SYNCOPE: TODAY AND TOMORROW

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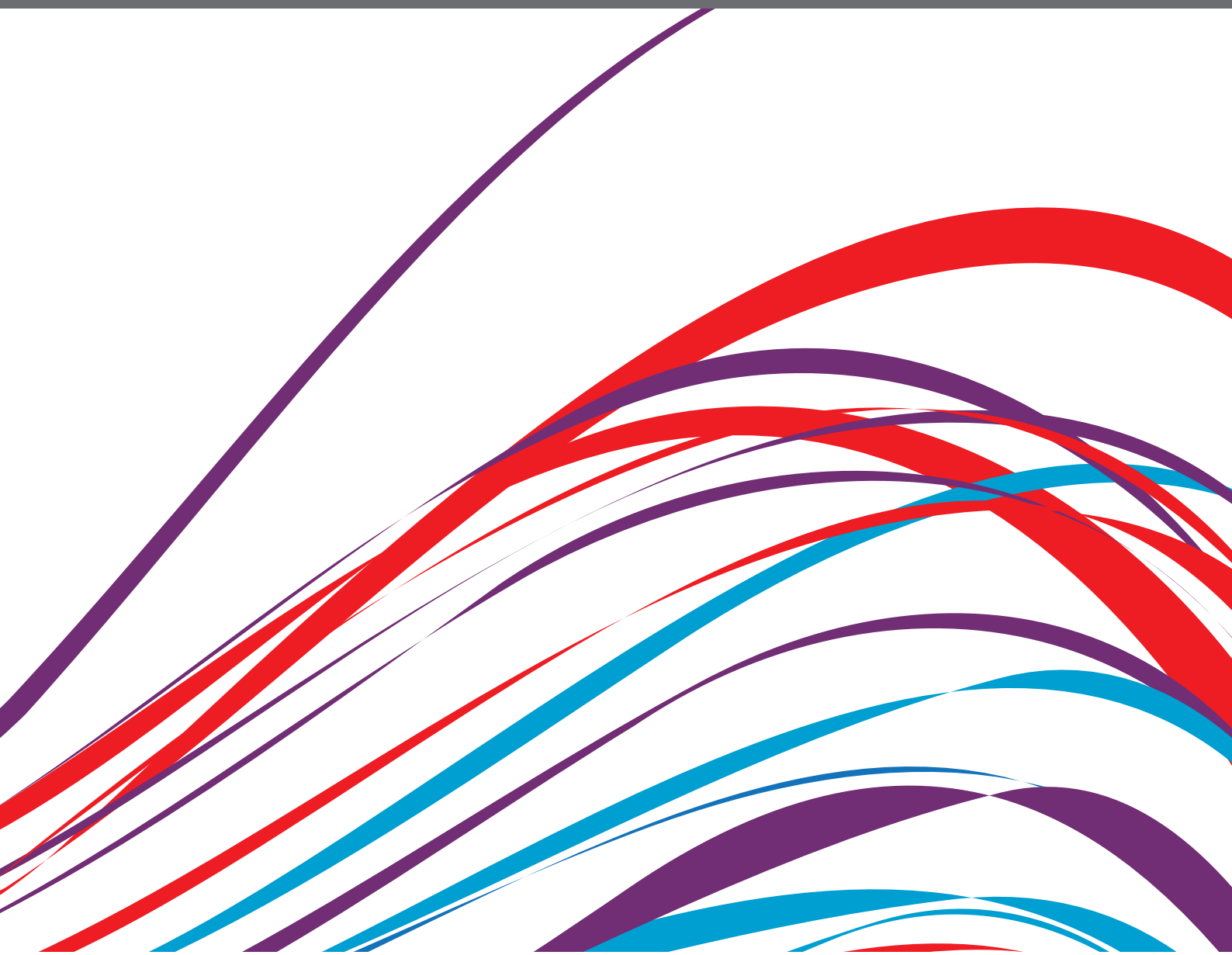

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SYNCOPE: TODAY AND TOMORROW

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EDITORIAL
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Editorial: Syncope: Today and Tomorrow

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Keywords: syncope genetics, syncope pathophysiology, syncope presentation, orthostatic hypotension, carotid sinus syndrome, pacing reflex syncope, syncope after pacing

Editorial on the Research Topic

Syncope: Today and Tomorrow

This volume of Frontiers Cardiovascular Medicine has been generated by the Editors with very close cooperation of many of the leaders in the field of syncope. The aim was to compile a substantial group of papers presenting recent work and contemporary reviews in the field. We felt a need to address a new focus on the genetics of vasovagal syncope (VVS) and aspects of its pathophysiology; notably, the role of the neuroendocrine system in the evolution of the event, the relative timing of circulatory and neurological events; new insights on the vexed problem of reflex atrioventricular block which really does exist despite denial in the recent past and the timing and depth of cerebral hypoxia. Further, we wanted to highlight aspects of the clinical presentation of syncope where developments have taken place. These are in the Emergency Department where a more collaborative approach reaps benefits; management of older patients presenting syncope requires particular care and thought and a thorough assessment of the interactions between syncope and head injury in the emergency presentation. Carotid sinus syndrome remains underappreciated and all too often ignored. Orthostatic hypotension also has new dimensions needing closer collaboration between neurologists and cardiologists as presently they seem to apply a different approach. In the last part, we felt that the difficult issues of how to pace and whom to pace is once again moving forward and the area of recurrent syncope in paced patients, another subject, unreasonably hitherto dismissed, required attention. Thanks to the contributors, we, the Editors, feel proud to have achieved our goal.

The volume begins with a section on the genetics of VVS in which Sheldon and Sandhu point to 3 candidate genes that are associated with VVS from a study of kindreds with high, multigenerational VVS prevalence.

A greater understanding of the pathophysiology of syncope follows with Benditt et al. in a wide-ranging review of neuroendocrine changes in vasovagal syncope. The most consistent literature finding, using tilt testing as a provocation, is a steep and early rise in epinephrine early in vasovagal reflex evolution. These authors raise the important question, yet to be answered, of whether this rise is a trigger or a response to evolving hemodynamics. It appears that this may only be revealed by much more frequent hormonal measurements during the induced attack.

van Dijk et al. show that in cardiac arrhythmias blood pressure falls more steeply than in VVS with syncope occurring in 8 s from the last systole in arrhythmias but may approach double this time in VVS from, in this case, onset of blood pressure fall.

Sutton addresses the reality and unexpectedly high frequency of reflex atrioventricular block (RAVB) in syncope, where 20% of older candidates for pacemaker therapy of VVS show this arrhythmia. Features of RAVB are described in order to aid diagnosis.

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The section closes with a review of non-invasive cerebral oximetry assessment in syncope and orthostatic intolerance syndromes, with tilt as provocation, emphasizing that there are important reductions in cerebral oxygenation before the onset of hemodynamic disturbance in VVS and in Postural orthostatic tachycardia without blood pressure fall (Kharraziha et al.).

The following section offers studies on clinical presentation of syncope including that in the Emergency Department from Canada in which Sandhu and Sheldon give great importance to cooperation between disciplines to achieve the best possible care for the emergency presentation of syncope and report that, within 30 days, ∼0.8% of patients die and 10.3% suffer a serious adverse event.

McCarthy et al. from Dublin, Eire report on nearly 5,000 older patients with syncope who were recruited into the Irish Longitudinal study of Aging. They found syncope to be common in the older patient, that its occurrence has an adverse effect of quality of life, most marked with two recent episodes, which is, in turn, influenced by fear of falling, a facet open to specific therapy.

A study of the problem of coincidence of syncope and head injury from Poland concludes that the short-term prognosis of syncope with head injury is similar to that of head injury alone but the long-term prognosis in these two conditions separates with syncope leading to head injury being substantially worse than head injury without syncope. In multivariable Cox regression analysis, syncope was one of the strongest independent predictors of long-term mortality (Furtan et al.).

The subsequent section is on Orthostatic hypotension (OH); drawing from the now very large series of patients in Malmö, Sweden who have been investigated for syncope and orthostatic intolerance. Torabi et al. separated classical OH from delayed OH finding surprisingly one-quarter of the whole group of patients present orthostatic hypotension of the two types. However, classical OH patients are older, more often have supine hypertension, pathologic Valsalva maneuver, Parkinson's disease, pacemaker-treated arrhythmia, and lower glomerular filtration rate. Classical OH is associated with increased vasopressin and epinephrine during head-up tilt, but blunted increase in norepinephrine. Their findings add to the distinction between the two clinical syndromes.

The second part of the section is on Carotid sinus syndrome which deserves much more attention than it receives. Parry, in his paper, elegantly recounts the history of this syndrome and considers whether pacing is ever required. This is a question not asked by Guidelines. Common misunderstandings are exposed. Carotid sinus hypersensitivity and carotid sinus syndrome are separated, implying different management approaches. Many old concepts are challenged, and the final recommendation is that pacing is probably indicated in some patients.

The final section on therapy provides reflections by Barón-Esquivias et al. on pacing for vasovagal syncope in the light of the SPAIN trial. They remain confident in the positive results of the SPAIN trial which showed pacing benefit in a randomized controlled methodology for younger patients than were included in previous trials without selection by insertable ECG loop recorder. The pacing system used a sensing system that detects right ventricular volume; a smaller volume triggers pacing at higher than the prevailing rate. A previous acute study has shown that this sensor permits earlier intervention by pacing than waiting for bradycardia which has been well-demonstrated to occur late in the evolution of VVS. The sensing system is known as closed loop (CLS) by Biotronik, Berlin, Germany. The current practice in Seville, Spain is to offer this type of dual-chamber pacemaker to 20% of their highly symptomatic referred patients.

The other study in this section raises another ignored problem that of recurrent syncope in patients who have been paced. The Malmö, Sweden group examine this in their large series of syncope and orthostatic intolerance patients. Thirty-nine patients (2.3% of the whole group, aged 65.6 years, 39% female) presented syncope recurrence after pacing from a database of 1,705 patients. In assessment of the cause none had pacemaker failure of any type; in 36 the cause was found by careful examination using cardiovascular autonomic testing which included Valsalva maneuver, active standing, carotid sinus massage, and tilt-testing. OH was the most common cause of recurrent syncope in 16 (41%) with VVS confirmed in 12 (31%). Three patients were not diagnosed. The authors advise a complete work-up such as this described in all paced patients with recurrent syncope (Yasa et al.).

We, the Editors, earnestly hope that, here, we have provided compelling reading for those interested in syncope.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Cardiovascular Autonomic Dysfunction Is the Most Common Cause of Syncope in Paced Patients

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Introduction: Syncope and orthostatic intolerance in paced patients constitute a common clinical dilemma. We, thus, aimed to determine the etiology of syncope and/or symptoms of orthostatic intolerance in paced patients.

Methods: Among 1,705 patients with unexplained syncope and/or orthostatic intolerance that were investigated by cardiovascular autonomic tests, including Valsalva *maneuver,* active standing, carotid sinus massage, and tilt-testing, 39 patients (2.3%; age 65.6 years; 39% women) had a cardiac implantable electronic device (CIED). We explored past medical history, diagnoses found during cardiovascular autonomic tests, and the further clinical workup, in case of negative initial evaluation.

Results: An etiology was identified during cardiovascular autonomic tests in 36 of the 39 patients. Orthostatic hypotension (n = 16; 41%) and vasovagal syncope (n = 12; 31%) were the most common diagnoses. There were no cases of pacemaker dysfunction. The original pacing indications followed guidelines (sick-sinus-syndrome in 16, atrioventricular block in 16, atrial fibrillation with bradycardia in five). Twenty-two of the 39 patients (56%) had experienced syncope prior to the original *CIED* implantation. Orthostatic hypotension was diagnosed in seven (32%) and vasovagal syncope in nine (41%) of these patients. Of the 17 patients that had not experienced syncope prior to the original CIED implantation, nine patients (53%) were diagnosed with orthostatic hypotension and vasovagal syncope was diagnosed in three (18%). Of the 39 patients, two had implantable cardioverter-defibrillators to treat malignant ventricular arrhythmias diagnosed after syncopal episodes.

Conclusion: Cardiovascular autonomic tests reveal the etiology of syncope and/or orthostatic intolerance in the majority of paced patients. The most common diagnosis was orthostatic hypotension (40%) followed by vasovagal syncope (30%), whereas there were no cases of pacemaker dysfunction. Our results emphasize the importance of a complete diagnostic work-up, including cardiovascular autonomic tests, in paced patients that present with syncope and/or orthostatic intolerance.

Keywords: pacemaker, pacing, syncope, orthostatic intolerance, cardiovascular autonomic tests

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INTRODUCTION

Syncope is defined as transient loss of consciousness (T-LOC) due to cerebral hypoperfusion, with a rapid onset, short duration, and spontaneous complete recovery (1, 2). For most syncopal events, three main mechanisms may be encountered: reflex syncope, orthostatic hypotension, and cardiac syncope, the latter including bradyarrhythmia as the predominant mechanism (1, 2). Although cardiac pacing is usually very successful in cardiac syncope due to bradyarrhythmia, with syncope recurrence rate of about 5% over 5 years (3, 4), successful pacemaker therapy in reflex syncope of cardioinhibitory type, meaning an asystole longer than 3 s or bradycardia below 40 beats per min, may be challenging (5). In case of concurrent hypotensive tendency, which may be observed as a significant decrease in blood pressure in standing position during head-up tilt test (HUT) (6), the syncope recurrence rate may be as high as 25–50%. In contrast, normal blood pressure response during HUT (tilt-negative) heralds pacing efficacy being almost the same as in primary bradyarrhythmia (5, 6). Thus, cardiac pacing is an effective treatment against syncope when applied in patients with either primary cardiac bradyarrhythmia or in the cardioinhibitory form of reflex syncope, with only a modest hypotensive tendency or so-called "vasodepressor reflex component".

This approach has been confirmed in the Syncope Unit Project (SUP)-2 reports (7, 8) and current guidelines recommend pacing reflex syncope in selected patients >40 years with recurrent attacks, absence of prodrome and traumatic falls (1). When syncope is unexplained, a stepwise algorithm has been proposed with cardiovascular autonomic assessment as initial stage, and prolonged ECG monitoring by insertable cardiac monitor (ICM) as the next stage, if required (8). However, unexplained syncope and/or orthostatic intolerance in patients with an already implanted pacemaker constitutes a diagnostic and therapeutic challenge and studies addressing clinical management in such patients are sparse. In the current study we, thus, explored the etiology of unexplained recurrent syncope and/or orthostatic intolerance in paced patients.

MATERIALS AND METHODS

Study Setting and Population

The patients in the current study were all from The Syncope Study of Unselected Population in Malmö (SYSTEMA). SYSTEMA was initiated to investigate systematically and manage patients with unexplained syncope (9). Between August 2008 and December 2016, a total of 1,705 patients with suspected syncope i.e., unexplained T-LOC by initial evaluation, who were referred to the tertiary Syncope Unit of Skåne University Hospital, Malmö, Sweden, were enrolled. All 1,705 patients underwent cardiovascular autonomic assessment including carotid sinus massage (CSM), HUT and Valsalva maneuver (1, 2). Along with the main syncope workup, additional tests may have been carried out, including exercise, and external long-term ECG, echocardiography, coronary angiography, brain imaging, and EEG, whenever appropriate. If carotid bruits were detected during admission or hospitalization, a carotid duplex ultrasonography was performed ahead of autonomic tests to rule-out significant carotid artery stenosis.

Cardiovascular Autonomic Test Examination Protocol

The patients were asked to take their regular medication and fast for 2 h before the test, although they were allowed to drink water without restriction. Prior to examination, the patients were asked to complete a questionnaire, which explored past medical history, duration, frequency and features of syncope-related symptoms, smoking status, and current pharmacological treatment. The cardiovascular autonomic tests included CSM, if appropriate (i.e., if age $\geq$ 40 years and no contraindications), according to Newcastle protocol (10). In brief, CSM was performed in the supine position using firm longitudinal massage of the right carotid sinus at the site of maximal pulsation 5–10 s while observing symptoms, blood pressure and RR-intervals. If right CSM in the supine position was non-diagnostic (i.e., no asystole $>$ 3 s and no fall in SBP $>$ 50 mmHg), left CSM was performed in the supine position, and then right and left CSM in 70° head-up tilt position.

Head-up tilt-table test was performed at 60–70° including optional nitroglycerin provocation according to the Italian protocol (11). Thus, nitroglycerin (400 μg spray sublingually) was administered first after 20 min of passive HUT if syncope had not occurred and the hemodynamic parameters were stable that is no hypotension (SBP<90 mmHg). Beat-to-beat blood pressure (BP) and electrocardiogram (ECG) were continuously monitored using a non-invasive validated method (Nexfin monitor, BMEYE, The Netherlands), and subsequently analyzed offline using a dedicated program provided by the monitor manufacturer. The Regional Ethical Review Board in Lund, Sweden accepted the study protocol (ref no. 82/2008), and all study participants gave their written informed consent.

Diagnostic Criteria of Orthostatic Hypotension, Carotid Sinus Syndrome, and Reflex Syncope

The following diagnostic criteria were applied: a) reproduction of symptoms (dizziness, lightheadedness, pre-syncope and syncope), if patients were able to recall conditions preceding syncope, and b) conventional criteria of orthostatic hypotension (OH), carotid sinus syndrome (CSS), and vasovagal reflex syncope (VVS) (1, 2). Briefly, OH was defined as a sustained decrease in systolic BP (SBP) $\geq$ 20 mmHg and/or decrease in diastolic BP (DBP) $\geq$ 10 mm Hg, or systolic BP $<$ 90 mmHg, CSS as a fall in SBP $\geq$50 mmHg and/or asystole $>$3 s with reproduction of syncope/symptoms, while VVS as a reproduction of syncope associated with a characteristic pattern of pronounced hypotension with or without bradycardia/asystole (1, 2). Moreover, an assessment of initial OH was performed by active standing test if the clinical history was suggestive of this disorder.

TABLE 1 | Patient characteristics (n = 1,705) at the time of initial evaluation stratified according to pacemaker status.

	Patients with pacemakers at the time of evaluation (n = 39)	Rest of SYSTEMA cohort (n = 1,666)	P-value
Age, years	65.6 (19.9)	51.8 (21.8)	<0.001
Sex, % female	38.5	60.7	0.005
Reported history of			
Syncope, %	84.6	91.5	0.127
Dizziness, *n* %	74.4	72.6	0.811
Number of syncope episodes, md [range]	5 [0–250]	4 [0–1,350]	0.278[a]
Duration of symptoms, years, md [range]	6 [0–48]	3 [0–77]	0.058[a]
SBP, mmHg	132.8 (18.7)	131.4 (22.5)	0.71
DBP, mmHg	68.8 (9.1)	71.6 (10.2)	0.091
Resting heart rate, bpm	67.2 (8.1)	70.3 (12.6)	0.028
Hypertension, %	51.3	28.5	0.002
CAD, %	30.8	6.4	<0.001
Atrial fibrillation, %	33.3	6.6	<0.001
Heart failure, %	25.6	3.3	<0.001

[a] *P-value for Mann-Whitney U-test. Continuous variables were compared between groups using Student's t-test and dichotomous variables were compared according to group using Pearson chi^2 test, if not otherwise indicated. md, median; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery ldisease.*

Calculations

Following evaluation in the autonomic laboratory (including Valsalva maneuver, active standing, carotid sinus massage, and tilt-testing), the most likely etiology judged by the investigating physician was compiled for all patients. If no likely diagnosis was established during cardiovascular autonomic testing, additional information was retrieved from the medical records of the patients.

The main characteristics of the study population were presented as mean and standard deviation for continuous variables, and percentages for categorical variables, unless otherwise specified. Continuous variables were compared between groups using Student's t-test when normally distributed and with Mann-Whitney U-test if not. Proportions among groups were compared using Pearson chi^2 test. A P-value < 0.05 was considered significant. All calculations were performed using IBM SPSS Statistics software version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA, USA, www.graphpad.com).

RESULTS

Of the 1,705 patients that were investigated due to unexplained syncope and/or orthostatic intolerance, 39 (2.3%) already had an implanted pacemaker at the time of the evaluation. The original pacing indications in these patients were sick-sinus-syndrome (SSS) in 16 (41%), atrioventricular block in 16 (41 %) and atrial fibrillation with bradycardia in five (12.8%). Twenty-two of the 39 patients (56%) had experienced syncope prior to the original pacemaker implantation. Two patients (one female and one male, aged 81 and 17 years, respectively) had implantable cardioverter-defibrillators due to malignant ventricular arrhythmias. Both these patients had experienced syncope prior to the implantation. Compared with the rest of the SYSTEMA cohort, the patients with a pre-existing pacemaker were older, more often men and were more likely to have cardiovascular disease (**Table 1**).

Following evaluation in the autonomic laboratory (including Valsalva maneuver, active standing, carotid sinus massage, and tilt-testing), an etiology was identified in 36 of the 39 patients, of which OH was the predominant diagnosis (**Figure 1**). Regarding the three patients in whom no etiology could be identified during tilt, further work-up demonstrated ventricular tachyarrhythmia in one; in another, vertigo, dementia and neurodegenerative changes were found and in the third, balance/gait disorder without haemodynamic basis, was considered causative.

Among the 22 patients that had experienced syncope prior to the original device implantation, orthostatic hypotension was diagnosed in seven (32%) and vasovagal syncope in nine (41%) patients. Of the 17 patients that had not experienced syncope prior to the original pacemaker implantation, nine patients (53%) was diagnosed with orthostatic hypotension whereas vasovagal syncope was diagnosed in three (18%). Statistical power calculations indicated insufficient power to detect any statistically significant differences in diagnoses between the 22 patients with prior syncope and the 17 patients without prior syncope.

All patients underwent pacemaker interrogation as an initial part of their assessment. There were no cases of pacemaker dysfunction. No paced patient received an ICM for diagnosis.

Most patients (28/39) were aged 60 years or more. In these patients, orthostatic hypotension was diagnosed in 50%, whereas vasovagal syncope was dominant in patients under 60 years of age. Cardiovascular autonomic tests indicated the etiology in all patients under 60 years of age. Results stratified according to age over/under 60–years appear in **Tables S1–S3**.

DISCUSSION

In the current study we have shown that:

I. A likely etiology of syncope and/or orthostatic intolerance in patients with pacemakers can be successfully identified by cardiovascular autonomic tests, including head-up-tilt, carotid sinus massage and Valsalva maneuver.
II. The most common etiologies in the unexplained group are orthostatic hypotension (preferentially in older subjects) and vasovagal syncope (preferentially in younger subjects). There were no cases of pacemaker dysfunction in our cohort.

The pacing literature has focused on symptoms and ECG diagnosis in order to select patients for successful pacing therapy. Recurrent syncope or orthostatic intolerance in paced patients has had less attention. Early series raised the possibility of autonomic causes, although a full range of autonomic

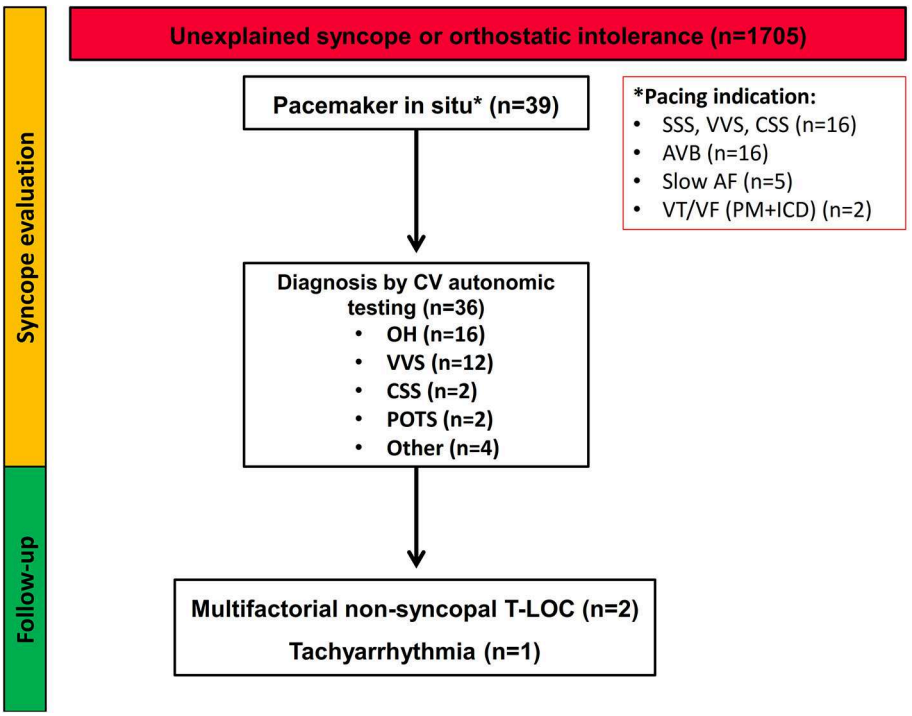

FIGURE 1 | Flow-chart of the study population. The diagram summarizes the diagnostic work-up and follow-up of patients presenting with unexplained syncope or symptoms of orthostatic intolerance. SSS, sick sinus syndrome; VVS, vasovagal syncope; CSS, carotid sinus syndrome; POTS, postural orthostatic tachycardia syndrome; AVB, atrioventricular block; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; PM, pacemaker; ICD, implantable cardioverter defibrillator; T-LOC, transient loss of consciousness.

investigations was not available to those investigators (12, 13). Using a prospective investigational protocol including cardiovascular autonomic tests, we have been able to provide insights into analysis of the etiology of recurrent syncope and/or orthostatic intolerance in paced patients. Orthostatic hypotension or vasovagal syncope was the etiology in seven of ten patients. Notably, orthostatic hypotension was more common among paced patients (41%) than in the rest of the SYSTEMA cohort (27%) and the proportion of patients in whom no cause could be identified during tilt was lower (8% compared with 22%). Regarding the finding of vasovagal syncope, sick sinus syndrome was a common original pacing indication (41%), thus, it should be considered that many of these paced patients show the "extrinsic" form (13), implying a reflex mechanism for syncope with a vasopressor component (1). Importantly, in paced patients with cardioinhibitory vasovagal syncope, the anti-bradycardia stimulation cannot treat the vasodepressor component, which was undetected, even on tilt if performed before implantation, by the severe bradycardia/asystole. Performance of tilt prior to pacing must now be considered as a risk of syncope recurrence tool, if positive, recurrence of syncope is substantially more likely (6). While the initial pacing indications followed guidelines in all patients, pacing offers little or no help for the vasodepressor component of vasovagal syncope and in orthostatic hypotension, thus constitutes the basis of recurrent syncope.

Of note, assessment of pacing function (performed in all patients) revealed no cases of dysfunction. Rather, our study affirms the importance of a comprehensive diagnostic work-up according to recent syncope guidelines (1, 2) also in patients with pre-existing pacemakers that present with recurrent syncope and/or orthostatic intolerance. Interestingly, cardiovascular autonomic tests indicated the etiology in all eleven patients under 60 years of age, suggesting that cardiovascular autonomic test may be particularly valuable in this age group. Concentrating expertise in a dedicated facility ("Syncope Unit") (1) offers increased diagnostic and therapeutic efficacy, as cardiovascular autonomic tests are not widely available and cardiologists may have limited knowledge of test interpretation.

In this study, we did not use Closed Loop pacing as was done in the SPAIN trial (14). This pacemaker senses right ventricular volume indirectly by measuring its impedance. When impedance increases by decrease in right ventricular volume, as occurs in vasovagal syncope due to diminishing cardiac output and venous return, pacing is triggered. This detected change precedes bradycardia/asystole in almost all vasovagal syncope, thus, the trigger for pacing is earlier in the reflex than waiting for later occurring bradycardia. The favorable results of the SPAIN trial suggest that this means of triggering pacing may offer more benefit. The BIOSYNC study, a randomized controlled trial of CLS vs. standard DDD pacing has almost completed recruitment (15).

We acknowledge some study limitations. Firstly, this is a single-center observational study with limited sample size, requiring our results to be confirmed. Secondly, our study is of a selected group referred to a tertiary syncope unit, thus, it may not reflect the etiology of a wider syncope population. The relatively low proportion of patients with an existing pacemaker at the time of entry into the cohort (2.3%) may be explained by the fact that only subjects with unexplained syncope and/or orthostatic had been referred to the syncope unit. Thus, the SYSTEMA population is a selected group in whom syncope etiology could not readily be determined and/or the patient adequately managed by the referring physician. Thirdly, our examination protocol did not include additional autonomic tests such as the Valsalva maneuver or baroreceptor sensitivity test in all patients.

CONCLUSION

In conclusion, we have shown that cardiovascular autonomic tests indicate the etiology of syncope and/or orthostatic intolerance in the majority of paced patients. The most common diagnosis is orthostatic hypotension (40%) followed by vasovagal syncope (30%), which emphasizes the importance of a full diagnostic work-up in paced patients that present with recurrent syncope and/or orthostatic intolerance.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Regional Ethical Review Board in Lund, Sweden (ref no. 82/2008). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EY, RS, AF, and VH: concept and design. EY, FR, HH, TP, OM, RS, AF, and VH: data analysis, interpretation, drafting article, critical revision of article, and approval of article. AF and VH: statistics. OM, AF, and VH: funding secure. EY, TP, and AF: data collection. FR, HH, and TP: other.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2019.00154/full#supplementary-material

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MINI REVIEW
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Cerebral Oximetry in Syncope and Syndromes of Orthostatic Intolerance

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Cerebral autoregulation is crucial for maintaining cerebral blood flow and perfusion. In recent years, the importance of cerebral oxygenation in syncope and orthostatic intolerance (OI) has received increased attention. Cerebral tissue oxygenation can be measured by using near-infrared spectroscopy (NIRS), which determines the ratio of oxygenated hemoglobin to total hemoglobin in cerebral tissue. NIRS is non-invasive technology using near-infrared light, which displays real-time cerebral tissue oxygenation. Normal values of cerebral tissue oxygenation in healthy subjects are 60 to 80%. Head-up tilt test (HUT) offers the opportunity to observe the haemodynamic changes precipitating syncope and is, today, the standard method for the evaluation of syncope and orthostatic intolerance syndromes. In previous studies where NIRS was applied during HUT, a significant decrease in cerebral tissue oxygenation both prior to and during loss-of-consciousness in vasovagal syncope (VVS) has been observed. Interestingly, cerebral tissue oxygenation appears to decrease even before haemodynamic changes can be observed. Apart from VVS, cerebral tissue oxygenation decreases during orthostatic provocation in patients with orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS), in the latter even in the absence of hypotension. Importantly, decline of cerebral tissue oxygenation in VVS and POTS during HUT may not correlate with hemodynamic changes. In this mini review, we summarize the current knowledge of the application of cerebral oximetry in syncope and orthostatic intolerance syndromes, discuss its likely value as a clinical diagnostic tool and also emphasize its potential in the understanding of the relevant pathophysiology.

Keywords: syncope, vasovagal syncope, cerebral oxygenation, hemodynamics, postural orthostatic tachycardia syndrome, head-up tilt

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INTRODUCTION

Syncope and orthostatic intolerance (OI) involve a variety of clinical syndromes on the basis of cardiovascular disease or autonomic dysfunction (1). These clinical entities range from benign sporadic episodes, such as vasovagal syncope (VVS), to severely disabling symptoms of autonomic failure in advanced forms of orthostatic hypotension (OH) (1, 2). Syncope and OI are often provoked by orthostatic stress accompanied by debilitating symptoms of cerebral hypoperfusion (3). Although, a number of methods, including long-term ECG-monitoring, head-up-tilt-test

(HUT) with continuous haemodynamic measurements and other specific cardiovascular autonomic tests are available, the identification of triggers for syncope and OI in a specific case may create a challenge for a clinician (1). In such setting, the measurement of cerebral tissue oxygenation may add important diagnostic information and therapeutic clues. In this mini review, we summarize the current knowledge of the application of cerebral oximetry in syncope and OI, discuss a possible role in diagnosis and its value in understanding the pathophysiology of VVS and syndromes of OI.

THE TECHNICAL BACKGROUND OF CEREBRAL TISSUE OXYGENATION MEASUREMENT

There are several methods that can be used in measuring the cerebral circulation, including ultrasound-based techniques such as transcranial doppler. In recent years, the use of near infrared spectroscopy (NIRS) has gained increased attention since it offers the opportunity to observe absolute values of cerebral oxygenation (4). NIRS measures the ratio between oxygenated hemoglobin and total hemoglobin (Hb) which reflects a proportional mix of arterial and venous blood in the outer regions of the brain (5). Near infrared light (700–1,000 nm) passes through tissues such as skin and bone with minimal absorption whereas hemoglobin (Hb) has a well-defined absorption spectrum that is influenced by the binding of O_2. Because oxygenated Hb and deoxygenated Hb have different absorption spectra, their proportion can be calculated (5). The principles of NIRS methodology in the measurement of cerebral tissue oxygenation are shown in **Figure 1**. In a population of healthy individuals, normal cerebral tissue oxygenation has been established to be between 60 and 80% (6).

NIRS technology combined with so called diffuse correlation spectroscopy permits direct monitoring of cerebral blood flow in addition to oxygenation (7). In short, the diffuse correlation spectroscopy flow-oximeter uses near infrared light to detect motion of moving scatters, primarily red blood cells, to directly and non-invasively measure local cerebral blood flow (7). This method is less commonly used in the field of autonomic dysfunction but may emerge as a potent assessment in the future. Absolute cerebral blood flow can also be measured with techniques such as functional magnetic resonance imaging and positron emission tomography. In addition, absolute measurements of cerebral blood flow using NIRS have been performed with tracer tracking techniques. The two main tracers have been oxyhemoglobin and indocyanine green (4).

MONITORING OF CEREBRAL OXIMETRY IN SYNCOPE PATIENTS

Head-up tilt test (HUT) is an established method for the evaluation of unexplained syncope and orthostatic intolerance by its opportunity to observe the haemodynamic changes during orthostatic provocation (8). By applying cerebral oximetry during orthostatic provocation by HUT it can be observed that cerebral tissue oxygenation decreases also in normal subjects, even though the decrease is small (9–11). In contrast, a more pronounced decrease in cerebral tissue oxygenation has been observed during HUT in patients with syncope and symptoms of orthostatic intolerance. The magnitude of this decrease is dependent both on the underlying diagnosis as well as the timing of the measurement in relation to the time of pre-/syncope (9, 12–15). Vasovagal syncope (VVS) is the most common cause of syncope (16). The underlying pathophysiological mechanisms of VVS are not fully understood but it has been proposed that reduction in cardiac output rather than reduction in systemic vascular resistance is the main cause of hypotension in VVS (17). The reduction in cardiac output may affect cerebral perfusion by increased cerebral vascular resistance, indicating that cerebral perfusion is dependent on a sufficient cardiac output and arterial inflow pressure (18). Thus, it is also likely that cerebral autoregulation, which aims to maintain constant cerebral blood flow over a mean arterial blood pressure (MAP) range of 50–150 mmHg (19), has a significant role in VVS pathophysiology.

When standing up, venous blood is pooled in the lower extremities and splanchnic area which leads to decreased venous return and reduced cardiac output. In turn, decreased cardiac output initiates various autonomic responses that if insufficient or impaired, ultimately may result in decreased cerebral perfusion and syncope (18). The implementation of cerebral oximetry in syncope patients has led to several important discoveries, including the ability to predict the onset of VVS before obvious changes in haemodynamic parameters are manifest by showing a gradual decrease in cerebral oxygenation

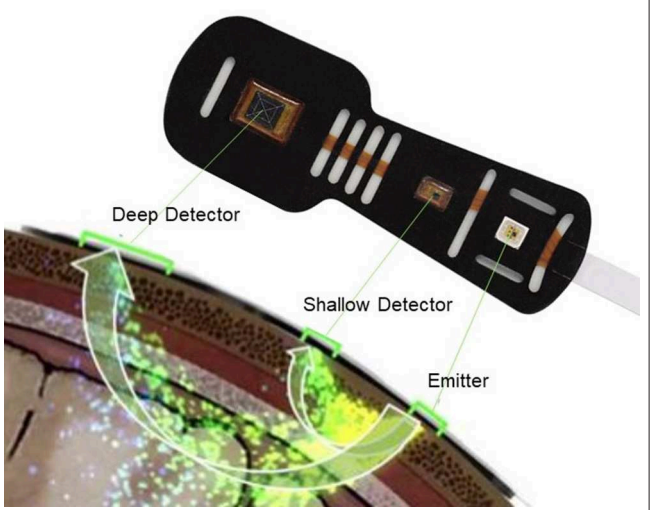

FIGURE 1 | Measurement of cerebral tissue oxygenation with near infrared spectroscopy. The NIRS probe is attached to the forehead. Near infrared light from the emitter, passes through tissues such as skin and bone with minimal absorption whereas hemoglobin (Hb) has a well-defined absorption spectrum that is influenced by the binding of O_2. Light attenuation is detected by the deep and shallow detectors as shown in this figure. Because oxygenated Hb and deoxygenated Hb have different absorption spectra, their proportion can be calculated. In healthy human normal cerebral tissue oxygenation is 60–80%. Edwards Lifesciences Corp, Irvine, CA, USA images archive.

prior to syncope (9, 11). The Bachus et al. (9) study reported a significant decrease in cerebral tissue oxygenation 1 min prior to reflex activation in contrast to MAP which did not show a significant decrease at this time. Another interesting finding from the same study was that syncope occurred when cerebral tissue oxygenation had fallen below 60% (9) (**Figure 2**). Hence, the fall in cerebral tissue oxygenation may explain the discrepancy between symptoms reported by the patient and haemodynamic parameters, for instance, in the prodrome of VVS or unexplained symptoms of orthostatic intolerance.

Another study using diffuse correlation spectroscopy flow-oximetry found that a threshold of ∼50% cerebral blood flow decrease during HUT can be applied in order to separate pre-syncopal patients from controls. Potentially, continuous monitoring of cerebral tissue oxygenation and blood flow may provide predictive information for impending VVS during HUT, possibly both shortening the test and avoiding the need for induction of syncope (20, 21).

Cerebral oximetry may also offer the possibility to analyse the syncope mechanism in potentially overlapping diagnoses such as VVS, postural orthostatic tachycardia syndrome (POTS), or OH by providing characteristic signal patterns during HUT (9, 11) (**Figure 2**). Different patterns of cerebral tissue oxygenation may aid in distinguishing between autonomic failure and reflex activation. In a previous study using diffuse correlation spectroscopy flow-oximetry, two stages of physiological responses were observed in pre-syncopal patients during HUT including gradual changes in cerebral blood flow during Stage I followed by rapid and dramatic cerebral blood flow changes during Stage II (20) associated with failure of physiological autoregulation. This two-stage pattern, characteristic of VVS, has also been reported in a study using NIRS only (9).

MONITORING OF CEREBRAL OXIMETRY IN ORTHOSTATIC INTOLERANCE AND POTS

An issue with HUT is the apparent high false-positive and false-negative rates in adults (22) although alternative explanations

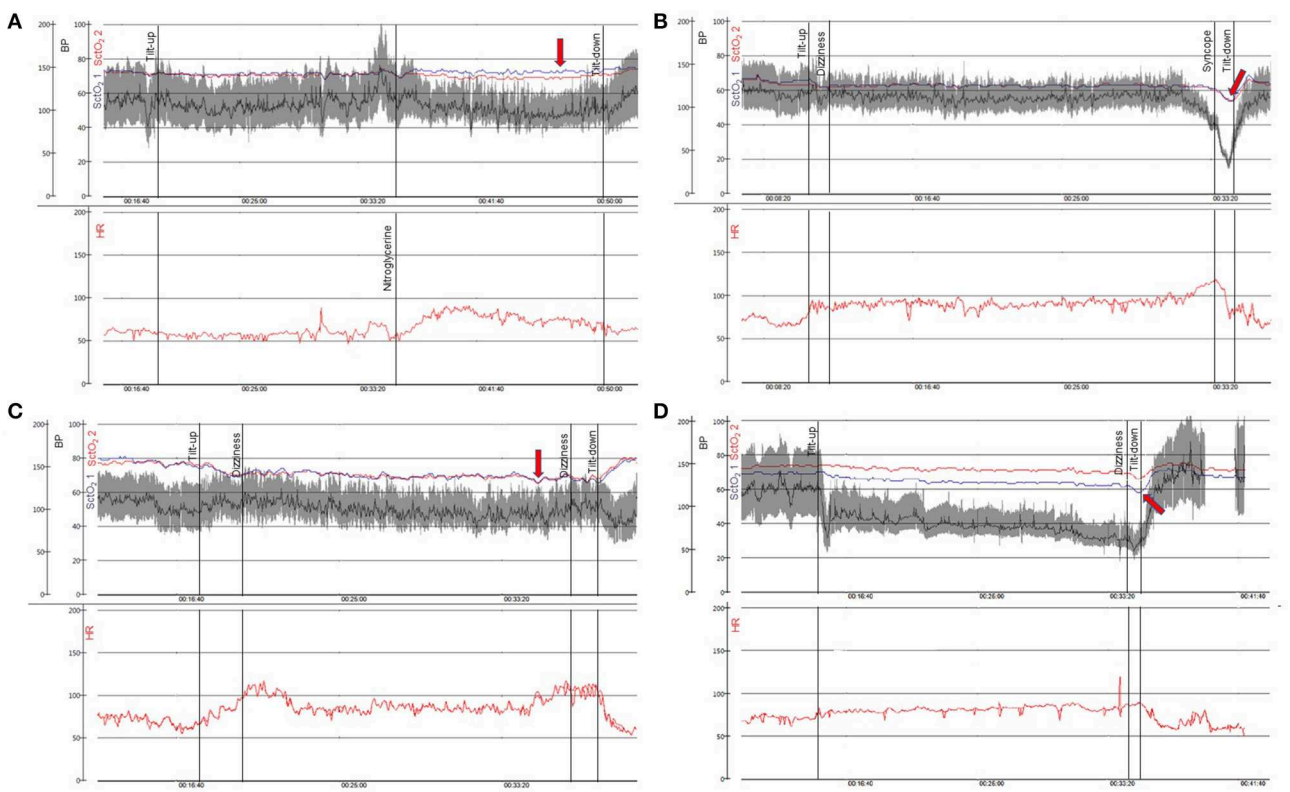

FIGURE 2 | Cerebral oximetry during head-up tilt in patients with syncope and orthostatic intolerance. In **(A–D)** two panels are shown: blood pressure in gray/black (BP—mmHg—0–200) and cerebral tissue oxygen oxygenation in blue and red ($SctO_2$-%—0–100) are plotted above with time scale denoted. Heart rate shown in red (HR—bpm—0–200) is demonstrated simultaneously in the panel below. **(A)** 61-year-old woman with syncope while driving. There is a normal response to head up tilt and preserved cerebral tissue oxygenation (red arrow). **(B)** 20-year-old woman with history of recurrent syncope. Vasovagal syncope during head up tilt occurs when cerebral tissue oxygenation falls below 60% (red arrow). **(C)** 23-year-old man with orthostatic intolerance. This patient fulfills diagnostic criteria of postural orthostatic tachycardia syndrome with pronounced decrease in cerebral tissue oxygenation during head up tilt of more than 10% associated with subjective symptoms (dizziness, red arrow). **(D)** 77-year-old man with Parkinson's disease and orthostatic hypotension. The symptoms of cerebral hypoperfusion are intolerable when cerebral tissue oxygenation falls below 60% (red arrow). BP, blood pressure; SctO2, cerebral tissue oxygenation; HR, heart rate. SctO2 1 measures the left side of the frontal lobe and SctO2 2 measures the right side of the frontal lobe.

have been provided (23). By adding NIRS during HUT, clinicians can detect early changes in cerebral oxygenation and thereby signs of cerebral hypoperfusion. During orthostatic provocation, cerebral tissue oxygenation decreases even in healthy patients (24, 25) but to a lesser degree. Patterns are relatively easy to detect when monitored in association with hemodynamics.

Kim et al. (11) using cerebral oximetry, found that total cerebral Hb (oxygenated Hb and deoxygenated Hb) after tilt-up decreases temporally during orthostasis, even in healthy controls. However, compared with healthy controls, the recovery of Hb concentration to baseline values seems to occur later in patients with OI, even in those who experience a normal response to HUT. The point at which the total Hb concentration recovered was 200 s after tilt-up in controls in contrast to patients with orthostatic intolerance where the blood volume continued to fall for ∼450 s. This delay in total Hb recovery may indicate a delay in return to cerebral homeostasis compared with healthy controls and perhaps impaired cerebral autoregulation. Hence, by adding cerebral oximetry during HUT, cerebral effects of orthostatic intolerance can be detected (11). This finding may also have relevance to that of McCrory et al. who found that the speed of recovery of blood pressure after active stand in community dwelling older adults offered valuable prognostic information concerning aging and mortality (26).

Cerebral tissue oxygenation declines during orthostasis in patients with POTS (10, 15) (**Figure 2C**). POTS is a disorder predominately found in subjects <40 years and is characterized by orthostatic intolerance and heart rate increase ≥30 bpm during orthostasis in the absence of OH. In addition to reduced orthostatic tolerance, patients with POTS frequently experience debilitating symptoms such as light-headedness, nausea, blurred vision, fatigue, mental confusion ("brain-fog"), chest pain and gastrointestinal problems (27). Syncope may occur in some patients although pre-syncopal symptoms are more common (28). Light-headedness and cognitive deficits are among the most disabling symptoms in POTS and have been assumed to be a result of cerebral hypoperfusion despite normal blood pressure (29). Several studies have measured changes in cerebral blood flow velocity with transcranial doppler in POTS patients during active standing test or HUT, but the findings are inconsistent (15, 29–32). However, it has recently been demonstrated that POTS patients experience lower cerebral tissue oxygenation during HUT compared with HUT negative patients (10). Interestingly, the decrease in cerebral tissue oxygenation in POTS correlated weakly with heart rate increase, implying that other factors may be responsible for the lower cerebral tissue oxygenation (10). Another study using both NIRS and transcranial doppler on POTS patients revealed a decrease in cerebral oxygenated Hb during HUT but no significant decrease in cerebral blood flow velocity compared with controls (15). In conclusion, cerebral oximetry appears to detect a dysfunctional response to orthostatic provocation where transcranial Doppler does not. The lower cerebral tissue oxygenation detected in POTS patients prompts a hypothesis of disrupted homeostasis of cerebral oxygenation. However, it is not known whether lower cerebral tissue oxygenation in POTS patients is a consequence of or a partial cause of POTS symptoms.

ADVANTAGES AND LIMITATIONS OF CEREBRAL OXIMETRY

NIRS and diffuse correlation spectroscopy flow-oximetry have definite potential for practical measurements of cerebral perfusion. They are both safe, non-invasive, applicable at the bedside, and suitable for quantitative measurements and continuous monitoring with little operator-dependency. Wireless NIRS devices have recently been validated in animals (33) and are soon anticipated to be approved for human use. Other non-invasive techniques that monitor cerebral blood flow, including magnetic resonance imaging, positron emission tomography and single photon emission computed tomography are all limited by availability, cost and the difficulty of making continuous bedside measurements. These imaging techniques also involve ionizing radiation. Transcranial doppler is operator-dependent and has wide inter-examiner variability (4).

The limitations of cerebral oximetry are mainly technical. NIRS does not measure cerebral blood flow directly, unless some form of flow tracer is used, e.g., a short breath of 100% oxygen or an injection of a contrast agent (4). As previously mentioned, diffuse correlation spectroscopy flow-oximetry does not have this problem. Another limitation of NIRS is the risk of measuring the saturation of overlying tissues or deeper regions of the brain (34). Although changes in cerebral tissue oxygenation have been correlated with circulatory responses induced by orthostatic blood pressure changes (9, 13, 25), the skin blood flow shift from head to lower body induced by orthostasis could also affect NIRS measurements. The risk of measuring superficial tissue can be diminished by adding detectors at multiple distances from the emitted light source. Other factors that can affect the signal are motion artifacts, melanin pigmentation in hair and bilirubin in patients with jaundice. Melanin content in skin does not affect the results as it is limited to the superficial part of the skin (34).

Further, NIRS displays a great variety in the human anatomy of vessels and non-vascular tissue, where baseline values vary by ∼10% between individuals. Thus, cerebral oximetry is more suitable for detecting intra-individual rather than inter-individual changes (34). Also, there is an issue of reproducibility in cerebral oximetry. However, according to a small study (24), deoxygenated Hb measured by NIRS seems to be reproducible and may therefore be used in follow-up studies.

Finally, cerebral oximetry with NIRS measures oxygen saturation levels in the regions where the probes are located and does not provide information on cerebral saturation in remote parts of the brain. A significant redistribution of the cerebral blood flow values during HUT has previously been found (35), with a reduction in frontal and an increase in postcentral areas. This frontal flow decrease was greater in OH patients than in healthy controls. However, another study found the reduction of brain perfusion during orthostatic stress to be global (36),

which may indicate that the issue of redistribution is not of great significance provided that the scalp electrodes are placed on the same regions. In addition, previous studies have found NIRS to be comparable with functional magnetic resonance imaging and positron emission tomography which both measure changes in cerebral blood flow globally (37, 38).

FUTURE APPLICATIONS OF CEREBRAL OXIMETRY IN SYNCOPE AND ORTHOSTATIC INTOLERANCE

As described in this review, cerebral oximetry has been increasingly used in various experimental settings in the recent years. However, cerebral oximetry is yet to find its role as an established method in the clinical settings of syncope and orthostatic intolerance. The future applications of cerebral oximetry can be broadly divided into two partly overlapping major goals: First, cerebral oximetry may aid in the understanding of pathophysiological mechanisms underlying syncope and orthostatic intolerance, the relationship between haemodynamic changes and cerebral autoregulation, and also serving as a complement to the current methods of cerebral circulation assessment. The cerebral oximetry may be applied for better monitoring of coupling between haemodynamic changes and characteristic symptoms observed in both VVS (9, 11, 20) and the complex syndromes of orthostatic intolerance, such as POTS (10, 15). Second, cerebral oximetry may aid in the clinical diagnosis and possibly in tailoring therapy against syncope and orthostatic intolerance.

As an example, monitoring of cerebral tissue oxygenation may provide predictive information for impending VVS during HUT, avoiding the need for induction of syncope (20, 21). The treatment implications conferred by cerebral oximetry are highly related to the ability of the method to enhance our understanding of the underlying mechanisms of syncope and orthostatic intolerance. However, since it is likely that there exists inter-individual threshold for when low cerebral tissue oxygenation causes symptoms, it cannot be excluded that cerebral oximetry in itself may also prove useful for targeting preventive therapy in syncope and orthostatic intolerance, despite this reasoning being highly speculative at this stage.

CONCLUSION

Cerebral oximetry with near infrared spectroscopy is a harmless, non-invasive technique which provides the opportunity to measure real-time regional cerebral tissue oxygenation. With the addition of diffuse correlation spectroscopy, simultaneous estimation of cerebral blood flow can be made. These techniques are able to demonstrate different patterns of cerebral deoxygenation during orthostatic provocation in patients with various types of syncope and orthostatic intolerance, before any haemodynamic changes can be observed. Furthermore, the addition of cerebral oximetry to the established head up tilt test allows a more sensitive detection of orthostatic intolerance and may reflect disrupted homeostasis of cerebral oxygenation in POTS. With increasing use in research, cerebral oximetry may be able to provide information about factors related to cerebral hypoperfusion as well as clues to hitherto unknown factors behind syndromes associated with recurrent syncope and orthostatic intolerance.

AUTHOR CONTRIBUTIONS

Concept and design, drafting the article, critical revision of the article, and approval of the article: IK, HH, EB, FR, RS, AF, and VH. Funding secured by: AF and VH. Other: IK and AF.

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The Search for the Genes of Vasovagal Syncope

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Only humans faint, and not all do so. Syncope tends to recur, and the predisposition to syncope can persist over many decades. Observations such as these have suggested that there may be a genetic predisposition to vasovagal syncope. It seems to have a high prevalence in some families; having a parent who faints increases the likelihood of an offspring fainting, and this is increased even further if both biological parents faint. Numerous studies have correlated a number of genotypes with positive tilt tests. However, the control subjects are usually those who faint, but have negative tilt tests, making the conclusions about association with the clinical phenotype less certain. Twin studies, highly focused genome-wide association studies, and gene duplicate studies all suggest there are sites in the genome that associate with vasovagal syncope, although the specific genes, pathways, and proteins are unknown. A recent large, candidate gene study of kindreds with high, multigenerational prevalence of the vasovagal syncope identified 3 genes that associate with vasovagal syncope. Our understanding of the genetic correlates of vasovagal syncope is in its infancy, with much to be understood.

Keywords: vasovagal syncope, genetics, kindreds, candidate gene, genome-wide association, syncope, vasovagal

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INTRODUCTION

There are several reasons to suspect a genetic origin of vasovagal syncope. First, this appears to be a uniquely human response. First, there are no animals that faint (1), including closely related great apes. Second, not everyone faints. In countries such as Canada (2), the Netherlands (3), and Malaysia (4) there are similar proportions of lifetime syncope cumulative incidence, in the range of 25–35%. Therefore, only a proportion of people appear to have vasovagal syncope. Third, the predisposition to syncope lasts decades for many people and the predisposition to syncope is an enduring phenotypic trait. Most fainters start fainting by age 30, and many clinical studies report syncope recurrences over subsequent decades (5). Similarly, the predisposition to faint on tilt table testing is generally reproducible (6). Similarly, non-inducibility is also stable. Furthermore, the degree of bradycardia induced by tilt testing is reproducible (6). Lastly, yet less persuasively, vasovagal syncope has no clearly associated autoimmune or infectious etiology.

Taken together, these 4 factors—the absence of syncope in other animals, only an affected minority of the population, persistent clinical, and physiologic phenotypes, and no apparent other cause—suggest a genetic origin for vasovagal syncope in humans.

More direct evidence for genetic associations with vasovagal syncope is accumulating. The essence of genetic analysis is to test the statistical strength of the association with the phenotype compared to a control population. These methods studying families with fainting members, testing the association of pre-specified candidate genes with the phenotype, and performing genome-wide

association studies. These different methodologies can be applied in kindred studies, conceptually related syndromes, and population-wide studies. Most reports of vasovagal syncope have been candidate gene studies of the surrogate outcome of fainting on a tilt test. Uncovering genetic associations with vasovagal syncope may provide insights into the physiology of the reflex, and perhaps new targets for therapy. We'll review the evidence critically and suggest some approaches that could be explored, as well as potential limitations of these approaches.

FAMILY PEDIGREE STUDIES

Family pedigree studies examine how the phenotype occurs in multigenerational families, the likelihood that parents will appear to pass on the trait to their children, and occasionally the association of genotype and phenotype. The latter is helped because families share most other genes and this reduces background genetic variability, the noise in the signal. One important conceptual limitation is a statistical one: if vasovagal syncope has a lifetime cumulative incidence of 35%, then if stochastic and not genetic there will be families with more than one fainting member, and the apparent inheritance pattern will be autosomal dominant. Simply reporting aggregated family histories cannot address this completely.

Phenotypic Pedigrees

Kleinknecht and Lenz (7) reported that 66% of people who fainted during exposure to blood or injury had at least one fainting parent compared to only 41% of control subjects ($p < 0.01$). In a related study (8) Kleinknecht et al. reported that 94% of subjects with syncope in the absence of aversion to medical situations also had a family history of syncope. Marquez et al. (9) and Newton et al. (10, 11) have documented multigenerational pedigrees of families with numerous fainting members. The patterns were compatible with incomplete penetrance of an autosomal dominant pattern.

Ensemble Family Histories

With a lifetime cumulative incidence of 25–40% many families would be expected to have multiple fainting members by chance alone. Pooling family data is one approach to estimate the risk conferred by family histories on its members. Mathias et al. (12, 13) reported that 36–51% of fainting patients had a family members who fainted, compared to 28% of controls. Camfield and Camfield (14) reported an apparently autosomal dominance pattern the families who had children in school. Almost all fainting children had close family members who fainted, while only 33% of non-fainting probands had a family members who fainted. In contrast, Newton et al. (10) reported that fainting probands had only a 19% likelihood of fainting family members.

These studies have a number of limitations. Most had patients as index cases, raising the possibility of inclusion bias. Few had controls and or reproducible diagnostic criteria. None featured actuarial analysis, which is important in a syndrome in which the likelihood of fainting at least once increases with age. Finally, recall bias may be common, particularly in family histories of fainting.

We reported a community-based study of family histories of vasovagal syncope (2), featuring consenting second-year medical students and their first-degree relatives. The diagnosis of vasovagal syncope was confirmed with the Calgary Syncope Score, which has been used repeatedly and successfully in randomized clinical trials. By age 60 the likelihood of syncope was estimated to be 37%, with 42% of females and 31% of males fainting. The likelihood of offspring fainting depended significantly on whether their parents fainted. For example, a man with two fainting parents is nearly 8-fold more likely to faint than one neither of whose parents faint. Therefore, the likelihood of an individual fainting depends significantly on both sex and whether and how many parents faint. This does not prove that fainting is due to genes alone, and there almost certainly are substantial environmental factors.

TWIN STUDIES

Twins provide an interesting opportunity for efficient assessment of genetic sources of phenotypic traits. They are siblings, and therefore share not only much of their genetic information but also usually their environmental, social, educational, and financial background. Furthermore, they provide a unique experiment in nature of gene dosing: monozygotic genes share all their genetic information while non-identical twins share only half their genes.

Marquez et al. (9) and Arikan et al. (15) reported three sets of monozygotic twins with recurrent vasovagal syncope. One pair of female twins had fainting family members while the male twins did not. One set of monozygotic male twins both had documented asystole during syncope. Klein and Berkovic performed a much larger same-sex twins study (16) in which 51 sets of twins were recruited through the Australian Twins Registry, and in which at least one subject had fainted. The 19 identical (monozygous) twin pairs had significantly higher concordance in their histories of syncope, and 7 of these pairs had multiple affected family members. Taken together the twins data are compatible with a genetic association with vasovagal syncope, but far from establish its reality.

CANDIDATE GENE ANALYSES

A candidate gene analysis tests a specific hypothesis: does a particular allele associate significantly with a specific phenotypic trait? Typically a population of patients with the abnormal phenotype is compared to a control group. These have been very popular studies but are prone to several problems. They are univariable analyses, and usually do not include other and possibly important genotypic or phenotypic information. Candidate gene association studies by their nature study only the families at hand, making them are susceptible to local imbalances between the fainting and control groups, and external validity concerns when comparing the study population to different populations. Replication is critical (17). The generally small sample sizes mean that only relatively common alleles can be studied, with a minor allele frequency usually exceeding 10%.

Finally there is a persistent concern here as elsewhere about publication bias: well-done but negative studies struggle to find a home.

Most candidate gene studies of vasovagal syncope compared patients with positive tilt tests to those with negative tilt tests; in essence, a surrogate biomarker. We took a complementary approach by directly testing the association of 12 candidate gene alleles with clinical vasovagal syncope in 7 kindreds (18). The advantages of this approach are that we are studying clinical presentations and not surrogate markers, and kindred studies reduce the background variability in both genetic and environmental influences. We performed a candidate gene association study of 12 allelic variants with plausible connections to vasovagal syncope. The candidate alleles were targeted based on genetic and physiologic plausibility, and vasovagal syncope was ascertained with a validated questionnaire. One insertion/deletion promoter variant and 11 SNPs, including 2 promoter variants, were selected because they had a known physiologic effect, were plausibly relevant to vasovagal syncope physiology, and had a minor allelic frequency of at least 15%. This frequency was chosen based on the results of an earlier family history study and a Mendelian model of autosomal dominance (2).

In this Candidate Gene section we'll review studies of vasovagal syncope and other disorders of hemodynamic control, using both surrogate studies and direct comparisons of patients and asymptomatic control subjects. **Table 1** contains a compilation attempts to demonstrate associations between specific candidate genes and the susceptibility to the induction of vasovagal syncope on tilt tests.

TABLE 1 | Associations between candidate gene alleles and susceptibility to induction of vasovagal syncope on tilt table tests.

Gene	Protein	Genotype-phenotype association
ACE	Angiotensin converting enzyme	Two negative (19, 20)
AGT	Angiotensinogen	Negative (20)
ATR1	Angiotensin 2 receptor	Negative (20)
EDN1	Endothelin 1	Positive (21), negative clinical
EDNRA	Endothelin type A receptor	Negative (21)
GNAS1	G protein alpha	One positive (22), one negative (23)
GNB3	G protein Beta3	One positive (24), four negative (22, 23, 25, 26)
GNG2	G protein γ2 subunit	Negative (27)
RGS2	G protein signaling regulator	Three negative (22, 23, 28)
ADRA1A	Alpha1 adrenergic receptor	One negative (25), one positive (29)
ADRB1	Beta1 adrenergic receptor	Two positive (29, 30), two negative (25, 31)
ADRB2	Beta2 adrenergic receptor	Negative (25)
ADORA2A	Adenosine receptor A2A	Positive (32)
SERT	Serotonin transporter	Two negative (20, 25)
DBH	Dopamine beta hydroxylase	Negative (25)
CHRM2	Muscarinic M2 receptor	Negative (27)
KCNJ3	Potassium inwardly rectifying channel, subfamily J, member 3	Negative (27)
KCNJ5	Potassium inwardly rectifying channel, subfamily J, member 5	Negative (27)

Alpha Adrenergic Receptors

The *alpha adrenergic 1 receptor* ADRA1A 1039T>C variant is involved in sympathetic transduction, and the Arg/Arg genotype of *ADRA1A* 1039 T>C significantly associated with positive tilt tests when comparing vasovagal syncope patients to asymptomatic controls with negative tilt tests (29). However, it was unclear if the clinical variable was the vasovagal syncope phenotype or the positive tilt test. We found no evidence that this allele associates with vasovagal syncope subjects compared to unaffected family members (18). Our results suggest that the ADRA1A variant associates with positive tilt tests, but not with vasovagal syncope.

Beta Adrenergic Receptors

The *beta adrenergic receptor* ADRB1 1165G>C (30) and 145A>G (25) variants are involved in sympathetic transduction, might be involved in the vasovagal reflex. The genotypes of the *beta adrenergic receptor gene ADRB1 1165G>C* associated with positive tilt tests in syncope patients (30). However, the control population was syncope patients with negative tilt responses, not unaffected controls. Furthermore, neither we (18) nor others (25, 31) detected an association of the ADRB1 1165G>C alleles with the clinical vasovagal phenotype when compared with unaffected control subjects.

Marquez et al. (30) studied the *β1-adrenoceptor polymorphism (Gly389Arg)* in 50 syncope patients who had tilt tests. These polymorphisms were studied because of the role of beta adrenergic stimulation in inducing vasovagal syncope during tilt testing (33), and because the 389Arg allele may increase sensitivity to β-adrenergic stimulation (34). The results were in complete contrast to the apparent hypothesis, and in fact the allele was equally prevalent in syncope patients and in larger normal populations. In the candidate gene kindred analysis (18) there was no evidence for the association of either allele with vasovagal syncope. Therefore, the Arg389Gly allele of the β1-adrenoceptor may make a positive tilt test more likely but does not seem to predispose to clinical vasovagal syncope.

G Protein Signaling

The beta-adrenergic G alpha subunit GNAS1 351C>T variant (35) is involved in sympathetic transduction, and is linked to orthostatic intolerance. We found no evidence that this allele associates with vasovagal syncope subjects compared to unaffected family members. Our results suggest that the ADRA1A variant is not associated with vasovagal syncope. Similarly, the TT genotype of GNAS1 T393C associates with less hypotension in patients with orthostatic hypotension (35), but

not with tilt test outcome in patients with presumed vasovagal syncope (23). Finally, Lelonek et al. reported that 825TT genotype of GNB3, the G protein beta 3 subunit predicts negative tilt test result in syncope patients (23). We did not test this genotype. They also reported the association of the 825T allele with atypical histories of vasovagal syncope.

Adenosine Receptors

The *adenosine 2A receptor ADORA2A 1083T>C (formerly 1364 T>C)* variant (32) is involved in adenosine transduction, and is linked to orthostatic hypotension and bradycardia. The C/C genotype of the *adenosine receptor ADORA2A 1083T>C* associates with positive tilt tests (32). We found no evidence that this allele associates with vasovagal syncope subjects compared to unaffected family members (18). Our results indicate that the ADORA2A variant associates with positive tilt tests, but not with vasovagal syncope.

Vasoactive Receptors

Newton et al. (19) reported that a polymorphism in the angiotensin-converting enzyme was approximately equally prevalent in syncope patients with a positive tilt test and in the normative population, making it an unlikely candidate for a gene that causes vasovagal syncope. Arterial vasoconstriction is impaired in young vasovagal syncope patients, and that this is prevented by NOS inhibition (36). eNOS3 (−786)T>C and 894T>G variants associate with Postural Tachycardia Syndrome (37). However, we found no evidence that this allele associates with vasovagal syncope subjects compared to unaffected family members (18).

Serotonin Signaling

We identified 3 gene variants in serotonin and dopamine signaling that appear to be associated with the phenotype of vasovagal syncope. The serotonin 5HT1A receptor is linked to vasodilation, might be involved in the vasovagal reflex (38–40), and the (-1019) G>C promoter variants regulate receptor levels. The serotonin reuptake transporter long/short promoter variant modulates serotonin signaling, and is linked to positive tilt test phenotype (41). Catecholamine O-methyltransferase degrades dopamine, and thereby reduces serotonin release into the synapse (42, 43). The serotonin 5HT1A receptor (-1019) G allele strongly associates with syncope in males but has the opposite effect females ($p = 0.005$). The serotonin transporter promoter long alleles associate with a decreased likelihood of fainting in males but increased in females. Males with homozygous long and short promoter alleles had 25 and 47% likelihoods of fainting, respectively, while in females had the likelihoods were 75 and 50%. The catechol O-methyltransferase c.472 A alleles were significantly linked with a decreased likelihood of fainting in males but the opposite in females ($p = 0.017$). This effect of serotonin signaling alleles on vasovagal syncope supports the serotonin hypothesis of the physiology of vasovagal syncope.

Candidate Genes and Serotonin Model

These findings support a model in which serotonin binding to post-synaptic 5HT1A receptors causes vasovagal syncope by inducing hypotension and bradycardia (40, 41). The possible interactions of serotonin signaling and vasovagal syncope have been noted for decades. One of the clearest series studies demonstrated that acute intravenous administration of clomipramine, a highly specific serotonin transporter inhibitor, provoked vasovagal syncope on tilt tests (41, 44, 45). Therefore, acutely increased intrasynaptic serotonin is associated with the vasovagal response. Randomized clinical trials of serotonin transport inhibitors have provided mixed results (46–48), but two good studies have been positive. Our work does provide one conceptual framework for this field, but much uncertainty remains.

GENOME-WIDE ASSOCIATION STUDIES

Genome-wide association studies, or GWAS, rely on the presence of millions of single nucleotide polymorphisms, or SNPs, scattered in the genome, all of whose positions on chromosomes are known. Studies search for highly significant statistical significance between specific SNPs and the phenotypes of interest. Generally because so many SNPs are studied simultaneously the threshold for statistical significance is extraordinarily high, often 10^{-8} or higher. As well, GWAS studies usually require replication, and usually thousands or tens of thousands of subjects are required in both the trait and control populations. It is not uncommon to have very many SNPs have phenotype associations with statistical significances of 10^{-6}. Although initially this was thought to be simply generated by the very large number of SNPs being studied this might not be so. The understanding that phenotypes arise from networks of gene and protein interactions has led to the concept of omnigenics (49), which proposes that very high numbers of genes underlie traits. In this paradigm GWAS studies target only the most influential of many genes.

Copy Number Variants

Copy number variants are contiguous sequences of several 100 kilobases that occur in more than 2 copies per genome. Demir et al. (50) studied the distribution of copy number variants throughout the genome of 16 subjects with vasovagal syncope and 3 controls, all within 4 families. In this small study there were 26 copy number variants whose distributions varied between syncope subjects, controls, and a publicly referenced database. The interpretation was made difficult because the variants occurred on all chromosomes, the distributions differed among all subjects, some increased in number while others decreased, and some had longer contiguous stretches while others decreased in length.

Biobank GWAS

Hadji-Turdeghal et al. (51) attempted to use GWAS to identify a genetic locus for syncope. They studied very large biobanks and databases in the United Kingdom and Denmark. The Danish population had a majority of patients with at least one of six major mental illnesses such as autism and schizophrenia. Only one locus, at chromosomal location 2q32.1, was highly significantly associated with identified syncope. The nearest

known structural gene was ZNF804A, which codes for a zinc finger regulatory protein. However, only 2.2% of the UK population and 6.5% of the Danish population were identified as having syncope, suggesting that syncope was under-reported in the control populations. The biological relevance of this is tantalizing but its clinical reality and significance are yet to be determined.

Single Family GWAS

Klein et al. (52) studied 44 Australian families with a familial history of syncope and identified 6 families with apparent autosomal dominant inheritance. Microsatellite markers identified in the largest family an apparent locus in chromosome locus 15q26, but sequencing of nearby candidate genes did not reveal mutations. Four affected members in this family did not carry the 15q26 haplotype, and the two next largest affected families did not carry this haplotype either. The relevance of this isolated finding remains to be determined.

FUTURE PERSPECTIVES

The evidence to date is compatible with one or more genetic sources of the vasovagal reflex. However, the studies to date are plagued by incomplete case finding, inadequate and irreproducible case definitions, limited definition of what is normal, low sample sizes, the use of surrogate outcomes that have not been substantiated in clinical studies, and the predominance of univariable candidate gene analyses. It may also be that the omnigenic or heavily polygenic paradigms are the case, and numerous genes each with small effects combine to predispose people to the vasovagal reflex. However, if there is a small number of genetic loci involved then the following criteria should be met to decide that a genetic locus is importantly involved.

1. The diagnosis should be established firmly in subjects with syncope by an evidence-based history or tilt test or documented vital signs during a syncopal spell;
2. The core abnormal allele should be present in all subjects with vasovagal syncope;
3. The core abnormal allele should be absent in most subjects without vasovagal syncope;
4. The difference between subjects with vasovagal syncope and controls should be based on clinical history and not a surrogate outcome such as a tilt table test;
5. Control subjects should be at least 50 years old, given that most (but not all) subjects with vasovagal syncope have a first syncopal spell before age 50;
6. The genetic locus should be associated with syncope in both sexes and in multiple ethnic populations;
7. There may be modifying loci that differ between males and females;
8. The findings must be reproducible in adequately powered studies.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Syncope in the Emergency Department

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Syncope is a common presentation to Emergency Departments (EDs). Estimates on the frequency of visits (0.6–1.7%) and subsequent rates of hospitalizations (12–85%) vary according to country. The initial ED evaluation for syncope consists of a detailed history, physical examination and 12-lead electrocardiogram (ECG). The use of additional diagnostic testing and specialist evaluation should be based on this initial evaluation rather than an unstructured approach of broad-based testing. Risk stratification performed in the ED is important for estimating prognosis, triage decisions and to establish urgency of any further work-up. The primary approach to risk stratification focuses on identifying high- and low-risk predictors. The use of prediction tools may be used to aid in physician decision-making; however, they have not performed better than the clinical judgment of emergency room physicians. Following risk stratification, decision for hospitalization should be based on the seriousness of the underlying cause for syncope or based on high-risk features, or the severity of co-morbidities. For those deemed intermediate risk, access to specialist assessment and related testing may occur in a syncope unit in the emergency department, as an outpatient, or in a less formal care pathway and is highly dependent on the local healthcare system. For syncope patients presenting to the ED, ∼0.8% die and 10.3% suffer a non-fatal severe outcome within 30 days.

Keywords: syncope, emergency department (ED), initial evaluation, risk stratification, outcomes

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INTRODUCTION

Syncope is a frequent reason for Emergency Department (ED) visits. Although estimates are largely influenced by studies reflective of specific populations, the accuracy of data collection and the definition of syncope used, numbers range from 0.6 to 1.0% in North America and 0.9–1.7% in Europe (1–3). The rates of subsequent admission to the hospital from the ED also vary depending on country, ranging from 12 to 15% in Canada (4, 5), 31–38% in Italy (6, 7), 49% in the United Kingdom (8), and 46–86% in the United States of America (9, 10).

Syncope is a symptom that may be the final presentation for a variety of conditions ranging from benign to life threatening. The most common causes of syncope seen in the ED are due to reflex syncope (35–48%) followed by orthostatic hypotension (4–24%), cardiac (5–21%), non-syncope transient loss of consciousness (TLOC) causes and anywhere from 17 to 33% of syncope presentations may remain unexplained (11–15).

INITIAL ED EVALUATION

An initial assessment in the ED involves a detailed history, physical exam (including standardized orthostatic vitals defined as blood pressure and heart rate changes in lying and sitting positions, on immediate standing and after 3 min of upright posture) and a 12-lead electrocardiogram (ECG) to determine whether an underlying cause of syncope can be identified and to help with prognostication (16, 17). Further diagnostic testing including blood work, cardiac and neurological tests and specialist evaluation should be mainly driven by the initial evaluation and a differential diagnosis that makes the extent and context of an additional work-up appropriate.

RISK STRATIFICATION

The role of risk stratification that occurs during the ED evaluation is important for several reasons: (i) it helps to estimate prognosis, (ii) influences triage decisions, (iii) establishes urgency for additional tests and specialist evaluation, and (iv) ensures appropriate discussions occur with patients. Yet, no optimal approach to risk stratification exists and as a result different approaches are being utilized.

Numerous prediction tools exist to help reduce unnecessary hospitalizations and healthcare costs related to syncope care. Examples of risk stratification tools evaluated in prospective studies are shown in **Table 1**. However, these scores have not been widely adopted into clinical practice because of important limitations including inconsistent definitions of syncope, outcomes, outcome time frames, and predictors, inclusion of "obvious" serious causes, small sample size, and limited external validation. To try and address some of those limitations, an individual patient data meta-analysis was performed to externally validate the available syncope prediction tools and compare them with clinical judgment (23). Syncope risk stratification tools did not show better diagnostic yield or prognostic yield in predicting serious short-term outcomes compared with clinical judgment. This study used older risk scores. A new syncope risk score was recently developed, the Canadian Syncope Risk Score (CSRS), which incorporates clinical factors, ECG and elevated troponin (>99th percentile of normal population) and assumed diagnosis in the ED (22). The CSRS performed better when comparing area under the curve (AUC) than not only cardiac biomarkers at predicting death and adverse outcomes but also cardiac biomarkers combined with older risk scores (24). The work underlying the scores do consistently identify certain predictors from the history, physical exam and ECG that are associated with a worse prognosis at 1–2 years follow up. Identifying those factors as either high-risk (suggesting serious condition) or low-risk (suggesting benign condition) has also been used for risk stratification (17). Precise definitions for high-, intermediate-, and low-risk patients evaluated in the ED after a syncope event do not exist. Available data makes this challenging because of variability in risk markers, study endpoints and adverse event rates among studies. An alternative to this approach has been to use risk markers from history, physical exam, laboratory investigations, and ECG to divide patients according to short-term risk (adverse outcome in the ED or post-30 days after ED discharge) and long-term risk (up to 1-year) (16).

DISPOSITION FROM ED

Following risk stratification, a decision regarding disposition must occur.

The decision for hospitalization is primarily based on the seriousness of the identified diagnosis or based on high-risk features identified during the initial evaluation. There is no strong evidence that hospitalization improves outcomes and in patients without a serious condition (e.g., reflex syncope or low-risk features) hospitalization has not been shown to improve short- and long-term outcomes and therefore these patients should be managed in an outpatient setting. The main role of hospitalization should be to expedite treatment or further diagnostic work-up (9, 25).

The optimal triage strategy for the "intermediate" risk patient remains a challenge. One proposed strategy is the syncope unit, aimed at reducing rates of under/misdiagnosis, hospital admission and costs (26). The key to a syncope unit is having advanced access to specialist assessment and related testing using an evidence-based approach. The unit may be located in the inpatient (cardiology or internal medicine department or ED) or outpatient setting (i.e., Rapid Access Blackout Clinic or Faint/Fall clinic) with referrals coming from the ED or community practitioners/cardiologists, depending on the location and the interaction can occur with an in-person or web-based evaluation. There are only two small, randomized clinical trials that have evaluated ED-based syncope units compared with usual care (27, 28). The results demonstrate higher diagnostic yield, lower hospital admission, reduced costs and no increase in adverse outcomes in patients randomized to the syncope unit. The ability to integrate a syncope unit is highly dependent on the structure and funding of an individual healthcare system and may not be required universally. A proposed strategy for disposition for the ED taking into consideration different healthcare systems is shown in **Figure 1**.

The European Heart Rhythm Association task force (26) developed preliminary quality indicators, based on consensus, for evaluation of a syncope unit and includes:

(i) An absolute rate of undiagnosed TLOC should be reduced by 20%.
(ii) <20% of low-/intermediate-risk TLOC patients should be admitted from the ED.
(iii) The syncope unit should have a 20% reduction in costs relative to usual practice and improved outcomes (i.e., <5% readmissions for syncope and <20% of paced patients with recurrence at 1-year).

For example, in Canada, two of these quality indicators (<20% low-/intermediate-risk TLOC patients should be admitted from the ED and <5% readmissions for syncope at 1-year) have been met without introduction of a syncope unit (4, 5, 29). More studies are needed to assess the clinical and

TABLE 1 | Example of syncope risk scores evaluated in prospective studies.

Study/year	Cohort (*N*)	Risk factors	Score	Endpoint	Results
Martin et al. (18)	252	Age > 45 years Abnormal EKG Ventricular arrhythmia Heart failure	0–4 (1 point each item)	1-year severe arrhythmias or arrhythmic death	0% score 0
Colivicchi et al. (19)	270	Age > 65 years Abnormal EKG Cardiovascular disease Lack of prodrome	0–4 (1 point each item)	1-year mortality	0% score 0 0.6% score 1 14% score 2 29% score 3 53% score 4
Quinn et al. (20)	684	Abnormal EKG Heart failure Shortness of breath Hematocrit < 30% SBP < 90 mmHg	No risk: 0 items Risk: ≥ 1 item	Serious events at 7 days	98% sensitive, 56% specificity
Brignole (21)	260	Palpitations (+4) Abnormal EKG/CVD (+3) Syncope effort (+3) Syncope supine (+2) Autonomic prodrome (−1) Predisposing factors (−1)	Sum of + and – points	2-year mortality Cardiac syncope probability	2% score < 3 21% score ≥ 3 2% score < 3 13% score 3 33% score 4 77% score >4
Reed et al. (8)	550	BNP ≥ 300 pg/mL HR ≤ 50; q waves EKG Fecal occult blood Hemoglobin ≤ 90 g/L Chest pain with syncope O_2 ≤ 94% room air	No risk: 0 items Risk: ≥ 1 item	1-month serious events or death (occurred in 7.1%)	87% sensitive, 65% specificity, 98% negative predictive value
Thiruganasambandamoorthy et al. (22)	4,030	Predisposition VVS symptoms (−1) History of heart disease (+1) SBP <90 or >180 mmHg (+2) Elevated troponin (+2) QRS axis < −30″ or >100″ (+1) QRS duration > 130 ms (+1) QTc interval > 480 ms (+2) Diagnosis of VVS in ED (−2) Diagnosis of cardiac syncope in ED (+2)	Add the + and – points (from −3 to 11)	Serious events at 30 days	0.4–0.7% score −2 to −3 1.2–1.9% score 0 to −1 3.1–8.1% score 1–3 12.9–19.7% score 4–5 28.9–83.6% score 6–11

economic effectiveness of these different approaches compared to usual care.

GUIDELINE COMPARISON FOR ED EVALUATION OF SYNCOPE

The initial syncope evaluation of a detailed history, physical exam (including orthostatic vitals) and 12-lead ECG is a class I recommendation in the 2017 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines while the European Society of Cardiology (ESC) document gives no class recommendation.

A key role to perform in the ED evaluation of syncope is risk stratification. When the underlying cause of syncope has been identified in the ED then risk stratification is more apparent. However, when the diagnosis is not clear then several approaches have been proposed for risk stratification including identifying risk factors with or without categorizing patients as low-, intermediate-, or high-risk, risk stratification tools or clinical judgment. Both guidelines give a class IIb recommendation (weak evidence) for use of ED prediction tools. One of the most marked distinctions between the guidelines is disposition from the ED for patients deemed "intermediate" risk. The ESC guidelines provide a strong recommendation (class I) for an ED or outpatient syncope unit evaluation instead of admission to the hospital for this subgroup. While the ACC/AHA/HRS guidelines suggest use of a structured ED observation (class IIa) can be an effective strategy. Both recommendations are based on the same limited studies.

OUTCOMES

Among studies that have evaluated short-term (7–30 day) outcomes of patients presenting to the ED with syncope, the composite estimate for death was 0.8% and 10.3% had suffered a non-fatal severe outcome (significant new diagnosis, a clinical deterioration, serious injury with recurrence, or a significant therapeutic intervention) (17). Approximately 6.9%

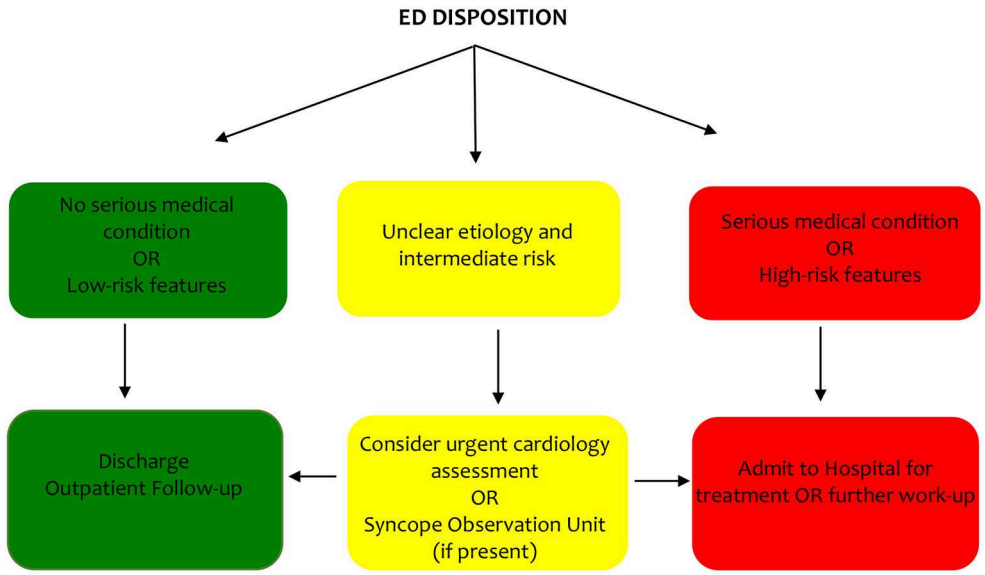

FIGURE 1 | Proposed disposition strategy from ED.

had a non-fatal severe outcome while in the ED and another 3.6% of syncope patients after ED discharge. In a meta-analysis of consecutive patients presenting to the ED, pooled estimates for mortality at 1-year was 8.4% (95% CI 6.7–10.2%), 8.9% (95% CI 7.4–10.6%) at 1.5 years, and 11.0% (95% CI 7.0–16.8%) at 2-years (30). In addition to high heterogeneity or few studies, many of these observational studies included patients both discharged or admitted from the ED. An Italian study (31) evaluating mortality based on disposition found 1.8% of syncope patients who were discharged from the ED died compared to 14.7% who were admitted. Almost half of admitted patients were 65 years or older and had significantly higher burden of cardiovascular comorbidity compared to those patients discharged from the ED. A study from Canada demonstrated both short- and long-term mortality rates among syncope patients discharged from the ED were very low (30 day 0.4% and 1-year 3.0%) (5). Among admitted patients, mortality rates were at least four times higher at 30 day and at least three times higher at 1-year among admitted patients compared to those who were discharged.

HEALTHCARE UTILIZATION

There are few data that report on the costs of syncope care exclusively for syncope patients in the ED. A study that examined costs of patients with syncope admitted and discharged from the ED found of the total costs (530 million CDN) over a 6-year period, the highest proportion was attributed to patients discharged from the ED (317 million CDN) because this cohort represented 85% of the study population (5). The highest proportion of annual costs were due to hospitalizations for each of the cohorts (admitted/discharged with syncope, admitted/discharged with an alternative diagnosis, discharged from the ED); however, for syncope patients who were discharged home from the ED, outpatient plus physician claims costs equaled those of hospitalization costs.

AUTHOR CONTRIBUTIONS

RKS wrote the content of the manuscript. RSS provided critical review.

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Syncope, Fear of Falling and Quality of Life Among Older Adults: Findings From the Irish Longitudinal Study on Aging (TILDA)

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Objective: Syncope is a prevalent condition that has a marked impact on quality of life. We examined the association between syncope and quality of life (QoL) and whether this association was explained by fear of falling (FoF).

Methods: We examined data from Wave 3 of The Irish Longitudinal Study on Aging (TILDA), of adults aged ≥50 years (n = 4,946) who were asked to report syncope and who completed the CASP-12 QoL instrument. Analyses were stratified by age and gender.

Results: Over 20% of participants reported having a previous syncopal episode, while 8% reported a faint, blackout or unexplained fall in the last year. QoL scores decreased as the burden of syncope increased: linear regression models adjusted for covariates showed that those having had two or more syncopal episodes in the last year reported a significantly lower CASP-12 score compared to those with none ($p = 0.011$). FoF partially mediated the association between syncope and QoL, particularly among younger participants.

Conclusions: Syncope is a common condition among older adults that has a deleterious effect on QoL, with ≥2 recent syncopal episodes having a particularly adverse impact on QoL. FoF is a potential pathway which may both explain this association and allow therapeutic interventions by health practitioners.

Keywords: syncope, quality of life, TILDA, CASP-12, fear of falling (FOF)

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INTRODUCTION

Syncope has been defined by the European Society of Cardiology as a transient loss of consciousness due to transient global cerebral hypoperfusion, characterized by rapid onset, short duration and followed by a spontaneous and complete recovery (1). All forms of syncope are thought to occur due to a sudden decrease of cerebral blood flow but there are numerous mechanisms for this, ranging from the benign, such as vasovagal syncope (VVS), whereby cerebral hypoperfusion is induced by reflex bradycardia and/or peripheral vasodilatation, to potentially life-threatening causes such as those involving an underlying cardiac dysrhythmia (2). The causes range in prevalence from 60% reflex to 15% cardiac with treatments varying depending on the underlying cause (3). Other causes of syncope include, but are not limited to, orthostatic hypotension and

structural heart disease. The cause of syncope may be multifactorial or indeed may not be identified at all, however, more recently, with the advent of newer technologies to aid investigations, rates of unexplained syncope have reduced to between 14 and 17.5% (4, 5).

Increasing incidence of syncope with advancing age can be accounted for by gradual age-related physiological impairments, namely "neuro-cardiovascular instability"—the regulation of heart rate, blood pressure, and cerebral blood flow (6), particularly with postural changes, in combination with increasing incidence of co-morbidities and polypharmacy that impair cardiovascular compensation (7).

Public policy is increasingly focused on the issue of successful aging in the hope of enabling individuals to lead enjoyable lives into old age. Quality of life (QoL) is an important feature of successful aging and it is vital that we better understand the health and related factors that affect QoL. Chronic disease and co-morbidity are features of aging (8) and their prevalence has increased along with life expectancy. This has been shown to be deleterious to QoL as people age (9). Less is known about the associations between individual conditions and QoL and how QoL is affected; for instance, through physical symptoms, functional limitations, or psychological effects, any of which could negatively impact upon physical and mental abilities, mood and social participation. It has been shown that a variety of factors including demographics, health, and social characteristics are associated with changes in QoL over time and that QoL is not just a function of aging or declining health but influenced by factors such as loneliness and social participation (10) which themselves may or may not be impacted by ill health. Improving our understanding of the different factors that influence QoL in the context of co-morbidity is vital in optimizing successful aging.

While maximizing QoL is an accepted aim for individuals and on a population level, a consensus is lacking on how best to define or measure QoL. Many measures of QoL include indicators of physical health and function which can make it more difficult to disentangle the associations between chronic disease and QoL, especially in older populations where chronic disease and co-morbidity are more prevalent and where health has often been used as a proxy for QoL rather than being simply a factor that influences it. The CASP-19 measure uses a broader definition of QoL, specifically developed for use with older people, consisting of 19 Likert-scaled items, encompassing four domains; control, autonomy, self-realization, and pleasure, the initials of which make up its acronym. It aims to assess the degree to which human needs are satisfied and can be affected by multiple factors including, but not limited to, health as measure of QoL (11) and has been shown to be a useful scale for measuring QoL in older people (12).

The QoL in syncope patients has largely been studied only in small groups, mainly in referral centers. Syncope has been shown to have moderate to severe effects on QoL from both a health and functional point of view, especially in patients with a recent onset of symptoms, with 33% having reported functional impairments with daily activities, which was clinically as well as statistically significantly worse than the reference population (13). QoL associated with recurrent syncope has been reported as equivalent to chronic conditions such as severe rheumatoid arthritis and chronic lower back pain (14) with 76% reporting that syncope interfered with their life or activities of daily living, with driving and employment also frequently affected. Syncope, even benign VVS, can result in not only loss of consciousness but also postural tone, which depending on one's occupation may be very hazardous—for instance when driving a truck/bus, working at heights or in proximity to flames or hot/dangerous materials/machinery. Indeed, even pre-syncope may result in falls or occupational accidents. Complexities around identifying causes and potential diagnoses may result in undue caution and unjustified delays in returning to work or driving (15). Syncope, regardless of one's occupation, can result in physical injuries and can be fatal, with those suffering from syncope experiencing increased healthcare utilization, unwanted change in employment status, driving restrictions, decreased social participation, and subjective decrease in self-worth, all of which impair QoL.

While one study found that syncope leads to a greater psychosocial than physical impairment (14) another found a greater impact of physical impairment than psychosocial (16). Whereas, both groups recruited participants from a syncope referral center, Linzer's group was smaller, older, more predominantly female and had a higher frequency of syncopal episodes compared to Rose's (62 participants vs. 136, mean age 49 $\pm$ 19 vs. 40 $\pm$ 17, 29% male vs. 42%, median 10 syncopal episodes in median 11 months vs. median 7 in 60). Different QoL measurement tools were used also, the strengths and weaknesses of which were discussed in detail in Rose's paper. Is it possible that age and/or sex may influence the associations between syncope and QoL?

Fear of falling (FoF) has been found to be associated with recent experience of falls and decreased QoL (17), lower activity levels, fewer social contacts (18), and reduced functional capacity (19). Those with severe FoF were also less likely to include leisure activities into their daily lives (20). FoF is associated with poor health and institutionalization (21). When 12 studies were summarized syncope was found to account for <1% of all causes of falls, however dizziness and vertigo, some of which may be attributable to pre-syncope, account for a mean of 13% (22). Even though syncope is a known cause of falls and impaired QoL, and that FoF is also known to have a detrimental effect on functional status, social participation and QoL there is very little known about the relationship between syncope and FoF and how it relates to QoL. Is FoF a mechanism through which syncope affects QoL or is it independent of it? Any intervention to reduce FoF in the context of syncope could potentially improve aspects of social participation, functional limitations, and may even improve rates of institutionalization.

This study sought to investigate the relationship between syncope and QoL in an older community-dwelling population,

Non-standard abbreviations: CAPI, Computer Assisted Personal Interview; CASP, Control, Autonomy, Self-realization and Pleasure; CIDI, Composite International Diagnostic Interview; FoF, Fear of falling; QoL, Quality of life; SCQ, Self-Completion Questionnaire; TILDA, The Irish Longitudinal Study of Aging; UCLA, University of California, Los Angeles; VVS, Vasovagal syncope.

compared to findings previously observed in small samples of participants recruited from specialist referral centers. In addition, we aimed to further investigate this relationship by taking into account features of the syncopal history such as timing (recent vs. distant) and frequency (number of syncopal events). We also aimed to investigate possible age and/or sex differences and explored the possible role of FoF in mediating the relationship between syncope and QoL.

METHODS

Sample

This observational study is based on data from the third wave of The Irish Longitudinal Study of Aging (TILDA), a prospective study of the health, social and economic circumstances and representative of community-dwelling adults aged ≥50 in Ireland. The third wave of data was collected between 2014 and 2015 with the data collection process being described in detail elsewhere (23, 24). As part of the study participants completed a Computer Assisted Personal Interview (CAPI), conducted in participants' homes by trained interviewers and a paper-based Self-Completion Questionnaire (SCQ) completed privately by participants at each wave. Those under the age of 50 were excluded.

Outcome Variable—QoL

QoL was measured as part of the SCQ where participants were asked to complete the CASP-12 instrument, a revised version of the CASP-19 QoL scale which has been shown to be a useful scale for measuring QoL in older people (12), has been recommended for use ahead of the CASP-19 as it has been shown to have stronger measurement properties than the original CASP-19 (25) and it has been shown to be psychometrically valid in TILDA (26). Participants rated how often they feel a particular way about their life, on 12 Likert-scaled items, ranging from often to never, with regards to the four domains of QoL measured by CASP; control, autonomy, self-realization, and pleasure, with possible scores ranging from 0 to 36 with a higher score indicating a better QoL (**Table 1**). CASP-12 was the outcome variable in this study.

TABLE 1 | Measures of control, autonomy, self-realization and pleasure in the CASP-12.

Scale	Description	Item	Score range
Control	Ability to actively participate in one's environment	My age prevents me from doing the things I would like to I feel that what happens to me is out of my control I feel free to plan for the future I feel left out of things	0–12
Autonomy	Right of the individual to be free from the unwanted interference of others	I feel that I can please myself in what I can do My health stops me from doing things I want to do Shortage of money stops me doing things I want to do	0–9
Self-realization	Fulfillment of one's potential	I feel satisfied with the way my life has turned out I feel life is full of opportunities	0–6
Pleasure	Sense of happiness or enjoyment derived from engaging with life	I look forward to each day I feel that my life has meaning I enjoy being in the company of others	0–9

Main Independent Variables—Syncope and FoF

A section of the CAPI asked participants "Have you ever had a blackout or fainted?" or "Since your last interview, have you had a blackout or fainted?" Those who had reported a positive response to the equivalent question in the CAPI from wave 2 were fed forward and given a positive response. Those who had not answered the question in wave 2 or who had not previously answered positively were given the options yes, no, don't know or refuse to answer. Those who answered yes were added to those fed forward from wave 2 and these participants were classed as having had "previous syncope." Previous syncope is the first predictor variable and includes previous blackouts and faints.

Another question asked, "Have you fallen in the last year/since your last interview?" with options being yes, no, don't know or refuse to answer. Those who answered yes were instructed to continue to "How many times have you fallen in the last year" and then "Was this fall/were any of these falls non-accidental, i.e., with no apparent or obvious reason?" with the same set of options available for responses as before. Those who answered yes were classified as having had an "unexplained fall in the last year."

Participants who had a positive response to "Since your last interview, have you had a blackout or fainted?" were asked "Approximately how many times have you had a blackout or fainted in the last year?" while those participants who were fed forward with a positive response to the equivalent question from wave 2 were asked the same question. Those participants who answered anything ≥1 were classified as having had a "blackout or faint in the last year/since last interview". Those participants were added to any with an "unexplained fall in the last year" and combined were classified as having had a syncopal episode in the last year or "recent syncope." Recent syncope is the second predictor variable and includes faints, blackouts, and unexplained falls.

Participants who were asked "Approximately how many times have you had a blackout or fainted in the last year?" and answered ≥1 were classified as having had a "blackout or faint in the last year" with participants categorized as having none, one, or two or more recent blackouts or faints or "recurrent syncope in the last year." Recurrent syncope in the last year is the third predictor variable and includes blackouts and faints but not unexplained falls as this could not be quantified separately to any type of fall. Those participants who reported any unexplained fall in the last year but not a faint or blackout were excluded from the "none" category for recent blackout or faint.

In the CAPI, participants, regardless of responses to previous questions about falls, were asked "Are you afraid of falling?" Those who responded positively were defined as having "FoF." FoF is the fourth predictor variable.

Covariates

Socioeconomic characteristics including age, sex, education and marital status were recorded.

History of chronic disease was obtained through a self-reported doctor-diagnosed history of diabetes and cardiovascular disease (heart attack, heart failure, stroke, Transient Ischemic Attack, atrial fibrillation, hypertension, and/or angina). The level of non-cardiovascular physical co-morbidity was categorized as 0, 1, or ≥2 self-reported doctor-diagnosed chronic conditions including cataracts, glaucoma, age-related macular degeneration, chronic lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer disease, venous ulcers, liver disease, thyroid disease, kidney disease, anemia, or any type of incontinence. Chronic disease has been shown to affect QoL, directly and indirectly, through increased deficits in physical function and activity (11) while self-reported doctor diagnoses have been shown to be a reliable measure of disease burden compared to medical records (27).

The total number of regular prescribed medications was recorded and coded using the World Health Organization Anatomical Therapeutic Chemical index with those participants taking 5 or more regular medications excluding supplements being defined as being subject to "polypharmacy." Smoking status was also recorded.

In terms of non-physical issues that may affect QoL, a self-reported history of having suffered either childhood physical or sexual abuse was obtained, as was loneliness and depression, all of which have been shown to have a negative effect on QoL (28). Apart from the impact it may have on later life QoL childhood trauma has been shown to have an association with increased cardiovascular risk in mid-life (29) and has also been linked with a lifelong tendency for syncope (30). The degree of loneliness or social isolation participants perceived was recorded using the University of California Los Angeles (UCLA) loneliness scale, on 5 Likert-scaled items ranging from hardly ever or never to often with scores summed to create a range from 0 to 10 with higher scores indicating greater levels of loneliness (31). A current or recent depressive disorder was measured using the Composite International Diagnostic Interview-Short Form (CIDI-SF) whereby participants dichotomously did or did not fulfill criteria for a major depressive episode in previous 12 months. CIDI-SF has been shown to correctly classify CIDI cases of major depressive episodes with an accuracy of 93% and generalized anxiety disorder with an accuracy of >99% (32).

Statistical Analysis

Stata/MP 14.1 software was used for all statistical analysis (33).

Ordinary Least Squares equal-interval scale linear regression models were used to examine the associations between syncope (previous, recent, and recurrent), QoL and FoF.

Cross-sectional weights were applied to account for attrition between waves and to adjust the sample making it more representative of the population according to age, sex, education, and location compared to known census data compiled by the Central Statistics Office.

Separate models were run with groups stratified by sex and age (<75 and ≥75) in a step-wise manner, initially adjusted for the covariates age, age squared (to account for the non-linear relationship observed between age and CASP score) (28), sex, marital status, and education (Model 1), before being further adjusted for smoking status, cardiovascular disease, diabetes, chronic disease, polypharmacy, history of childhood physical or sexual abuse, loneliness, and depression (Model 2). Finally, the models were adjusted for FoF (Model 3) to examine its effect and relative importance.

RESULTS

There were 6,454 participants ≥50 years of age who completed the CAPI. Of these participants, 76.6% ($n = 4{,}946$) had complete CASP-12 data, of which 2.1% ($n = 103$) were missing data for any of the variables of interest, with those participants excluded, resulting in a final sample of 4,933 participants for model 1 and 4,843 for models 2 and 3. These 4,843 participants were characterized overall before being stratified according to sex and age.

Over one in five (21.7%, SE: 0.767, 95% CI: 20.27–23.29) reported a previous syncopal episode while nearly one in twelve (8.07%, SE: 0.471, 95% CI: 7.19–9.04) reported a recent syncopal episode. Both previous and recent syncope were more commonly observed among women with the incidence of recent syncope being higher among those 75 or older for both sexes (**Table 2**).

There was no significant difference on CASP-12 scores between the "overall" group (Mean CASP-12 score 26.73, SE: 0.095, 95% CI: 26.55–26.92) and either sex when grouped as total number for each sex regardless of age. When stratified by age <75 or ≥75, younger females (26.93, SE: 0.145, 95% CI: 26.64–27.21) had better QoL than older (25.82, SE: 0.257, 95% CI: 25.31–26.32). There was no difference for men regardless of age group.

Of the 6,454 participants ≥50 years of age included in the study who completed the CAPI 4,072 had complete CASP-12 data, relevant covariates, as well as information relating to the number of recent blackouts or faints or "recurrent syncope" (once those who reported any unexplained fall but not a faint or blackout were excluded). **Table 3** shows characteristics of the different categories for recurrent syncope in the last year.

There was no significant association between previous syncope and QoL, overall or in any of the sex and age stratified groups.

Results for the weighted linear regression models showing associations of QoL with recent syncope are summarized in **Tables 4–6** showing Models 1, 2, and 3, respectively.

Fully adjusted weighted linear regression including the participants for whom all data was complete ($n = 4{,}843$) showed that recent syncope had a significant association with QoL ($\beta = -0.95$, SE: 0.277, 95% CI: −1.50 to −0.41, $p = 0.001$). This significance was maintained when adjusted for FoF ($\beta = -0.81$, SE: 0.277, 95% CI: −1.36 to −0.27, $p = 0.004$) and while the negative effect of syncope on QoL was reduced by FoF, it remained negative with the coefficient reducing from −0.95 to −0.81.

When stratified by sex, the association between recent syncope remained significant for males ($\beta = -1.63$, 95% CI: −2.47 to −0.79, $p < 0.001$) but not females ($\beta = -0.27$, 95% CI: −0.95 to 0.40, $p = 0.426$).

TABLE 2 | Distribution of key characteristics of the 4,843 participants included in Model 2 and 3 with standard errors and confidence intervals.

			Std. Err.	95% CI	*N*
Gender	Male	45.87%	0.623	44.65–47.10	4,843
	Female	54.13%	0.623	52.90–55.35	
Mean age (years)	Overall	64.83	0.196	64.44–65.21	4,843
	Male	65.20	0.218	64.77–65.63	2,172
	Female	64.51	0.246	64.03–65.00	2,671
	Male≥75	79.88	0.221	79.44–80.31	430
	Female≥75	80.26	0.210	79.85–80.68	473
	Male<75	62.18	0.161	61.87–62.50	1,742
	Female<75	60.73	0.175	60.38–61.07	2,198
Highest level of education obtained	Primary or below	28.38%	0.913	26.62–30.20	4,843
	Secondary	46.75%	0.855	45.08–48.43	
	Tertiary or above	24.87%	0.801	23.33–26.48	
Marital status	Married	72.33%	0.812	70.71–73.90	4,843
	Never married	7.77%	0.467	6.90–8.74	
	Separated/divorced	6.97%	0.422	6.18–7.84	
	Widowed	12.93%	0.554	11.88–14.06	
Level of co-morbidity	0 chronic conditions	39.62%	0.843	37.98–41.29	4,843
	1 chronic condition	31.11%	0.749	29.66–32.59	
	≥2 chronic conditions	29.27%	0.793	27.74–30.85	
Proportion who had a recent syncopal event	Overall	8.07%	0.471	7.19–9.04	4,843
	Male	6.13%	0.557	5.13–7.32	2,172
	Female	9.70%	0.676	8.45–11.11	2,671
	Male≥75	11.35%	1.684	8.43–15.11	430
	Female≥75	16.57%	1.872	12.20–20.58	473
	Male<75	5.06%	0.575	4.04–6.32	1,742
	Female<75	8.05%	0.685	6.81–9.50	2,198
Proportion who had previous syncopal event	Overall	21.74%	0.767	20.27–23.29	4,843
	Male	19.22%	0.965	17.39–21.19	2,172
	Female	23.88%	1.041	21.90–25.98	2,671
	Male≥75	16.11%	1.970	12.59–20.37	430
	Female≥75	25.75%	2.274	21.53–30.47	473
	Male<75	19.86%	1.069	17.84–22.04	1,742
	Female<75	23.43%	1.125	21.29–25.71	2,198
Mean CASP-12 score	Overall	26.73	0.095	26.55–26.92	4,843
	Male	26.76	0.132	26.50–27.02	2,172
	Female	26.71	0.127	26.46–26.96	2,671
	Male≥75	26.55	0.255	26.05–27.06	430
	Female≥75	25.82	0.257	25.31–26.32	473
	Male<75	26.80	0.152	26.51–27.10	1,742
	Female<75	26.93	0.145	26.64–27.21	2,198

When stratified by age (but not sex), there was a significant association between recent syncope and QoL for both groups, with FoF having a greater impact on the reduction in the coefficient for those <75 ($\beta = -0.81$, 95% CI: −1.52 to −0.09, $p = 0.027$ to $\beta = -0.65$, 95% CI: −1.37 to 0.06, $p = 0.073$) than the older group ($\beta = -1.33$ 95% CI: −2.12 to −0.53, $p = 0.001$ to $\beta = -1.21$, 95% CI: −2.02 to −0.40, $p = 0.003$) with a reduction in coefficient of 19.8 vs. 8.7%. While significance was maintained for the ≥75 group when adjusted for FoF this significance was lost when adjusted for FoF for those <75.

TABLE 3 | Distribution of key characteristics of the 4,072 participants included in Model 2R and 3R with standard errors and confidence intervals.

	Number of faints or blackouts in past year		Std. Err.	95% CI	*N*
Proportion of total males (%)	0	96.94%	4.427	95.94–97.70	1,872
	1	1.95%	3.343	1.39–2.72	
	≥2	1.11%	2.631	0.70–1.77	
Proportion of total females (%)	0	95.92%	4.966	94.82–96.79	2,200
	1	2.91%	4.135	2.20–3.85	
	≥2	1.17%	2.967	0.71–1.92	
Mean age (male) (years)	0	64.95	0.235	64.48–65.41	1,812
	1	67.62	1.747	64.08–71.17	39
	≥2	66.85	1.687	63.30–70.39	21
Mean age (female) (years)	0	63.92	0.262	63.41–64.44	2,117
	1	67.47	1.799	63.87–71.08	60
	≥2	68.24	2.953	62.04–74.44	23
Mean CASP12 Score (male)	0	27.00	0.144	26.71–27.28	1,812
	1	25.55	1.225	23.06–28.03	39
	≥2	22.53	1.452	19.48–25.58	21
Mean CASP12 score (female)	0	26.88	0.144	26.60–27.17	2,117
	1	25.51	1.050	23.41–27.62	60
	≥2	23.76	1.078	21.50–26.03	23

TABLE 4 | Model 1—weighted linear regression model showing associations of QoL with recent syncope adjusted for age, age-squared, sex, marital status, and education.

Category (*n*)	Coefficient (95% CI)	Std. Err.	*P*-value	R^2
Overall (4,933)	−2.31 (−3.01, −1.61)	0.355	<0.001	0.051
Male (2,213)	−2.90 (−4.00, −1.79)	0.561	<0.001	0.059
Female (2,720)	−1.97 (−2.84, −1.09)	0.446	<0.001	0.047
Male ≥ 75 (448)	−3.23 (−4.76, −1.69)	0.779	<0.001	0.076
Female ≥ 75 (484)	−1.50 (−2.81, −0.19)	0.668	0.025	0.035
Male < 75 (1,765)	−2.68 (−4.11, −1.24)	0.730	<0.001	0.059
Female < 75 (2,236)	−2.18 (−3.29, −1.07)	0.564	<0.001	0.048

TABLE 5 | Model 2—weighted linear regression model showing associations of QoL with recent syncope adjusted for Model 1 covariates plus cardiovascular disease, diabetes, chronic health conditions, smoking, polypharmacy, history of childhood physical abuse, history of childhood sexual abuse, depression, and loneliness.

Category (*n*)	Coefficient (95% CI)	Std. Err.	*P*-value	R^2
Overall (4,843)	−0.95 (−1.50, −0.41)	0.277	0.001	0.381
Male (2,172)	−1.72 (−2.57, −0.87)	0.433	<0.001	0.378
Female (2,671)	−0.45 (−1.13, 0.23)	0.346	0.190	0.392
Male ≥ 75 (430)	−1.81 (−2.98, −0.64)	0.593	0.002	0.342
Female ≥ 75 (473)	−1.15 (−2.12, −0.17)	0.495	0.021	0.360
Male < 75 (1,742)	−1.78 (−2.88, −0.69)	0.557	0.001	0.391
Female < 75 (2,198)	−0.18 (−1.11, 0.74)	0.469	0.694	0.405

A significant association between recent syncope and QoL was observed for males both <75 and ≥75. Males <75 had a lesser negative coefficient ($\beta = -1.66$, 95% CI: −2.75 to −0.58, $p = 0.003$) compared with the older male group ($\beta = -1.77$, 95% CI: −2.93 to −0.62, $p = 0.003$) with FoF again accounting for a larger reduction as a proportion in the size of the coefficient for the younger group than the older (reduction in coefficient of 6.7 vs. 2.2%).

There was no significant association between recent syncope and QoL observed for women <75, whereas there was for women ≥75 ($\beta = -1.15$, 95% CI: −2.12 to −0.17, $p = 0.021$), however its statistical significance was lost once adjusted for FoF ($\beta = -0.96$, 95% CI: −1.97 to 0.04, $p = 0.06$).

The results for Model 3 are summarized graphically in **Figure 1** while results for the weighted linear regression models showing associations of QoL with recurrent syncope are summarized in **Tables 7–9** showing Models 1R, 2R, and 3R, respectively.

These fully adjusted models showed that ≥2 syncopal episodes in the past year were associated with a significantly lower QoL, but when stratified by sex this significance was only seen in males ($\beta = -3.71$, 95% CI: −6.05 to −1.37, $p = 0.002$). One recent syncope did not have a significant effect on QoL overall or for either sex when examined individually. **Figure 2** shows that two or more syncopal episodes in the past year, in a male

TABLE 6 | Model 3—weighted linear regression model showing associations of QoL with recent syncope adjusted for Model 2 covariates plus FoF.

Category (*n*)	Coefficient (95% CI)	Std. Err.	*P*-value	R^2
Overall (4,843)	−0.81 (−1.36, −0.27)	0.277	0.004	0.386
Male (2,172)	−1.63 (−2.47, −0.79)	0.428	<0.001	0.380
Female (2,671)	−0.27 (−0.95, 0.40)	0.345	0.426	0.400
Male ≥ 75 (430)	−1.77 (−2.93, −0.62)	0.589	0.003	0.344
Female ≥ 75 (473)	−0.96 (−1.97, 0.04)	0.510	0.060	0.371
Male < 75 (1,742)	−1.66 (−2.75, −0.58)	0.552	0.003	0.393
Female < 75 (2,198)	−0.01 (−0.92, 0.91)	0.464	0.990	0.412

population, was observed to have a similar impact on QoL as a current or recent depressive episode and more so than having a single chronic disease from a list including conditions such as chronic lung disease, arthritis, osteoporosis, cancer, Parkinson's disease, liver disease, kidney disease, or any type of incontinence. This relationship would appear to be stronger in younger males.

DISCUSSION

This study sought to investigate the relationship between syncope and QoL in a large, nationally representative, community-dwelling older population. We observed that syncope was found to have an adverse significant effect on QoL on those who have had a self-reported episode of faint, blackout, or unexplained fall, which is consistent with what has been observed previously in those presenting for assessment at a specialist syncope referral center (13, 14, 16).

We found that a history of a syncopal event, rather than a recent syncopal event, had no significant association with QoL which would indicate that there is not necessarily a prolonged relationship between syncope and QoL. It has been shown previously that QoL improved significantly at 1-year follow up, compared with presentation for syncope (34) but less so for those with recurrent episodes. These results combined suggest it is the frequency of syncopal episodes and how recent they are that affects QoL.

As to why a distant history of a syncopal event, rather than a recent syncopal event, had no significant association with QoL may depend on the type of syncope experienced at different stages of life. Classical VVS, one of the most common subtypes of syncope, usually starts at a young age (35). It is benign and with education about the condition, the precipitating factors and recognition of the prodromal symptoms, the frequency often decreases with age or stops altogether. It would be reasonable that VVS accounted for a significant proportion of syncopal events for the more than 1-in-5 who reported having had a syncopal event in this study. It would also be reasonable that a benign event potentially decades previously would have minimal impact on current QoL.

With regard to whether there were any differences in the relationship observed between syncope and QoL depending on age and sex, a history of a recent syncopal event was found to have an association with QoL for men only. In relation to whether the number of recent syncopal events correlated with QoL, it was found that, while an isolated episode has no effect, ≥2 in the past year has a marked impact on QoL, the degree of which would compare with a current or recent depressive episode.

With regard to the possible mediating effect of FoF on the relationship between syncope and QoL, for those with a recent syncopal event, FoF was observed to have more than twice the effect, in terms of proportion of reduction in the coefficient, for men in the <75 years bracket compared with those ≥75, suggesting it has a higher relative importance with regards QoL for the younger male group. The significance recent syncope had on QoL for women aged ≥75 was lost when FoF was added to Model 3.

Questions raised by our results include why does syncope impact QoL of men more so than women and why does FoF impact younger men more so than old?

Why syncope impacts the QoL of men more than women may be due to the subtype of syncope experienced differing between sexes. For instance, it has been shown (36) that the incidence of cardiac causes of syncope are nearly twice that among men than women (13.2 vs. 6.7%) and that the risk of recurrence was especially high among those with cardiac causes (multivariable-adjusted hazard ratio 30.0; 95% CI: 14.9–60.3) suggesting that, while the prevalence of syncope is higher in women, recurrent syncope is more prevalent in men. Male sex has been shown previously to be a risk factor for recurrent syncope (multivariate hazard ratio 1.18; 95% CI: 1.12–1.24) (37). For those <75, of which 45.1% were male, we observed males accounted for 53.1% of those with ≥2 syncopal episodes in the past year.

Another route in which men may be affected more than women could be the impact syncope may have on social participation which has been shown to play a vital role in healthy aging (38). Strict regulations relating to recent syncope may have direct effects on social participation via restrictions on driving and use of heavy machinery that an episode may have—this may be directly, through its impact on general independence and social participation, or indirectly through subsequent inability to work due to restrictions for those who need to drive as part of their employment. Gaggioli et al. stated that "restrictive measures regarding the resumption of work are often inappropriate given the rarity of recurrences" (39) and while it has been shown that 52% of those presenting to Emergency Departments with syncope are of working age (18–65) only 60% of those employed at the time of syncope returned to their previous job after discharge, with the risk of syncope recurrence highest within 6 months at 9.2% overall (40). Unemployment or working in the home significantly reduced CASP-19 (28).

Driving, rather than being a passenger, is associated with better social participation and well-being whereas relying on lifts was found to be associated with poorer psychosocial well-being (41). The male group were observed to be more likely to be employed (42% for males vs. 33% for females) and there are some professions dominated by one sex or other, such as farming, where farm owners/managers were >88% male in

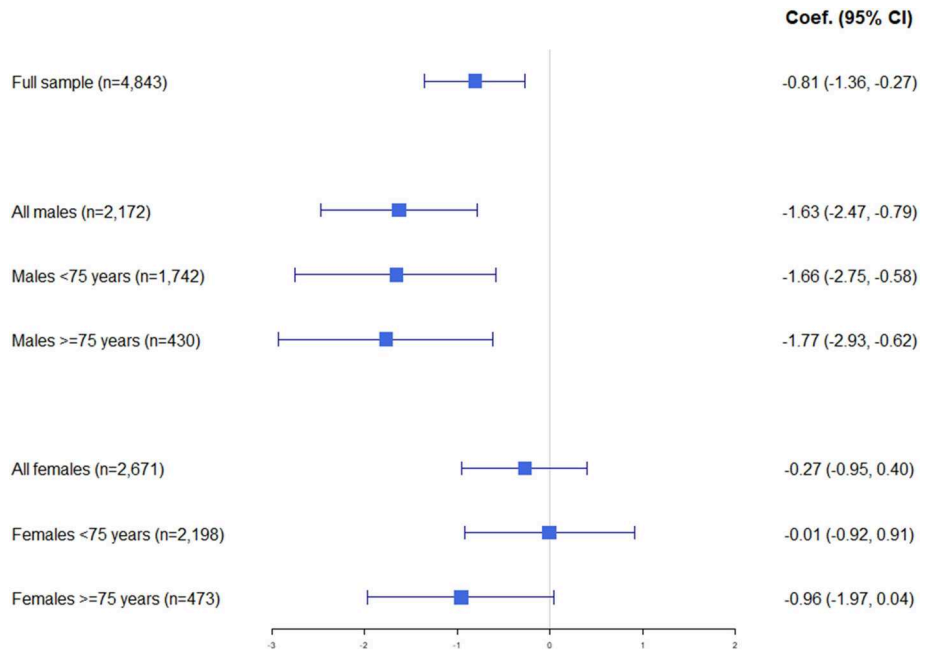

FIGURE 1 | Graphical summary of results of weighted linear regression Model 3 with coefficient and 95% confidence intervals.

wave 3, while conversely, >99% of those who reported their current employment situation as "looking after home/family" were female. There are other professions such as taxi/bus driving and in the shipping/freight industry which would have a stereotypically male dominated workforce, particularly among older generations, where restrictions on one's license to drive or operate heavy machinery would reduce their ability to work resulting in economic loss, all of which would have a negative effect on QoL. Previous observations in TILDA have shown that income is positively associated with QoL in older age with a mean CASP-12 score of 29.6 for individuals in the highest quintile of household income compared with 26.2 for those in the lowest (42).

With regard to FoF affecting younger men's QoL more so than older men, it has been shown that mental health was a bigger determinant of QoL for a younger age group than older (albeit 50–64 rather than 50–74) with anxiety having a more negative impact than depression when fully adjusted (28). The anxiety around FoF may overlap with poorer mental health as a result of recent syncope potentially unaccounted for with the depression variable in our models. The fact that a large proportion of syncopal episodes never have a confirmed cause may heighten any anxiety and FoF given the level of uncertainty that may bring. As discussed previously, in the age category ≥50, younger men are more likely to have cardiac causes of syncope, more life-threatening causes of syncope and more likely recurrent syncope. Syncope caused by arrhythmias often has little or no prodrome, preventing warning of an event and is more likely to be injurious. All of this may heighten anxiety and FoF when compared with older men or women of any age who have syncope and this may lead to apprehension about returning to certain forms of employment and/or driving, potentially even when unjustified.

Sub-group analyses would suggest that recurrent syncope has an effect on men's QoL, not seen for women, similar to what was observed for recent syncope, with younger men being affected more than older. However, the numbers included in these analyses are small and while they should be interpreted with caution, they merit further consideration and future investigation. Possible reasons for these results may again lie in the subtype of syncope experienced being different between sexes and at different ages and the impact this has on employment status/social participation. Cardiac causes of syncope have been shown to be more prevalent in a more middle-aged pre-retirement group (mean age 56 years) than older, with 10% felt to have ventricular dysrhythmias as the cause of syncope (2). This compared with no syncopal episode at all being attributed to ventricular dysrhythmia in an older group (mean age 87) which would suggest selective survival of individuals without life-threatening dysrhythmias (7). Participants in the Framingham Heart Study (36) with cardiac syncope had lower survival (∼55% 5-year survival compared with approximately 85% 5-year survival for the group containing vasovagal, orthostatic, medication-induced and other infrequent causes of syncope) which was consistent with another study that suggested cardiac syncope is associated with increased risk of premature death and cardiovascular events (43). If those with a cardiac cause of syncope are more likely to be younger men, less likely to survive to an older age, and more likely to have recurrent episodes while alive, it could be deduced that their QoL would be worse than

TABLE 7 | Model 1R—Weighted linear regression model showing associations of QoL with recurrent syncope adjusted for age, age-squared, sex, marital status, and education.

Category (*n*)	Number of episodes	Coefficient (95% CI)	Std. Err.	*P*-value	R^2
Overall (4,146)	1	−1.09 (−2.60, 0.42)	0.768	0.156	0.047
	≥2	−3.05 (−4.65, −1.46)	0.812	<0.001	
Male (1,903)	1	−1.45 (−3.89, 1.00)	1.243	0.245	0.052
	≥2	−3.59 (−6.37, −0.81)	1.416	0.011	
Female (2,243)	1	−0.86 (−2.76, 1.03)	0.965	0.371	0.043
	≥2	−2.62 (−4.50, −0.75)	0.955	0.006	
Male ≥ 75 (377)	1	−3.33 (−6.95, 0.30)	1.840	0.072	0.053
	≥2	−2.71 (−5.91, 0.50)	1.627	0.097	
Female ≥ 75 (371)	1	1.62 (−0.01, 3.24)	0.824	0.050	0.029
	≥2	−1.80 (−6.26, 2.65)	2.263	0.426	
Male < 75 (1,526)	1	−0.40 (−3.54, 2.75)	1.600	0.804	0.056
	≥2	−3.69 (−6.93, −0.46)	1.647	0.025	
Female < 75 (1,872)	1	−1.83 (−4.38, 0.71)	1.297	0.158	0.049
	≥2	−2.89 (−4.52, −1.26)	0.831	0.001	

TABLE 8 | Model 2R—weighted linear regression model showing associations of QoL with recurrent syncope adjusted for Model 1R covariates plus cardiovascular disease, diabetes, chronic health conditions, smoking, polypharmacy, history of childhood physical abuse, history of childhood sexual abuse, depression, and loneliness.

Category (*n*)	Number of episodes	Coefficient (95% CI)	Std. Err.	*P*-value	R^2
Overall (4,072)	1	0.17 (−0.87, 1.21)	0.530	0.744	0.384
	≥2	−1.95 (−3.31, −0.58)	0.695	0.005	
Male (1,872)	1	0.28 (−1.21, 1.76)	0.756	0.714	0.376
	≥2	−3.82 (−6.13, −1.51)	1.177	0.001	
Female (2,200)	1	0.11 (−1.29, 1.51)	0.713	0.875	0.401
	≥2	−0.40 (−1.72, 0.93)	0.675	0.558	
Male ≥ 75 (362)	1	−1.67 (−3.37, 0.03)	0.865	0.055	0.342
	≥2	−2.12 (−4.81, 0.58)	1.369	0.123	
Female ≥ 75 (364)	1	1.08 (−0.80, 2.97)	0.957	0.260	0.378
	≥2	−0.70 (−4.07, 2.67)	1.710	0.683	
Male < 75 (1,510)	1	0.94 (−1.03, 2.90)	0.999	0.350	0.391
	≥2	−4.35 (−6.94, −1.77)	1.316	0.001	
Female < 75 (1,836)	1	−0.23 (−2.10, 1.64)	0.954	0.810	0.412
	≥2	−0.03 (−1.71, 1.66)	0.857	0.975	

older men who are less likely to have cardiac causes of syncope and recurrent syncope.

In conclusion, syncope is a common condition among older adults that has a deleterious effect on QoL, with ≥2 recent syncopal episodes having a particularly adverse impact. FoF is a potential pathway which may both explain some of this association and allow therapeutic interventions by health practitioners. The overall well-being of the general population, rather than just their health, is becoming more of a focus for policy-makers (44). Optimizing health outcomes with primary and secondary prevention/intervention should continue to be first line for healthcare professionals but overall care strategies should also encompass policies that facilitate and sustain social participation of older people in the community. With that in mind, given the results of our investigations, it could be suggested to increase or ear-mark resources to allow for expedition of

TABLE 9 | Model 3R—Weighted linear regression model showing associations of QoL with recurrent syncope adjusted for Model 2R covariates plus FoF.

Category (*n*)	Number of episodes	Coefficient (95% CI)	Std. Err.	*P*-value	R^2
Overall (4,072)	1	0.24 (−0.82, 1.30)	0.540	0.659	0.390
	≥2	−1.82 (−3.22, −0.42)	0.712	0.011	
Male (1,872)	1	0.36 (−1.15, 1.87)	0.768	0.638	0.379
	≥2	−3.71 (−6.05, −1.37)	1.191	0.002	
Female (2,200)	1	0.15 (−1.27, 1.56)	0.722	0.840	0.410
	≥2	−0.26 (−1.59, 1.07)	0.678	0.704	
Male ≥ 75 (362)	1	−1.58 (−3.30, 0.13)	0.871	0.071	0.345
	≥2	−1.97 (−4.84, 0.90)	1.457	0.177	
Female ≥ 75 (364)	1	1.17 (−0.77, 3.11)	0.987	0.237	0.391
	≥2	−0.63 (−4.02, 2.75)	1.717	0.712	
Male < 75 (1,510)	1	1.02 (−0.99, 3.03)	1.023	0.320	0.394
	≥2	−4.25 (−6.84, −1.65)	1.322	0.001	
Female < 75 (1,836)	1	−0.21 (−2.10, 1.68)	0.963	0.828	0.420
	≥2	0.15 (−1.57, 1.87)	0.874	0.863	

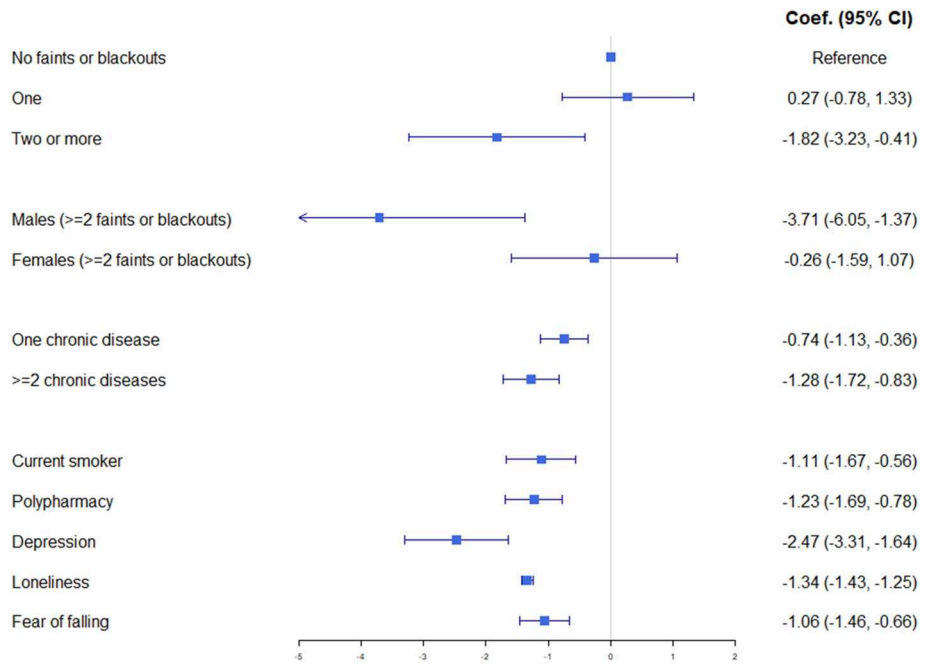

FIGURE 2 | Graphical summary of weighted linear regression Model 3R with coefficient and 95% confidence intervals including those for selected significant covariates for comparison.

investigations of syncope where appropriate, such as external loop recorders and echocardiograms for those in employment with the aim of minimizing potential delays before diagnoses and treatment thus reducing the length of driving restrictions and economic losses. Provision of group physical therapy, like cardiac rehabilitation post myocardial infarction, or other similar interventions such as psychological counseling, where appropriate, with the aim of reducing FoF and its impact on QoL may also be advisable.

LIMITATIONS

While TILDA is a longitudinal study the data used here was cross-sectional, so causality cannot be inferred.

The self-report nature of most measures may have introduced a degree of error or bias. While self-reported doctor diagnoses have been shown to be reliable (27) this may not apply to participants' reporting of self-made "diagnoses" relating to falls, blackouts or faints when having not attended a doctor.

Missing information was a limitation − 4,946 participants completed the CASP-12, 76.6% of the original sample size of 6,454, with fewer again (4,843) being included for Models 2 and 3 once those missing data for the remaining covariates of interest were excluded.

While anyone reporting an unexplained fall, blackout, or faint was defined as having had syncope, its subtype is unknown (vasovagal, cardiogenic, pseudo-syncope etc.) and the outcome may be different for different classes of syncope. It has been shown that those with an underlying neurological or psychogenic cause of syncope have a poorer QoL (34) and it is possible that participants with a pre-existing poor QoL somatise with consequential psychogenic syncope.

The CAPI had no question relating to history of unexplained falls beyond the last year or since last interview. Therefore, while those reporting recent syncope were classified as anyone with a positive answer to recent unexplained fall, blackout or faint, those reporting previous syncope were classified as those with a positive answer to history of blackout or faint. They are therefore not directly comparable.

Similarly, while the CAPI quantified the burden of recent syncopal events by asking about the number of recent faints or blackouts, the burden of unexplained falls was not quantified individually, instead being quantified within the number of falls as a whole. The recurrent syncope predictor variable in our models includes only those reporting a blackout or faint in the past year and not those with unexplained falls, so this would need to be considered when interpreting results and again it is not directly comparable with our recent syncope analyses.

As mentioned in the discussion, while it was observed that the burden of recent faints or blackouts had a significant relationship with QoL with a marked decrease in QoL for men having 2 or more events in the past year, it should be noted that the absolute numbers in the different categories are low (when stratified by sex and age having excluded those with unexplained falls and participants missing data on all covariates of interest). A total of 44 participants reported ≥2 syncopal episodes in the past year, 21 male (17 < 75), 23 female (15 < 75), therefore particularly the analyses for those ≥75 should be interpreted with caution.

The mean age of this group at baseline was 64.8 which is approaching the age when prevalence of syncope begins to rise sharply peaking around 70 years of age (45). Therefore, it would be valuable to follow up this cohort of participants in further waves and evaluate their QoL as syncope becomes more prevalent.

DATA AVAILABILITY STATEMENT

TILDA datasets are in a publicly accessible repository: The datasets analyzed for this study can be found at http://www.ucd.ie/issda/.

ETHICS STATEMENT

Ethical approval was obtained from the Faculty of Health Science Research Ethics Committee at Trinity College Dublin. Informed written consent was obtained from all participants. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RK is the Principal Investigator and project coordinator of the TILDA study. KM, MW, and RK designed the study and analyzed the data. KM wrote the initial draft of the manuscript. MW, RR, and RK critically revised the manuscript. All authors had responsibility for accuracy of the final content and read and approved the final manuscript.

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REVIEW
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Pacing for Patients Suffering From Cardioinhibitory Vasovagal Syncope Using the Closed-Loop System

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One in three vasovagal syncope (VVS) patients has syncopal recurrence after diagnosis, despite the standard recommendations for the avoidance of a recurrence, and one in five patients has more than one syncopal recurrence in the medium term. Given the high prevalence of VVS, there is a large population that continues to need effective treatment. There are numerous studies that use the implantable loop recorder (ILR) to document a cardioinhibitory response during VVS, with one study, ISSUE-3, demonstrating the efficacy of pacing using the rate-drop-response algorithm to trigger pacing and prevent syncopal recurrence in this population. There are more uncertainties in the studies that have used head-up tilt test (HUT) to select the population for pacing. We have recently performed the SPAIN randomized, controlled clinical trial using HUT to select the patients for pacing. The conclusion of the study was that, with the closed-loop system to introduce pacing, there was a significant reduction in the burden of syncope and a seven-fold increase in the time to first recurrence of syncope, which was greater than in the ISSUE-3 study. Since the completion of the SPAIN trial and its inclusion in the European guidelines, in our daily clinical practice, the use of this therapy is still recommended with caution in the context of the available literature, but it has increased our confidence in so doing. One in five patients with VVS needs treatment because of a high syncopal load. If an ILR is used to select the patients for pacing, the rate-drop-response algorithm can be recommended. In patients who have asystole on HUT, pacing with the closed-loop system has higher success and must now be considered as a tenable option for VVS patients.

Keywords: vasovagal syncope, cardioinhibition, pacing, rate-drop-response, closed-loop system, syncope

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INTRODUCTION

Vasovagal syncope (VVS) is generally considered as a benign disease. Up to 40% of the population experience at least one syncope in a lifetime, with most patients having no more than a single episode (1). Considering the patients who are referred to cardiologists, their number of syncopes is typically three, ranging from one to five episodes, and in those with recurrent episodes,

their quality of life is reduced (2, 3). The most important aspect of the management of these patients is to explain and reassure them about what happens in an episode and to emphasize physical counter-measures and changes in lifestyle (4). Although no clinical studies have compared these recommendations with controls, there is a consensus that they have a beneficial effect in reducing the syncopal recurrences (4). After diagnosis, a third of patients presenting to specialized syncope facilities have recurrences, and one in five patients have more than one recurrence, which implies that 14% require some additional treatment beyond the standard measures (4, 5). The most pressing cases requiring additional treatment are those who have recurrent syncope with short or absent prodromes and those who sustain VVS during high-risk activities.

The studies of pacing in VVS using head-up tilt test (HUT) for patient selection were published in the 1990s and early 2000s, while findings for those guided by implantable loop recorder (ILR) followed. Both sets of studies served to deepen the knowledge of VVS. Cardioinhibition observed during induced and spontaneous VVS prompted the use of pacemakers (PMs) as treatment for these patients. However, the use of HUT to decide on the necessity of pacing is actually in doubt based on published data (6, 7). The number of VVS patients treated by pacing based on HUT findings has fallen substantially. It was frequent in the 1990s, but it has reduced to be exceptional today. A study by our group conducted between 1990 and 2000 reported PM implantation in 58 (17.5%) of 330 patients with recurrent VVS and positive HUT (8). Additionally, in a Swedish study conducted between 2008 and 2016, only 41 (4.4%) of 933 patients with VVS and positive HUT received a pacemaker as the preventive syncope treatment (9).

VVS TREATMENT BASED ON ILR RESULTS

The introduction of ILR as a diagnostic tool opened the doors to the design of studies that, based on ILR findings, selected pacing as a therapy for these patients. The International Study of Syncope of Unknown Etiology (ISSUE) series of studies included patients with syncope and documentation of spontaneous cardioinhibition on ILR during syncope; they were thus selected for pacing. In ISSUE-2, the recurrence per year in 53 patients who received pacing therapy was 10% compared with 41% in patients without specific therapy (80% reduction in relative risk for patients, $p = 0.002$, and 92% for syncope burden, $p = 0.002$) (10). The 1-year recurrence rate in patients with pacemakers was 5%. This study was a registry rather than a randomized, double-blind, controlled trial (10). ISSUE-2 thus prompted ISSUE-3 (11), which was designed as a multicenter, prospective, randomized, and double-blind trial to evaluate the effectiveness of dual-chamber pacing (DDD) with the rate-drop-response algorithm (RDR) to prevent the recurrence of syncope. These patients, aged >40 years, presented documented asystole in the spontaneous ILR recordings of VVS. Seventy-seven patients were randomly assigned to DDD–RDR stimulation or to the group who will have only sensing without pacing. The recurrence of syncope during follow-up occurred in 27 patients, 19 of whom had been assigned to the sensing mode and eight to the active pacing. At 2 years, syncope recurrence occurred in 57% with an implanted device in sensing mode and in 25% with active pacing, representing 57% reduction in recurrence. ISSUE-3 was the first trial with a strong design to show the pacing benefit in VVS. These findings were used to justify the Class IIa indication for pacing in patients >40 years old who suffer from recurrent VVS and have documented asystole on ILR during spontaneous VVS (4, 12).

However, the use of pacing bases its effectiveness on the fact that the patient suffering from VVS has a predominant cardioinhibition since it is not anticipated to be effective in preventing vasodilation and hypotension. In a substudy of ISSUE-3, an asystolic response during HUT predicted asystole during spontaneous syncope as documented by ILR, with a positive predictive value of 86% (13). A meta-analysis including four studies on patients with syncope and documented asystole on ILR showed that the benefit of pacing was less in those patients who had a positive response during HUT although the confidence interval was large (13–53%), preventing a definitive conclusion regarding the benefit of pacing in these patients (14).

Finally, in the SUP-2 study (5, 15), an Italian registry study from 10 syncope units employing a uniform algorithm for the management of older patients (mean age 73 years) with clinically likely reflex syncope, in those patients undergoing HUT, 38 of whom had a dominant cardioinhibition (mean asystole of 22 ± 16 s), the syncopal recurrence after pacing was 3% at 1 year, 17% at 2 years, and 23% at 3 years. These percentages were less than those observed in the untreated patients in the study. The strategy of the SUP-2 study consisted of three progressive steps based on recent guidelines: first, the carotid sinus massage in which, if positive with cardioinhibition, pacing was selected; second, HUT, where if positive likewise with cardioinhibition, pacing was selected; third, ILR, where again if positive with cardioinhibition, pacing was chosen, and if not positive or if cardioinhibition is absent, ILR monitoring was continued (4, 15, 16) (**Figure 1**).

VASOVAGAL SYNCOPE TREATMENT WITH CLOSED-LOOP STIMULATION

It is well-known that the physiological sensors in pacemakers can optimize their function (17–20). The so-called closed-loop system (CLS) sensor tracks the variations in intracardiac (right ventricular) impedance during the systolic phase of the cardiac cycle (21). These changes in intracardiac impedance are closely correlated both with the right and left ventricular dP/dt and right ventricular volume, making this system a detector of both the contractility and the right ventricular volume in the early phase of VVS (22, 23). The first study looking at "neuromediated inotropic pathophysiology" showed a significant increase in heart contractility in nine patients in the minutes preceding the HUT-induced neurally mediated syncope (NMS), also corroborated by what is known concerning the epinephrine rise in this period (24–26). It was suggested that the contractility changes

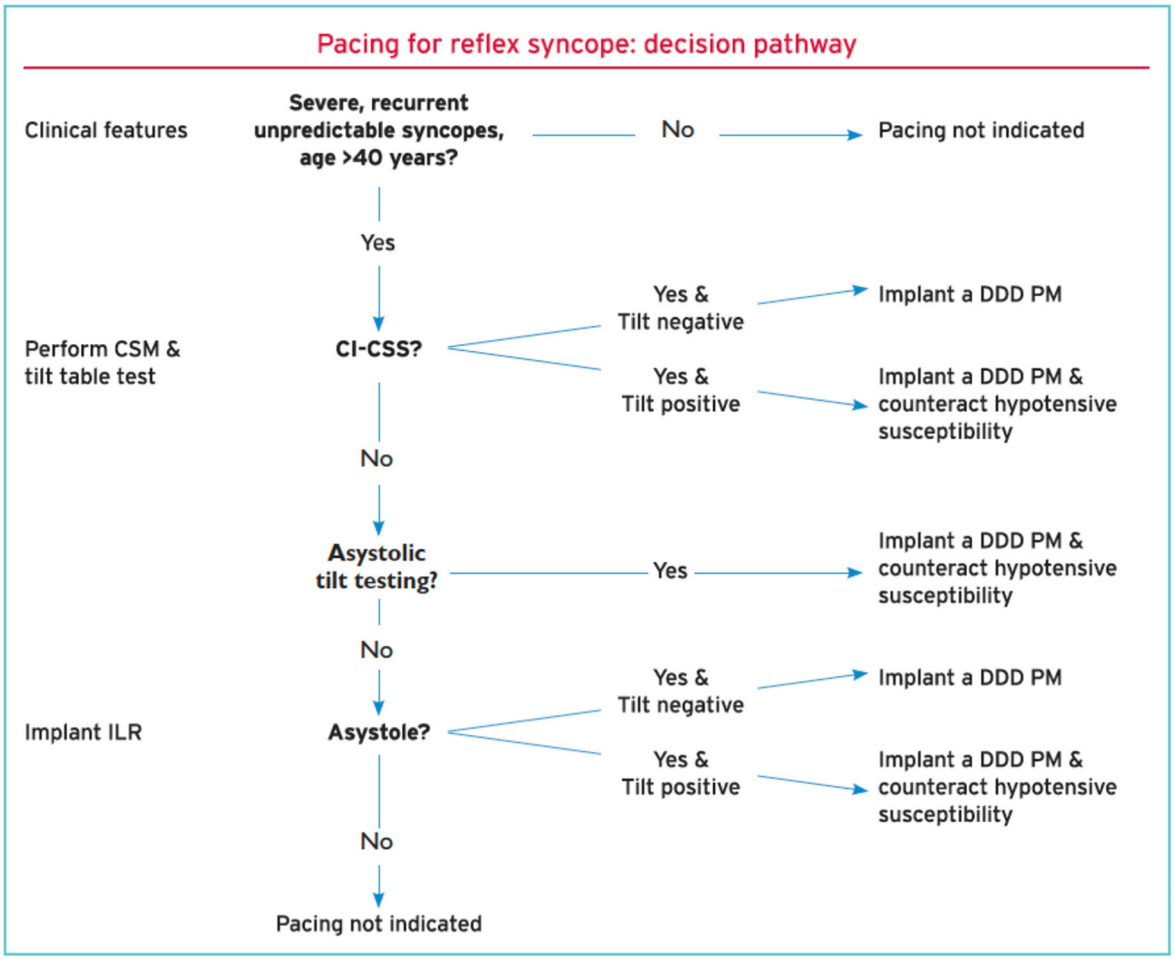

FIGURE 1 | An algorithm decision tree for the selection of patients with severe recurrent vasovagal syncope who are eligible for pacemaker therapy as recommended by the European guidelines (4).

might be used for triggering a rate-adaptive pacemaker when cardiac pacing is indicated to prevent NMS (27). Later, the same authors performed a single-blind, randomized, crossover study comparing DDDR vs. DDI and concluded that, in patients with recurrent VVS, the symptomatic recurrences were less frequent during contractility-driven DDDR pacing than during DDI pacing (28).

The value of DDD stimulation with a CLS sensor in patients suffering from VVS was first described in 1998 (29). The reason for this benefit was assumed to be based on the CLS detecting the increase in contractility in the initial stage of VVS, which could activate the dual-chamber pacing that anticipates the large decrease in sympathetic tone and counteracts it, thus avoiding arterial hypotension, bradycardia, and possibly syncope. This hypothesis was supported by a study in which DDD-CLS significantly reduced the incidence of HUT-induced syncope when compared with DDD triggered by rate-drop-response. Pacing in DDD-CLS began 8 min earlier than in DDD, which may reflect sensing of reduction of the right ventricular volume occurring even before the rise in dp/dt (30). There remains a lack of sufficient data concerning the relative timing of blood pressure fall and epinephrine rise due to the epinephrine measurements being infrequent (24–26). However, it appears likely that the blood pressure fall due to reduced venous return precedes the contractility changes, and the CLS device is able to detect this (30). The early work of Italian researchers in a prospective registry showed encouraging results that heralded the value of this sensing system in VVS (31–33).

Since then, there have been six studies, some prospective, that have included patients with cardioinhibition during HUT, and all have suggested the usefulness of DDD-CLS stimulation to reduce the recurrence of VVS (summarized in **Table 1**). The first of these was the INVASY study, which was multicenter, prospective, randomized, and controlled but single-blind. It compared DDD-CLS stimulation with DDI mode at 30 bpm (essentially ineffective pacing), with the patients crossing over to the other stimulation mode after the second recurrence of syncope. DDD-CLS stimulation was more effective than DDI in preventing the recurrence of syncope during a mean follow-up of 19 months, and no recurrence was observed in the group of

TABLE 1 | Characteristics of studies using the DDD CLS mode in vasovagal syncope after HUT cardioinhibitory response.

References	Methods	Blind	Patients	Follow-up (months)	Recurrences
Occhetta et al. (34)	Multicenter, randomized, controlled, prospective	Single	50	19	DDI 78% DDD-CLS 0%
Kanjwal et al. (35)	Single-center, non-randomized, retrospective		44	9	DDD-RDR 83% DDD-CLS 59%
Bortnik et al. (36)	Single-center, prospective		35	61	DDD-CLS 17%
Palmisano et al. (37)	Single-center, retrospective		41	53	DDD-RDR 38% DDD-CLS 4%
Russo et al. (38)	Single-center, prospective cross-over	Single	50	36	DDD-CLS off 16% DDD-CLS on 2%
Palmisano et al. (30)	Multicenter, prospective randomized	Single	30		HUT-induced syncope DDD 76.7% DDD-CLS 30%

patients assigned to DDD-CLS (34) despite a number of protocol violations being there.

In a retrospective North American study with 35 patients that received 44 devices, 12 received a standard stimulation mode (RDR or simple-rate hysteresis), and 32 were stimulated with a DDD-CLS unit, where the recurrence was less (59 vs. 83%) and the reduction in syncope burden was greater (25 vs. 84%, $p = 0.002$) in those stimulated with a DDD-CLS device (35). Bortnik et al. (36) reported a prospective study including 35 patents with VVS, 83% of whom became asymptomatic when stimulated in the DDD-CLS mode.

A further retrospective, single-center study included 41 patients, 25 of them with DDD-CLS pacemakers and 16 of them with DDD-RDR, and only one patient (4%) in the DDD-CLS group compared with six patients (38%) in the DDD-RDR group had a recurrence of syncope (37).

Another Italian group conducted a prospective, randomized, single-blind, and cross-sectional study with 50 patients, all with DDD-CLS pacemakers randomized to pacemaker-ON vs. pacemaker-OFF for 18 months in each mode, with a total follow-up of 36 months. They showed a reduction in the number of syncopes (2 vs. 15; $p = 0.007$) and presyncopes (5 vs. 30; $p = 0.004$) in patients when they were stimulated with CLS vs. when they were not stimulated (38).

The most recent work has also been multicenter, prospective, randomized, and single-blind, including 30 patients with cardioinhibition during HUT who had been previously implanted with a DDD-CLS pacemaker for VVS. All were subjected to two new HUTs with a week between them: one in DDD-CLS mode and the other in DDD mode. The patients were randomly and blindly assigned to two groups, where in one group the first HUT was performed in DDD-CLS ($n = 15$) and in the other in DDD ($n = 15$). Compared with DDD, DDD-CLS significantly reduced the incidence of HUT-induced syncope (30.0 vs. 76.7%, $p < 0.001$). In patients with syncope, the DDD-CLS stimulation significantly delayed the onset of syncope during HUT (from 20.8 ± 3.9 to 24.8 ± 0.9 min; $p = 0.032$).

SPAIN STUDY

To try to answer all of the previous questions, in 2006 the Syncope Working Group of the Spanish Society of Cardiology designed a randomized, double-blind, cross-over, prospective, and multicenter study that has attempted to verify the value of the DDD-CLS pacemaker against the DDI mode at 30 bpm in patients with recurrent VVS. Fifty-four patients ≥40 years old with cardioinhibition on HUT were included, 46 of whom completed the protocol. The patients were randomized to either DDD-CLS pacing for 12 months followed by sham DDI mode pacing at 30 ppm for 12 months (group A) or sham DDI mode for 12 months followed by DDD-CLS pacing for 12 months (group B). The patients in both arms crossed over after 12 months of follow-up or when a maximum of three syncopal episodes occurred within 1 month. During 22 months of follow-up, there was an overall ≥50% reduction in syncopes in 29 patients. In 72% of patients with DDD-CLS therapy vs. 28% with DDI in group A and in all group B patients, a reduction of ≥50% of syncopes was demonstrated once they crossed over from DDI therapy to DDD-CLS during the second year ($p = 0.0003$). Four (8.7%) patients suffered syncope while stimulated in DDD-CLS vs. 21 (45.65%) patients when they were in DDI (hazard ratio 6.72, odds ratio 0.11; $p < 0.0001$). A Kaplan–Meier analysis showed a significant prolongation of time until the first syncope with DDD-CLS vs. DDI ($p < 0.0001$ in both groups). The study concluded that DDD-CLS reduces the syncope burden and prolongs the time until the first syncope recurrence by seven-fold in patients >40 years with recurrent syncope and cardioinhibition during HUT compared with back-up DDI pacing (39).

In addition to this study, our group has recently published a pre-specified SPAIN subanalysis on the quality-of-life (QoL) data

TABLE 2 | ISSUE-3 and SPAIN trials compared.

	ISSUE-3	SPAIN
Diagnostic tool	Implantable loop recorder	Head-up tilt table
Number of patients included	77	54
Design	Double-blind, randomized, placebo-controlled, and parallel	Double-blind, randomized, placebo-controlled, and cross-over
Pacing mode	DDD-rate drop response	DDD-closed loop stimulation
Follow-up (months)	24	12
Recurrence rate in placebo arm (%)	57	45.7
Recurrence rate in pacing arm (%)	25	8.7
Relative risk reduction (%)	57	89
Absolute risk reduction (%)	Unknown	37
NNT	Unknown	2.7

of the SPAIN study. QoL was assessed using the Short Form-36 (SF-36) health survey before randomization (baseline) and at 12 and 24 months of follow-up. Each SF-36 domain was scored from 0 to 100, with 100 representing the best perception of QoL. The change in QoL relative to the baseline was assessed and compared between the pacing algorithms (DDD-CLS vs. DDI). The mean SF-36 scores were significantly increased from baseline on DDD-CLS pacing across eight domains with the exception of "bodily pain." QoL was significantly improved with DDD-CLS in "general health," "vitality," and "emotional role" (change in score of 9.6, 9.8, and 15.2, respectively; $p < 0.05$). Comparing the two pacing algorithms, the mean SF-36 scores were higher in the DDD-CLS group compared with the DDI group for the eight domains, and the differences in "physical role," "bodily pain," and "vitality" were statistically significant.

The analysis of the component summary scores indicated that DDD-CLS positively impacted both the mental and physical components, with significant differences in the physical component score, when compared with the DDI group. This pre-specified analysis of QoL in the SPAIN trial clearly demonstrates that the reduction in syncope burden and the extended time to the first syncope recurrence promoted by DDD-CLS translate into a significant and clinically relevant improvement in QoL. The DDD-CLS improved the perception of patients across both mental and physical components (40).

A recent meta-analysis has examined eight controlled trials (including 291 patients) that evaluated the CLS pacemaker therapy in patients with vasovagal syncope and cardioinhibitoion during HUT. They found that the use of CLS pacing was associated with a reduced risk of syncope (OR 0.08; 95% CI 0.03–0.18; I^2 32%) and presyncope (OR 0.34; 95% CI 0.18–0.63; I^2 0.00%). Using proportion meta-analysis, the summary estimate of the proportion of cases that developed syncope during CLS pacing was similar between the RCTs and the prospective studies (3.2 and 3.1%, respectively). This is much lower than the rate of recurrence in the control arm of RCTs at 33.7%. The sensitivity analyses yielded similar results. The authors concluded that, for patients with recurrent cardioinhibitory syncope confirmed by HUT, CLS pacing reduces the recurrent syncope and may improve the quality of life. Based on the findings of this analysis, "it should be considered" for patients who meet these criteria (41).

A new randomized trial called BIOSync is currently underway, which includes patients with VVS and cardioinhibition on HUT and who are randomized to DDD-CLS ON vs. OFF, and is hoped to confirm the findings of SPAIN (42), the results of which are expected in 2021.

ISSUE-3 vs. SPAIN

There are similarities and differences between the ISSUE-3 and SPAIN trials. SPAIN required asystole/severe cardioinhibition on HUT, but in ISSUE-3, HUT was not required. However, 87% of ISSUE-3 patients underwent HUT, allowing the data to be available for subsequent analysis. ISSUE-3 required the finding of asystole on ILR (**Table 2**). A question must be asked concerning why there were differences in the pacemaker efficacy between these two studies. Firstly, ISSUE-3 included patients that had experienced more than or equal to three syncopal episodes in the previous 2 years, while in SPAIN the patients had more than or equal to five episodes and more than or equal to two episodes in the past year; so the SPAIN patients were much more symptomatic.

Secondly, the pacing mode was RDR in ISSUE-3, while SPAIN used the DDD-CLS mode. The recurrence rate in the paced arm was 25% in ISSUE-3, while it was only 8.7% in SPAIN. This suggests that the pacing mode was the main reason for the difference, but a randomized, controlled trial of the two pacing modes would be needed to conclude this point.

Finally, two other differences may have played a part in the different results between the two studies: parallel groups (ISSUE-3) vs. crossover (SPAIN) design and 24 (ISSUE-3) vs. 12 (SPAIN) months of follow-up. Both trial design features are important in a condition such as the vasovagal syncope with its infrequent but cluster-prone behavior. Both are relevant when comparing ISSUE-3 and SPAIN and future trial designs.

NEGATIVE ASPECTS

There are potentially deleterious effects of the permanent stimulation using a rate-responsive mode in a population of relatively young patients. It is well-known that the patients may occasionally experience side effects related to the so-called hyperchronotropism induced by rate-responsive modes. Further, the very long-term use of pacemakers, again in a relatively young population, must be expected to show complications, such as lead failure and infection at generator change, with predictable adverse effects. Finally, the resolution of even severe symptoms is

known to occur without a specific treatment in the medium-term follow-up (43).

CONCLUSIONS

It appears that the dual-chamber pacing with closed-loop system sensing has advantages over the rate-drop-response in the effectiveness of treatment of older (>40 years) patients with severe recurrent vasovagal syncope. The mechanism may be such that the closed-loop system introduces pacing earlier in a vasovagal episode. Evidence is available for the earlier stimulation by CLS in the vasodepression phase of vasovagal syncope, while RDR must wait for the later onset of bradycardia (cardioinhibition). The timing of onset of pacing may be the critical discriminator.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Classical and Delayed Orthostatic Hypotension in Patients With Unexplained Syncope and Severe Orthostatic Intolerance

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Background: Orthostatic hypotension (OH) is a major sign of cardiovascular autonomic failure leading to orthostatic intolerance and syncope. Orthostatic hypotension is traditionally divided into classical OH (cOH) and delayed OH (dOH), but the differences between the two variants are not well-studied. We performed a systematic clinical and neuroendocrine characterization of OH patients in a tertiary syncope unit.

Methods: Among 2,167 consecutive patients (1,316 women, 60.7%; age, 52.6 ± 21.0 years) evaluated for unexplained syncope and severe orthostatic intolerance with standardized cardiovascular autonomic tests including head-up tilt (HUT), we identified those with a definitive diagnosis of cOH and dOH. We analyzed patients' history, clinical characteristics, hemodynamic variables, and plasma levels of epinephrine, norepinephrine, C-terminal-pro-arginine-vasopressin (CT-proAVP), C-terminal-endothelin-1, mid-regional-fragment of pro-atrial-natriuretic-peptide and pro-adrenomedullin in the supine position and at 3-min HUT.

Results: We identified 248 cOH and 336 dOH patients (27% of the entire cohort); 111 cOH and 152 dOH had blood samples collected in the supine position and at 3-min HUT. Compared with dOH, cOH patients were older (68 vs. 60 years, $p < 0.001$), more often male (56.9 vs. 39.6%, $p < 0.001$), had higher systolic blood pressure (141 vs. 137 mmHg, $p = 0.05$), had lower estimated glomerular filtration rate (73 vs. 80 ml/min/1.73 m^2, $p = 0.003$), more often pathologic Valsalva maneuver (86 vs. 49 patients, $p < 0.001$), pacemaker-treated arrhythmia (5 vs. 2%, $p = 0.04$), Parkinson's disease (5 vs. 1%, $p = 0.008$) and reported less palpitations before syncope (16 vs. 29%, $p = 0.001$). Supine and standing levels of CT-proAVP were higher in cOH ($p = 0.022$ and $p < 0.001$, respectively), whereas standing norepinephrine was higher in dOH ($p = 0.001$). After 3-min HUT, increases in epinephrine ($p < 0.001$) and CT-proAVP ($p = 0.001$) were greater in cOH, whereas norepinephrine increased more in dOH ($p = 0.045$).

Conclusions: One-quarter of patients with unexplained syncope and severe orthostatic intolerance present orthostatic hypotension. Classical OH patients are older, more often have supine hypertension, pathologic Valsalva maneuver, Parkinson's disease, pacemaker-treated arrhythmia, and lower glomerular filtration rate. Classical OH is associated with increased vasopressin and epinephrine during HUT, but blunted increase in norepinephrine.

Keywords: orthostatic hypotension, syncope, catecholamines, arginine vasopressin, tilt-table test

INTRODUCTION

Orthostatic hypotension (OH) is the most common manifestation of cardiovascular autonomic dysfunction leading to orthostatic intolerance and syncope. Orthostatic hypotension has multiple etiologies and is traditionally divided into neurogenic or non-neurogenic types. Neurogenic OH is caused by primary neurodegenerative disorders or is secondary to endocrine and autoimmune diseases or renal failure. Non-neurogenic causes include drugs, volume depletion, venous pooling, and heart failure (1).

The prevalence of OH increases with advancing age and comorbidities, such as diabetes, Parkinson's disease or kidney failure, ranging from around 3% in younger individuals, to 35% and more in individuals above 75 years (1). In the majority of patients, OH is asymptomatic, but it can cause symptoms of cerebral hypoperfusion, such as dizziness, fatigue, head and neck pain, nausea, visual disturbance, and ultimately syncope. Symptoms of OH are present when there is a critical reduction of mean arterial pressure and cerebral perfusion (1, 2).

Studies have shown that OH is independently associated with increased mortality, cardiovascular events, incident heart failure, atrial fibrillation, and renal failure (2, 3).

Orthostatic hypotension is clinically classified into classical OH (cOH) and delayed OH (dOH). Classical OH is defined as a sustained decrease in systolic blood pressure (SBP) $\geq$20 mmHg and/or diastolic blood pressure (DBP) $\geq$10 mmHg, within 30 s−3 min of active standing or head-up tilt (HUT). In dOH, the progressive fall in systolic blood pressure occurs after 3 min (1). Delayed OH was first described by Streeten and Anderson (4) but there is limited data on the pathophysiology of dOH and the differences between classical and delayed OH.

Given the scarcity of data, we aimed to perform a systematic clinical, hemodynamic, and neuroendocrine characterization of patients presenting with OH in a tertiary syncope unit.

We asked the following questions: what are the differences in clinical characteristics between cOH and dOH? Do patients with cOH and dOH have detectable neuroendocrine and hemodynamic differences during supine rest and HUT?

MATERIALS AND METHODS

Patient Population

The present study is a part of the previously described SYSTEMA project (5, 6) and was conducted from September 2008 through October 2018. Briefly, patients with unexplained syncope or severe orthostatic intolerance were referred to the tertiary syncope unit at Skåne University Hospital in Malmö from hospitals and outpatient care in southern Sweden.

The definition of unexplained syncope was a transient loss of consciousness without an established diagnosis after the initial evaluation according to the current syncope guidelines (7, 8). During the study period, 2,167 consecutive patients (1,316 women, 60.7%; age, 52.6 $\pm$ 21.0 years) were enrolled. We identified 248 cOH and 336 dOH patients (27% of the entire cohort); of these 111 with cOH and 152 with dOH had blood samples collected both in supine position and at 3 min of HUT as per the initial SYSTEMA study protocol (2008–2014) (6). The flowchart of the study is illustrated in **Figure 1**.

Examination Protocol

Patients were requested to take their regular medications and fast for 2 h before the test but were allowed to drink water. A self-administered questionnaire was used to collect data about past medical history and the characteristics of syncope-related symptoms.

The examination included basic cardiovascular autonomic testing (Valsalva maneuver and active standing) and a standard HUT according to the Italian protocol (9) i.e., a drug-free HUT phase of 20 min or until syncope occurred. If the drug-free phase was negative, 400 μg sublingual nitroglycerin was administered and the patient was monitored for another 15 min. This part of the protocol was reserved for patients with unexplained syncope, in whom the passive phase was inconclusive and standing systolic BP was over 90 mmHg. The hemodynamic response during the drug-potentiated HUT phase was not a part of OH evaluation. Classical OH was defined as a sustained decrease in SBP $\geq$20 mmHg or DBP $\geq$10 mmHg during first 3 min of head-up tilt (HUT), whereas dOH as SBP/DBP fall $\geq$20/10 mmHg occurring first after 3 min of tilt testing (10), excluding the obvious pattern of vasovagal reflex i.e., typical prodrome and bradycardia preceding or coinciding with a significant BP fall. A pathologic Valsalva maneuver was defined as the absence of an increase in heart rate during phase II, absence of late phase

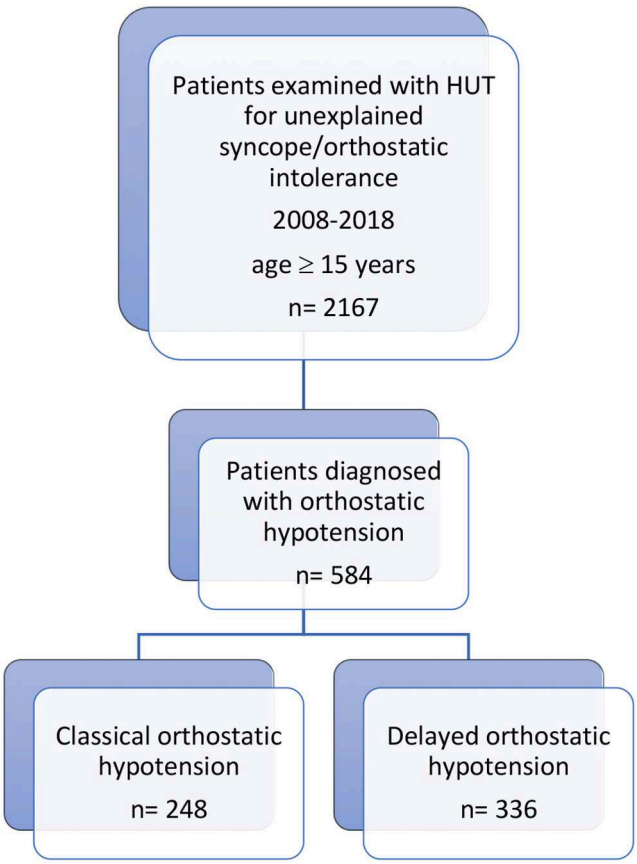

FIGURE 1 | Study design and patient selection process. From the cohort of patients investigated in 2008–2018 for unexplained syncope/orthostatic intolerance with head-up tilt testing (HUT), 2,167 consecutive patients were included. Of these, 584 were diagnosed with orthostatic hypotension, 248 with classical orthostatic hypotension (cOH) and 336 with delayed orthostatic hypotension (dOH). Of these, 111 with cOH and 152 with dOH had blood samples collected both in supine position and after 3 min of HUT and were included in the analysis of neuroendocrine hormones.

II blood pressure recovery and delayed blood pressure recovery without the characteristic overshoot during phase IV (7).

All disputable or difficult to interpret cases were resolved by adjudication involving one syncope and autonomic expert, and the examining physician.

Beat-to-beat blood pressure and electrocardiogram were monitored continuously by a validated non-invasive method (Nexfin monitor; BMEYE, Amsterdam, Netherlands or Finapres Nova, Finapres Medical Systems, PH Enschede, Netherlands) (11, 12).

Blood samples were collected from an intravenous line, both in supine position and at 3 min of HUT. The decision to collect blood at 3 min of HUT was based on previous studies (13) indicating that the central blood volume displacement to the lower body, heart rate, and total peripheral resistance reach a steady state at 3 min of orthostasis, which implies that the initial neuroendocrine responses are then fully developed.

Neuroendocrine Measurements

Measurement of plasma neuroendocrine concentrations has previously been described (6). In brief, we analyzed blood samples in supine position and at 3 min of HUT concentrations of epinephrine, norepinephrine, and non-active peptides C-terminal-pro-arginine-vasopressin (CT-proAVP), C-terminal- endothelin-1 (CT-proET-1), mid-regional-fragment of pro-atrial-natriuretic-peptide (MR-proANP), and mid-regional-fragment of pro-adrenomedullin (MR-proADM). The non-active peptides are generated from the pro-neuroendocrine molecule in ratio 1:1 to the active neuropeptide and are more stable and suitable for analysis compared with their corresponding biologically active substances. High-performance liquid chromatography with fluorescence detection method was used for epinephrine and norepinephrine (14). For measurement of CT-proAVP, CT-proET-1, MR-proANP, and MR-proADM, ThermoScientific BRAHMS assays (BRAHMS GmbH, ThermoFisher Scientific, Neuendorfstrasse 25, 16761 Hennigsdorf, Germany) were used according to the manufacturer's instructions (15, 16).

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

The main characteristics of the study population are presented as mean and standard deviation for normally distributed continuous variables, as median and interquartile range for non-normally distributed variables and percentages for categorical variables. Intergroup differences were analyzed using ANOVA test for non-categorical variables and Pearson's chi-square test for categorical variables. Neuroendocrine concentrations were log-transformed and standardized (expressed per 1 standard deviation). Logistic regression model adjusted for age and gender was applied to test inter-group differences in neuroendocrine concentrations.

Statistical analyses were carried out using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). All tests were two-sided and $p < 0.05$ was considered significant.

RESULTS

The main characteristics of the study population are presented in **Table 1**.

Compared with dOH, patients with cOH were older (68 vs. 60 years, $p < 0.001$), taller (173 vs. 171 cm, $p = 0.004$), more likely men (56.9 vs. 39.6%, $p < 0.001$), had higher supine blood pressure (141 vs. 137 mmHg, $p = 0.05$), lower estimated glomerular filtration rate (73 vs. 80 ml/min/1.73 m^2, $p = 0.003$), reported less palpitations before syncope (16 vs. 29%, $p = 0.001$), more often had a pathologic Valsalva maneuver (86 vs. 49 patients, $p < 0.001$), a pacemaker (5 vs. 2%, $p = 0.04$), and Parkinson's disease (5 vs. 1%, $p = 0.008$). Patients with cOH had a more pronounced fall in systolic (88 vs. 99 mmHg, $p < 0.001$) and diastolic (56 vs. 63 mmHg, $p < 0.001$) blood pressure during HUT than those with dOH. **Figure 2** displays typical hemodynamic responses during HUT in the two forms of OH.

TABLE 1 | Clinical characteristics of the study population.

Characteristic	All *n* = 584	Classical OH *n* = 248	Delayed OH *n* = 336	*P*-value
Age, years	64 ± 18	68 ± 14	60 ± 20	**<0.001**
Sex (male), *n* (%)	274 (47)	141 (57)	133 (40)	**<0.001**
Height (cm)	172 ± 10	173 ± 10	171 ± 10	**0.004**
Body mass index (kg/m^2)	25 ± 4	25 ± 4	26 ± 5	0.121
Palpitations before syncope, *n* (%)	110 (23)	31 (16)	79 (29)	**0.001**
History of orthostatic dizziness, *n* (%)	439 (76)	183 (74)	256 (77)	0.439
History of syncope, *n* (%)	527 (90)	220 (89)	307 (91)	0.270
Nr of previous syncope episodes (median, interquartile range)	4 (2–10)	4 (2–8)	4 (2–10)	0.160
History of falls, *n* (%)	319 (55)	137 (56)	182 (55)	0.502
Atrial fibrillation, *n* (%)	76 (13)	29 (12)	47 (14)	0.437
History of coronary artery disease, *n* (%)	62 (11)	28 (11)	34 (10)	0.649
Pacemaker therapy, *n* (%)	20 (3)	13 (5)	7 (2)	**0.04**
Parkinsons disease, *n* (%)	16 (3)	12 (5)	4 (1)	**0.008**
Supine systolic blood pressure, mmHg	139 ± 24	141 ± 26	137 ± 22	0.051
Supine diastolic blood pressure, mmHg	74 ± 12	75 ± 12	73 ± 11	0.155
Supine heart rate, beats/min	70 ± 12	69 ± 12	70 ± 12	0.272
Lowest systolic blood pressure during HUT, mmHg	95 ± 22	88 ± 22	99 ± 20	**<0.001**
Lowest diastolic blood pressure during HUT, mmHg	60 ± 13	56 ± 13	63 ± 12	**<0.001**
Max heart rate during HUT (beats/min)	83 ± 16	82 ± 17	85 ± 16	0.069
Pathologic Valsalva maneuver, *n* (%)	135 (29)	86 (43)	49 (18)	**<0.001**
Estimated GFR (mL/min/1.73 m^2)	77 ± 22	73 ± 21	80 ± 22	**0.003**
Reduced ejection fraction, *n* (%)	119 (21)	42 (18)	77 (24)	0.068
Diabetes, *n* (%)	59 (10)	25 (10)	34 (10)	0.969
Use of betablockers, *n* (%)	153 (26)	62 (25)	91 (27)	0.519
Use of calcium channel blockers, n (%)	96 (17)	38 (15)	58 (18)	0.508
Use of RAAS-antagonists *n* (%)	95 (16)	44 (18)	51 (15)	0.450
Use of loop-diuretics, *n* (%)	63 (11)	32 (13)	31 (9)	0.171
Use of alphablockers, *n* (%)	27 (5)	16 (6)	11 (3)	0.075

OH, orthostatic hypotension; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system. Data are presented as mean ± SD unless indicated otherwise. Values in bold are significant (p > 005).

Clinical characteristics that did not differ between the cOH and dOH groups were history of falls, history of previous syncope and number of previous syncope episodes, diagnosis of atrial fibrillation, supine heart rate, maximum heart rate during HUT, occurrence of reduced ejection fraction (below 55%), coronary artery disease, and medications (betablockers, calcium channel blockers, RAAS-antagonists, loop-diuretics, alpha-blockers).

The plasma levels of neuroendocrine markers are shown in **Table 2**. Supine and 3-min HUT levels of CT-proAVP were higher in cOH compared with dOH ($p = 0.022$ and $p < 0.001$). In contrast, at 3 min of HUT, norepinephrine was higher in dOH ($p = 0.001$). Further, Δepinephrine ($p < 0.001$) and ΔCT-proAVP ($p = 0.001$) (i.e., 3 min of HUT minus supine values) were higher in cOH, whereas Δnorepinephrine was higher in dOH ($p = 0.045$) compared with cOH.

The plasma levels of CT-proET-1, MR-proANP, and MR-proADM were not different between the cOH and dOH groups.

DISCUSSION

This study examined the differences in clinical characteristics, hemodynamic variables, and plasma concentrations of neuroendocrine hormones in patients with classical and delayed orthostatic hypotension. We found that patients with classical OH were older, more likely men, more often hypertensive, treated with pacemaker, had lower kidney function and more often pathologic Valsalva test, Parkinson's disease, and reported less palpitations before syncope. Compared with delayed OH, classical OH was associated with increased levels of vasopressin and epinephrine during HUT, whereas norepinephrine increased more during HUT in delayed OH.

Moving from supine to standing position causes an immediate redistribution of up to 1 l of blood to the capacitance vessels of the legs and splanchnic/pelvic circulation. This prompts a decrease in venous return and cardiac output, which, in the healthy individual, is counteracted by the baroreflex, causing increased sympathetic outflow and vagal inhibition. Heart rate, cardiac contractility, and peripheral vascular resistance increase to maintain blood pressure. During prolonged standing, transcapillary fluid filtration into the interstitial space can reduce plasma volume up to 20% (17). Neuroendocrine responses, primarily mediated by the renin-angiotensin-aldosterone system cause volume expansion and become important during prolonged orthostatic stress. Vasopressin-secretion by the hypothalamus has a smaller role in maintaining blood pressure in the normovolemic state in healthy individuals (18).

In patients with autonomic dysfunction, norepinephrine release from postganglionic sympathetic nerves is reduced or insufficient, causing inadequate peripheral arteriolar vasoconstriction and subsequent hypotension during orthostasis (17). This process may be associated with compensatory mechanisms governed by different neuroendocrine systems.

Neuroendocrine Changes and Orthostatic Hypotension

Vasopressin

Vasopressin is released in response to hyperosmolarity and reduced arterial pressure, leading to renal water reabsorption and vasoconstriction (19). Vasopressin acts as a backup system to the renin-angiotensin and sympathetic systems, and is not critical for hemodynamic stability as long as the former are intact (19). Blockade of V1 receptors caused a larger fall in blood pressure in patients with diabetic autonomic dysfunction compared with

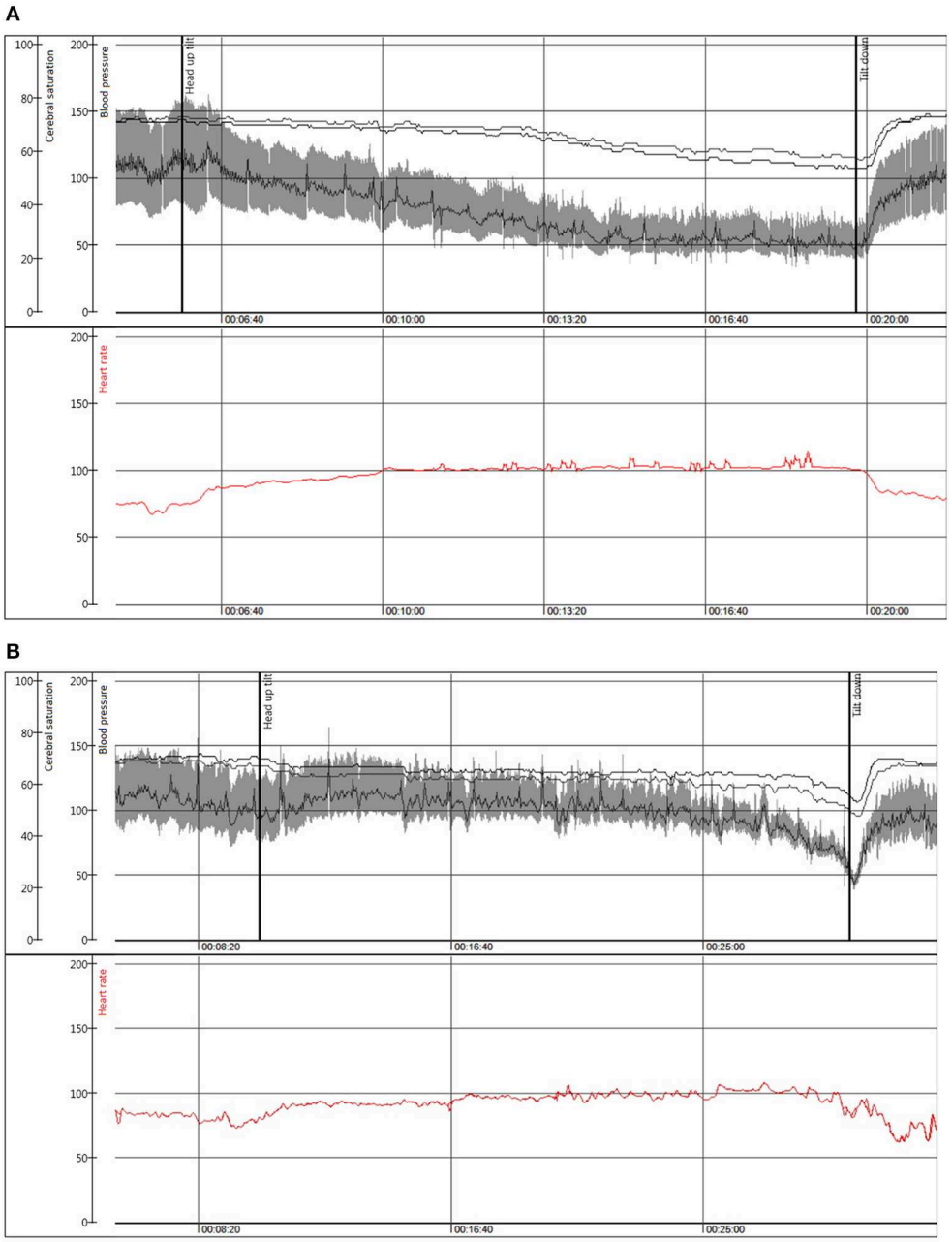

FIGURE 2 | Beat to beat blood pressure (mmHg), and cerebral oxygen saturation (%) in the upper panel with heart rate (beats/min) depicted in red in the lower panel during head-up tilt in a representative patient with **(A)** classical orthostatic hypotension, woman, 50 years; **(B)** delayed orthostatic hypotension leading to an onset of vasovagal reflex and syncope, man, 80 years.

controls, showing that these patients are more dependent on vasopressin to maintain blood pressure (20).

Vasopressin levels increased 3-fold in healthy subjects during HUT (21, 22) and a similar increase was seen in patients with autonomic failure and falling blood pressure on HUT, but the increase was not sufficient compared with the magnitude of blood pressure fall (21). Studies have shown that the subnormal vasopressin response in patients with autonomic dysfunction is caused by a defect in the baroreflex arc (23, 24).

Our findings are consistent with previous studies. Patients with cOH had more pronounced falls in systolic and diastolic blood pressure than those with dOH. The supine and standing levels of CT-proAVP were significantly higher in cOH compared to dOH. The fall in blood pressure and right atrium filling stimulates vasopressin secretion. Vasopressin was measured

TABLE 2 | Plasma concentrations of assessed neuroendocrine hormones.

Hormone	All $n = 263$	Classical OH $n = 111$	Delayed OH $n = 152$	*P*-value*
Epinephrine (0) (nmol/L)	0.15 (0.09–0.24)	0.14 (0.09–0.21)	0.15 (0.09–0.24)	0.954
Epinephrine (3) (nmol/L)	0.22 (0.08–0.35)	0.22 (0.13–0.44)	0.22 (0.13–0.32)	0.128
Norepinephrine (0) (nmol/L)	2.30 (1.60–3.10)	2.20 (1.50–3.10)	2.40 (1.70–3.20)	0.263
Norepinephrine (3) (nmol/L)	3.40 (1.80–4.60)	3.10 (1.90–4.70)	3.60 (2.63–4.56)	**0.001**
CT-proAVP (0) (pmol/L)	8.18 (4.53–14.4)	9.42 (6.01–16.3)	7.30 (3.94–12.3)	**0.022**
CT-proAVP (3) (pmol/L)	8.38 (4.57–16.1)	10.5 (6.24–22.5)	6.55 (3.77–12.4)	**<0.001**
CT-proET-1 (0) (pmol/L)	61.8 (50.8–74.2)	63.0 (52.2–74.6)	61.1 (49.9–70.8)	0.406
CT-proET-1 (3) (pmol/L)	56.0 (43.2–71.1)	58.8 (44.5–72.5)	55.0 (41.9–67.4)	0.908
MR-proANP (0) (pmol/L)	109 (65.9–161)	109 (67.3–150)	109 (61.3–168)	0.940
MR-proANP (3) (pmol/L)	109 (61.6–152)	111 (64.6–150)	108 (58.3–173)	0.758
MR-proADM (0) (pmol/L)	0.68 (0.50–0.91)	0.74 (0.50–1.06)	0.63 (0.50–0.85)	0.132
MR-proADM (3) (pmol/L)	0.59 (0.42–0.83)	0.64 (0.44–1.00)	0.56 (0.40–0.81)	0.233

The concentrations of neuroendocrine hormones given as median (interquartile range) for supine (0) and 3 min HUT (3). CT-proAVP indicates C-terminal-pro-arginine-vasopressin, CT-proET, C-terminal-endothelin-1, MR-proANP, mid-regional-fragment of pro-atrial-natriuretic-peptide and MR-proADM mid-regional-fragment of pro-adrenomedullin.
**P-values for log-transformed concentrations.*
Values in bold are significant (p > 005).

after 3 min of HUT, when the hemodynamic impairment is fully developed in cOH but not in dOH. Consequently, vasopressin response after 3 min of standing was greater in cOH.

Epinephrine

In healthy volunteers, epinephrine initially increased 3-fold during standing, and normalized after prolonged orthostasis (22). In a study comparing older OH males with controls, no difference was seen in epinephrine concentrations at the end of HUT (25).

We found that the change in epinephrine concentration at 3 min of HUT was more pronounced in cOH compared with dOH. A variety of stressors induce higher plasma epinephrine increases than those in norepinephrine, indicating a greater adrenomedullary than noradrenergic system response (26). Since blood pressure fall during HUT was higher for cOH than dOH, it is reasonable to assume that a steeper orthostatic blood pressure fall would evoke a more significant epinephrine response at 3 min of HUT. Moreover, the compensatory release of epinephrine through adrenomedullary mechanisms might be more pronounced in the presence of impaired function of the autonomic nervous system due to neurodegenerative processes affecting the release of norepinephrine from neural endings (27).

Norepinephrine

In healthy subjects, plasma norepinephrine concentration doubles within 5 min of standing (22). Orthostatic hypotension is associated with impaired norepinephrine release (27, 28) whereas in dOH norepinephrine levels are normal or increased (4).

Consistent with previous studies, we found that orthostatic norepinephrine concentration was higher in dOH and that it increased more on HUT compared with cOH. These data would indicate dOH as a milder form of sympathetic autonomic dysfunction compared with cOH.

Clinical Features of Orthostatic Hypotension

Consistent with previous reports, we found that patients with dOH were younger than those with cOH, supporting the idea that dOH might be an early presentation of autonomic dysfunction, preceding cOH (29). Another finding that supports this is that cOH patients more often had a pathologic Valsalva maneuver than dOH patients. It has been reported that cOH is associated with more severe autonomic dysfunction compared with dOH (30). Conditions that that are associated with autonomic dysfunction and OH, such as Parkinson's disease (31, 32) and reduced renal function (33, 34), were also more common in the cOH group. Surprisingly, diabetes, which is a common cause of secondary OH, was equally prevalent in the two groups.

Orthostatic hypotension is frequently associated with supine hypertension (35, 36). Goldstein found that OH was associated with supine hypertension in patients with primary neurodegenerative diseases. These patients also had low plasma concentrations of norepinephrine, indicating that the supine hypertension in OH is caused by other mechanisms than the hyperactivation of the sympathetic nervous system (35). The observation that cOH patients more frequently have supine hypertension implies that cOH is associated with more severe abnormalities of both autonomic and neuroendocrine control mechanisms.

Studies have shown that cOH is associated with increased risk of cardiovascular disease (3, 37), which can explain the higher incidence of pacemaker treatment in cOH patients. Autonomic dysfunction with sympathetic denervation of the heart that caused sick sinus syndrome has been reported (38). Cardiac denervation could be a possible explanation for the observation that cOH patients reported less palpitations before syncope.

Delayed OH was first described by Streeten and Anderson (4) and has been viewed as a benign condition, but more recent studies indicate otherwise. Gibbons and Freeman followed individuals diagnosed with cOH and dOH for 10 years and discovered that 54% of patients with dOH eventually developed cOH, and 31% developed alpha-synucleopathies (39). Mortality in dOH was increased compared with controls, but not as high as in cOH. Such long-term data indicate dOH not to be a benign non-progressive condition, but in the majority of cases, is an early presentation of cOH.

Better characterization of classical and delayed orthostatic hypotension can have implications for diagnosis, prevention, and treatment of these conditions. In clinical practice, delayed

orthostatic hypotension is often overlooked although there are similar clinical consequences in both variants such as syncope as indicated by this study. Whether delayed and classical orthostatic hypotension represent a sequential worsening of the same disease, or constitute two different entities of cardiovascular autonomic dysfunction with different therapeutic approaches, warrants further research.

STUDY LIMITATIONS

There are several important limitations that should be acknowledged. One is that this a single-center study and another is that there is no healthy control group. Vasoactive medications were not withdrawn before HUT as the tests were performed to detect syncope etiology in the real-life scenario, meaning without discontinuing the regular medication. The amount of water ingested prior to HUT, which may have potentially introduced a bias in the measured neurohormone levels, was not recorded. Neuroendocrine hormones were only measured in supine position and at 3 min of HUT. Other changes in the levels of these hormones might have occurred after prolonged orthostasis. Other neuroendocrine hormones that were not included in this study may have a significant role in OH pathophysiology. Finally, plasma norepinephrine concentration represents the spillover from synapses. The concentration is dependent on both the release into plasma and removal by reuptake into nerve terminals and might not accurately reflect the rate of sympathetic nerve traffic.

CONCLUSION

Compared with delayed orthostatic hypotension, patients with the classical form are older, more often have supine hypertension, autonomic dysfunction, Parkinson's disease, pacemaker-treated arrhythmia, and lower glomerular filtration rate. Classical orthostatic hypotension is associated with increased levels of vasopressin and epinephrine during head-up tilt, but blunted increase in circulating norepinephrine. These findings suggest that classical orthostatic hypotension, compared with the delayed form, is associated with more severe abnormalities of both autonomic and neuroendocrine control mechanisms and can be regarded as a more advanced and severe condition.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Ethical Review Board in Lund (82/2008). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All the coauthors conceived and designed the study. PT, AF, FR, and VH reviewed the literature. RS gave a critical input for the analyses. PT, AF, and VH collected the data for the study. PT, AF, and FR performed the statistical analyses. PT and AF drafted the manuscript. FR, VH, and RS performed the critical review of the manuscript. All coauthors accepted the final version. AF provided the founding for the study.

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REVIEW
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Timing of Circulatory and Neurological Events in Syncope

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Syncope usually lasts less than a minute, in which short time arterial blood pressure temporarily falls enough to decrease brain perfusion so much that loss of consciousness ensues. Blood pressure decreases quickest when the heart suddenly stops pumping, which happens in arrhythmia and in severe cardioinhibitory reflex syncope. Loss of consciousness starts about 8 s after the last heart beat and circulatory standstill occurs after 10–15 s. A much slower blood pressure decrease can occur in syncope due to orthostatic hypotension Standing blood pressure can then stabilize at low values often causing more subtle signs (i.e., inability to act) but often not low enough to cause loss of consciousness. Cerebral autoregulation attempts to keep cerebral blood flow constant when blood pressure decreases. In reflex syncope both the quick blood pressure decrease and its low absolute value mean that cerebral autoregulation cannot prevent syncope. It has more protective value in orthostatic hypotension. Neurological signs are related to the severity and timing of cerebral hypoperfusion. Several unanswered pathophysiological questions with possible clinical implications are identified.

Keywords: syncope, tilt table test, vasovagal syncope, transient loss of consciousness, pathophysiology

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INTRODUCTION

Two key features of syncope are that is a form of transient loss of consciousness and that it is due to cerebral hypoperfusion (1, 2). The cerebral hypoperfusion in syncope is global in nature, so it may affect all brain functions, though not necessarily always or all at once. This global cerebral hypoperfusion stems from a failure of the systemic circulation to keep arterial blood pressure high enough to perfuse the brain adequately.

This paper provides an overview of the timing of cardiovascular and neurological events in syncope. The discussion of reflex syncope will address some general aspects that apply to all forms of syncope. These will not be repeated in the discussion of cardiac syncope and syncope due to orthostatic hypotension. Some unanswered questions will be identified.

REFLEX SYNCOPE

The Reflex Pathway

Transient loss of consciousness (TLOC) in syncope is the result of a temporary low blood pressure. As arterial blood pressure (BP) is the product of cardiac output and total peripheral resistance (TPR), and as cardiac output is the product of stroke volume (SV) and heart rate (HR), BP is the product of all three: $BP = SV \cdot HR \cdot TPR$. This simple equation means that a decrease of any one of these three parameters can in principle cause syncope, provided the decrease is severe enough, lasts long enough and is not compensated for sufficiently by an increase of any of the other parameters.

The terms "reflex syncope" and its synonym "neurally mediated syncope" indicate that syncope is evoked by a trigger setting afferent nerve impulses in motion. However, reflex syncope does not only involve the nervous system. Hormonal factors are likely to play a role as well. There are obvious similarities between neuronal reflex and endocrinological mechanisms of regulation: both involve the detection of a disturbance and a corrective response. The sections below focus primarily on autonomic nervous system responses, and provide a short overview of humoral influences.

The array of possible triggers in reflex syncope comprises extremely diverse elements; examples are thinking unpleasant thoughts, eating a heavy meal, stretching, stopping with running, coughing, being stuck with a needle, or simply standing still. It is hard to understand why such diverse impulses would all evoke a very similar response, and yet they do. Clinical experience suggests reflex syncope is more likely to occur when several risk factors occur at the same time. It seems likely that a low circulating volume or an already low blood pressure feature in this set of common factors, but it is unknown whether any one factor is obligatory in triggering reflex syncope.

The neuronal efferent responses in reflex syncope can be identified with more confidence because their specific efferent circulatory effects are also involved in normal baroreceptor blood pressure control. The nuclei transmitting the efferent impulses are the dorsal vagal nucleus and the nucleus tractus solitarii. These control two effector mechanisms that are normally involved in blood pressure control. In reflex syncope these two mechanisms can both lower blood pressure: they are the cardioinhibitory (CI) and vasodepressive (VD) pathways.

Cardioinhibition

CI concerns an increase of vagal stimulation of the heart, resulting in a decrease of HR. The severity of CI ranges from a slight HR decrease to long asystole. Asystole during tilt table testing (TTT) may last about 1 min, but that is not the typical duration. Asystole, defined as a pause of at least 3 s. duration, occurred in 21 of 69 TTT cases (30.4%) selected for the occurrence of full syncope; the mean duration of asystole was 9.1 ± 6.4 s (3). The duration and asystole rate in TTT depend on test characteristics such as the duration of tilting back (4). Note that the inhibitory effects of CI not only concern the sinoatrial (SA) node affecting HR, but also the atrioventricular (AV) node: in tilt-induced VVS, the occurrence of AV escape beats suggests that the AV node is less inhibited than the SA node (5). In contrast, a complete AV-block, also occurring in VVS, suggests stronger inhibition of the AV than the SA node. These observations in turn strongly suggest that the common presentation of asystole without any electrical heart activity is due to complete inhibition of both nodes.

A decrease of HR can lead to a quick decrease of BP, as is evident from the sudden cardiac standstill that occurs in complete AV-block. BP may then be halved in just 3 s. after the last beat; after about 10–15 s. of persistent asystole, BP becomes stable at 10–20 mmHg (6). At this extremely low BP, there is no longer a pressure difference between the aorta and right ventricle, so systemic blood flow stops altogether. The available evidence suggests that loss of consciousness starts about 8 s. after the last heart beat (6, 7). Patients are typically not aware of anything amiss for the first 3 of 4 s. of that time; those who do sense something amiss have only a few s. to lie down before consciousness is lost and they fall.

Vasodepression

Vasodepression (VD) can be interpreted as any mechanism in reflex syncope apart from CI that causes blood pressure to decrease. As explained below, a decrease in venous return is one such cause. The other is a decrease of sympathetic vasoconstriction of arterioles, and some authors restrict VD to this mechanism. This decrease allows arterioles to dilate, resulting in a decrease of Total Peripheral Resistance (TPR). The shortest time in which sympathetic effects can affect BP through this mechanism is probably a few heart beats, whereas vagal effects on HR can operate within one heartbeat.

CI and VD in Reflex Syncope

In reflex syncope, VD and CI may occur together to varying degrees, making it difficult to determine how much either contributes to the decrease of BP. Even so, it is safe assumed that asystole, if it lasts long enough, will always cause the circulation to come to a halt and cause syncope; this will occur irrespective of any additional VD.

The nature and severity of CI differs between types of reflex syncope. In swallow syncope asystole due to an AV-block has been frequently described (8), although a selection bias cannot be ruled out. This "reflex AV-block" differs in some respects from an intrinsic AV-block, and is probably due to stronger inhibition of the AV- than the SA-node. Age plays a part too, as asystole in VVS occurs more often in younger patients than in older ones. This is most obvious in the so-called "pallid breath holding spells" of toddlers, in which bradycardia and asystole cause LOC (9). Note that these sadly misnamed spells do not involve abnormal breathing, in contrast to "cyanotic breath holding spells" (10). The "pallid" spells are in fact nothing other than cardioinhibitory VVS (1). In adults with VVS, CI occurs more in younger people than in elderly ones (11–13).

Over the last 15–20 years the concept that reflex syncope involves CI and VD in the shape of reduced arteriolar vasoconstriction had to be revised substantially for VVS. As these studies mostly concerned TTT, the results hold for VVS induced by standing ("orthostatic VVS"). The existence of CI remained undisputable in view of obvious bradycardia and asystole. But a decrease of TPR was not consistently present. In many of these studies Modelflow was used, a technique relying on analysis of the arterial pressure waveform of individual heart beats (14). TPR did not consistently decrease before syncope: although a decrease in TPR was reported in young people (15), an increase was been described too (15). Moreover, TPR could increase before syncope in some patients but not in others (16). Finally, during actual syncope TPR even proved to be increased rather than decreased in adults (17–19) and children (20). The increase of TPR at syncope in these Modelflow studies seems to contradict studies using another technique, "muscle nerve sympathetic activity" (MSNA). The latter technique records

sympathetic vasoconstrictor nerve impulses to blood vessels in leg muscles. Most MSNA studies show a cessation of such impulses during syncope (21, 22), but this does not occur in all cases (23, 24). There is therefore an apparent discrepancy between Modelflow and MSNA techniques. Solving this probably require a simultaneous assessment of clinical characteristics of syncope, Modelflow and MSNA.

Instead of the expected decrease in TPR, a decrease in SV emerged as a consistent finding in the minutes before syncope in tilt-induced VVS (15, 18, 25–28). This low SV was usually attributed to a decrease of venous return, in turn due to venous pooling in the lower limbs, abdomen or pelvis (15, 18, 28–30). The current concept of the circulatory events in the minutes before VVS holds that venous pooling causes a decrease in SV that in turn leads to a slow decrease in BP. CI occurs much later in the course of this process, but not in all cases. CI may well be triggered by the ongoing venous pooling and resulting decrease in blood pressure. Whether VD must be present for CI to occur is uncertain: findings in toddlers suggest that CI can occur without antecedent VD (9).

While it has become clear that venous pooling acts as the starting point of orthostatic VVS, it is not clear why this occurs at some times, and its place in the "reflex" concept is not clear. It may be seen as the triggering process rather than as part of the response. If it is a trigger, then the neuronal reflex may in fact only become active at the moment when CI starts. Whether the reflex then also has a component of a reduction of arteriolar vasoconstriction (low TPR), is not yet clear.

At any rate the question may be asked whether the term "vasodepression" should be limited to a sympathetically mediated release of arteriolar vasoconstriction. A wider concept of VD, comprising both arterial and venous components, has already been proposed (31). The arteriolar component of VD would then appear as a decrease of TPR, while the venous one is reflected in a decrease of SV.

The Timing and Importance of CI in Reflex Syncope

In tilt-induced VVS, BP may start to decrease several minutes before syncope, while CI typically starts later, a minute or less before syncope. As said, CI may be triggered by a secondary abnormality related to the ongoing venous pooling. Putative secondary triggers may be sought in consequences of venous pooling, such as a reduction of blood volume in the thorax, likely to alter the filling, flow or pressure in thoracic blood vessels and in the heart itself. The "empty heart hypothesis" sought to explain the origin of CI in mechanoreceptors in the walls of the near-empty ventricles (32); however, evidence against this theory was later reported (33, 34). Over 20 years later, what triggers CI in tilt-induced VVS still remains unknown.

It should be understood that a lowering of HR at a time when BP is decreasing contradicts the normal behavior of the baroreflex. This reflex normally aims to keep BP constant by manipulating HR as well as TPR. Normally a lowering of BP elicits a rise in HR, and a BP increase will evoke a HR decrease. After CI sets in, BP and HR decrease together, showing that normal baroreflex control is lost (35). Baroreceptor control is in fact already abnormal earlier, when subjects became symptomatic (36).

While tilt-induced VVS appears to be a good model for orthostatic VVS (37), its findings need not apply to other forms of reflex syncope. Which roles the three factors CI, arterial and venous VD, play in emotional VVS and other forms of reflex syncope such as carotid sinus syncope remains to be studied. However, the differing rates of CI between forms of reflex syncope provide evidence that CI can systematically differ in strength between forms. The relative contributions of arterial and venous VD probably also differ: for instance, massage of a carotid artery can result in syncope in such a short time that a slow build-up of venous pooling is very unlikely. Unraveling the relative size and timing of these three effects is likely to have practical consequences, as this may impact pacemaker therapy.

CI and VD can each cause syncope on their own: VD can cause LOC in the absence of any decrease of HR (7), and can even cause EEG flattening (see below) as evidence of profound cerebral hypoperfusion (3). Asystole, if long enough, will cause LOC regardless of any degree of VD. Unfortunately, a consequence of the occurrence of simultaneous VD and CI is that preventing or shortening asystole need not prevent syncope. Given that VD can cause syncope on its own, and that CI and VD often occur together, a pacemaker is then not a failsafe way to prevent syncope.

The relative strength of CI and VD is not the only important factor in determining whether syncope will occur; their time of onset also determines the outcome (31). The timing of CI was studied in cases of tilt-induced syncope, documented with continuous blood pressure monitoring as well as video-EEG, excluding cases with presyncope only or the use of nitroglycerin. In one third of the resulting 35 cases, asystole started either after the onset of LOC or <3 s. before it, short enough to mean that asystole could not have caused LOC that quickly. In those with late asystole, the median BP at the onset of asystole was 32.0 vs. 45.5 mmHg in those with early asystole. This suggested that VD had already lowered BP severely in those with late asystole. These results help explain some of the failures of pacemakers to prevent syncope, and strongly suggest that relying on HR alone is likely to overestimate the importance of asystole as the cause of syncope (31).

Humoral Influences

For a detailed review of the possible roles of neurohormones in VVS we refer to Benditt et al. (38). Here, a very short summary must suffice. The best known alterations of hormones in syncope concern adrenalin and noradrenalin in orthostatic VVS. A general finding during presyncope is that the ratio of adrenalin to noradrenalin rises, due to a large increase of adrenalin and a very limited or no increase of noradrenalin (38). Higher ratios were linked to a shorter time to syncope (39, 40). Adrenalin may have different vasoconstrictor effects on different vascular beds, while noradrenalin is a potent vasoconstrictor. The high adrenalin to noradrenalin ratio may therefore induce vasodilation is some vascular beds. As such, this hormonal shift might contribute to the venous pooling observed in VVS. It

probably does not explain most of the pooling, as adrenergic blockers did not significantly prevent VVS (41).

Various other hormones and circulating agents have been investigated, such as vasopressin and natriuretic peptides. At present it remains to be seen whether hormonal alterations are a response to a circulation that is slipping out of autonomic control, or whether they contribute to it (38).

Cerebral Perfusion in Reflex Syncope

Blood will only flow through an organ if two conditions are met: firstly, there must be a pressure difference between the arteries and veins supplying the organ. Secondly, the vessels in between must be open (42). For flaccid vessels such as veins, the main force that keeps them open is intraluminal pressure. These simple principles suggest that two aspects can critically lower organ perfusion. The first is that veins are more likely to be occluded than arteries, as their intraluminar pressure is lower. Secondly, the phase of the heart beat is important, as intraluminar pressure is lower during diasystole than systole. Blood flow through organs is generally lower during diastole than systole, but the brain is exceptional in having a substantial diastolic flow (43). The combined result of these effects is that perfusion is most at risk in veins and during diastole. Arrayed against intraluminal pressure as the one force opening vessels are two closing forces: vessel wall tension and tissue pressure. In the brain, tissue pressure equals intracranial pressure (**Figure 1**). As venous and intracranial pressures are normally very low, arterial pressure normally is the predominant force in cerebral perfusion.

The comparison of opening with closing forces helps explain brain perfusion in abnormal conditions. A surprising consequence of this is that cerebral flow in imminent brain death resembles that in syncope. In brain death intracranial pressure is so high that the closing forces gain the upper hand. A reflex increase of systemic blood pressure counters the high intracranial pressure in part, but beyond a certain point intracranial pressure will approach blood pressure. Transcranial Doppler (TCD) then shows that diastolic flow velocity decreases before systolic velocity does; this is because the opening forces are at their weakest in diastole. In syncope BP is so low that the closing forces again win, but now because the opening forces are very weak. Again, TCD shows that systolic flow velocity remains nearly normal while diastolic velocity is markedly reduced.

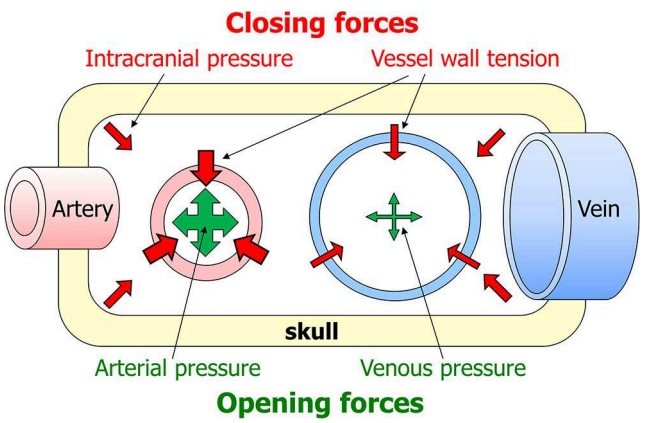

FIGURE 1 | Factors affecting cerebral blood flow. Blood will only flow through the brain if two criteria are met: there must be a pressure difference between the arteries and veins supplying the brain, and the vessels in between must be open. The latter depends on a summation of forces opening and closing the vessels. The main opening force is the pressure in the lumen of the vessel. The two closing forces are intracranial pressure and vessel wall tension.

Cerebral Autoregulation in Reflex Syncope

Cerebral autoregulation describes the ability of brain perfusion to counteract changes in arterial BP: when BP decreases, the forces that close vessels decrease to keep cerebral perfusion constant. Likewise, when BP increases, vessels must constrict to increase the closing forces in parallel with the increase in the opening force. Cerebral autoregulation has a lower limit of regulation of about 60 mmHg. If B falls below this level, cerebral perfusion will decrease in parallel with BP (43). Cerebral autoregulation depends on endothelial, myogenic metabolic and neurogenic factors. It is considered to have static and dynamic components; the latter one acts on a time scale of 2 to 10 s (44).

The time scale of autoregulation is critical for reflex syncope. In case of a sudden asystole, BP will fall below the lower level of autoregulation before that autoregulation has had the time to exert its full effect. When BP decreases slowly, as may happen with pure VD, autoregulation has more time to counteract the effects of decreasing BP. An elegant study found that cerebral resistance to flow was markedly reduced at syncope, meaning that autoregulation indeed opened vessels to compensate for low BP (45), confirmed later (46, 47). These saving attempts are likely to fail in the end, as the decrease of BP in reflex syncope not only continues but typically even accelerates (1, 7, 35). Both an overly quick BP decrease and a very low BP will therefore eventually overcome the compensatory effects of autoregulation.

The Clinical Characteristics of Reflex Syncope

Not all symptoms and signs associated with syncope are due to cerebral hypoperfusion (6). Some symptoms instead reflect the cause of syncope, which can be very useful for diagnosis. For instance, syncope preceded by palpitations and chest pain points strongly to cardiac syncope, while the prodromes of nausea, sweating and facial pallor strongly suggest a reflex mechanism. Although the latter are sometimes described as "autonomic activation," they need not all depend on the autonomic nervous system. Humoral factors may well play a role. Further discussion will be limited to signs of cerebral hypoperfusion.

Signs of Cerebral Hypoperfusion

In tilt-induced VVS, the first observable signs of LOC were motor ones, i.e., a vacant expression or dropping of the head and jaw (3). From that point on, a large number of phenomena could be witnessed (3, 48). A specific order of progression was observed, although the time of onset of signs varied between individuals [(3); **Figure 2**]. The signs proved to be linked to the two EEG patterns of syncope: with mild hypoperfusion the EEG shows slowing ("S") only, whereas more severe hypoperfusion results in a slow-flat-slow pattern ("SFS") (3, 49). The EEG concerns

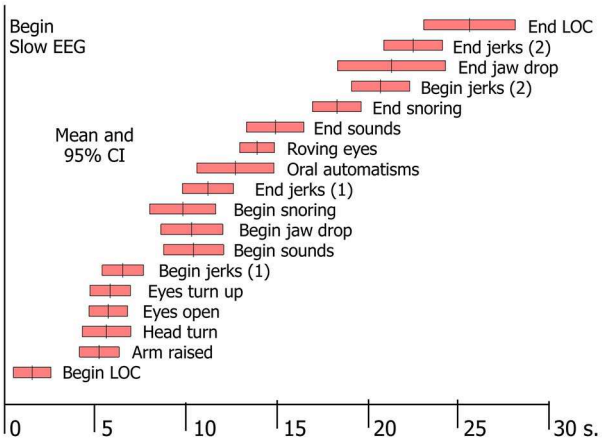

FIGURE 2 | Signs in tilt-induced VVS. Each bar represents the mean value and the 95% confidence intervals for a range of signs, determined by analysis of video-EEG records of 69 cases of tilt-induced VVS [These data conform to Table 2 in Van Dijk et al. (3)].

cortical functions only, so any conclusions regarding basal ganglia or brainstem dysfunction are wholly based on clinical observations. Brainstem signs appeared later than cortical ones, because the brainstem is more resistant to ischaemia. Some signs were strongly associated with EEG flattening, and are therefore likely to concern brainstem activity: making sounds, snoring, upward deviation of the eyes and roving eye movements (3). We later added tonic posturing of the arms to this list (48), either flexion or extension. As more severe cerebral hypoperfusion was associated with lower minimal BP and asystole (3), these signs should increase suspicion of deep hypoperfusion, in turn likely due to CI or arrhythmia.

Some syncopal signs indicate a loss of neuronal function whereas others can only be interpreted as abnormal excessive neuronal activity, probably due to a lack of inhibition. Examples of the latter are mumbling, pointing to cortical disinhibition, and roving eye movements, suggesting brainstem disinhibition (3). Both the cortex and the brainstem appear to go through a sequence in which a loss of some activity and disinhibition happen first, followed by a complete loss of activity [(48), **Figure 3**].

Cardiac Syncope

"Cardiac syncope" is usually taken to comprise both specific cardiac causes as well as disorders of the great vessels, such as pulmonary embolism (1). The two main groups are arrhythmia and structural heart disease. An arrhythmia concerns an abnormal rhythm of heart beats, consisting of irregular beats, too fast beats (tachycardia), and too slow beats (bradycardia). Arrhythmias may be permanent or paroxysmal. Syncope in arrhythmia is usually die to a sudden onset of an arrhythmia, leading to an abrupt decrease of cardiac output and hence of blood pressure. In bradycardic arrhythmia, low HR causes cardiac output to fall. Bradycardia with HR below 30 bpm for 15–30 s. cause syncope more often than tachyarrhythmias. In tachycardia, there is too little time to fill the heart in diastole, so SV falls precipitously, more than is accounted for by the high HR. Arrhythmias often occur without a recognizable trigger, although some occur during exercise (see below). Arrhythmias generally occur regardless of posture. This is important clinically: forms of syncope that primarily depend on non-cardiac BP abnormalities tend to occur more readily while standing, and sitting or lying down helps prevent syncope. But if the circulation stops altogether, syncope occurs regardless of posture. This explains why syncope in the supine position is a danger sign for cardiac syncope.

Structural heart disease concerns heart diseases, other than coronary heart disease, of a mechanical nature, including valvular disease, septum defects, and cardiomyopathy. Structural heart disease impairs the mechanical efficiency of the heart. This becomes most problematic when there is a discrepancy between the demands for a high cardiac output and a failure to deliver it. This helps explains why syncope in relation to exercise is a cardiac danger signs. However, if low cardiac output were the only mechanism, patients might be expected to experience a slow inability to perform physical work. Instead, the typical history is a sudden LOC with little or no warning. The explanation for the latter pattern may be a susceptibility to respond to hypotension with syncope, so the mechanism in structural cardiac syncope may in fact partly be reflex syncope (7, 37, 50).

In many cases cardiac syncope develops very quickly, resulting in the same clinical signs as in sudden complete CI in reflex syncope: patients may only have a few s. to become aware of a problem before they lose consciousness. But the situation may be more complicated when the pumping action is not lost entirely, so cardiac output is decreased but not nil. We have noted patients becoming aware of "weakening" or "dizziness" without LOC, even in cases of ventricular tachycardia.

Sudden Cardiac Death

The term "convulsive syncope" appears to be used to indicate a perceived high severity of syncope, and suggests that it is based on the presence of myoclonic jerks. However, jerking of the arms did not occur significantly more often with severe cerebral hypoperfusion, i.e., EEG flattening, then without such flattening (3), so there is no evidence that the presence of myoclonic jerks in syncope indicates severe hypoperfusion. However, it arrhythmic syncope might last much longer than tilt-induced syncope, and it is possible that extremely long-lasting syncope causes neurological signs that are not observed during TTT. Unfortunately, there appear to be no reports on the clinical signs of such long syncope. Personal communications from physicians familiar with resuscitation in emergency rooms (S Peeters) or the intensive care (J Maas) do not suggest that recovery from long-lasting cardiac standstill is accompanied by dramatic abnormal movements. In contrast, movements then appear to be absent altogether.

There are recent observations of sudden cardiac death, taken from publicly available video records of sports players (51–55).

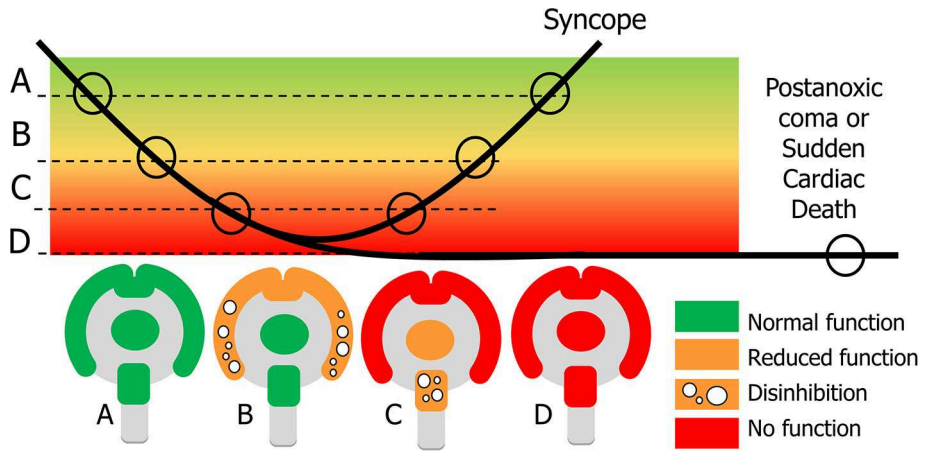

FIGURE 3 | Explanation of signs in syncope and sudden cardiac death. In syncope cerebral perfusion (bold line) temporarily decreases below the normal level **(A)**. Clinical signs depend on the severity of cerebral hypoperfusion. Dysfunction becomes apparent in two ways: normal function can be decreased or completely lost, and new actions may appear, caused by neuronal disinhibition. With mild hypoperfusion this occurs for the cortex, while the basal ganglia and brainstem still function normally: state **(B)** appears at the beginning and end of syncope. With more severe hypoperfusion all cortical function is lost, and new signs concern a decrease of function and disinhibition of the brainstem **(C)**. If recovery takes too long, there will be cerebral damage such as the postanoxic coma; if there is no circulatory recovery at all, the result is sudden cardiac death **(D)**.

One report mentioned that all six observed players had their eyes wide open with a fixed gaze and fixed pupils (55). This led the authors to conclude that a sudden unexpected LOC in an athlete in action and a fixed gaze were key features of sudden cardiac death. As these signs do not differ from those in severe tilt-induced VVS (3), we suggest that they in fact point to severe cerebral ischaemia, regardless of cause. It is the occurrence of these signs in relation to exercise is the tell-tale feature that should raise suspicion of a potentially deadly cause. It is also noteworthy that most observed cases of sudden cardiac death during sports did not occur during intensive action, but shortly after it or during non-intensive action (52, 53). Hence, syncope just after cessation of exercise may not be safely assumed to be due to VVS or orthostatic hypotension.

SYNCOPE DUE TO ORTHOSTATIC HYPOTENSION

There are three types of orthostatic hypotension (OH); the initial, classical and delayed types: iOH, cOH, and dOH (1). Note that the definition of cOH conforms to previous definitions of "OH". The distinction between types of OH became necessary because of the growing recognition of iOH and dOH as separate entities. To avoid using the same term "OH" for the entire group as well as for one of its parts, "OH" now is an umbrella term. The discussion will center on cOH; for iOH and dOH we refer to other sources (56–58).

Definitions and Causes of cOH

The definition of cOH (1, 59) describes a sustained fall of at least 20 mmHg for systolic BP, or of at least 10 mmHg for diastolic BP, within 3 min of standing up or of being tilted upwards. The ESC criteria added an absolute systolic BP of <90 mmHg (1). In daily practice the systolic criterion may have more value than the diastolic one (60). Note that the definition does not state whether or not the BP decrease should be accompanied by symptoms. It merely describes a measurement result that points to a failure to keep BP at the desired level in the upright position.

The causes of cOH are a failure to control arteriolar vasoconstriction, hypovolemia or both. The most common cause of cOH is medication. When the cause concerns structural damage to the sympathetic nervous system, the resulting cOH is often labeled "neurogenic OH" [nOH; (61)]. The damage may be a secondary effect of nerve damage, as in diabetes, amyloidosis, or auto-immune autonomic neuropathy, or it may concern primary autonomic failure, in which the autonomic nervous system suffers primary damage. Primary autonomic failure causing cOH consists of pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease with OH (PD-OH), and Lewy body dementia (LBD).

Pathophysiology of cOH/nOH

The central defect of nOH is an inability to bring about arteriolar vasoconstriction (62). In terms of the factors governing BP, i.e., HR, SV, and TPR, this concerns an inability to increase TPR when needed. To understands its effects the normal events in standing up must be understood: standing up is associated with a fall in SV due to a downwards movement of blood. The normal physiological response to this consists of compensatory increases in HR and TPR. The overall effect is usually an increase in diastolic BP and a slight increase or no change in systolic BP. As said, the prime abnormal event in cOH is a failure of TPR to increase in the upright position, but the situation is more complicated: the failure of arterial vasoconstriction causes a secondary venous pooling, perhaps exacerbated by a failure

to control the volume in the venous vascular beds (62). This venous pooling will become apparent as a low SV, further decreasing BP. The only remaining mechanism to repair BP would be an increase of HR, but damage to the autonomic nervous system may also involve an inability to control HR adequately. If so, neither HR and TPR can rise, while SV is low.

BP measurements in patients with cOH/nOH exhibit two features that point to even more complicated processes: supine hypertension (63) and a BP overshoot when patients lie down or are tilted back after head-up tilt (64). Supine hypertension may be present at every occasion a patient lies down during the day, and may also be present throughout the night. Its existence suggests that attempts to compensate for low upright BP keep on functioning for hours in the supine position. The BP overshoot after head-up tilt also suggests a tendency toward a high pressure, and shows that BP can in fact increase very quickly, gaining as much as 60 mmHg within 1 or 2 min. These observations mean that the pathophysiology of cOH is not straightforward and that the primary defect may appear buried under secondary abnormalities.

One unexpected finding in nOH was a decrease of TPR in the upright position, measured from a baseline supine position (64–67). This upright decrease in TPR, apparently stronger in PAF than in MSA, was unexpected because a change to the upright position should cause TPR to increase, or at least remain the same if it cannot increase. Hence, the decrease of TPR requires an additional explanation. One was that the TPR calculations might be incorrect (68), which would however not explain why there were differences between MSA and PAF (64, 66), even when both groups had similar BP falls (64). Another explanation is that there are additional vasodilatory influences that only become active while standing. In physical exertion and indeed active standing a degree of muscular vasodilation occurs that is normally counteracted by the autonomic system, but not if that is damaged (69). A second possibility concerns hyperventilation; this normally causes peripheral vasodilation, but this is again normally countered by the autonomic nervous system. When that is damaged, the vasodilation of hyperventilation may remain unchecked (70, 71).

Cerebral Autoregulation in OH

Patients with nOH may be fully conscious at remarkably low BP values, suggesting excellent autoregulation (72). Cerebral autoregulation depends on some factors that do and some that do not involve the autonomic nervous system, so the question arises whether autonomic damage can also compromise autoregulation. One approach reasons that good autoregulation would mean that cerebral flow would stay stable even if BP varies; its dysfunction would mean that cerebral blood flow would follow fluctuations in BP. Studies along these lines were conflicting: some pointed to defective autoregulation (65, 73), whereas others showed good function (72, 74–77). Whether the differences depend on the cause of autonomic failure has not been elucidated.

Signs in OH

As said, signs and symptoms in syncope may either be related to the cause of syncope, or to cerebral perfusion. In nOH, examples related to the cause of syncope include the absence of "autonomic activation" as occurs in reflex syncope. Another example is the occurrence of complaints in the standing position, often exacerbated during exercise or just after it (78, 79). Some patients will report an immediate worsening of symptoms on raising the arms above the head, effectively meaning that the arms compete with the brain for blood flow. Another example is "coat hanger pain," i.e., pain in the neck and shoulders in the upright position, relieved quickly by lying down (80). It is attributed to local muscle ischaemia.

The signs of cerebral hypoperfusion in syncope are in principle irrespective of the cause. Whether they are perceived and reported depends critically on the speed of the blood pressure decrease. When this is very fast, patients often report either no awareness of anything amiss at all, or a non-descript yet recognizable feeling for a few seconds. In cOH, the BP decrease can be quick initially, but the rate of decrease typically diminishes and BP tends to become stable at a lower level. If that level is below that needed to maintain consciousness, syncope ensues; if it is higher, there may be no symptoms or signs. Because BP decreases slowly in cOH, most patients learn to heed the warning signs and learn to prevent syncope. One sign occurs fairly often in nOH: an "inability to act." In nOH, BP is then too high to cause unconsciousness, but too low to allow higher cortical functions such as deciding to sit down (**Figure 4**) (81). The result is that patients freeze in their position, either sitting or standing, and may not act until someone pulls them on a chair or a bed. We suspect that this condition in nOH is often mistaken for motor problems or for sleep. This inability to act can in fact also occur in quickly developing syncope, but then only lasts a few seconds (82).

CONCLUSIONS AND FUTURE RESEARCH

Conclusions

The above discussion shows that the speed and timing of circulatory and neurological events is of prime importance to understand the signs and symptoms of syncope. Syncope concerns a change from fully functional alertness and awareness to, in the most severe forms, one in which cortical functions have stopped altogether while the brainstem is on the way to equal that state. The quickest natural way to reach that state is probably a sudden asystole, leading to LOC in about 8 s., in which patients may only realize that something was wrong when they regain consciousness after the fact. At the other end of the spectrum lies the slow BP decrease in nOH, in which patients may perceive a slow progression of symptoms over minutes, in which an inability to rectify the situation may precede a loss of vision and finally LOC. Important factors in the equation are the occurrence of bradycardia or asystole on the cardiovascular side, and cerebral autoregulation on the cerebral end.

The timing and speed not only have consequences for the clinical presentation of syncope, but also for therapy. Whether attempts to rectify CI with a pacemaker will prevent syncope in

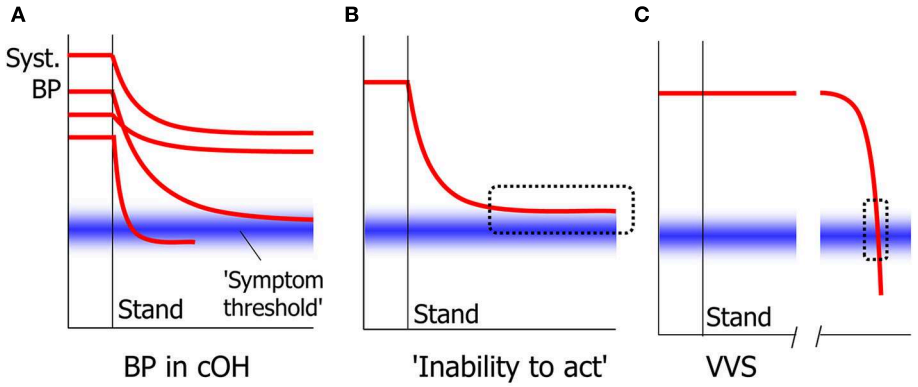

FIGURE 4 | Signs in slow and quick cerebral hypoperfusion. In cOH, BP decreases after standing up to a varying degree and with varying speed in different people **(A)**. The general tendency is for BP to decrease quickly at first and slower later. Whether symptoms and signs appear depend on whether a symptom threshold of cerebral perfusion is crossed. One result of this is that BP may stabilize at a level too high for syncope to occur, yet too low for patients to act volitionally, causing an "inability to act" **(B)**. In VVS, BP decreases slowly at first, but accelerates thereafter. This means that the critical level at which symptoms such as the inability to act occur, is crossed very quickly that this phase is usually not noted **(C)**.

reflex syncope will critically depend on simultaneous VD. The fact that CI started too late to cause LOC in one third of cases with tilt-induced reflex syncope, suggests that pacing will fail at least that same rate, if started at the onset of asystole (31).

Gaps in Knowledge and Possible Solutions

The above overview helps delineate a number of gaps in the understanding of the processes that lead to LOC in reflex syncope.

The first is limited knowledge concerning the pathophysiology of emotional VVS and other forms of syncope. The reason is very likely that orthostatic VVS can be evoked with relative ease with a TTT, while the other forms, in particular emotional VVS, are difficult to evoke. TTT studies on VVS have clarified that the original scheme of a dual parasympathetic and sympathetic reflex action, respectively causing bradycardia and too little arteriolar vasoconstriction, is at best incomplete. Instead, venous pooling causing a reduction in SV seems to be the prime abnormality starting the complex process of orthostatic VVS. As other forms of reflex syncope are triggered much swifter, these may not rely on the slow process of venous pooling. Hence, studying other forms of reflex syncope may clarify pathophysiological differences between the various types.

A second problem is why and how excessive venous pooling occurs in orthostatic VVS. This reflects an excessive shift of blood from the thorax to lower regions of the body. At present the assessment of venous pooling relies mostly on indirect deductions of its presence from a reduction in SV, i.e., it relies on measurements that concern the arterial system. Instruments that would allow direct measurements of venous filling or the distribution of blood across body regions might yield as much new information regarding the venous system as continuous blood pressure measurements did for the arterial system. Impedance measurements should help fill his gap, and have shown important results, but are not used widely (29, 83).

A third and fundamental problem is why the autonomic nervous system seems incapable of countering venous pooling in orthostatic VVS. The reduction in SV leads to a slow decrease in BP, meaning that this decrease is for some reason not countered by adequate increases in sympathetic arteriolar vasoconstriction nor heart rate. Are there conflicting demands on the autonomic nervous system that prevent it from acting normally, or is there perhaps a mismatch between humoral and nervous actions?

Fourth, it is difficult to assess which of the processes CI and VD affect BP the most when both act together. In the well-known equation BP = SV·HR·TPR, HR represents CI, and SV and TPR may represent venous and arterial VD. The multiplicative nature of this relation suggests that it should be possible to determine how much each parameter contributes to a given decrease in BP. If such comparisons would for instance reveal that over half of a BP decrease is due to a HR decrease, pacing attempts become more promising then when CI hardly explains any BP decrease. Clearly, not only the relative severity of VD and CI, but also their relative time of onset is important for the occurrence of syncope: in about one third of cases of tilt-induced VVS, asystole occurred too late to cause syncope (31). Treatment decisions regarding pacing, at least in orthostatic VVS, should therefore ideally not be based on ECG records only. Measuring VD at the same time would be helpful, provided the problem of assessing the relative contributions of VD and CI is solved first. At present there are no practical ways to measure BP continuously. However, there is one parameter that can be measured continuously and easily, and that is whether the trunk is positioned vertically or horizontally. If the body is still vertical when asystole starts, there is a chance that pacing might prevent syncope and falling, while there is no such chance if the body has already fallen to a horizontal position. Equipping ILR devices with position sensors would be an obvious first step to test this concept, perhaps later leading to smarter pacing.

The pathophysiological studies on nOH reveal that it is surprisingly complex, with an apparent mixture of primary

defects and secondary reactions. The paradoxical occurrence of an apparent decrease in TPR in the standing position is a case in point. Studying it and its as yet unidentified mechanisms might help alleviate the orthostatic BP decrease.

AUTHOR CONTRIBUTIONS

JD: main concepts, outline, writing, and revising. IR: critique and writing. RT: critique and writing.

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MINI REVIEW
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Reflex Atrioventricular Block

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Reflex atrioventricular block is well-recorded although it is considered rare. Recent data suggests that it is less rare than has been supposed. It has been shown to occur in both vasovagal and carotid sinus reflexes. It has to be distinguished from paroxysmal atrioventricular block due to ventricular conduction tissue disease. Low chronic adenosine levels combined with adenosine release may mimic reflex atrioventricular block. Explanations of the mechanism of these phenomena have been lacking until the recent past. The relevance of reflex atrioventricular block to clinical decision-making is as a possible indication for pacing the heart with consideration given to the vasodepressor component of the reflex.

Keywords: atrioventricular block, vasovagal reflex, carotid sinus reflex, cardiac pacing, cardiac conduction system disease, adenosine

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INTRODUCTION

Atrioventricular block (AVB) is a well-recognized condition due in most cases either to idiopathic disease of ventricular conduction tissue, the His-Purkinje system, or to ischemic damage to this tissue. Amongst the less common causes are invasion of calcification from calcific aortic valve stenosis and congenital. As AVB became better understood, particularly by employing increasingly sophisticated electrocardiographic monitoring, it became evident that lesser examples of the disease, such as bundle branch block, tended to progress over months or years. Progression often presented evidence of paroxysmal atrioventricular block heralding permanent block. Evidence also emerged in 1980s and 1990s that paroxysmal AVB could be part of carotid sinus or vasovagal reflexes (1–5) **(Figure 1)**.

Reflex AVB, a form of paroxysmal AVB, was less well accepted (1–5) as it may be difficult to distinguish from progression of ventricular conduction system disease (2). More recently, another form of paroxysmal AVB has been attributed to adenosine release in chronic hypoadenosinemia (6, 7). Thus, there are at least three possible pathophysiological mechanisms of paroxysmal AVB.

Conservative thinking concerning reflex AVB has been very strong with a tendency to deny the existence of two of these three mechanisms, namely reflex and hypoadenosinemic types, despite presentation of 4 clear cases of reflex AVB in the Lancet in 1988 (8, 9). Even a recent and very extensive assessment of Danish data in patients of <50 years found that in approximately half of the 1,027 patients receiving a pacemaker in that country between 1996 and 2015 the etiology of AVB was unknown (10) and given the relative youth of the patients reflex causes may have accounted for many. Moreover, they showed that the unknown etiology cases progressively increased in number over the study period.

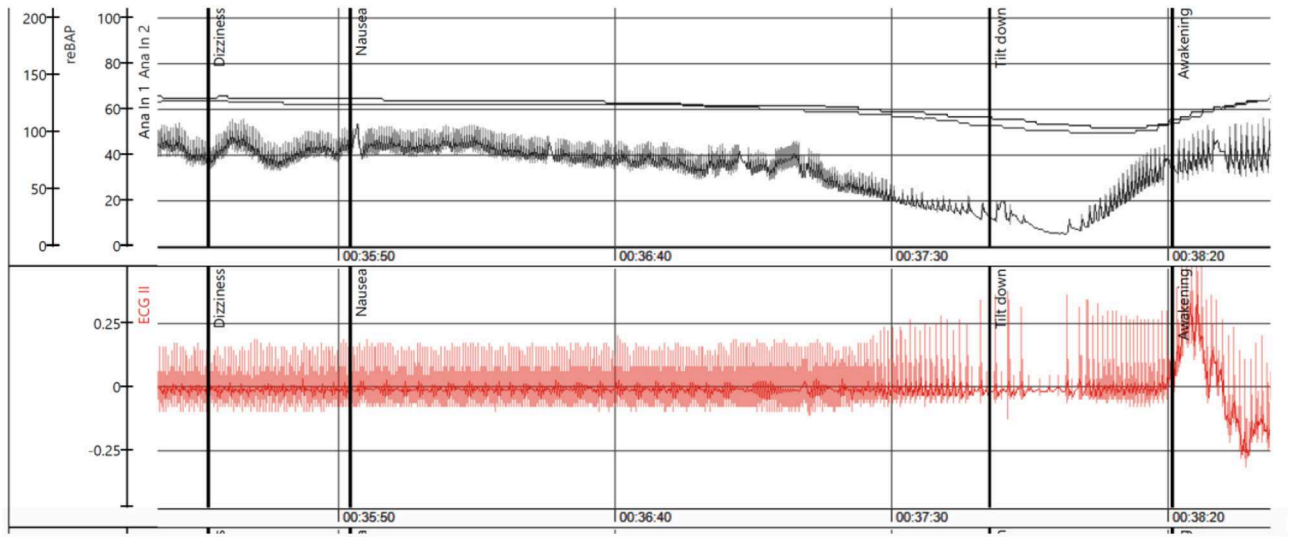

FIGURE 1 | The figure illustrates a positive tilt test in a young female patient. The upper panel shows the beat-to-beat blood pressure recorded by a photoplethysmographic method. The first vertical heavy black line denotes onset of dizziness followed by nausea at the second vertical heavy black line. The third vertical heavy black line denotes tilt down at severe hypotension and loss of consciousness. Rapid recovery follows. The lower panel shows the ECG. There is sinus rhythm until about 20s before tilt down when AVB begins and evolves asystole at tilt down. In recovery there is sinus tachycardia. This is indisputably reflex paroxysmal AVB. Time in minutes and seconds is indicated below (Recording courtesy of A Fedorowski).

CAUSES AND MECHANISMS OF PAROXYSMAL ATRIOVENTRICULAR BLOCK

This matter of cause of AVB was particularly illustrated in the opposition of reviewers to publication of the ISSUE (International study of syncope of unknown etiology) 3 study (11) on the basis that the study had only shown a progression of conduction system disease which is expected to respond well to pacing. The authors arguments eventually overcame the objections and the study was published. Nevertheless, at nearly every congress session on this subject the same criticisms arise, i.e., the wrong diagnosis has been made and this is not paroxysmal reflex AVB but progression of ventricular conduction system disease. At the time of publication of the ISSUE 3 (11) and its sub-studies (12, 13) there had been no evidence of progression of AVB in any case, even those that showed complete AVB on insertable loop recorder (ILR) during an episode of syncope.

Analysis of the ILR recordings during syncope in the ISSUE 2 study (4) surprised the investigators, myself included, with the incidence of AVB. Prior to this analysis we had made a classification of rhythm disturbances that occurred on ILR during syncope or symptoms in ISSUE 2 patients (14). This proposal included three types of asystole, **Table 1**.

The description type 1c raised a question of ventricular conduction tissue disease in the minds of the classification's proposers. Thus, this finding in ∼20% of the clinically determined reflex (vasovagal) was unexpected raising the possibility of a different mechanism, namely intrinsic disease of the His-Purkinje system as observed in Stokes-Adams attacks. At this time, even the ISSUE 2 investigators did not completely appreciate that such findings could be compatible with reflex AVB. When the ILR recordings were available from the ISSUE 3 study (8) a very similar finding of type 1c pattern of AVB was made in similar numbers to that seen in ISSUE 2 (4). This consistency was striking but progression to more obvious ventricular conduction system disease was absent in contrast to the ISSUE 1 study of Brignole and colleagues that set out to monitor by ILR patients with bundle branch block finding progression of conduction tissue disease in 42% (15) in 3–15 months of monitoring. In contrast, ISSUE 3 (11) included 2 years of follow-up without such findings where pre-existing conduction system disease was an exclusion from the study.

Following the results of the ISSUE 2 study, the literature again contained definite examples of reflex AVB (3) and evidence also became available for an additional and previously unconsidered form of paroxysmal AVB (6). The latter syndrome was one of "benign" paroxysmal AVB combined with syncope without prodrome, a normal heart and normal ECG but a low adenosine level. It was hypothesized that the low chronic level of adenosine rendered the atrioventricular conduction system very vulnerable to adenosine release precipitating narrow complex AVB. These patients respond very well to pacing. The syndrome of low adenosine AVB has been fully reviewed (7).

Thus, paroxysmal AVB can be considered to be of three types as put forward in the review by Aste and Brignole (16), **Table 2**.

DIFFERENTIAL DIAGNOSIS

In making a differential diagnosis, these aspects require consideration:

TABLE 1 | The ISSUE classification of arrhythmias on implantable/insertable ECG loop recorders relating to bradycardia and AVB.

Type 1a: slowing sinus rhythm followed by sinus arrest and ventricular asystole; Type 1b: Progressive sinus bradycardia to <30 bpm followed by AVB with severe bradycardia/asystole; Type 1c: sudden onset of AVB with concomitant increase in sinus rate.

ISSUE, International study of syncope of unknown etiology; AVB, atrioventicular block.

TABLE 2 | Types of paroxysmal atrioventricular block.

1. Reflex AVB (due to vasovagal or carotid sinus mechanisms).
2. Progression of ventricular conduction tissue disease.
3. Hypoadenosinemia.

- other associated reflex features e.g., nausea; coincident vasodepression;
- evidence of already existing ventricular conduction tissue disease e.g., bundle branch block;
- plasma adenosine level
- lack of prodrome.

Vasodepression as an integral part of reflex syncope must always be considered because it is always present (17). Not only does it begin much earlier than cardioihibition, by many minutes, but also may be sufficient to drive the blood pressure so low as to cause loss of consciousness before cardioinhibition with AVB occurs (18, 19). It is likely that hypotensive drugs, commonly prescribed in older populations with a hypertensive tendency, actually exaggerate vasodepression. Attention has been given to this in a small trial, STOP-VD, that shows evidence of symptomatic improvement by reduction in hypotensives in a vasovagal syncope, paced group of patients (20).

Unfortunately, adenosine has been a difficult to acquire measurement in routine clinical practice. However, shortly, a simple easily performed test will become available. It has been shown that there are clear differences between vasovagal patients (normal or raised plasma adenosine levels) and those with low adenosine. Carotid sinus syndrome (CSS) patients show similar low adenosine levels to those presenting hypoadenosemic AVB (7). This may explain some differences in behavior between CSS and VVS as yet not fully investigated. It is anticipated that the soon to be greater availability of measurement of plasma adenosine levels and more experience of the lack of progression of conduction tissue disease in reflex AVB compared with already documented, ventricular conduction system disease will clarify this situation.

RELEVANCE OF CARDIAC PACING TO PAROXYSMAL ATRIOVENTRICULAR BLOCK

How do these findings influence a decision to pace the heart? Complete AVB with or without asystole is generally considered an indication for permanent pacing whatever its mechanism. In the case of progression of ventricular conduction system disease the indication to pace is clear when complete AVB or asystole occurs. The relatively new findings reviewed here, reflex and hypoadenosinemic AVB prompt a reassessment of the indications for pacing.

In vasovagal syncope even more than in CSS consideration needs to be given to the timing of bradycardia and timing of loss of consciousness, as vasodepression starts many minutes before cardioinhibition, which might prevent or markedly reduce pacing benefit (17–19). These observations may override that of simply pacing AVB. They may also account for the apparently better results of sensing volume ± contractility of the right ventricle in the closed loop system of Biotronik (Berlin, Germany) rather than simply the onset of bradycardia as in the Rate-drop-response of Medtronic (Minneapolis, MN, USA) (11, 21, 22).

In hypoadenosinemia, the experience is, so far, small but pacing seems to be very effective (23) although it is possible that theophylline treatment could also be effective (24).

SUMMARY AND CONCLUSIONS

In summary, reflex atrioventricular block is more common than previously thought as evidenced by the ISSUE 2 and 3 studies (11, 14). It may be an indication to pace but account must be taken of the timing of both bradycardia and loss of consciousness within the reflex episode when making a decision in favor of pacing. Accompanying vasodepression in reflex atrioventricular block also needs consideration as there may be a need to reduce hypotensive medication to improve pacing benefit.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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frontiers in Cardiovascular Medicine

MINI REVIEW
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Should We Ever Pace for Carotid Sinus Syndrome?

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Carotid sinus syndrome has been associated with transient loss of consciousness for millennia, and while steeped in cardiovascular lore, there is little in the way of solid evidence to guide its main treatment modality, permanent cardiac pacing. This article reviews the history of the condition in the context of its contemporary understanding before examining three key concepts in the consideration of what constitutes a manageable disease: first, is there a pathophysiologic rationale for the disease (in this case carotid sinus syndrome)? Second, is there a good diagnostic test that will identify it reliably? And finally, is there a convincingly evidence-based treatment for the disease? Relevant literature is reviewed, and recommendations made in how we view pacing in the context of this intriguingly opaque condition.

Keywords: pacemaker, carotid sinus syncope, neurally mediate syncope, syncope - etiology, treatment - contemporary views

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HISTORICAL CONTEXT

The association of the carotid sinus with impaired consciousness stretches back over several millennia. The ancient Assyrians used carotid compression to dull the pain associated with ritual circumcision (1), while one of the Parthenon's metopes from the 5th century BC illustrates the offensive use of carotid compression by a centaur to cause unconsciousness in an opposing Lapith soldier (**Figure 1**). Six centuries later, the ancient Greek physician and philosopher Galen (AD c 130–210) wrote of the loss of consciousness caused by the compression of nerves surrounding the carotid arteries (2), while the Greek recognition of the physiologic significance of the carotids is evident, the name being derived from the Greek *karotides*, the plural of *karotis*, meaning drowsiness, which itself was derived from the verb *karoun* (to stupefy). The Persian Muslim father of modern medicine Avicenna (c 980–1037; **Figure 2**) later commented on falling and unconsciousness induced by carotid sinus pressure by hammams in public baths (3, 4), while the French barber surgeon to several kings Ambroise Paré (c 1510–1590) noted that "(the) two branches which they call carotides or soporales, the sleepy arteries, because they being obstructed, or any way stopt we presently fall asleep" (5).

However, it was not until 1799 that the English physician and friend of Edward Jenner (initiator of the smallpox vaccine), Caleb Hillier Parry (**Figure 3**), made the more causal observation between carotid pressure and syncope, noting that "in patients, whose hearts have been beating with undue quickness and force, I have often, in a few seconds, retarded their motion many pulsations in a minute, by strong pressure on one of the carotid arteries," though he took this to be a sign of coronary artery disease (6). In 1862, further observations were recorded by Waller on the effect of pressure over the carotid artery posterior to the ramus of the mandible: "The heart beat at first increases in number with decreased power followed by a retardation of the heart action of about four to five beats a minute. . . .," an action he attributed to vagal activation (6).

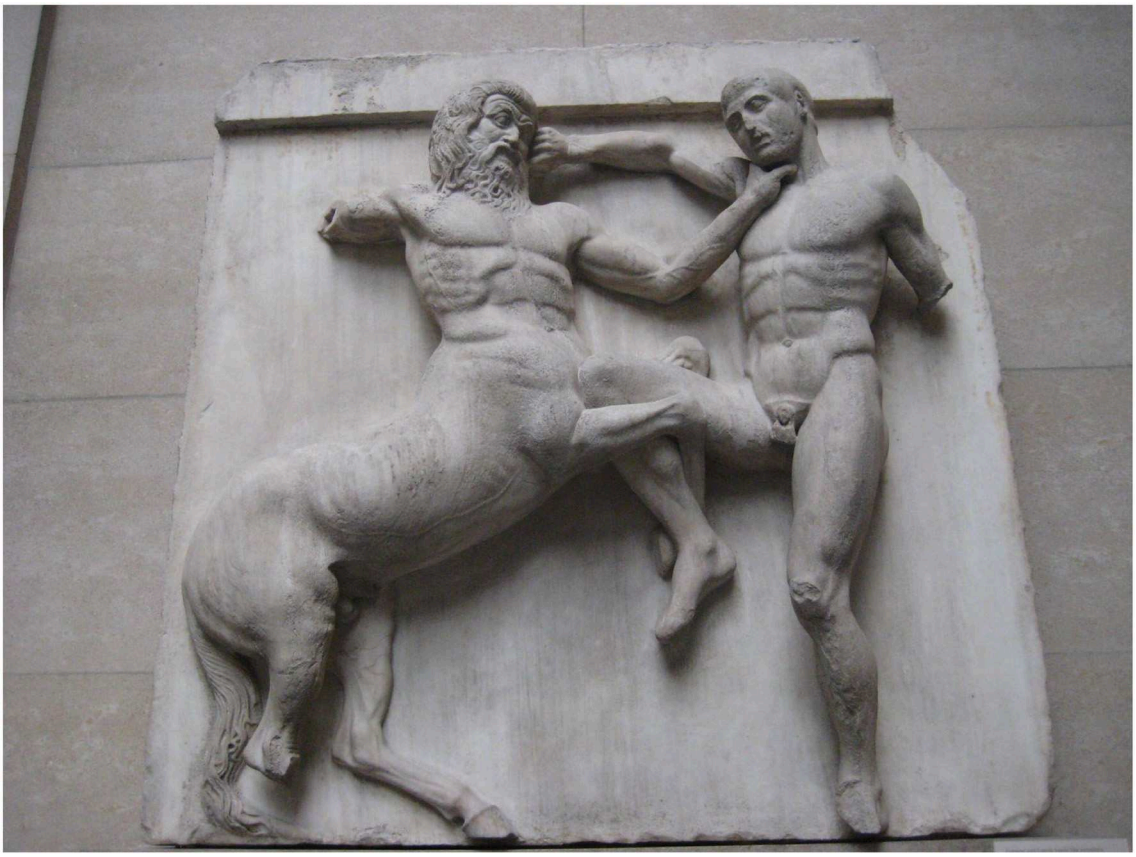

FIGURE 1 | Centaur and Lapith, 31st Metope, The Parthenon. By Claire H., originally posted to Flickr as Centaur and Lapith, CC BY-SA 2.0 (https://commons.wikimedia.org/w/index.php?curid=5123552).

Waller noted with great insight that "it is easily ascertained that the symptoms above described are not owing to *compression* of the carotid artery, as they may be produced without obliteration of the calibre of the artery; or vice versa the course of the blood may be completely interrupted in the artery without producing any of the symptoms enumerated," (7) providing an early distinction between the pathologic and the physiologic reflexive hemodynamic changes and the importance of symptoms in attributing causation in the clinical setting. Four years later, these observations were expanded upon by the Austrian physiologist Czermak (8), who found that self-induced carotid pressure at the level of the upper margin of the sternocleidomastoid muscle caused temporary slowing of the heart rate, which was more pronounced on the right than on the left. Czermak's conclusions regarding the mechanism of cardiac slowing attributed to vagal pressure in the region of the carotid sinus held sway for much of the ensuing 50 years, with the test itself denoted as the "vagus druckversuch" or "vagus pressure test" (9).

In 1912, Sollman and Brown showed that traction on the carotid arteries caused a relative bradycardia and fall in blood pressure independent of vagal stimulation (10), but it was not until a decade later that Hering showed that mechanical pressure at the bifurcation of the common carotid artery caused cardioinhibition, even when the vagus was dissociated from the artery (11, 12). Hering's associate Koch (13, 14) confirmed these observations, while de Castro (15) and Heymans (16) showed that the carotid sinus was richly supplied with sensory receptors (15, 16) found predominantly in its adventia, emerging as spiral fibers which unite to form the carotid sinus nerve, Hering's nerve (12), or the intercarotid nerve of de Castro (15). Sunder-Plassman (17) later showed the union of the carotid sinus nerve with the hypoglossal nerve, conclusively demonstrating the direct afferent connection between the carotid sinus and the brainstem.

Clinical studies on the physiology and the pathophysiology of the carotid sinus in human subjects only really began following the discovery of a reflexive role for the sinus independent of the vagus nerve. Koch (13) studied the effect of carotid sinus pressure on 50 predominantly male subjects, 28 of whom had a resultant fall in systolic blood pressure at a mean of 23% of the baseline level. As the fall in blood pressure was independent of cardiac slowing, Koch assumed that a depressor vasomotor reflex was in operation (13). Mehrmann confirmed these observations, noting a particularly marked fall in blood pressure in patients with arteriosclerotic disease (18), as did Mandelstamm and

FIGURE 2 | Avicenna (Ibn Sina). From Wikimedia Commons, *via* Bibliotheque Interuniversitaire (https://www.commons.wikimedia.org/wiki/Category:Media_contributed_by_the_Biblioth%C3%A8que_interuniversitaire_de_sant%C3%A9).

Lifschitz (19), who also demonstrated a particularly marked fall in blood pressure in subjects with hypertension as well as arteriosclerosis.

Mandelstamn and Lifschitz were also the first to associate the more pronounced hemodynamic consequences of carotid sinus stimulation in relation to advancing age; the 103 retired Russian workers studied had an average fall in systolic blood pressure of 37 mmHg with carotid sinus pressure, while 106 healthy young soldiers had only a 5-mmHg vasodepressor response (19). They also noted that the degree of heart rate slowing did not necessarily correlate with that of the fall in blood pressure and that the fall in heart rate occurred earlier and lasted for a much shorter time than the blood pressure fall (19). Moreover, Mandelstamm and Lifschitz (19) were the first to emphasize the need for uniformity in the technique of carotid sinus pressure in man. The patient should lie supine, with the head elevated, just overhanging a support and turned slightly to one side, the sinus being located at the angle of the jaw and at the upper border of the thyroid cartilage (19).

The first case report of syncope and pre-syncope caused by a pathological carotid sinus reflex was published by Roskam in 1930, along with the original use of the term "hypersensitivity" ("*hyperreflectivité*") (20). The 53-year-old man described had recurrent syncope first elicited by stretching of the skin while shaving. During clinical examination, the compression of the carotid sinus caused more than 15 s of asystole with loss of consciousness and "convulsions," as graphically described by Roskam: "…pendant cette syncope que se prologea plus de quinze secondes apres la fin de l'attouchement, j'auscultai avec la plus grande attention la region precordiale: silence absolu. Finalement, survinrent des convulsions epileptiformes generalisees. Puis brusquement, le coeur se remit a battre sur un rythme accelere, a 120 pulsations environ a la minute, des extrasystoles venant frequemment entrecouper la succession precipitee des systoles regulieres" (20)*. Repeated light carotid sinus pressure resulted in 16 s of asystole, again with syncope and convulsions. The patient was treated successfully with atropine and remained symptom-free at follow-up (20).

[** "…as syncope occurred for more than 15 sec. following discontinuation of pressure, I auscultated attentively over the praecordium: absolute silence. Finally, generalised epileptiform convulsions ensued. Then, abruptly, the heart began to beat with an accelerated rhythm, at around 120 beats per minute, with initial frequent extrasystoles interrupting the succession to normal sinus rhythm"]

The millennia-long foundations had therefore been laid for Soma Weiss and James Baker's landmark case series in carotid sinus hypersensitivity (CSH) published later in 1933, describing "the carotid sinus reflex in health and disease" and "its role in the causation of fainting and convulsions" (21). Fifteen subjects with CSH, all with symptom reproduction during carotid sinus pressure of variable degrees and duration, were described in detail, with the division of responses to carotid stimulation designated as "vagal" where marked bradycardia or asystole occurred, "depressor" where arterial pressure fell independently of cardiac slowing, and "cerebral" where syncope occurred with no hemodynamic changes, although this last type soon proved secondary to cerebral anterior circulatory compromise caused by carotid artery obliteration during carotid sinus massage (CSM) in the presence of hemodynamically significant contralateral carotid stenosis (22, 23).

While the lack of standardization of carotid sinus stimulation, *ad hoc* subject selection, and absence of diagnostic definitions hamper Weiss and Baker's original paper, their contribution, in terms of drawing attention to the pathologic role of the carotid sinus and making some sense of the presentation, natural history, and management of the condition, is unique. One of the case reports presented in the paper was on a 65-year-old Boston streetcar driver (**Figure 4**) with fainting and dizziness upon turning his head from side to side to look out for traffic, which has passed into medical folklore. The patient was found to have reproducible CSH, and the characteristic hemodynamic responses were later reproduced with the celluloid high collar he used for work, with all symptoms

FIGURE 3 | Caleb Hillier Parry. Engraving by P. Audinet after J. H. Bel; from Welcome Images, *via* Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Caleb_Hillier_Parry._Engraving_by_P._Audinet_after_J._H._Bel_Wellcome_V0004501.jpg, original at http://catalogue.wellcomelibrary.org/record=b1171293).

resolving with the use of a soft collar! (21) As Mehrmann (18), Mandelstamm and Lifschitz (19), and Nathanson (24) had noted, the hypersensitive response was more common in patients with arteriosclerotic disease, with all but one of Weiss and Baker's subjects being so affected (21). They also noted that "pressure on the sinus regularly brought on fainting more quickly when the patient was standing than when he was lying down" (21), a finding confirmed and reinforced since (25).

The stage was thus set for further clinical exploration of Weiss and Baker's "syndrome of dizziness, fainting and convulsions due to a hyperactive carotid sinus reflex" (21). The management of carotid sinus syndrome (CSS; CSH in response to CSM culpably associated with symptoms of syncope, dizziness, drop attacks, or unexplained falls vs. CSH in isolation, which is not associated with such symptoms) was initially with vagolytics or carotid sinus denervation (26) until the first permanent pacemaker was implanted for CSS almost

FIGURE 4 | 1930s Boston streetcar. A two-car train of center-entrance streetcars on Tremont Street at Upton Street (just north of Dartmouth Street), probably in the 1930s. From City of Boston Archives, West Roxbury, USA, via Wikimedia Commons (https://www.commons.wikimedia.org/wiki/File:Streetcars_on_Tremont_Street_opposite_Upton_Street,_1930s.jpg).

half a century ago (27). This treatment strategy for the management of CSS' cardioinhibitory and mixed subtypes has continued ever since and is supported by international consensus guidance to this day (28–32). However, a growing body of evidence from a number of epidemiologic, experimental, and observational studies has questioned whether CSS is a disease state in need of treatment or a coincidental finding (33–36). Alongside this, international systematic reviews and meta-analyses consistently and inconveniently demonstrate the lack of high-quality evidence for permanent pacing in the management of CSS (30, 32).

So how to disentangle fact from fiction (or at best supposition) in the question of whether we should ever pace for CSS? Before trying to establish a final answer, it is instructive to decide whether there is a disease process at work, as without a disease (or at minimum, a symptomatic deviation from normal function), there is no case for treatment. While the Oxford Dictionary definition of disease as "a disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms or that affects a specific location and is not simply a direct result of physical injury" (37) may seem to fit CSS, a more practical and informative definition might flow logically from the following questions:

1. Is there a pathophysiologic rationale for the disease (in this case CSS)?
2. Is there a good diagnostic test that will identify it reliably?
3. Is there a convincingly evidence-based treatment for the disease?

In the remainder of this paper, I will discuss each of these in the context of the CSS subtypes for which permanent pacing is indicated (cardioinhibitory and mixed) before attempting to synthesize the answers into a coherent response to its title. Vasodepressor CSS is not the subject of this review.

IS THERE A PATHOPHYSIOLOGIC RATIONALE FOR CAROTID SINUS SYNDROME?

It is evident from the historical overview above that, first, the stimulation of the carotid sinus provokes exaggerated heart rate and blood pressure changes in normal humans (carotid sinus hypersensitivity), and second, that in some individuals, stimulation through the carotid sinus pressure or massage can provoke syncope (carotid sinus syndrome). What is less evident is what might cause the conversion of the asymptomatic state to the symptomatic state. The basic functional neuroanatomy of the carotid sinus reflex has an afferent component from the sinus *via* neuronal projections to the brainstem [in particular, the nucleus tractus solitarius (38, 39)] via Hering's nerve and the glossopharyngeal nerve, while the efferent expressions of CSH are mediated by the vagus nerve in cardioinhibitory carotid sinus hypersensitivity (40–42) and by sympathetic withdrawal, with subsequent vasodilatation and arterial hypotension in mixed carotid hypersensitivity and vasodepressor carotid hypersensitivity (**Figure 5**) (42–45). Why the exaggerated hemodynamic responses are triggered is not

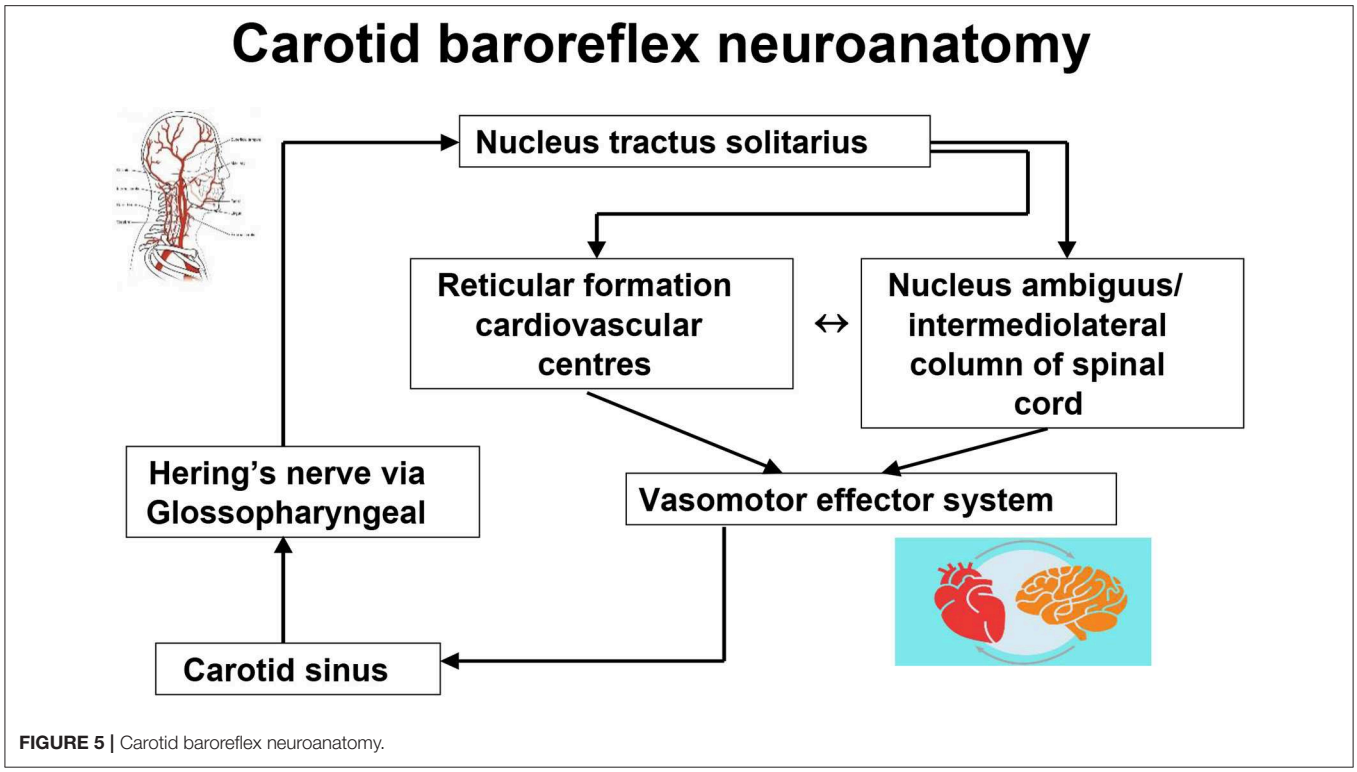

FIGURE 5 | Carotid baroreflex neuroanatomy.

understood. Certainly the carotid sinus and its projections are unlikely culprits as the histology of the intima and the nerve terminals in CSS is essentially normal (38, 46), and both the vasodepressor and the cardioinhibitory effects of CSM continue despite the termination of carotid stimulation (and carotid sinus neural output) (40, 43), Furthermore, denervation of the carotid sinus is not always a successful intervention in the management of CSH (47, 48). Although the sinus itself may be an unlikely primary source of the hypersensitive response, Tea et al. (49) and later Blanc et al. (50), working in the same laboratory, found a powerful (and unexpected) association between electromyographically demonstrated sternocleidomastoid muscle denervation and CSH during CSM (49, 50). The authors suggest that the chronic loss of innervation of the sternocleidomastoid muscles may cause an increased sensitivity of the baroreflex arc and hence CSH, although the link is tenous (49). However, causality in the opposite direction must be considered—there is no evidence to refute the possibility of sternocleidomastoid denervation as a *consequence* of CSH. This important work has never been replicated or explored further.

One study showed hyperphosphorylated tau accumulation baroreflex-associated neurons in a controlled neuroanatomical study of 12 patients with CSH compared to 14 controls (51), so there is some evidence to support a central neuropathologic culprit in CSH, although this finding has not been examined elsewhere. The efferent limb of the carotid baroreflex arc appears to be intact given the exaggerated vasodepression and normal bradycardic response to muscarinic stimulation with edrophonium seen in CSH (5). By exclusion, a central brain-stem-level abnormality in the modulation of central baroreflex gain is therefore likely and indeed was suggested three decades ago (52), although interestingly Tea et al.'s study found no abnormalities of the central neurophysiological parameters in subjects with CSH (49). One hypothesis suggests that central alpha-2 adrenoceptor upregulation provides the substrate for this baroreflex gain (53), with reduced arterial compliance secondary to carotid arteriosclerosis associated with ageing, hypertension (54), or atheroma resulting in diminished mechano- and baroreceptor stimulation and thus a decrease in afferent neural traffic to the brain stem, resulting in the upregulation of medullary alpha-2 adrenoceptors, which are known to regulate negative feedback hypotensive and bradycardic responses (55).

This "physiologic" denervation hypersensitivity then causes the overshoot bradycardia and hypotension following carotid sinus stimulation that is clinical CSH (53). We tested this hypothesis with a double-blind, placebo-controlled cross-over study of the centrally active alpha-2 adrenoceptor antagonist yohimbine administered during CSM in patients with documented CSS (56). If the alpha-2 adrenoceptor hypothesis was true, the hemodynamic responses to yohimbine should be markedly attenuated—this was not the case (**Figure 6**) (56). More recently, 10 older adults with CSH had higher arterial stiffness and reduced arterial baroreflex sensitivity compared to those without, further providing no evidence to support the upregulation of the arterial baroreflex in patients with CSH (57).

There is thus a small but inconclusive evidence base to suggest neuroanatomical abnormalities as the underpinnings of CSS.

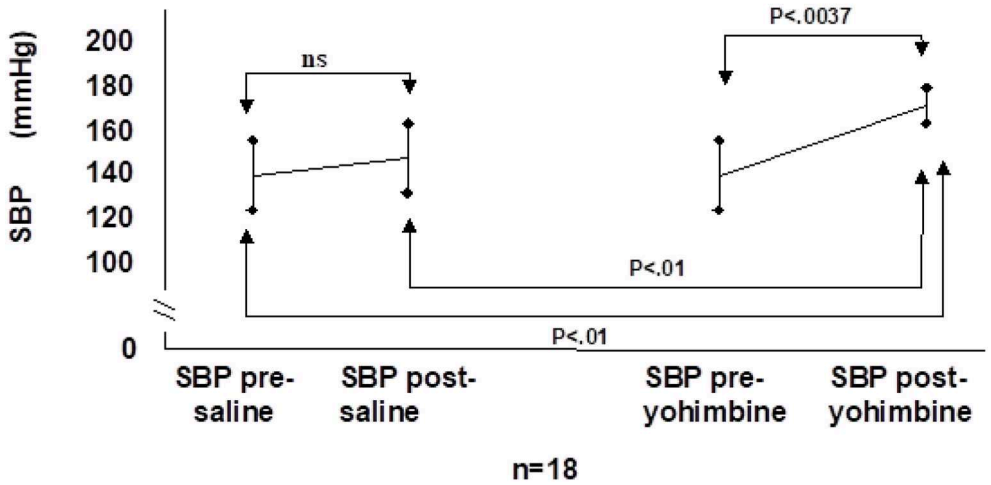

FIGURE 6 | Change in systolic blood pressure post-intravenous yohimbine and saline. SBP, systolic blood pressure; ns, not significant [from Parry et al. (56)].

What about a more functional disorder analogous to psychiatric disease in the absence of overt brain pathology? One possibility is disordered cerebral autoregulation, a candidate catalyst for the conversion of asymptomatic CSH to CSS, with linked studies by Leftheriotis et al. (58, 59) showing that hypotension secondary to CSM caused the delayed onset of transcranial Doppler ultrasonographically (TCD)-measured cerebral autoregulation which was more prominent with increasing asystole duration. Dual-chamber pacing ameliorated the response. However, the studies were small, uncontrolled, and provided no method of distinguishing cerebral autoregulatory derangements specific to carotid sinus stimulation from the effects of profound arterial hypotension, during which cerebral autoregulation falters and fails (60). We sought to overcome these limitations through a comparison of changes in cerebral autoregulation (as measured by TCD) in response to controlled lower body negative pressure-induced hypotension in subjects with CSS, those with asymptomatic CSH, and in healthy controls in a series of studies (61, 62). In both studies, we found evidence of deranged cerebral autoregulation, in the first particularly through differences in cerebrovascular resistance and in the second in cerebral blood flow velocity between patients with CSS and controls (61, 62). However, the findings have not been replicated elsewhere and suffer from the small sample sizes as well as the many limitations of the TCD method of estimating cerebral autoregulation. Further work is needed before definitive conclusions can be drawn.

If cerebral autoregulation abnormalities are the ultimate expression of the cause of symptoms in CSS, a strong candidate for the mediating mechanism would be the same underlying process, autonomic dysfunction. Morley and Sutton found abnormal baroreflex sensitivity in CSS and sick sinus syndromes as measured by the phenylephrine pressor test (63). Almost three decades later, we studied baroreflex sensitivity and heart rate variability in 22 patients with CSS, 18 with CSH, and 14 normal controls only to find that both CSS and CSH patients had increased resting sympathetic activity and baroreflex sensitivity compared to controls (35). Whether this reflects a generalized mild autonomic dysfunction associated with aging or a pathologic state remains unknown. We further explored the autonomic hypothesis through meta-iodo benzyl guanidine scanning of cardiac sympathetic activity in patients with CSS, patients with CSH, and asymptomatic controls (64). Cardiac sympathetic neuronal activity was increased in patients with CSS, but not in the other two groups (64), adding more weight to the suggestion that CSS is a clinical manifestation of autonomic dysregulation in older individuals.

IS THERE A GOOD DIAGNOSTIC TEST THAT WILL IDENTIFY CAROTID SINUS SYNDROME RELIABLY?

Consensus guidelines state that the current standard diagnostic test for CSS is 10 s of bilateral, sequential, and longitudinal CSM, right then left (as the hypersensitive response is more likely to occur on the right), during electrocardiographic and (preferably beat-to-beat) blood pressure monitoring (29, 31, 65). The process should be repeated in the upright position in order to avoid missing up to a third of cases (25), with diagnosis of CSS confirmed by the presence of prolonged asystole with reproduction of usual symptoms (29, 31, 65, 66). The

duration of asystole deemed as diagnostic was unspecified early on, 3 s or more for half a century, but now more than 6 s, following recent arguments detailing the duration of cardiac pause needed to induce loss of consciousness (67). However, this consensus certainly masks an absolute dearth of rigorous experimental effort to support it, alongside the fact that the distinction between carotid sinus pressure (Weiss and Baker's original method) and massage gained traction in the late 1960s (68) and became commonplace only in the 1980s (52, 63, 69). Moreover, the duration of massage similarly has little basis in scientific methodology, with durations of up to 30 s of pressure or massage for much of the 1930s to 1980s (68, 70), and 5 s in many laboratories (66) and recent American syncope guidelines (28). Added to this, despite confidently quoted anatomical landmarks (65, 66), the carotid sinus' position can vary considerably, with the estimated location missing the actual location by up to 1.5 cm (71), and post-mortem evaluation shows a high variation in sinus location, with an asymmetric location in 34% (72). The implications for further diagnostic ambiguity are clear, particularly regarding false-negative tests.

IS THERE A CONVINCINGLY EVIDENCE-BASED TREATMENT FOR THE DISEASE?

The short answer to this question is no, if the standard of evidence required is that of the randomized controlled trial (RCT). Two recent high-quality reviews of pacing intervention in CSS, where syncope is the presenting complaint, found no high-quality evidence to support pacing as a treatment of choice (30, 32) despite the consensus guideline strength of recommendation being set at IIa or IIb (28, 29, 31). However, this masks the dearth of RCTs on which to base gold-standard treatment recommendations and the wealth of observational data supporting pacing as an effective intervention (26, 29, 73–75). Such data come with considerable methodologic baggage and innumerable biases and need further investigation. There is little further clarity where CSH has been associated with unexplained falls, although not according to the method of symptoms (i.e., in the absence of symptom reproduction during positive CSM). Several studies have examined the role of pacing in this context (76–78). The SAFE PACE study showed a significant reduction in fall rates in those paced vs. those without pacing intervention in CSH fallers, although the magnitude of intervention (surgical procedure vs. no intervention) makes interpretation more difficult (76). The latter SAFE PACE 2 study, with a more rigorous study design (pacing vs. implantable loop recorder, so both arms had device intervention), showed no such benefits (77). Similarly, the only randomized, double-blind, placebo-controlled pacing intervention study in this area (indeed in any CSS study) showed no reduction in fall rates with pacing, although the study was marginally underpowered (78). The mechanism of causality, and whether pacing is effective or not in unexplained falls, is thus as unclear as in syncope.

SHOULD WE EVER PACE FOR CAROTID SINUS SYNDROME?

"The truth is rarely pure, and never simple"
(Oscar Wilde, The Importance of Being Earnest, Act I, 1895)

Truth, in the sphere of day-to-day existence as much as in classic 19th century comedy, is seldom absolute. As the reader will be aware from the discussion so far, Wilde's pithy observation on the nature of truth has a particular resonance in attempting to answer the question posed by the title of this paper. Our putative disease, CSS, on balance from the small number studies and patients involved in trying to understand the physiologic bedrock of this elusive condition, appears to have some basis in autonomic dysfunction. What is less apparent is whether this represents a disease in need of management (at least in the sense of the word as here defined) or whether this is part of the autonomic spectrum of normal aging. On balance, the former seems more likely, although a definitive

BOX 1 | Pacing in Carotid Sinus Syndrome: European Society of Cardiology (29) and American College of Cardiology/American Heart Association/Heart Rhythm Society (28) Consensus.

Patient characteristics

Age 40 or over, presenting with syncope*

No recent stroke, transient ischaemic attack or myorcardial infarction and no significant carotid stenosis (>70% in ESC guidance (29), though neither advocates routine carotid Doppler study screening prior to carotid sinus massage)

Carotid sinus massage and interpretation of test result

Locate carotid sinus as point of maximal carotid pulsation between the angle of the jaw and the cricoid cartilage

Ten seconds$^{\pm}$ bilateral, sequential, longitudinal carotid sinus massage, right then left, supine then upright with continuous ECG and beat-to-beat blood pressure monitoring

Positive test

Symptom reproduction during more than six seconds$^{\pm}$ asystole

- Cardioinhibitory CSS: asystole without significant vasodepression (i.e., 50 mmHg fall in systolic blood pressure)
- Mixed CSS: asystole with significant vasodepressor response.§

Management

Modification of culpable medication where feasible

Dual chamber pacemaker implantation may be indicated for cardioinhibitory or mixed CSS sub-types

Guidance

*While neither guideline expressly suggests massage in patients with unexplained fall or drop attacks that are likely to be syncopal, it is our centre's practice to do so in such individuals given the discussion above

$^{\pm}$Five seconds massage, and more than three seconds asystole for test positivity in North American guidelines (28)

§The European guidelines suggest repeated CSM with intravenous atropine injection to distinguish predominant cardioinhibition from vasodepression in mixed sub-type CSS (29) in order to characterise more accurately the relative contributions of asystole and non-asystole related hypotension

§Levels of evidence for pacing intervention are IIa in North American (28) and IIb in European guidelines (29)

answer is not possible from the data so far available, with the distinction between CSH and CSS proving particularly difficult from a pathophysiologic perspective. To further make the waters muddy, there is considerable observational evidence to suggest that there are large numbers of older people who have CSH in the absence of symptoms. Kerr et al. systematically evaluated a random sample of community-dwelling elders and found that 39% had CSH overall, with a cardioinhibitory response in 24%—in the absence of any culpable symptoms (33). Older studies with thousands of subjects found that 4–41% had CSH (24, 79, 80), with a particularly high prevalence in those with coronary artery disease (81) with or without culpable symptoms.

More troublesome is the changing face of the technique and criteria used to diagnose this apparent disease, morphing from "pressure" of up to 30 s to the current 10 s of longitudinal massage over the course of the last eight or nine decades. Current guidance, on very sound physiologic principles, defines the cutoff for CSS diagnosis as 6 s of asystole, ignoring the troublesome fact that many of the intervention studies since the 1980s used the 3 s criterion (26, 28, 30, 73) to establish the diagnosis. Additionally, current consensus guidelines on pacing in CSS base their entire (fairly strong) recommendation on such observational studies with apparently successful pacing in patients with CSS—diagnosed using the 3 s criterion, many with 5 s massage. So, while pacing may reduce syncope burden in CSS, there is little high-quality evidence supporting that it does so.

The answer to the question posed therefore is … probably. There is some evidence of disordered physiology in need of a remedy to treat the symptoms, although the test to diagnose is not a good one and the evidence supporting the intervention is arguably weaker than the strength of the recommendations for its use. Without a doubt, much further work is needed, with more detailed work on pathophysiology to guide treatment strategies, a better diagnostic test, and more clear phenotyping of symptom presentation that then aligns with potential pacing intervention. In addition, given the differences in test performance and interpretation as well as evidence level recommendations, it would be useful to develop world-wide consensus on the diagnosis and management of CSS (**Box 1**). Newer potential treatments for CSS' sister, neurally mediated condition vasovagal syncope, may offer additional therapeutic benefit and need evaluation, for example, autonomic modulation using parasympathetic cardiac ganglionic plexi ablation (82) and drug treatment with the norepinephrine transporter inhibitor atomoxetine (83).

If a slavish adherence to a gold-standard evidence base is to be the sole guiding principle, pacing cannot be recommended for CSS. However, in the real world of patient care where clinical experience chimes with the weight of history, while further evidence is rigorously sought, it is not unreasonable to follow imperfect but sensible consensus guidance until an unambiguous verdict is reached (**Box 1**).

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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Neurohormones in the Pathophysiology of Vasovagal Syncope in Adults

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Vasovagal syncope (VVS) is the most common cause of syncope across all age groups. Nonetheless, despite its clinical importance and considerable research effort over many years, the pathophysiology of VVS remains incompletely understood. In this regard, numerous studies have been undertaken in an attempt to improve insight into the evolution of VVS episodes and many of these studies have examined neurohormonal changes that occur during the progression of VVS events primarily using the head-up tilt table testing model. In this regard, the most consistent finding is a marked increase in epinephrine (Epi) spillover into the circulation beginning at an early stage as VVS evolves. Reported alterations of circulating norepinephrine (NE), on the other hand, have been more variable. Plasma concentrations of other vasoactive agents have been reported to exhibit more variable changes during a VVS event, and for the most part change somewhat later, but in some instances the changes are quite marked. The neurohormones that have drawn the most attention include arginine vasopressin [AVP], adrenomedullin, to a lesser extent brain and atrial natriuretic peptides (BNP, ANP), opioids, endothelin-1 (ET-1) and serotonin. However, whether some or all of these diverse agents contribute directly to VVS pathophysiology or are principally a compensatory response to an evolving hemodynamic crisis is as yet uncertain. The goal of this communication is to summarize key reported neurohumoral findings in VVS, and endeavor to ascertain how they may contribute to observed hemodynamic alterations during VVS.

Keywords: vasovagal syncope, neurohormone, neuroendocrine, catecholamines, tilt-table testing

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INTRODUCTION

Vasovagal syncope (VVS) is the most frequently encountered form of reflex syncope, and is the most common cause of syncope across all age groups (1, 2). Although the clinical importance of VVS has been widely acknowledged for more than a century, and despite considerable investigational effort, its pathophysiology remains incompletely understood. In this regard, several reports have examined neurohumoral changes accompanying VVS (primarily VVS induced during head-up tilt table testing) in an attempt to gain insight into the basis of the hemodynamic alterations associated with VVS episodes. For the most part, studies have focused on changes in circulating

catecholamines prior to and during VVS. However, a number of other neurohormones have also been the subject of study, including vasopressin, endothelin-1, adrenomedullin, brain and atrial natriuretic peptide (BNP, ANP) and serotonin. In this report we aim to summarize the key reported neurohumoral changes that have been observed during VVS, and endeavor to relate them to its pathophysiology.

OVERVIEW OF VVS PATHOPHYSIOLOGY

VVS pathophysiology remains a subject of active study with many residual unknowns (1–4). From a clinical perspective it is understood that susceptibility to VVS varies both among and within individuals over time. In this regard, multiple different VVS triggers (e.g., emotional upset, pain, venipuncture, and volume depletion), may initiate an event. However, even though it is believed that all humans (but not other species) are believed to be appropriately "wired" to permit VVS, certain individuals seem to be more susceptible to VVS triggers than are others. Additionally, VVS induction is inconsistent. The same stimuli do not always initiate episodes, even in individuals in whom VVS has previously occurred under similar circumstances.

Genetic predisposition may account in part for inter-individual variability of VVS susceptibility, but genetics cannot not readily address temporal variations of susceptibility within individuals. On the other hand, as yet poorly understood variations of both neural and neuroendocrine responses to triggers may play a role in determining whether a VVS event is initiated. With respect to neurohormone contributions to VVS (the subject of this communication), the relative magnitude of release of various endogenous vasoactive substances and their interaction at a given time, might be expected to vary, and thereby contribute to variation in the likelihood of VVS occurring at any point in time or in response to a particular "trigger." In this regard, a number of neuroendocrine changes have been identified as being associated with VVS events; however, whether they have a causation role, or are predominantly bystander (possibly even compensatory given ongoing hemodynamic changes) effects remain subjects of ongoing study.

Certain clinical observations are relevant to the understanding of VVS pathophysiology. Most importantly, VVS events tend to occur while the affected individual is in an upright position, and are extremely rare when patients are supine. Thus, it is reasonable to assume that gravity contributes, and that venous pooling is a crucial element of the pathophysiological process; in large measure the ability of head-up tilt (HUT) table testing to trigger VVS relies on this aspect of VVS physiology. However, whether the pathophysiology of VVS induced by head-up tilt is representative of VVS associated with other triggers (e.g., pain, emotional upset, dehydration) is unknown.

The pooling of blood below the diaphragm (i.e., in the thighs, buttocks, splanchnic bed, and possibly the pelvic organs) during upright posture inevitably diminishes venous return to the heart. The consequence is decreased right atrial volume, reduced pulmonary artery blood flow, and ultimately diminished cardiac output.

Reduction in venous return and an inappropriate reduction of cardiac output (CO), would be expected to trigger an increase in efferent sympathetic neural tone in an attempt to increase heart rate (a compensatory means to restore CO) and vascular tone in order to maintain both organ perfusion and systemic blood pressure (3, 5–8). The main drivers of these compensatory responses are primarily afferent signals from cardiac and vascular baroreceptors to central nervous system cardiovascular control centers in the mid-brain. Attempts have been made to discern which of the pressure/stretch receptors (i.e., atrial, arterial) are the more important for initiating VVS, but this has proved difficult. In any case, the afferent signals are directed to the nucleus tractus solitarii in the medulla oblongata, where integration with other incoming inputs takes place (3). Subsequently, in an evolving VVS there is a sequence of neural and hormonal changes that are reasonably interpreted at least initially as a compensatory attempt to prevent hypotension. Not infrequently, the compensation is effective in stabilizing the circulation, and syncope does not occur. Nevertheless, patients may experience certain "warning" symptoms that spontaneously resolve including palpitations, abnormal temperature sensations and gastrointestinal upset. However, if compensation fails, then the VVS episode progresses to include diminished cardiac output with hypotension.

Reports vary regarding the changes in sympathetic nerve activity that occur VVS in susceptible patients (4). Some studies suggest that diminution of sympathetic tone as assessed by microneurographic sympathetic nerve activation (MSNA) recordings cause loss of venous and arterial tone (i.e., vasodepression) resulting in progressive reduction of venous return and arterial pressure (3). On the other hand, others have noted preservation of MSNA throughout an evolving VVS has also been observed until the development of syncope. The apparent discordance in MSNA observations during induced VVS requires further study. In this regard a few possible explanations merit investigation, including: (1) unknown factors, other than sympathetic nerve activity, determine vascular resistance status, and (2) MSNA recordings, by virtue of being able to assess a limited number of accessible nerves, may not be recording those nerves most pertinent to the evolving hypotension, (3) despite maintenance of MSNA, hypotension may occur if NE release is impaired at the synapse or NE re-uptake is enhanced.

The late phase of VVS is associated with an increase in parasympathetic tone. The latter, tends to result in a marked or relative cardioinhibition, thereby undermining any attempt to provide a compensatory chronotropic response in the face of evolving hypotension.

SPECIFIC NEUROHUMORAL ALTERATIONS ACCOMPANYING VVS

A wide range of neurohumoral changes have been reported to be associated with evolving VVS episodes. Most findings have been observed using head-up tilt (HUT) triggered VVS, while a few

have been obtained during VVS induced by lower body negative pressure (LBNP).

Alterations of circulating catecholamines during evolving VVS have been the subject of study since the mid-1960s, with some difficult-to-explain differences being reported. The first observations are usually credited to Chosy and Graham (9) who noted higher urinary epinephrine (Epi) levels in blood donors who went on to faint than in others who did not faint. Subsequently, others provided more detailed evaluation of catecholamine changes in VVS, along with assessment of a variety of other neurohumoral agents to be discussed later. The principal observations are summarized here.

Catecholamines

The possibility that circulating catecholamines play a role in VVS pathophysiology has been the subject of interest for more than 30 years (3, 6–20). The most consistent finding has been a relatively early increase in circulating epinephrine (Epi) during head-up posture prior to the faint. The basis for this Epi increase is as yet unexplained.

In most instances, the Epi concentration at time of syncope was higher than baseline and much higher than observed after comparable periods of head-up posture in non-fainters. However, in a few reports the Epi levels were not significantly increased (13, 15). Reasons for the differing outcomes remain unclear, although in the report by Vanderheyden et al. (15), the mean value of Epi did increase but the standard deviations in a relatively small population was large and may have obscured any statistically significant change.

In terms of key studies examining catecholamines during induction of VVS, Fitzpatrick et al. (10) observed a substantial increase of circulating epinephrine (Epi) concentrations in association with an imminent faint in 7 tilt-table induced fainters, but not in 2 control subjects and 2 other individuals who had a fainting history, but in whom the HUT did not trigger an event. Further, Epi concentrations were somewhat higher in fainters at baseline and at 10 min of tilt when hemodynamics were stable, However, in close temporal relation to the faint, epinephrine concentration was substantially higher in HUT-positive fainters than in HUT-negative non-fainters. Norepinephrine (NE) also increased during HUT but did not differ significantly in the 2 groups for the duration of the test. These same investigators also identified a marked increase in circulating arginine vasopressin (AVP) and pancreatic polypeptide (PPP) during upright posture in fainters compared to controls, topics that will be addressed more fully later.

In the report by Sra et al. (11), a somewhat larger population was studied (30 individuals; 19 VVS subjects and 11 controls). These researchers also observed that NE increments with head-up posture were comparable in VVS patients and controls, but that Epi increments were much greater in the VVS subset (∼5-fold increase) compared to minimal change in control subjects. The authors concluded that VVS is associated with diminished neuronal sympathetic NE release, and enhanced adreno-medullary activity.

The most detailed early evaluation of hemodynamic and neurohumoral changes in evolving VVS was provided by Jardine et al. (14) using prolonged head-up tilt at 60 degrees. Norepinephrine (NE) and epinephrine (Epi) increased early during upright posture to a greater extent in fainters than controls. However, in proximity to syncope the Epi level continued to rise while NE fell back to control values. Ermis et al. (16, 17) found that the NE values continued to rise throughout the HUT but were similar in both fainters and controls, with no fallback in the fainter group at the time of symptoms. However, consistent with most of the reports summarized above, Epi continued to rise, and reached values 6 to 15 times baseline depending on the site from which the blood was drawn (i.e., femoral vein, aorta, renal vein-vena caval junction) (**Figure 1**). In essence, near the time of head-up tilt induced faint, all reports agree that the Epi/NE ratios were much higher in fainters than was the case at baseline in the same individuals or in comparable control subjects.

Using lower body negative pressure method, Lenders et al. (18) concluded that there was larger synaptic norepinephrine "spillover" (i.e., NE which reaches the circulation) in non-fainters than fainters. This observation implies several possibilities in non-fainters compared to fainters: (1) greater NE production, (2) more NE being released at the synapse, or (3) less NE being re-captured by the synaptic re-uptake process. The latter observation suggested that perhaps there was a defect of neural NE production in fainters or an unexpected augmentation of NE reuptake in the synapse.

In regard to the NE neural production issue, Vaddadi et al. reported reduced tyrosine hydroxylase activity, an important rate-limiting step in NE synthesis in VVS subjects (20). The latter occurred predominantly in patients who presented with a low blood pressure phenotype of VVS as initially described by Mathias et al. (21). The same investigators also observed higher NE transporter (i.e., increased re-uptake capability within the synapse) in the normotensive blood pressure phenotype of VVS patients. Both of these functional sympathetic nerve defects would be expected to reduce NE spillover into the circulation, and thereby be consistent with the diminished NE levels summarized above. On the other hand, if these NE production and/or NE re-uptake issues are confirmed to be prevalent in VVS susceptible subjects, it raises the issue of why VVS only occurs intermittently and not reproducibly. Potentially, NE production/re-uptake may vary with time, a possibility that would be very difficult to study.

The apparent disturbance of NE release and/or uptake was further assessed by Ermis et al. (16, 17), who also noted that while circulating NE rose throughout HUT, the increments with upright posture in fainters were similar to that in controls and much less than might have been expected given the hemodynamic crisis. However, they also observed that to some extent NE release at the level of the renal/adrenals may provide some element of compensation (**Figure 1**). Specifically, Ermis et al. (16) reported that there was near doubling of NE concentrations near the time of syncope between femoral venous sites and supra-renal sites in fainters but not in non-fainters (714 ± 476 pg /ml vs. 385 ± 166 pg/ml, $P < 0.05$). The authors speculated that this latter NE increment was derived from the kidneys or adrenal gland and may have provided some

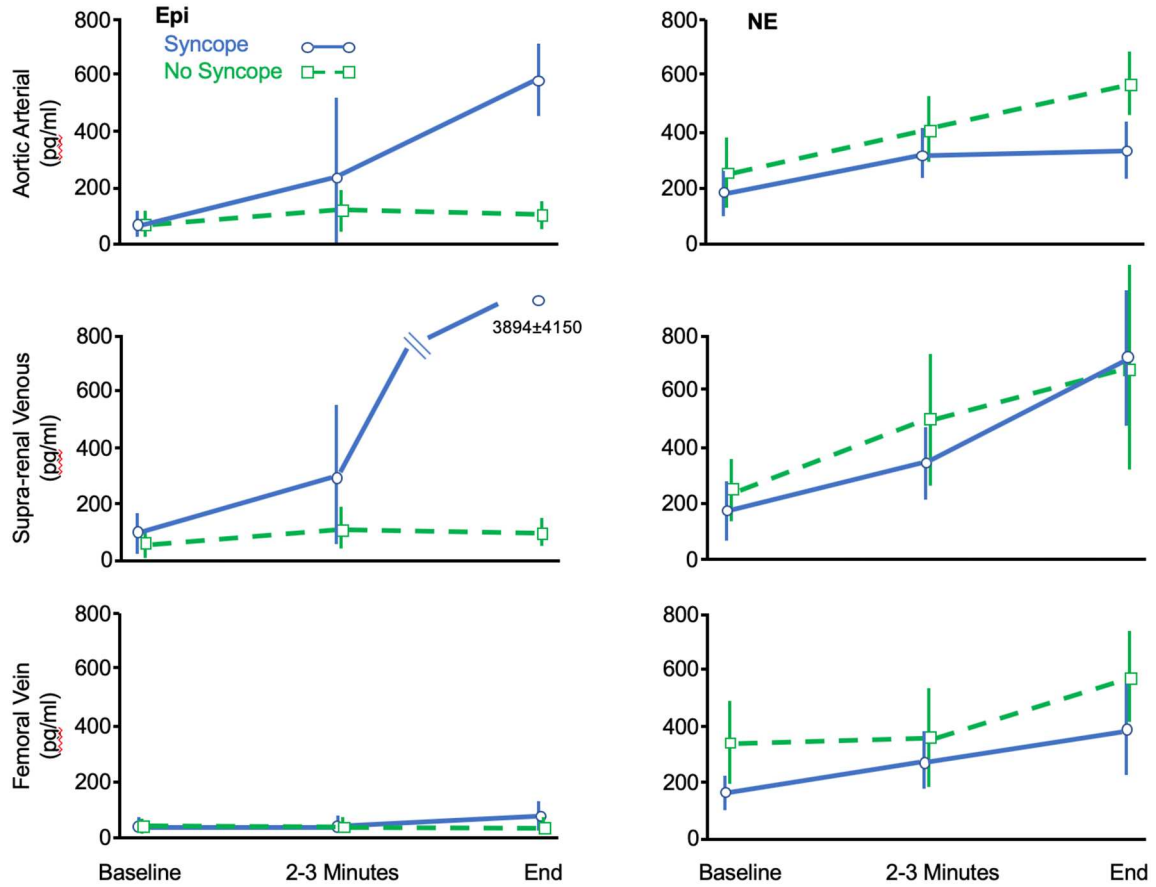

FIGURE 1 | Data adapted from Ermis et al. (16) showing change of circulating Epi and NE concentrations (ordinate: pg/ml) measured at various anatomic sites during the course of HUT-induced syncope (Blue) or HUT without syncope (Green). See text for details.

compensation for failure of synaptic NE contribution to maintain hemodynamic stability. It also suggests that the drivers for NE release may differ at the neural synapse vs. adrenal/renal sites; if that were the case, perhaps any postulated issues with NE production/re-uptake noted earlier, may not apply to the same extent in the adrenal glands or kidney. At present, the basis for this seeming difference between neural and organ NE overflow is unknown.

More recently, the relationship between tilt-induced increase of circulating catecholamines (particularly Epi) and time to HUT-induced VVS (i.e., the latter being used as a surrogate measure of "susceptibility" to VVS) has been introduced for use in the clinical laboratory. Kohno et al. (19) observed a significant correlation between higher baseline and 2-min plasma Epi level and shorter time to syncope (baseline: R-Squared = 0.12, P = 0.048, and 2 min : R-squared = 0.33, P = 0.001) (**Figure 2**). Similarly, there was a significant correlation between greater Epi/NE ratio at 2 min and shorter time to syncope (R-squared=-0.49, P = 0.007). Finally, a greater increase of Epi levels from baseline to 2 min of HUT (i.e., difference 2-min Epi minus baseline Epi) was associated with a shorter time to syncope (R = -0.58, P = 0.001). On the other hand, with respect to NE alone, neither 2-min HUT levels nor change from baseline values correlated with time to syncope.

In an even more recent study of a large group of VVS susceptible individuals, Torabi et al. (22) reported findings very similar to those of Kohno et al. (19).

In summary, VVS triggered by head-up posture appears to be associated with marked increases in circulating catecholamines even prior to hypotension; circulating epinephrine levels seem to increase particularly dramatically. However, whether these changes are causal remains uncertain. An epinephrine (Epi) relation to VVS susceptibility seems likely given the consistency of the finding of increased Epi levels across many studies. However, if Epi or NE changes contribute directly to VVS pathophysiology, the manner in which they participate is as yet uncertain. One initial concept was that Epi/NE enhance ventricular force of left ventricular contraction and thereby stimulate myocardial wall mechanoreceptor afferent signaling, with a subsequent reflex lowering of heart rate and blood pressure. However, this mechanism is not widely held given the observation of VVS after heart transplantation. Potentially, other non-cardiac arterial receptors may be operating in parallel thus maintaining a modified version of the basic theory. In any case,

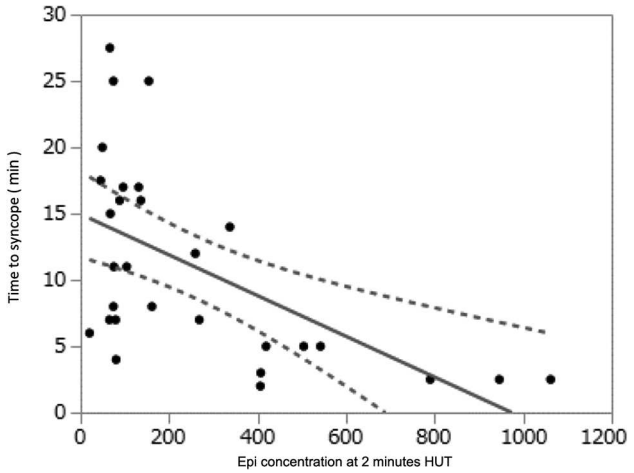

FIGURE 2 | Data derived from Kohno et al. (19) showing that the time to syncope during HUT was shorter (Time in Minutes on ordinate) as the Epi concentration increased (abscissa, pg/ml).

while at best only an indirect argument in favor, the physiologic actions of a greater Epi/NE ratio is appropriate to lead to clinical features consistent with VVS (e.g., vascular dilatation in some beds with constriction in others such as the skin). Nevertheless, this interpretation of the role of catecholamines has not been without controversy, especially given the failure of adrenergic blockers to show a universal clear preventative benefit in VVS susceptible patients (23).

Vasopressin

Arginine vasopressin (AVP), is an endogenous nonapeptide hormone synthesized in the hypothalamus and subsequently transported via neuronal axons to the posterior pituitary gland where it is able to access the circulation (24, 25). Release into the circulation from pituitary capillaries is facilitated by their lack of blood-brain barrier. At usual circulating concentrations, AVP's action is primarily antidiuretic (hence its other common name: antidiuretic hormone). However, at higher than physiologic levels such as might be expected during a hypotensive crisis, AVP is a potent vasoconstrictor (26).

In health, AVP is not deemed important for maintaining cardiovascular homeostasis. However, in a crisis (e.g., severe hemorrhage), endogenous circulating AVP may increase sufficiently to provide compensatory benefit. AVP interacts with 3 receptors (V1: predominantly vascular effects, V2:which mainly act to retain water, and V3: which are mainly in neurons, particularly the adenohypophysis leading to ACTH release) (24, 25). On the other hand, acting centrally, AVP enhances baroreceptor sensitivity. The expected result of the latter action would be increased vagotonia and lower sympathetic tone relative to the level of blood pressure (this may be important in VVS as discussed later).

Increased levels of AVP in association with VVS were first reported by Riegger and Wagner (27) and Fitzpatrick et al. (10), and again somewhat later by others including Jardine et al. (14) and Theopistou et al. (28), Rash et al. (29) and Nilsson et al. (30). The report by Fitzpatrick et al. (10), although encompassing a small patient population, indicated that baseline AVP was higher in fainters and that remained the case at 10 min of HUT when hemodynamics were still stable. With syncope, AVP was markedly increased. Jardine et al. (14) and Theopistou et al. (28) similarly noted that AVP increased during HUT in fainters, although only modestly or not at all in the early stages of the procedure when hemodynamics were stable. However, at the time of syncope, AVP was 20-fold higher than baseline (28). On the other hand, Rash et al. (29) did not observe any evident baseline AVP differences among 3 groups of patients (VVS, epilepsy and controls) but they did not provide measures during or in proximity to syncope events. Finally, Nilsson et al. (30) found AVP to be higher in patients who fainted spontaneously during HUT compared to those who fainted after nitroglycerine stimulation. The pathophysiologic implication of this latter set of observations is not immediately evident.

In summary, Fitzpatrick et al. (10), Jardine et al. (14) and Torabi et al. (22) observed moderately increased AVP values early in HUT in VVS prone patients suggesting a potential marker of susceptibility, but others did not detect baseline differences (28, 29, 31). Nonetheless, all confirmed that AVP increased abruptly in close proximity to the faint itself. Thus, while one cannot yet be certain, it appears that the elevated AVP levels are more likely reactive to evolving hypotension rather than a marker of susceptibility. On the other hand, as discussed below, AVP may ultimately contribute as an additional provocateur, not so much as a compensatory actor.

The role of AVP in blood pressure control is not fully settled (24, 32), and assessing its actions in a setting in which catecholamines are also increased is particularly problematic. Most investigators agree that short-term blood pressure control is primarily neurally-mediated rather than humoral. AVP, as a vasoconstrictor, may only become important during a hemodynamic crisis (26). In regard to VVS, and based on the preponderance of observations summarized above, it seems that a substantial AVP rise occurs primarily in response to a serious hypotensive crisis (i.e., the final phase of the VVS event). The latter is consistent with the findings of Goldsmith et al. (26) showing that in humans AVP release to levels that may have vasoconstrictive capability (i.e., potentially compensatory in the setting of VVS-induced marked hypotension) is only triggered by very severe drops in systemic pressure. Nonetheless, whatever the trigger for marked AVP release near the end of a VVS event, it is inadequate to reverse the progressive and often dramatic blood pressure fall in patients destined to faint.

Why AVP fails to reverse the hypotensive trend even when finally released in substantial concentrations is not immediately obvious. However, the explanation may lie in the net outcome of two potentially contrary AVP actions: (1) a direct AVP constriction effect, and (2) reflex effects initiated by AVP-induced increase in central venous pressure that triggers low pressure atrial mechano-receptors (see earlier). In brief, Aylward et al. (24) noted that exogenous AVP infusion to levels known to have an antidiuretic effect had little hemodynamic impact in healthy men. Further reflex changes induced by neck pressure,

neck suction, or lower body negative pressure (LNBP) were unaffected. However, at higher AVP doses, there was unexpected forearm vasodilation; this being a vascular bed that seems to be strongly influenced by low pressure atrial receptors (24). Further, reflex vasodilation triggered by release of LBNP was augmented in the presence of AVP. Thus, under certain conditions in humans, the net effect (i.e., constriction vs. baroreceptor anti-sympathetic action) of AVP may facilitate reflex vasodilation. If that occurs in an evolving VVS scenario in which (like LNBP) there is diminished venous return, AVP may exacerbate the blood pressure (BP) problem. However, as BP plummets, the AVP reflex anti-sympathetic action may diminish and peripheral resistance may then have an opportunity to increase and restore hemodynamic stability.

In conclusion, multiple studies are consistent in reporting marked increase of AVP in temporal proximity to a VVS event. However, resting AVP levels do not appear to be a marker of VVS susceptibility, as they are not consistently different in VVS susceptible patients and controls. Consequently, the terminal-VVS AVP rise in fainters is most likely a reaction to serious systemic hypotension. However, and paradoxically perhaps, the marked AVP rise in the setting of reflex hypotension may exacerbate the drop in pressure via an effect on baroreceptor sensitivity. The latter are active in the basal state, providing vagal tonus and sympathetic inhibition. AVP may enhance these effects by increasing central venous pressure. In other non-reflex hypotensive circumstances (e.g., severe hemorrhage) in which a central venous pressure fall cannot be readily reversed by AVP, the net action of an increased AVP level may be of compensatory value. Clearly, further study of AVP action in VVS is needed.

Endothelin-1

Endolthelin-1 (ET-1) is a 21 amino acid peptide vasoconstrictor and pro-inflammatory agent derived from a 39 amino acid precursor through an endothelin converting enzyme (33). ET-1 is one of 3 isoforms (ET-1, ET-2, ET-3), but is the most important from a cardiovascular perspective.

ET-1 which is primarily derived from endothelial cells, may be viewed as balancing the effects of nitric oxide (NO). Its release is also inhibited by NO, atrial natriuretic peptide (ANP), and by prostacyclin. Conversely, ET-1 release may be promoted by humoral factors including AVP, angiotensin II, as well as physical factors such as vascular shearing forces. Under pathological conditions, ET-1 may be produced by other cells including vascular smooth muscle cells and cardiac myocytes. ET-1 effects act through 2 receptors (ET_A, ET_B), with the net effect (constriction vs. NO release by ET_B) being determined by the location and balance between receptor sites (33).

Several studies have examined ET-1 in VVS patients. Rash et al. (29) found no difference in baseline ET-1 levels among syncope, seizure and control subjects. Magerkuth et al. (34) found elevated ET-1 in tilt-test positive patients both on the day of the test and at other times suggesting that ET-1 may be a marker for susceptibility. However, baseline differences were not found by either White et al. (35) or Kaufmann et al. (36). The former noted that orthostatic stress increased ET-1 in controls, but not in VVS positive patients, while Kaufmann et al. found ET-1 to rise similarly with upright tilt in VVS patients and in controls, but not at all in autonomic failure patients. They concluded, that during orthostatic stress the ET-1 increase is mediated by ET-1 released from the neurohypophysis rather than the vascular periphery. In this regard, Fedorowski et al. (37) came to an analogous conclusion suggesting that increased ET-1 is more consistent with neurogenic non-VVS orthostatic cause of syncope, while low ET-1 is a marker of VVS. While such a conclusion requires more evidence, these three reports are consistent (34–37); in essence, lower ET-1 levels were associated with greater likelihood of initiating VVS. Presumably, diminished ET-1 induced vasoconstriction may enhance VVS susceptibility.

Adrenomedullin

Adrenomedullin (ADM) is a 52-amino acid multifunctional peptide vasodilator (acting via NO) and natriuretic agent that was first isolated from pheochromocytoma tissue in the early 1990s (38). It is widely accepted that measurement of the mid-regional fragment (MR-proADM) is a useful surrogate for ADM itself. High ADM levels have been associated with POTS in children (39).

The role of ADM in VVS has been the subject of several reports but currently its impact remains unclear. Plasek et al. (40) did not observe a significant difference in ADM levels in a study comparing of 14 HUT-positive patients with a cohort of 14 HUT-negative control group. Gajek et al. (41) observed ADM to rise substantially in patients who developed VVS during the passive phase of HUT (but not if nitroglycerin-induced) On the other hand, Hamrefors et al. (42) observed that in patients >40 years of age, lower supine MR-pro-ADM predicted asystolic VVS on HUT, although orthostatic levels of the biomarker were not assessed. They also noted a tendency toward a relationship between ADM levels and tendency to cardioinhibitory forms of VVS; in brief, lower ADM levels were associated with greater likelihood of cardioinhibition. The highest ADM levels were noted in HUT-negative subjects. More recently, Torabi et al. (22) found that higher baseline MR-pro-ADM during HUT was associated with longer time to syncope. Thus, for unclear reasons higher ADM levels appears to be "protective," whereas intuitively the opposite would be expected. In any case, in the largest study to date examining baseline ADM levels, Fedorowski et al. (37) in multivariable analysis did not find it to be an independent marker of VVS susceptibility.

Atrial (ANP) and Brain (BNP) Natriuretic Peptide

The potential contributions of brain and atrial natriuretic peptides (BNP and ANP) on VVS induced by HUT were first examined by Jardine et al. (14) in VVS patients and control subjects. In that study, BNP did not differ in the two patient groups, and did not change substantially throughout HUT and recovery; consequently, BNP has for the most part not been deemed relevant to VVS pathophysiology. However, it has been suggested that BNP may be a useful diagnostic marker in for cardiac syncope, but that issue will not be discussed further here.

In regard to ANP, Jardine et al. (14) found that while ANP levels are higher in syncope-prone patients compared to controls, they were not appreciably altered by whether syncope occurred or not. In fact, ANP levels tended to decline in both groups throughout the tilt procedure. Subsequently, Fedorowski et al. (37) examined mid-regional fragments of pro-atrial natriuretic peptide (MR-proANP); findings revealed that ANP levels tended to be lowest in patients prone to tilt-induced fainting and highest in non-fainters. Consequently, the role played by ANP, if any is unclear and difficult to explain. Specifically, while increased ANP levels in isolation may largely reflect atrial stretch status, the latter may be affected by other influences occurring at the same time analogous to the complex effects of AVP discussed earlier.

Galanin

Galanin is a neuropeptide that is widely distributed in the central and peripheral nervous systems (43). Galanin interacts with both sympathetic and vagal systems as well as with neurotransmitters, such as serotonin. In animals, galanin can lower blood pressure and attenuate vagally-induced slowing of the heart rate. In humans, the administration of galanin depresses basal norepinephrine and norepinephrine responses to both assumption of upright posture and insulin-induced hypoglycemia.

Bondanelli et al. (44) examined plasma galanin changes during HUT in healthy subjects and patients with recurrent VVS. In healthy subjects, galanin did not change during HUT. However, in VVS patients with a negative response to tilting (no syncope), galanin significantly ($P < 0.001$) increased and correlated positively with the increases in blood pressure (BP) and heart rate (HR). In control patients with a positive HUT response (i.e., false positive), galanin did not change either before the loss of consciousness or during syncope. Thus, circulating galanin levels progressively increased during a negative HUT in patients with a history of VVS, whereas they remain unchanged in healthy subjects. Moreover, in the patients with tilting-induced syncope galanin does not change either before or during loss of consciousness. Potentially increased Galanin acted to diminish VVS susceptibility.

Plasek et al. (40) obtained slightly different results. These authors observed an increase in plasma galanin for VVS patients during HUT, regardless of whether they developed syncope or not during the test. Conversely, orthostatic stress was associated with galanin decrease in controls. Thus, galanin might be useful as a marker for VVS susceptibility, but further evaluation is needed.

Pancreatic Polypeptide

Pancreatic polypeptide is a 36-amino acid peptide secreted from the pancreas. Its primary action is in the gastrointestinal system where its release is known in part to be mediated by vagal activity. It helps regulate pancreatic hormone release and may have satiety actions.

In regard to VVS, pancreatic polypeptide has been reported to be increased in conjunction with the faint (10, 14). Jardine et al. (14) observed a statistically significant greater increase in pancreatic polypeptide during HUT compared to controls in whom there was no change from baseline. Fitzpatrick et al. (10) observed no difference between HUT positive fainters and HUT negative controls during the tilt test procedure. However, pancreatic polypeptide increased markedly during HUT recovery in fainters but was unaffected in control subjects.

In summary, it is unlikely that pancreatic polypeptide has a mechanistic action in VVS, other than as a marker of increased vagal activity in temporal proximity to the faint. Perhaps an elevated measurement after recovery may be a marker of a recent VVS event, but further evaluation is needed before such an application can be recommended.

Others (Cyclic AMP, Opioids, Plasma Renin Activity, Angiotensin II, and Serotonin)

Cyclic AMP

Cyclic AMP (cAMP) is an intracellular second messenger, that transduces the effects of a number of hormones (e.g., epinephrine) that cannot enter cells themselves. Abe et al. (12) examined changes in cyclic-AMP during HUT-induced VVS. However, the use of isoproterenol in the HUT protocol somewhat complicates interpretation of the results, but HUT with isoproterenol was associated with a c-AMP increase with movement to upright posture and a further increase if syncope was induced. However, in terms of magnitude, the c-AMP increase of ∼16% was less in percentage terms than was the case for NE, being ∼44%. Beta-blockers, particularly propranolol, blocked both c-AMP changes and syncope induction in this report.

Mitro et al. (45) also examined c-AMP in VVS although they did not undertake a c-AMP measurement to determine if a premonitory change was evolving at the crucial point during upright posture when hemodynamics were stable to determine if a premonitory change was evolving. In their report, 61 syncope patients (age 35 ± 15 years) underwent a passive HUT. Blood samples for NE, Epi, and dopamine were obtained at baseline supine, at 5 min of HUT and at syncope or end HUT (45 min). cAMP values were obtained at baseline and at the end HUT. HUT was positive for VVS in 33 and negative for VVS in 28 patients. There were no significant neurohumoral baseline difference, but while NE, Epi and dopamine were higher with HUT at 5 min, there were no significant differences between the groups. As expected based on findings presented earlier, at the time of syncope, catecholamine levels in HUT-positive patients were higher than baseline levels and higher than in HUT-negative patients. Similarly, cAMP levels increased at syncope and were higher than in non-syncopal patients at the end of the HUT (607 ± 460 vs. 328 ± 297 nmol/ml).

In summary, while the investigators have raised the possibility that c-AMP may be relevant to the pathophysiology of an evolving VVS, it is reasonable at this point to conclude that c-AMP levels are primarily driven by the catecholamine changes summarized earlier.

Endogenous Opioids

Endogenous opioids have been considered as agents potentially triggering or otherwise contributing to VVS (13, 46). Several observations favor this possibility: (1) the high concentration

of neural opioids in the mid-brain cardiovascular centers, (2) previous findings indicating that naloxone diminishes baroreceptor sensitivity, (3) opioid agonists have been shown to trigger a vasovagal-like response to experimental hemorrhage, and (4) beta-endorphins have been shown to be increased in association with VVS. Further, in an initial study, Wallbridge et al. (13) noted beta-endorphin increase prior to the faint.

Perez-Paredes et al. (46) evaluated the role of endogenous opioids in neurally-mediated syncope. Head-up tilt test was performed on 35 patients with syncope of unknown origin. Subjects with a positive drug-free HUT showed a larger rise in plasma beta-endorphin concentrations at time of syncope (baseline 13.7+/-8.0 vs. syncope 41.4 $\pm$ 26.4 pmol/l; $P < 0.01$). On the other hand, patients with a positive isoproterenol-test showed no rise in plasma beta-endorphin levels as was also the case for subjects with negative HUT tests. However, intravenous naloxone at a dose of 0.02 mg/kg was not superior to placebo for preventing positive responses to baseline HUT.

In summary, the role that opioids may play in VVS is uncertain. However, given the lack of utility of opioid agonists for preventing VVS, it is unlikely that the opioid contribution is crucial to VVS pathophysiology.

Plasma Renin Activity and Angiotensin II

Jardine et al. (14) provided the first assessment of renin and angiotensin II in HUT-induced VVS. Findings show that renin increased substantially in control non-fainters, but only modestly in fainters. Similarly, angiotensin II increased somewhat in both groups, but remained higher in non-fainting controls. Gajak et al. (47) examined plasma renin activity (PRA) and found that it increased throughout the HUT procedure and was ∼2.5-fold greater than baseline at the time of syncope. However, there were no comparative control data offered. In this regard, Vanderheyden et al. (15) observed that patients with cardioinhibitory syncope exhibited blunted activation of the renin-angiotensin-aldosterone axis at syncope. Conversely, the renin-angiotensin-aldosterone axis is activated in patients with vasodepressor syncope and in patients with a negative result of head-up tilt test.

Angiotensin II antibodies and antiadrenergic antibodies have been postulated to play a role in postural orthostatic tachycardia syndrome. A similar finding might reasonably be anticipated in individuals susceptible to VVS. However, Yu et al. did not find this to be the case (48).

In brief, the role of PRA/angiotensin II in VVS pathophysiology remains unclear. Additional controlled observations are needed.

Serotonin

Serotonin (5-hydroxytryptamine) is derived from neural and gastrointestinal sites, with subsequent storage predominantly in platelets, and has a number of effects on the central nervous system as well as the endocrine and cardiovascular systems. Matzen et al. (49) raised the possibility that inasmuch as serotonin has been associated with BP regulation, and is well-represented in areas of the brain pertinent to VVS, it may be a contributor to VVS by virtue of central-mediated anti-sympathetic effects. In an initial study these authors found that serotonergic stimulation using the re-uptake inhibitor clomipramine (with prolactin and cortisol as biomarkers) resulted in a greater effect in patients with presumed VVS than in control subjects (49). Later, the same group reported the effects of clomipramine during HUT (50). In this report, all individuals had been previously tested using 60 degrees HUT for 30 min, and if negative, with isoproterenol provocation. Baseline HUT was positive in 23/55 cases (53%) patients and none of 22 controls. However, after clomipramine, HUT was positive in 80% of patients, but only one control subject. The authors concluded, based on these 2 studies, that enhanced serotonin responsiveness with clomipramine leading to a presumed (but not proven) greater sympatholytic effect, supports a mechanistic role for serotonin in the central pathways leading to VVS initiation.

Unfortunately, interpretation of the clomipramine observation is clouded by the fact that the drug impacts many other receptor sites (e.g., histamine H1, norepinephrine re-uptake [NET], and muscarinic sites). Further, clomipramine metabolites exhibit a greater blocking affinity for NET than for the serotonin re-uptake site. Consequently, studies with clomipramine can only be taken as suggestive of serotonin contribution to VVS. Furthermore, others have provided findings that seem to dispute an active role of serotonin in VVS. For example, Matzen et al. (49) found that while methylsergide (a serotonin receptor blocker) did alter a number of neurohumoral responses (e.g., NE, PRA) during HUT, it did not alter hypotensive responses. Similarly, Alboni et al. (51) did not find a substantial change in plasma or platelet serotonin levels during HUT-induced VVS. Consequently, the available literature does not support a crucial place for serotonin in the initiation of VVS.

In summary, a putative role for serotonin in VVS remains debatable. For the most part selective serotonin reuptake inhibitors (SSRIs) have not proved effective clinically for preventing VVS. Nevertheless, further evaluation of the serotoninergic pathways with more specific blockers is warranted.

POSSIBLE IMPLICATIONS OF NEUROHUMORAL AGENTS IN VVS PATHOPHYSIOLOGY

Humans are believed to be the principal if not the only species exhibiting VVS. However, VVS susceptibility does seem to differ among individuals, and also varies over time within affected persons. Thus, while 20–30% of humans report having had a presumed VVS event in their lifetime, only a much smaller proportion exhibit multiple episodes (1–4, 8). Further, even among patients in whom VVS is known to have occurred, repetitive exposure to the same stimulus may not consistently trigger an episode. The latter is exemplified, for example, by lack of reproducibility of VVS induction during HUT (52). Consequently, while inter-individual genetic issues may account for some differences among individuals, they cannot account

for intra-individual variations in susceptibility. In this regard, alterations in factors such as hydration, environmental exposure (e.g., temperature, stress, etc.) and neurohumoral status may be relevant.

Several hypotheses have been put forward in an attempt to understand VVS pathophysiology (see Ref #3 for summary). However, none provide a comprehensive explanation for how a VVS episode is first triggered, then evolves, and ultimately self-terminates. The understanding that does exist is principally based on observations obtained in VVS induced by upright posture or by LBNP (as opposed for example to emotional or pain triggers).

Initial VVS Stage

It is generally agreed that in orthostatic-triggered VVS the initial and perhaps crucial event is diminution of venous return to the heart with associated fall of stroke volume (SV) and cardiac output (CO). The venous reservoir below the diaphragm is very large and compliant; if dilated by neural and/or humoral agents, blood pooling may occur which is far in excess of the usual volume associated with movement to upright posture. The dependent sites which are particularly likely to pool blood are the thighs, buttocks, pelvic organs and very importantly the splanchnic bed.

Apart from the altered concentrations of circulating catecholamines (mainly Epi and NE) as VVS evolves, there is in addition a change in the Epi/NE ratio (see earlier discussion). Potentially, the greater the circulating Epi/NE ratio, such as has been documented in an evolving VVS event (see above), the greater the potential dependent pooling.

The functional impact of a greater Epi/NE ratio during an evolving faint is not proven but as pointed out by Goldstein et al. (6) it appears that activation of the sympathetic neural and adrenal sympathetic system do not necessarily operate in concert ("sympatho-adrenal imbalance"). Thus, while Epi is usually a predominant vasoconstrictor (alpha-adrenergic action) in the cutaneous circulation (which likely accounts for the pallor associated with VVS), the constrictor effect is not a universal Epi action. In the case of VVS, Epi concentrations in excess of NE may be expected to dilate certain skeletal muscle beds and thereby contribute to venous pooling. Further, at high concentrations Epi beta-adrenergic effects may be vasodilatory in both the splanchnic and hepatic circulation. The latter action may in part account for the abdominal sensation (often perceived as "nausea" or abdominal fullness) that often accompanies VVS.

A substantial increase in peripheral vasoconstrictor activity (e.g., exogenous NE infusion) may ameliorate or terminate the evolving VVS event in the initial stage of VVS, but with a higher than usual Epi/NE ratios, reversal of the evolving hemodynamic crisis may not occur unless the patient voluntarily assumes a gravitationally neutral posture.

Several reports note that the catecholamine changes begin at a time during HUT when patients are still hemodynamically stable, suggesting a contribution to the initiation of the event (10, 14, 53). Further, the increase is greater in subjects who go on to faint, than in those who do not. Moreover, among individuals who go on to faint, the greater the Epi increase and the higher the Epi/NE ratio early upon assuming upright posture, the greater the VVS susceptibility as measured by "time to syncope" (19, 22).

Despite the plausible role played by Epi and Epi/NE ratio in triggering VVS, there is also strong evidence pointing away from these agents being causative. For instance, Calkins et al. did not find Epi to be useful for triggering VVS during tilt-testing (3, 54). More importantly though, while a number of small, single-center observational studies have suggested that beta-adrenergic blockade may be beneficial prophylaxis in VVS patients, the broader clinical experience is that beta-adrenergic blockers typically do not provide protection against VVS recurrences in most patients (1, 2, 8, 23). In this regard, Sheldon et al. (23) observed only a trend toward utility of beta-adrenergic blockers in older (>42 years) but not younger VVS susceptible patients. On the other hand, as has been suggested by others (55, 56), older patients appear to release less epinephrine than do younger individuals. Perhaps, it may be possible to achieve adequate blockade with tolerable beta-blocker doses in older individuals, while that might not be achievable in younger patients.

Reduction of venous return to the heart diminishes SV and CO. In otherwise healthy individuals, this scenario not unexpectedly triggers an increase in heart rate (HR). The resulting presumably compensatory positive chronotropic drive, is most likely initiated by signals derived initially from low pressure cardiac receptors, as well as potentially somewhat later by higher pressure arterial receptors; the result is parasympathetic "withdrawal" and sympathetic neural activation. The role of neurohumoral agents at this stage is uncertain. However, the impressive rise of epinephrine levels early during the evolving faint is likely important.

Ultimately, diminished venous return prevents an increased heart rate from providing adequate hemodynamic support. Consequently, given the falling CO despite the attempted HR compensation, one might also expect total peripheral resistance (TPR) to rise in conjunction as sympathetic neural activation attempts (at least in healthy circulations) to maintain blood pressure (BP). However, while HR rises, TPR change is less clear-cut in VVS. Perhaps the explanation in part relates to the altered circulating Epi/NE ratio with constriction in some beds and vasodilation in others as noted earlier. However, as time goes by, other hormonal contributors may become important, particularly vasopressin (AVP).

Second Phase

As the VVS episode evolves, usually over several minutes, a modest but important downward BP trend has been well-described; this occurs typically at a time when HR is still higher than baseline (57–59). Why the heart rate is not driven to very high levels at this time is has not yet been fully explained. However, one may speculate that a balance is developing between the former Epi predominance, and resurgence of parasympathetic activity.

Finally, in this stage of the evolving faint, several factors may undermine any attempt by the vascular system to effect a sufficient increase of TPR to compensate for the low CO. In essence, as alluded to previously, sympathetic constrictor neural effects may be counteracted in critical portions of the

circulation by the adverse Epi/NE ratio. However, in addition, to the disadvantage of the circulation, other humoral agents may tilt the balance to a dilator direction (particularly, adrenomedullin and ANP being dilators) in conjunction with the diminished or ineffective humoral constrictor effects of agents such as ET-1 and AVP as discussed above.

Final Phase

As syncope approaches, there is a marked and usually abrupt drop in BP (55). HR at this stage (even with rapid pacing) cannot prevent hemodynamic collapse; in fact, a "relative" (vis-à-vis the magnitude of hypotension) or at times marked (asystole for often lengthy periods) bradycardia ensues. This reversal of HR trend (from relatively stable tachycardia to bradycardia) is often attributed to the action of ventricular mechanical receptors in the setting of a perceived "empty" ventricle (3). Whether the latter mechanism is valid or not, the HR slowing is well-known to be reversible with muscarinic blockade (i.e., atropine) (60) and thus reflects abrupt increase of parasympathetic tone. Nevertheless, it is rare that the BP fall is ameliorated by increasing HR. The moment at which a physiologically useful HR increment (whether by medication or pacing) can be introduced, is now past.

The basis for this apparent abrupt reversal of parasympathetic tone may be in part driven by humoral factors. As noted earlier, AVP increases markedly late in the VVS event; the trigger for this is uncertain but could be compensatory given AVP's combination of vasoconstriction and anti-diuretic actions. However, AVP in humans only exhibits vasoconstriction at high concentrations, and such high concentrations are likely reached only in the late stages of a VVS episode when its vasoconstrictive effect may be too late to be effective. More pertinent, however, vasopressin is also known to stimulate the baroreceptor system which diminishes sympathetic activity and on balance enhances parasympathetic influence (24, 32, 61). The net outcome might then not promote circulatory homeostasis, but in fact a contributor to hypotension.

Loss of consciousness usually leads to falling, with the individual assuming a horizontal position. The latter is a gravitationally neutral position that permits recovery of venous return, normalization of SV and ultimately of BP as sympathetic tone normalizes. Of note, a post-event overshoot of BP (as is seen in neurogenic orthostatic hypotension or with a normal Valsalva maneuver) is not a characteristic of VVS recovery. Consequently, while total peripheral resistance (TPR) increases toward normal after a VVS event, it does not seem to ever reach super-normal values such as commonly occurs with the more transient diminution of cardiac output and pulse pressure in the Valsalva maneuver. Nevertheless, the hemodynamic situation is precarious. If the patient is moved to an upright position, too soon, then a second faint may be triggered.

CONCLUSIONS

A number of neurohormonal agents have been studied to ascertain both how they change during posture-induced vasovagal faints and whether they contribute to the phenomenon. Nonetheless, despite the important insights that have been gained, many elements of the puzzle remain unclear. In particular, why VVS susceptibility varies between individuals and over time within known fainters remains a mystery that is not readily accounted for by either genetic, neural or hormonal differences. At this time, although there is reasonable evidence implicating Epi, NE and AVP changes in certain aspects of VVS, whether they or other neurohormones contribute directly to the evolving faint is still debatable. Further, whether better understanding of neurohumoral effects would enhance VVS prevention remains uncertain. Additional study is needed.

AUTHOR CONTRIBUTIONS

DB developed the manuscript and developed the text and Figures. JD provided critical information related to neurohormones. DK reviewed and corrected the text and offered key material. WA provided criticism and key revision. SS revised the text and provided key material.

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Prognosis of Syncope With Head Injury: a Tertiary Center Perspective

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Aim: Head injury is the most common trauma occurring in syncope. We aimed to assess whether syncope as cause of head-trauma affects short-and long-term prognosis.

Methods: From a database retrospective analysis of 97,014 individuals attending Emergency Department (ED), we selected data of patients with traumatic head injury including age, gender, injury mechanism, brain imaging, multiple traumas, bone fracture, intracranial bleeding, and mortality. Mean follow-up was 6.4 ± 1.8 years. Outcome data were obtained from a digital national population register. The study population included 3,470 ED head injury patients: 117 of them (50.0 ± 23.6 years, 42.7% men) reported syncope as cause of head trauma and 3,315 (32.2 ± 21.1 years, 68.5% men) without syncope preceding head trauma.

Results: Thirty-day mortality was low and similar in traumatic head injury with or without syncope. One year and long-term all-cause mortality were both significantly higher in syncopal vs. non-syncopal traumatic head injury (11.1 vs. 2.8% and 32 vs. 10.2%, respectively; both $p < 0.001$). In adjusted logistic regression analysis, death between 121st-day and 1 year in patients with head-trauma was associated with male gender [odds ratio (OR): 6.48; 95% CI: 2.59–16.25], advancing age (per year) (OR 1.09; 95% CI 1.07–1.11), Glasgow Coma Scale < 13 (OR: 6.18; 95% CI:1.68–22.8), bone fracture (OR 4.72; 95% CI 2.13–10.5), and syncope (OR 3.70; 95% CI: 1;48–9.31). In multivariable Cox regression analysis, syncope was one of the strongest independent predictors of long-term all-cause death (hazard ratio: 1.95; 95% CI 1.37–2.78).

Conclusion: In patients with head trauma, history of syncope preceding injury does not increase 30-day all-cause mortality but portends increased 1 year and long-term mortality.

Keywords: syncope, head injury, mortality, prognosis, Glasgow Coma Scale

INTRODUCTION

Injuries are the third commonest cause of death worldwide following circulatory diseases and cancer. About half of deaths due to injuries occur as a result of head trauma (1, 2). Loss of consciousness due to injury is a strong recommendation for head computer tomography (CT) scan (2). However, in patients presenting to ED with both syncope and head trauma, it is often difficult to decide whether head trauma was preceded by syncope or whether transient loss of consciousness (TLOC) was due to brain injury (3).

Most injuries that occur as a result of syncope are head injuries (4, 5). Falls as a result of syncope may vary in their severity; cardiac syncope results generally in a more rapid decrease in supply of blood to the brain than vasovagal syncope and may be associated with worse prognosis due to both the underlying cardiac mechanism of syncope and the severity of head injury, as it stems from the "dead weight" of an unprotected fall (5, 6). A fall due to syncope is usually from the patient's height, however, falls from height (steps, roof) are also possible. Moreover, high-energy injury may rarely be caused by driving accidents due to syncope (7, 8).

Traumatic injuries occur in 15–45% of syncopal patients, and severe injuries in 0.6–4.8% depending on the studied population (4, 9–15). Patients with traumatic injuries due to syncope have shown a higher 1 year mortality than other patients with syncope (11, 12). Less is known of the importance of syncope in the prognosis of the patients with traumatic head injury. The long-term prognosis in head trauma patients may be related not only to the severity of head injury but also to the underlying condition, which predisposes to trauma such as alcoholism, drug addiction, or concomitant chronic diseases (16–20). The aim of this study was to assess whether syncope as a cause of head trauma affects short- and long-term prognosis in patients presenting with head injury.

METHODS

We performed a retrospective analysis of medical records of 97,014 patients admitted during two periods—from January 2007 to June 2008 and from January 2009 to June 2010—to an emergency department (ED) in Zgorzelec, Poland, a regional trauma center with a catchment area of ∼200,000 citizens. We identified patients admitted because of traumatic head injury and retrieved the following data: age, gender, mechanism of injury (high or low energy), presence of multiple trauma, head computer tomography (CT), bone fracture, intracranial bleeding, and specialist consultations. Thirty-day, 1 year and survival at longest follow-up available were assessed using the data obtained from a Polish national population register (PESEL), including the date of death, if applicable. The study was approved by the Bioethical Commission of Wroclaw Medical University, Poland (No. 552/2012).

STATISTICAL ANALYSIS

Continuous variables were presented as mean and standard deviation and compared using Student's t-test, whereas discrete variables were presented as numbers and percentages, and compared using Pearson's ch^2-test. Logistic regression analysis was performed to identify factors associated with 1-month and 1 year survival, for the latter, after excluding patients who had died within 120-days of the index head injury. Further, logistic regression analysis was performed to identify factors related to intracranial hemorrhage. Rates of overall survival were estimated by means of the Kaplan–Meier method and were compared between head-trauma with and without syncope by log-rank test. A Cox proportional hazards analysis was used to calculate the adjusted hazard ratio of all-cause mortality by each variable. All recorded variables were forced to enter into the final model. We performed Schoenfeld's test to check the validity of proportional hazards assumptions and checked the validity of constant incidence ratios over the follow-up using Nelson-Aalen's cumulative hazard estimates. $P < 0.05$ was considered as significant. The statistical analysis was performed using IBM SPSS Statistics version 25.0 software (SPSS Inc. Chicago, Illinois, USA).

RESULTS

The study group consisted of 3,470 patients admitted to the ED because of head injury (3.6% of total patient population). Of those, 117 patients had reported that head trauma was preceded by a sudden loss of consciousness and muscle tone, and were classified as head trauma due to syncope. Thirty-eight patients (1%) were excluded due to incomplete or incorrect data, yielding the final study sample of 3,432 patients. Mean follow-up was 6.4 $\pm$ 1.8 years.

The main characteristics of syncopal ($n = 117$) and non-syncopal head-trauma patients ($n = 3{,}315$) are presented in **Table 1**. The syncopal head-trauma patients were older, more likely women, had more frequently undergone brain CT, were more likely to receive specialist consultations and, also, more likely to be admitted to hospital than those with non-syncope related head-injury.

Thirty-day mortality in patients without syncope not admitted to hospital, with syncope not admitted to hospital, without syncope admitted to hospital, and with syncope admitted to hospital was, respectively, 0.4, 0.0, 3.3, and 4.8% (**Table 2**).

One year mortality in patients without syncope who were not hospitalized was 1.9% whereas among those who were hospitalized was 6.7%. One year mortality in patients with syncope who were not hospitalized was 6.7% whereas among those who were hospitalized was 19.0% (**Table 3**).

In all head-trauma patients, 30-day mortality was related to older age (OR per year 1.05; 95% CI 1.03–1.07, $p = 0.01$), Glasgow Coma Scale (GCS) <13 (OR: 76.1; 95% CI 34.8–166.5 $p < 0.001$) presence of intracranial hemorrhage (OR 2.98; 95% CI 1.11–7.98, $p = 0.03$). Syncope preceding head injury was not predictive of short-term mortality.

TABLE 1 | Baseline demographics and clinical data of emergency department patients with and without syncope as the cause of head-trauma.

Covariates	Syncope + *n* = 117	Syncope− *n* = 3,315	*P*-value
Age, years	50.0+/−23.6	32.2+/−21.1	0.001
Male gender, *n* (%)	50 (42.7)	2,266 (68.5)	0.001
30-day mortality, *n* (%)	2 (1.7)	31 (0.9)	0.399
120-day mortality, *n* (%)	6 (5.1)	60 (1.8)	0.010
1 year mortality, *n* (%)	13 (11.1)	92 (2.8)	0.001
High energy mechanism of injury, *n* (%)	10 (8.5)	1.355 (40.4)	0.001
Alcohol abuse, *n* (%)	13 (11.1)	472 (14.5)	0.294
Bone fracture, *n* (%)	7 (6.0)	285 (8.6)	0.316
ICH at CT scan, *n* (%)	3 (2,6)	20 (0.8)	0.151
GCS < 13, *n* (%)	3 (2.6)	60 (2.1)	0.761
Unconsciousness immediately after head trauma, *n* (%)	117 (100.0)	406 (12.3)	0.001
Head CT, *n* (%)	48 (41.0)	480 (15.5)	0.001
Neurology consultation, *n* (%)	62 (53.0)	613 (18.5)	0.001
Neurosurgery consultation, *n* (%)	3 (2.6)	29 (0.9)	0.067
Cardiology consultation, *n* (%)	5 (4.3)	3 (0.1)	0.001
Hospital admission, *n* (%)	42 (35.9)	634 (19.2)	0.001

CT, computed tomography; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage.

Logistic regression analysis revealed that death between 121st and 365th days was predicted by male gender (OR: 6.48; 95% CI: 2.59–16.25 $p < 0.001$), older age (per year) (OR: 1.09; 95% CI: 1.07–1.11 $p < 0.001$), GCS < 13 at admission (OR: 6.18; 95% CI: 1.68–22.8 $p < 0.001$), syncope as a cause of trauma (OR:3.70; 95% CI: 1.48–9.31, $p < 0.001$), and bone fracture (OR:4.72; 95% CI: 2.13–10.52, $p < 0.001$). Logistic regression analysis showed that increased risk for intracranial bleeding was related to male sex (OR 5.4; 95% CI 1.6–17.8, $p < 0.006$), older age (OR per year 1.022; 95% CI 1.003–1.042, $p = 0.03$), and GCS < 13 (OR 99.0; 95% CI: 44.0–222.9, $p < 0.001$) at admission. Syncope was a borderline factor (OR 4.0; 95% CI: 0.92–17.3, $p = 0.06$).

Patients who died within 30-days were older and were more likely to have a GCS < 13 at admission, high-energy injury, and intracranial hemorrhage found on CT scan.

As shown by the Kaplan-Meier estimate, syncope-related head injuries were associated with significantly higher all-cause mortality compared with non-syncopal head injuries (Log-rank (Mantel-Cox): $p < 0.001$) (**Figure 1**). Furthermore, in multivariable Cox regression analysis, syncope, epilepsy, GCS < 13 and alcohol abuse were the strongest independent predictors of long-term all-cause mortality (**Table 4**).

TABLE 2 | Baseline characteristics of patients who died within 30-days and survivors at 30-days.

Covariates	Death within 30-days *n* = 33	Survivors at 30-days *n* = 3,399	*p*-value
Age, years	54.5 ± 22.1	32.6 ± 21.3	<0.001
Male gender, *n* (%)	26 (78.8)	2,290 (67.4)	0.17
GCS < 13, *n* (%)	19 (57.6)	52 (1.5)	<0.001
High-energy trauma, *n* (%)	20 (60.6)	1,332 (39.2)	0.007
Syncope, *n* (%)	2 (6.1)	115 (3.4)	0.40
Epilepsy, *n* (%)	2 (6.1)	62 (1.8)	0.07
Alcohol abuse, *n* (%)	5 (15.2)	480 (14.1)	0.87
Bone fracture, *n* (%)	4 (12.1)	288 (8.5)	0.45
ICH, *n* (%)	9 (27.3)	22 (0.7)	<0.001

GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage.

TABLE 3 | Baseline characteristics of patients who survived longer than 1 year and those who died between the 121st day after injury and 1 year.

Covariates	Survivors > 1 year *n* = 66	Survivors ≤ 1 year *n* = 3,366	*P*-value
Age, years	64,359	31,899	<0.001
Male gender, *n* (%)	32 (82.1)	2,240 (67.4)	0.052
Syncope, *n* (%)	7 (18.0)	104 (3.1)	<0.001
Epilepsy, *n* (%)	1 (2.6)	57 (1.7)	0.83
Alcohol abuse, *n* (%)	11 (28.2)	462 (13.9)	<0.001
Bone fracture, *n* (%)	10 (25.6)	273 (8.2)	<0.001
ICH, *n* (%)	1 (2.6)	19 (0.6)	0.57
Polytrauma, *n* (%)	3 (7.7)	111 (3.3)	0.29
High energy traumatic injury, *n* (%)	14 (35.9)	1,310 (39.4)	0.78
GCS < 13, *n* (%)	3 (7.7)	75 (1.4)	0.008

GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage.

DISCUSSION

In this study, we have observed that syncope precipitating head injury does not increase short-term mortality but is associated with increased longer-term mortality. The study also showed the rather more expected result that 30-day mortality in Emergency Department patients admitted after head injury is associated with older age, intracranial bleeding, and Glasgow coma scale < 13 at admission concordant with other similar studies (21).

Syncope as a cause of injury is not a factor typically associated with 30-day mortality in both single and multivariate analyses. These results indicate the significance of damage to the central nervous system in assessment of short-term prognosis. In patients with loss of consciousness the interview is difficult, if at all possible, rendering the identification of fainting as a cause of head injury often underestimated. In the present study of patients with syncope followed by head injury, the 30-day mortality rate was 1.7%. The short-term mortality of patients with syncope

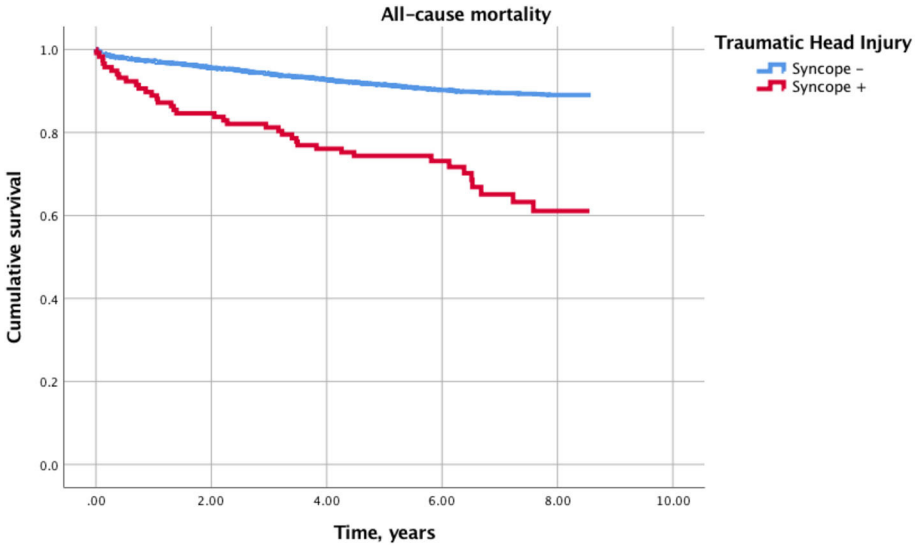

FIGURE 1 | Kaplan-Meier curves for cumulative incidence of all-cause death in syncopal vs. non-syncopal traumatic head injury.

TABLE 4 | Predictors of long-term all-cause mortality after head injury in a multivariable-adjusted Cox regression model.

Covariates	Hazard ratio	95% CI	*P*-value
Age, years	1.070	1.074–10.76	<0.001
Male gender, *n* (%)	1.573	1.232–2.009	<0.001
Syncope, *n* (%)	1.949	1.366–2.780	<0.001
Epilepsy, *n* (%)	2.039	1.156–3.597	0.014
Alcohol abuse, *n* (%)	1.929	1.508–2.467	<0.001
Bone fracture, *n* (%)	1.397	1.009–1.934	0.044
High-energy traumatic injury, *n* (%)	1.301	1.036–1.635	0.024
GCS< 13, *n* (%)	4.655	3.047–7.112	<0.001

GCS, Glasgow Coma Scale.

in other similar studies was also low (12). The presence of an injury is not a factor influencing the prognosis in patients after fainting. The risk of death during short-term observation is related not to the loss of consciousness itself, but to the illness that underlies syncope.

In STePS, 5 patients died from pulmonary edema, aortic dissection, pulmonary embolism and stroke, similarly 10 patients died in the EGSYS study, which was 1% of the study group (9, 12). The cause of death in this group was sudden cardiac in one patient, 2 patients had lung disease, advanced cancer in 3 patients and undetermined cause in 1 patient. Long-term prognosis was also associated with age, presence of cancer, cerebrovascular disease, structural heart disease, and ventricular arrhythmia (12).

In the analysis of 1 year survival in the subgroup of patients who achieved 4-month survival, the risk factors for death were age, male gender, syncope, bone fracture, decreased GCS scoring, and older age. High-energy injury was not an independent risk factor for death in this group of patients, however, the fracture that accompanied the trauma still remained a risk factor for death. Bone fracture that accompanies a head injury can be a sign of a significant force of injury. In the case of syncope, the occurrence of an injury is more frequent in cardiac syncope, in which a sudden "dead weight" fall occurs compared with reflex syncope where the decrease in blood pressure is usually slower resulting in a crumpling fall, usually accompanied by less injuries. Hino et al. reported that patients with loss of consciousness and maxillofacial fractures tend to have more severe maxillofacial injuries than those without loss of consciousness (22). The absence of links between bone fracture and long-term prognosis (after exclusion from analysis of patients who died within 4 months) indicates that bone fracture should be considered a surrogate of other factors related to long-term survival and not directly determining survival. These other factors may include not only the occurrence of cardiac syncope, but also the patient's lifestyle, increasing the risk of further injuries. Likewise, patients with traumatic injuries due to syncope who die during long-term observation have sustained more severe injury (23).

One of the important findings of this study is that syncope causing head trauma predicts mortality in patients who survive the first 4 months. Annual mortality in the whole group of patients admitted to ED after head injury who survive the first 4 months is 1% and is similar to the annual mortality of patients admitted to ED due to eye and ear diseases (24). In the subgroup of patients with syncope, mortality is over 6%. Syncope in this group in both single and multivariate analyses is an independent risk factor for death.

Mortality in a patient after head injury may depend on the direct effects of head injury, distant consequences of head injury, and coexisting conditions leading to syncope and injury. The assessment of each of these three seemingly obvious components can actually be very difficult.

The direct effects of a head injury can be assessed using the level of consciousness according to the GCS when admitted to the ED. However, it should be remembered that disturbance of consciousness is not always a direct consequence of brain injury but may be associated with consciousness disorders due to alcohol or psychoactive substance toxicity, postictal state following epileptic seizure or prolonged arrhythmia leading to central hypoxia (2, 25). Some of these factors may affect survival regardless of the injury. In the present study, the influence of low admission GCS score on the annual survival was still present after exclusion of patients who died within the first 4 months of injury. Moreover, the risk of fall-related injuries is increased among patients hospitalized for unexplained syncope, regardless of syncope mechanism (26).

Among mechanisms of head injury, we traditionally distinguish between high- and low-energy impacts. It is expected that greater impacts will lead to greater head damage. However, this dependency is not directly proportional. The direct effects of head injury depend not only on the force itself but also on the anatomical structure of the head and which parts are affected, concurrent anticoagulant therapy and the possibility of self-defense against the trauma. The relationship between syncope and injury may be further complicated by the fact that as a result of fainting or injury, the patient may have retrograde amnesia, which may lead to confusion regarding the facts relating to fainting and the injury scenario (27). Moreover, presence of manifest cardiovascular disease is a risk factor which increases, by a factor of 5–10, the mortality risk in patients with trauma (28, 29), and syncope may be a direct consequence of an acute circulatory disturbance caused by cardiovascular disease, undetected at ED presentation.

LIMITATIONS

There are some important study imitations that should be mentioned. The first of these is the retrospective nature of the study and inextricably related factors such as incomplete documentation. Second, the data regarding concomitant medications was not available in the available medical records. Third, due to the retrospective nature of the study, the ideal syncope history was not necessarily complete with only that recorded in the patient's file being available. Fourth, the study has been conducted only in one Eastern European country which may limit its generalizability. However, access to the digital national data on total mortality and the large group of analyzed patients increase the validity of our study findings.

CONCLUSIONS

1. Syncope-related head injury does not increase short-term mortality, but is associated with increased 1 year and long-term mortality compared with all patients admitted to the Emergency Department with head injuries.

2. Patients with syncope as the cause of head injury more frequently suffer low energy traumatic injury; CT scans and hospital admissions are both increased in this patient population compared with those who present head injury without preceding syncope.

3. Intracranial hemorrhage occurs slightly more often in patients after syncope, but syncope is not an independent risk factor for intracranial hemorrhage. However, older age, male gender, and lower Glasgow Coma Scale score on admission are important risk factors.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethical Commission of Wroclaw Medical University, Poland (Grant No. 552/2012). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SF, PP, DT, and DZ designed the study. SF, PP, and DZ collected the data. DZ, AF, and FR performed the statistical analyses. SF, DT, FR, RS, AF, and DZ searched the literature. SF, PP, DT, and DZ drafted the manuscript. FR, RS, and AF reviewed and corrected the manuscript. All authors take full responsibility for the contents of the manuscript.

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