI and VD patterns was similar in passive and TNG-potentiated TT when age-adjusted (*Figure 5*). Thus, both TT phases trigger a similar pattern of pathophysiological mechanisms. Our data indicate that reflex syncope pathophysiology varies with age, being mainly attributable to vagal hyperactivity in youth and to attenuated cardiovascular autonomic responses and impaired ventricular filling at older age.

Our study also demonstrated that TT-positivity rate tended to decrease with advancing age (*Figure 2*), especially due to fall in positive responses to passive TT (*Figure 4*). A similar age-related decline in positive responses was reported by previous studies using passive TT.[9,21] Conversely, age did not influence positive responses to isoprenaline potentiated-TT,[9] similarly to our observations on TNG-potentiated phase.

As previously hypothesized by Giese *et al.*,[22] higher systolic BP in older patients may offer greater BP reserve to maintain consciousness, allowing tolerance of longer upright periods. In support of this hypothesis, data from SYSTEMA cohort (Malmö) showed lower BP values in patients with positive responses during passive TT compared with those with drug-potentiated positive TT.[23] Consequently, older patients may require stronger stressors, provided by TNG, to induce TT positivity. These patients are likely to have higher susceptibility to abnormal venous pooling induced by TNG. Indeed, ageing is associated with increased ventricular wall stiffness impairing diastolic relaxation, compromising cardiac filling, and implying greater preload dependence.[24] This effect is potentiated when heart rate is increased, as is the case after TNG administration, with abbreviated diastolic filling leading to further reduction in stroke volume.[8]

Although progressively decreasing with advancing age, TT positivity showed a slight increase around the age of 50 years (*Figure 2*). The reason is unclear, but we may suppose that this modest peak is related to initial cardiovascular ageing and blunted autonomic compensatory responses, or initiation of anti-hypertensive therapy, which is frequently introduced at this age (*Table 1*).[25,26] If this were proven, it

would explain the common clinical presentation of the advent of syncope following the introduction of anti-hypertensive therapy, i.e. steep increase in overall syncope incidence after the age of 60 years.

Finally, we observed an age-related increase in the number of patients undergoing TT (*Figure 1*), which is likely to be related to a different clinical presentation of reflex syncope in older people. Indeed, older patients frequently show atypical presentations, including brief prodromes with slight intensity, retrograde amnesia, and unexplained falls.[27–29] Conversely, younger patients commonly report reflex syncope associated with typical predisposing situations and clear prodromes with nausea, palpitations, and sweating, which allow the diagnosis to be established based on clinical history alone without the need to perform TT. Therefore, the diagnosis of reflex syncope becomes more challenging with advancing age, which supports an important role of TT in the diagnostic work-up of older patients.

The majority of previous studies investigating TT responses was conducted in younger age samples including young- and middle-aged patients.[2,4,7–9,30] Our study was carried out in three experienced European Syncope Units where TT is only performed if syncope diagnosis remained unexplained after initial evaluation, thus determining a significantly greater TT use in older patients. In particular, in our study population the number of patients undergoing TT showed a sharp increase around age 50 (*Figure 1*), suggesting that the diagnostic process of reflex syncope complicates at this age, implying that the diagnostic relevance of TT increases.

The age-related differences in TT haemodynamic responses carry relevance to treatment strategies for reflex syncope. As hypotensive medications may exacerbate tendency to vasodepression, older patients may benefit more from revision of medical therapy and withdrawal/reduction of hypotensive medications. Such revision may achieve significantly less syncope recurrence.[31]

Limitations

A selection bias due to the long recruitment time and possible heterogeneity between and within cohorts cannot be excluded. However, it seems unlikely that it has significantly affected our results because of the very large study population and the wide age range of patients (randomly sampled by referral). Due to the retrospective nature of the study, we were unable to provide a patient log. We cannot exclude that, in our study population, some patients may have had cardiac syncope, especially among those with negative TT. The focus of this article was on positive TT among patients with high pre-test probability of reflex syncope. By definition, reflex syncope is diagnosed when suspected reflex syncope (high pre-test probability) is confirmed by positive TT. As regards negative TT, these patients should continue with syncope investigation according to current syncope guidelines, e.g. using implantable loop recorder. However, these patients were not prospectively followed up and a more detailed discussion of possible final syncope diagnoses in tilt negative patents is beyond the scope of this study.

Conclusions

The haemodynamic response to TT modifies with age. Younger patients manifest vagal hyperactivity, whereas older patients tend to develop vasodepression which is explained by age-related impaired ventricular filling and attenuated cardiac autonomic compensatory mechanisms. Thus, reflex syncope pathophysiology evolves as patients age, starting from age 50. Similarly, the diagnostic role of TT modifies with age, being more relevant in older patients as atypical presentation of reflex syncope becomes more frequent.

Conflict of interest: Richard Sutton reports acting as Consultant to Medtronic Inc., membership of Speakers Bureau of Abbott Labs Corp (St Jude Medical), stockholder in Edwards LifeSciences Corp., and Boston Scientific Inc. Artur Fedorowski reports personal fees for lectures from Medtronic Inc. and Biotronik. All other authors have nothing to disclose.

Data availability

Data available on request.

References

1. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, ESC Scientific Document Group *et al.* 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:1883–948.
2. McGavigan AD, Hood S. The influence of sex and age on response to head-up tilt-table testing in patients with recurrent syncope. *Age Ageing* 2001;**30**:295–8.
3. Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, Musso G *et al.* Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. *Am J Cardiol* 1995;**76**:267–72.
4. Noormand R, Shafiee A, Davoodi G, Tavakoli F, Gheini A, Yaminisharif A *et al.* Age and the head-up tilt test responses in syncope patients. *Res Cardiovasc Med* 2015;**4**:e27871.
5. Kazemi B, Haghjoo M, Arya A, Sadr-Ameli MA. Predictors of response to the head-up tilt test in patients with unexplained syncope or presyncope. *Pacing Clin Electro* 2006;**29**:846–51.
6. Kurbaan AS, Bowker TJ, Wijesekera N, Franzén A, Heaven D, Itty S *et al.* Age and hemodynamic responses to tilt testing in those with syncope of unknown origin. *J Am Coll Cardiol* 2003;**41**:1004–7.
7. Schroeder C, Tank J, Heusser K, Diedrich A, Luft FC, Jordan J. Physiological phenomenology of neurally-mediated syncope with management implications. *PLoS One* 2011;**6**:e26489.
8. Verheyden B, Gisolf J, Beckers F, Karemaker JM, Wesseling KH, Aubert AE *et al.* Impact of age on the vasovagal response provoked by sublingual nitroglycerine in routine tilt testing. *Clin Sci (Lond)* 2007;**113**:329–37.
9. Baron EG, Pedrote A, Cayuela A, Valle JI, Fernandez M, Estepa MG *et al.* Age and gender differences in basal and isoprenaline protocols for head-up tilt table testing G. *Europace* 2001;**3**:136–40.
10. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del RA, Foglia MG *et al.* 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;**2**:339–42.
11. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N *et al.* New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. *Europace* 2000;**2**:66–76.
12. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, ESC Scientific Document Group *et al.* Practical instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:e43–e80.
13. Monahan KD. Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol* 2007;**293**:R3–R12.
14. Brodde OE, Leineweber K. Autonomic receptor systems in the failing and aging human heart: similarities and differences. *Eur J Pharmacol* 2004;**500**:167–76.
15. Pfeifer MA, Weinberg CR, Cook D, Best JD, Reenan A, Halter JB. Differential changes of autonomic nervous system function with age in man. *Am J Med* 1983;**75**:249–58.
16. Jones PP, Shapiro LF, Keisling GA, Jordan J, Shannon JR, Quaife RA *et al.* Altered autonomic support of arterial blood pressure with age in healthy men. *Circulation* 2001;**104**:2424–9.
17. Ndayisaba JP, Fanciulli A, Granata R, Duerr S, Hintringer F, Goebel G *et al.* Sex and age effects on cardiovascular autonomic function in healthy adults [published correction appears in Clin Auton Res. 2016 169-70]. *Clin Auton Res* 2015;**25**:317–26.
18. Sink KM, Evans GW, Shorr RI, Bates JT, Berlowitz D, Conroy MB *et al.* Syncope, hypotension, and falls in the treatment of hypertension: results from the

randomized clinical systolic blood pressure intervention trial. *J Am Geriatr Soc* 2018;**66**:679–86.
19. Sim JJ, Zhou H, Bhandari S, Wei R, Brettler JW, Tran-Nguyen J *et al.* Low systolic blood pressure from treatment and association with serious falls/syncope. *Am J Prev Med* 2018;**55**:488–96.
20. Rivasi G, Rafanelli M, Mossello E, Brignole M, Ungar A. Drug-related orthostatic hypotension: beyond anti-hypertensive medications. *Drugs Aging* 2020;**37**:725–38.
21. Folino AF, Buja G, Martini B, Bassan L, Nava A. Upright tilt test: correlation between results and patient clinical features. *Pacing Clin Electrophysiol* 1996;**19**: 1582–7.
22. Giese AE, Li V, McKnite S *et al.* Impact of age and blood pressure on the lower arterial pressure limit for maintenance of consciousness during passive upright posture in healthy vasovagal fainters: preliminary observations. *Europace* 2004;**6**: 457–63.
23. Nilsson D, Sutton R, Melander O, Fedorowski A. Spontaneous vs nitroglycerin-induced vasovagal reflex on head-up tilt: are there neuroendocrine differences? *Heart Rhythm* 2016;**13**:1674–8.
24. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. *Heart Fail Clin* 2012;**8**:143–64.
25. Gu Q, Paulose-Ram R, Dillon C, Burt V. Antihypertensive medication use among US adults with hypertension. *Circulation* 2006;**113**:213–21.
26. Johnson HM, Thorpe CT, Bartels CM, Schumacher JR, Palta M, Pandhi N *et al.* Antihypertensive medication initiation among young adults with regular primary care use. *J Gen Intern Med* 2014;**29**:723–31.
27. Duncan GW, Tan MP, Newton JL, Reeve P, Parry SW. Vasovagal syncope in the older person: differences in presentation between older and younger patients. *Age Ageing* 2010;**39**:465–70.
28. Ungar A, Mussi C, Ceccofiglio A, Bellelli G, Nicosia F, Bo M *et al.* Etiology of syncope and unexplained falls in elderly adults with dementia: syncope and dementia (SYD) study. *J Am Geriatr Soc* 2016;**64**:1567–73.
29. O' Brien H, Kenny RA, Department of Medical Gerontology, TCIN, St James's Hospital, Dublin, Ireland. Syncope in the elderly. *Eur Cardiol* 2014;**9**:28–36.
30. Sheldon R, Rose S, Flanagan P, Koshman ML, Killam S. Risk factors for syncope recurrence after a positive tilt-table test in patients with syncope. *Circulation* 1996;**93**:973–81.
31. Solari D, Tesi F, Unterhuber M, Gaggioli G, Ungar A, Tomaino M *et al.* Stop vasodepressor drugs in reflex syncope: a randomised controlled trial. *Heart* 2017; **103**:449–55.