

Clinical features of prolonged tilt-induced hypotension with an apparent vasovagal mechanism, but without syncope



Geoffrey L. Heyer*

Department of Neurology, Dell Medical School, Austin, TX, USA

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ABSTRACT

Background: A previous study of electroencephalography (EEG) changes with syncope led to a finding that some young patients develop prolonged periods of tilt-induced hypotension, but they do not lose consciousness. The present study aim was to compare patterns of hemodynamic changes, measures of duration, and sweating between these patients and patients with tilt-induced vasovagal syncope.

Methods: In an observational study, qualitative changes in hemodynamic parameters were compared between patients with prolonged hypotension ($n = 30$) and with syncope ($n = 30$). To demonstrate that periods of hypotension far-exceed the typical presyncope period, several parameters were used to compare the durations of events between groups. Differences in sweating patterns were explored.

Results: Parallels in hemodynamic changes were present in both groups suggesting similar vasovagal mechanisms. Patients with prolonged hypotension had longer durations of hypotension (165 ± 44 versus 57 ± 13 s, $p < 0.001$), diminished cardiac output (109 ± 38 versus 32 ± 9 s, $p < 0.001$), and EEG slowing (85 ± 31 versus 9 ± 4 s, $p < 0.001$) compared to patients with syncope. While all patients generated an increase in sweat rate, those with hypotension only developed a robust sweat response that always preceded the plateau in hypotension compared to 14 (47%) patients with syncope who developed an increase in sweating prior to syncope, $p < 0.001$.

Conclusions: Similarities are present among hemodynamic changes with prolonged hypotension and with tilt-induced vasovagal syncope, suggesting a possible vasovagal mechanism for prolonged hypotension. If true, understanding why some individuals develop a vasovagal response that does not culminate in rapid syncope may help to elucidate the physiologic underpinnings of the vasovagal reflex.

1. Introduction

Vasovagal (reflex) syncope is a common cause of transient loss of consciousness among children and adults, with a lifetime cumulative incidence estimated as high as 35–40% (Ganzeboom et al., 2006; Ganzeboom et al., 2003; Serletis et al., 2006). Syncope is defined as transient loss of consciousness caused by global cerebral hypoperfusion and rapidly followed by spontaneous and complete recovery (Shen et al., 2017; Moya et al., 2009; Freeman et al., 2011). While common, the physiologic mechanisms that cause syncope are poorly understood. The term “vasovagal” highlights that both arterial vasodilatation and heart rate slowing are mechanistically involved in the syncope response (Lewis, 1932).

In a previous study of the electroencephalographic (EEG) changes that correspond with syncope, young otherwise-healthy patients who experienced tilt-induced presyncope symptoms were asked to remain

upright until syncope occurred, although they could request table lowering at any point. (Heyer et al., 2016a). Some patients developed the signs and symptoms of imminent syncope, but they did not lose consciousness, even with prolonged periods of symptomatic hypotension (Heyer et al., 2016a). Since that initial study, whenever patients have developed tilt-induced hypotension without syncope during clinical tilt-table testing they were encouraged to remain upright until the symptoms became intolerable. The aim of the present study was to compare the patterns of hemodynamic changes between those patients with tilt-induced hypotension, but without syncope, and patients with tilt-induced vasovagal syncope. The hypothesis was that similarities would be identified in hemodynamic patterns between groups, supporting the view that prolonged hypotension without syncope has a vasovagal mechanism. To limit the likelihood that episodes of prolonged hypotension merely represent prolonged presyncope states (i.e., progressive hypotension culminating in syncope), the durations of EEG

* Department of Neurology, Dell Medical School, 1701 Trinity St., MC: Z0700, Austin, TX, 78712, USA

E-mail address: ghey@austin.utexas.edu.

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slowing and other hemodynamic changes were compared. Sweating changes were explored because sweating represents a purely sympathetic response and could lend some mechanistic insight. Understanding why some individuals develop a vasovagal response that does not culminate in rapid syncope may help to elucidate the physiologic underpinnings of the vasovagal reflex.

The terms “hypotension without syncope” and “hypotension only” are used interchangeably through the remainder of the manuscript to describe the phenomenon of prolonged hypotension, culminating in table lowering due to intolerable symptoms rather than loss of consciousness with syncope. The terminology is not meant to suggest that syncope could not occur eventually.

2. Materials and methods

2.1. Standard protocol approvals

The study was approved by the Institutional Review Board at Nationwide Children's Hospital. Written informed consent (parents and subjects ≥ 18 years of age) and assent (9–17 years) were obtained prior to any testing.

2.2. Subjects

An observational study was conducted between January 2015 and June 2018. Sequential patients were recruited prospectively for a pediatric orthostatic intolerance database. Reasons for database recruitment included refractory or frequent syncope, transient loss of consciousness of unclear etiology, positional tachycardia, and frequent orthostatic symptoms including “near-syncope”. The present study identified all database patients who had prolonged periods of tilt-induced hypotension without syncope (i.e., the prolonged period of hypotension was always aborted by table lowering) and a comparison group ($n = 30$) of sequential patients with tilt-induced syncope. Since some patients with tilt-induced syncope can experience a gradual and prolonged progression from the onset of hypotension to loss of consciousness, inclusion criteria for patients with hypotension only were ≥ 90 s from the onset of hypotension to tilt-table lowering and sustained alertness during the period of hypotension. Exclusion criteria for both cohorts were artifact or equipment malfunction that prevented interpretation of hemodynamic or sweat data, medicine provocation to induce syncope, hypotension onset within three minutes of tilt, and any medical disorder (genetic, autoimmune, or neuropathic) that could cause neurogenic orthostatic hypotension. None of the patients met diagnostic criteria for postural tachycardia syndrome (POTS). Five patients with hypotension only repeated a research protocol with additional monitoring and with the aim of extending their upright tolerance during the period of hypotension. Each patient who repeated a research protocol developed prolonged hypotension without syncope identical to their previous clinical testing. All patients had normal cardiac exams and normal 12-lead electrocardiograms prior to tilt-table testing.

2.3. Definitions

Tilt-induced syncope was defined as a transient loss of consciousness associated with hypotension, with or without bradycardia/asystole, and with the typical electroencephalography (EEG) changes of tilt-induced syncope (determined by visual inspection) (Heyer et al., 2016a; van Dijk et al., 2014). All patients with syncope (1) had at least two clinical signs suggestive of loss of consciousness (eyes opening when initially closed, eye deviation, loss of postural tone, myoclonus, or tonic posturing) and (2) acknowledged the perception of loss of consciousness upon recovery. We defined hypotension without syncope as a symptomatic drop in systolic blood pressure of > 20 mmHg from the initial tilted baseline, with or without bradycardia, but without apparent or perceived loss of consciousness. Visual inspection of the

Table 1

Demographic and clinical features of patients with hypotension only and patients with syncope.

	Hypotension only (n = 30)	Syncope (n = 30)	P-value
Age, years (mean \pm SD)	15.5 \pm 1.8	15.9 \pm 2.2	0.45
Sex, female	27 (90%)	23 (76.7%)	0.3
Previous “near syncope”	30 (100%)	28 (93.3%)	0.49
Previous syncope	2 (0.7%)	30 (100%)	$< 0.001^*$
Onset of hypotension with tilt-table testing, seconds	1261 \pm 603	1156 \pm 521	0.47

SD = standard deviation.

* Significant p-value.

corresponding EEG demonstrated high-amplitude slowing for all patients with hypotension only (Heyer et al., 2016a) which underscores that the drop in blood pressure was substantial enough to impair brain perfusion, yet syncope did not occur.

2.4. Protocol

All medicines that could affect orthostatic tolerance were discontinued ≥ 5 half-lives. Video EEG (Comet AS-40, GRASS systems, Warwick, Rhode Island, USA) was synchronized with continuous monitoring of heart rate and blood pressure (Finapres Medical Systems, Amsterdam, Netherlands) and sweat rate (WR Medical Electronics, Minnesota, United States). Sweat rates were measured from capsules placed at the left ankle, left thigh, mid-abdomen, and left wrist (Heyer et al., 2016b). Since an emotional form of sweating can overlap with the diffuse sweat response associated with hypotension and syncope (Heyer et al., 2016b), a sweat response was considered to be pre-event for any patient with an increase in sweat rate that preceded syncope or the initial period of plateau in hypotension when syncope did not occur, regardless of the presence of emotional sweating. Patients who did not have a change from the baseline sweat rate until after syncope or the initial hypotension plateau were counted as having a post-event sweat response.

The EEG video camera was mounted on the ceiling. A separate high-resolution video camera was attached by a bar welded to the tilt table, moving up and down as the table was raised and lowered, which helped to confirm signs of loss of consciousness with syncope, particularly eye opening and eye deviation. Following 30 min of recumbency, patients were tilted upright to 70 degrees. The table was lowered with syncope, intolerable symptoms, or after 45 min. Patients who developed hypotension without syncope were asked simple questions during the hypotensive period (e.g.: What is the name of this hospital? Who is the U.S. president?).

2.5. Statistical analysis

The Modelflow algorithm (Finapres Medical Systems, Amsterdam, Netherlands) was used to calculate relative changes in cardiac output and systemic vascular resistance. The patterns of systolic blood pressure changes were compared between groups. Each tracing was zeroed by subtracting the baseline (supine) blood pressure and then centered at the onset of hypotension. The onset of hypotension was defined as the earliest point where systolic blood pressure drops rapidly. This phase of plummeting blood pressure has been termed “terminal hypotension (phase 3)” by others (Stewart et al., 2017; Jardine et al., 2018) The initial onset of phase 3 was used to center blood pressure tracings.

The chi-square test or Fisher's exact-test was used to compare categorical variables, and the Student's t-test or Mann-Whitney *U* test was used to compare continuous variables between cohorts with syncope and with hypotension without syncope. The Pearson correlation

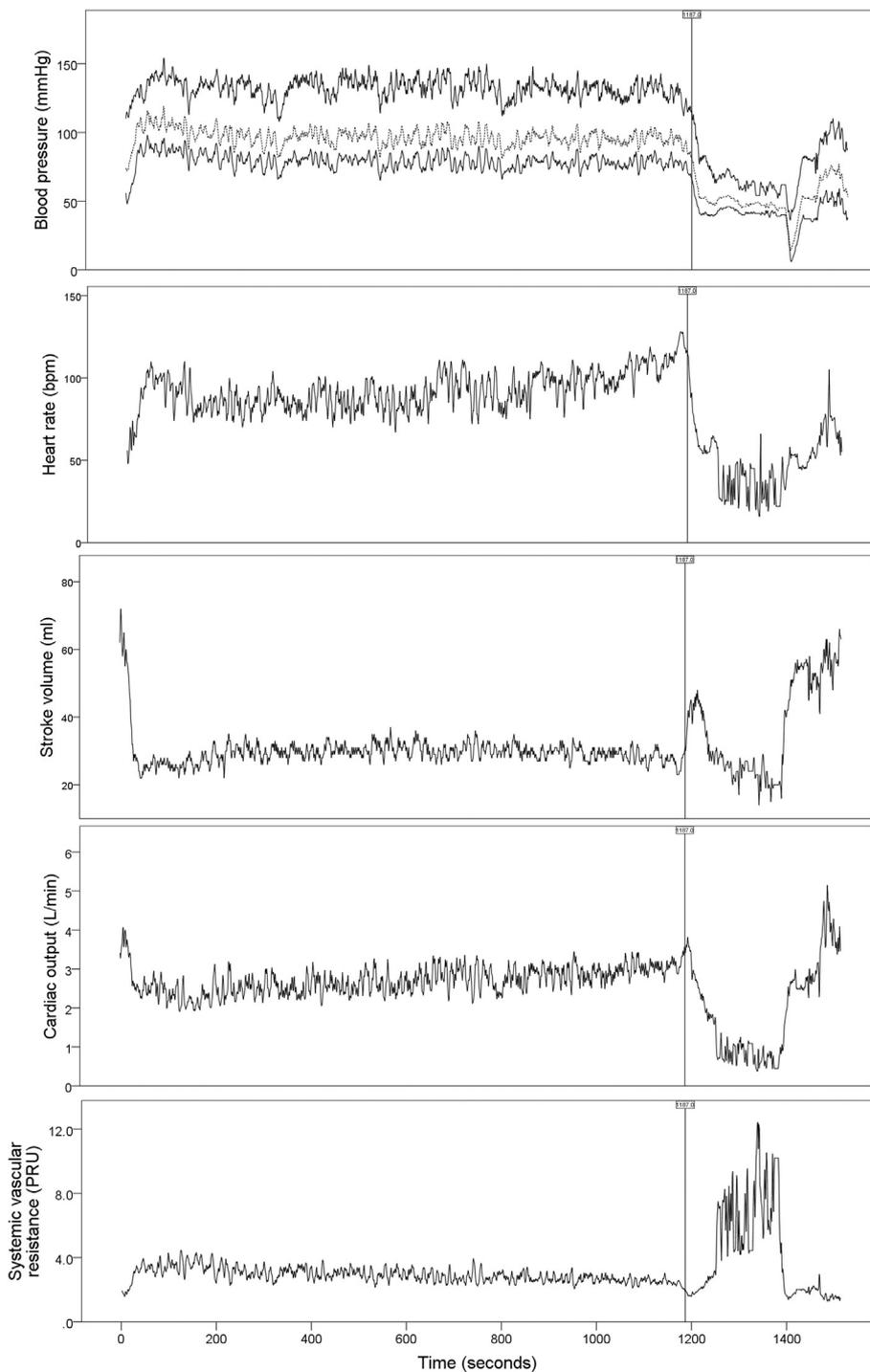


Fig. 1. Hemodynamic changes during tilt-induced hypotension without syncope parallel the changes with vasovagal syncope. The blood pressure tracing (top panel) demonstrates a rapid drop in blood pressure followed by a plateau period of hypotension lasting approximately 210 s. The onset of hypotension is estimated by the vertical line. There is a corresponding initial drop in systemic vascular resistance and a sustained drop in heart rate, each consistent with the vasovagal mechanism. The drop in cardiac output appears to be counterbalanced by a substantial (subsequent) increase in systemic vascular resistance. The hemodynamic changes closely parallel the changes with vasovagal syncope (Fig. 2) with the exception of the blood pressure plateau.

coefficient was used to characterize the relationship between hypotension duration and the duration of EEG slowing. Data are presented as mean \pm standard deviation or median (interquartile range; IQR). Analyses were 2-tailed where appropriate. All statistical analyses were performed using SPSS Version 25 (SPSS Inc., Chicago, IL, USA). The significance threshold was set at 5%.

3. Results

During the 42-month study period, 40 patients developed prolonged periods of symptomatic hypotension without syncope. Equipment malfunction or artifact precluded data interpretation for four patients, and six patients asked to be lowered prior to the 90-s minimum

duration of hypotension (mean 39 ± 7 s following hypotension onset). Data from the remaining 30 patients were analyzed.

Demographic and clinical features of patients with tilt-induced hypotension only and with syncope are presented in Table 1. All patients in both cohorts reported or acknowledged lightheadedness, visual dimming, warmth, and sweating with tilt-induced events. All patients with syncope reported nausea, while 27 patients (90%) with hypotension only reported nausea ($p = 0.24$). Each patient with hypotension only recognized that the tilt-induced symptoms were similar to the near-syncope episodes that prompted clinical referral; only two patients from the cohort reported prior syncope (i.e., definitive loss of consciousness), both during vein cannulation for blood draws. The earliest onset of hypotension (without syncope) occurred at 368 s of tilt.

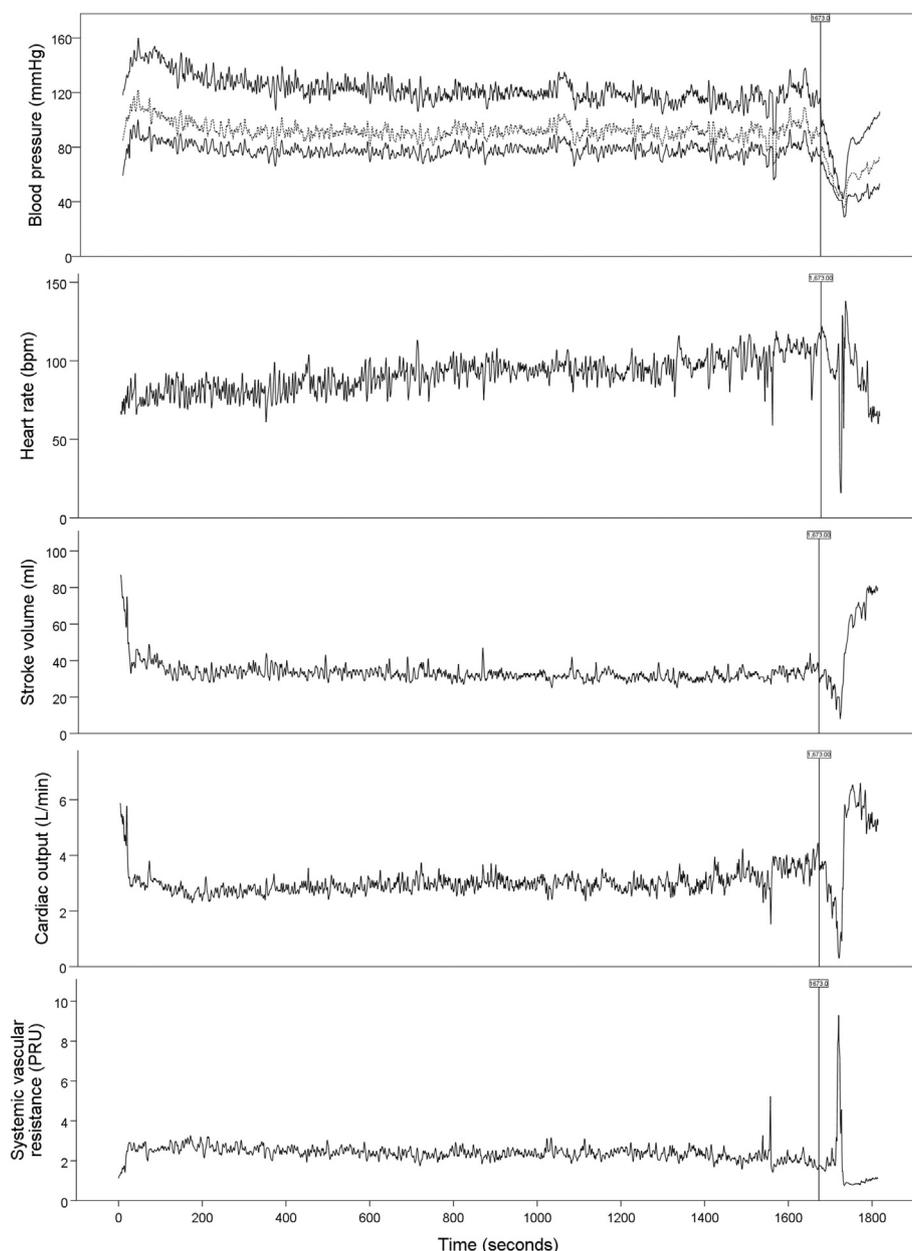


Fig. 2. Hemodynamic changes during tilt-induced vasovagal syncope. The onset of hypotension is estimated by a vertical line. There is an initial drop in systemic vascular resistance and heart rate, consistent with the vasovagal mechanism of syncope. In contrast with the plateau in hypotension demonstrated in Fig. 1, the blood pressure continues to drop precipitously until syncope. It then self corrects with table lowering back to the supine position.

3.1. Hemodynamic changes related to hypotension only versus syncope

The changes in hemodynamic parameters are depicted for a patient with tilt-induced hypotension without syncope (Fig. 1) and a patient with tilt-induced syncope (Fig. 2). The hemodynamic changes with hypotension only demonstrate features of a vasovagal mechanism in all patients, including an initial decrease in systemic vascular resistance (vasodilatation) and a corresponding decrease in heart rate (vagal response). The median heart rate with hypotension was 51 (IQR17) bpm (range 31–85 bpm), representing a median drop in heart rate of 11(IQR12) bpm from the supine baseline. A consequent drop in cardiac output appears to be counterbalanced by a substantial rise in systemic vascular resistance, leading to a plateau in blood pressure which persisted until the table was lowered. Fig. 3 displays the plots for individual and mean systolic blood pressure tracings. The evolution of hypotension appears similar initially. The tracings diverge as patients

with hypotension without syncope develop a plateau in blood pressure, while patients with syncope experience further decline in blood pressure, followed by recovery (coincident with lowering of the tilt table). None of the patients with syncope had the plateau in blood pressure that was present in all patients with hypotension only. Both cohorts had decreased cardiac output that paralleled the blood pressure tracings.

3.2. Measures of event duration

The overall duration of hypotension differed between groups (165 ± 44 versus 57 ± 13 s, $p < 0.001$). The range of hypotension duration was 95–252 s for patients with hypotension without syncope. Changes in cardiac output were used as an alternative method of comparing duration. The interval from the onset of diminished cardiac output to lowering of the tilt-table differed between patients with hypotension only and syncope (109 ± 38 versus 32 ± 9 s, $p < 0.001$).

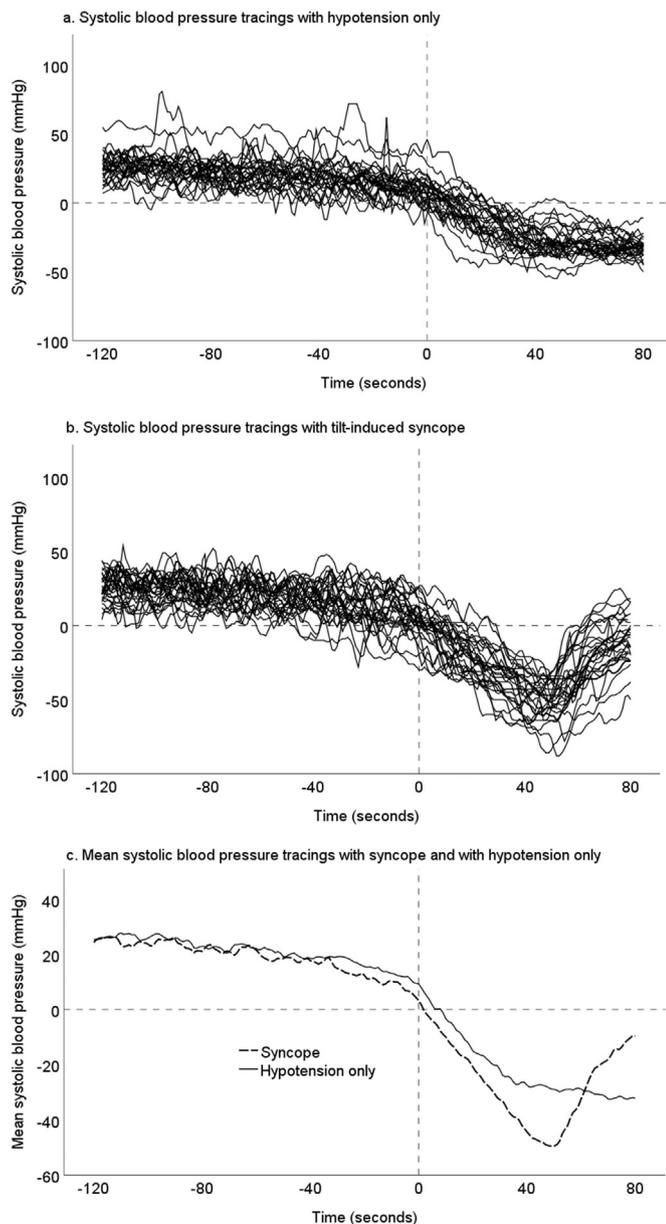


Fig. 3. Systolic blood pressure patterns with hypotension only and with syncope. The tracings are zeroed by supine blood pressure (0, y-axis) and centered at the onset of hypotension (0, x-axis) for each patient with hypotension only (3a) and with syncope (3b). The mean systolic blood pressure curves (3c) appear to have similar initial patterns. The curves diverge when the blood pressure plateaus among patients with hypotension only, but continues to descend and then correct (with table lowering and recovery) among patients with syncope.

Lastly, the duration of EEG slowing was compared because it represents a degree of hypotension that impairs adequate cerebral perfusion. Patients with hypotension only had longer periods of EEG slowing than patients with syncope (85 ± 31 versus 9 ± 4 s, $p < 0.001$). All patients with hypotension only were able to answer simple questions during the period of EEG slowing, but some responses were delayed, incomplete, or incorrect. Fig. 4 demonstrates the correlation between durations of hypotension and durations of EEG slowing in both groups (hypotension only, $r = 0.53$, $p = 0.003$; syncope, $r = 0.38$, $p = 0.007$).

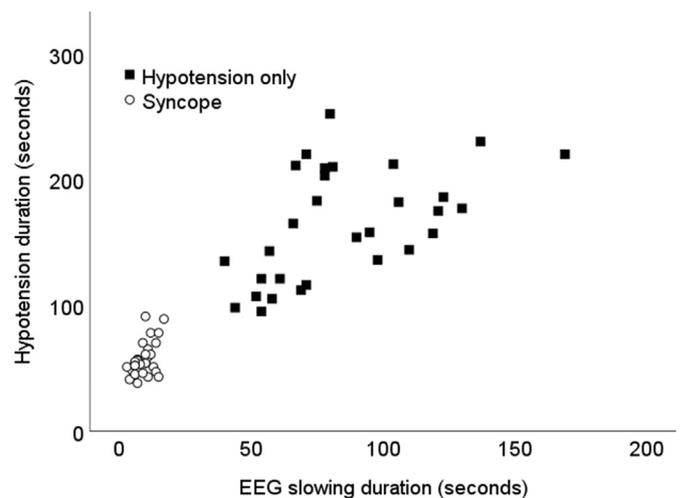


Fig. 4. The duration of hypotension positively correlates with the duration of EEG slowing among patients with tilt-induced syncope (empty circles) and with tilt-induced hypotension without rapid syncope (solid squares). Patients with hypotension only had significantly longer periods of hypotension and EEG slowing.

3.3. Sweat changes associated with prolonged hypotension without syncope and with syncope

All patients in both cohorts generated an increase in sweat rate consistent with prior research (Heyer et al., 2016a). Every patient with hypotension only (100%) had a pre-event increase in sweat rate compared to 14 (47%) patients with syncope, $p < 0.001$. Fig. 5a depicts a diffuse sweat response associated with hypotension without syncope. A plateau in sweat rate was present at some (or all) measured regions, suggesting that sweat production was maximal at that area and proportional to the density of sweat glands. The subsequent decrease in sweat rates occurred well-after tilt table lowering, so the durations were not compared between groups. Fig. 5b depicts a diffuse increase in sweat rate that preceded syncope.

4. Discussion

The present study demonstrates that some young patients develop a tilt-induced period of prolonged symptomatic hypotension with an apparent vasovagal mechanism, but without rapid progression to syncope. All patients generated a degree of hypotension substantial enough to cause EEG slowing, and the duration of hypotension far-exceeded the duration of syncope, arguing against a mere presyncope phenomenon. Unlike patients with syncope, those with hypotension only developed a plateau in blood pressure associated with a marked increase in systemic vascular resistance. A robust increase in sweat rate always preceded the plateau in hypotension.

The vasovagal response is complex and incompletely understood. Tilt-induced vasovagal syncope is characterized by a steep fall in cardiac output but not systemic vascular resistance (Jardine et al., 1997; Verheyden and Liu, 2008; Fu et al., 2012; Jardine et al., 2002). The drop in cardiac output reflects a decrease in cardiac stroke volume related to diminished venous return from orthostatic blood pooling and, in some cases, a decrease in heart rate (Fu et al., 2012). Systemic vascular resistance may decrease or remain unchanged through the pre-syncope period (Stewart et al., 2017; Fu et al., 2012), but it always eventually increases with syncope (Verheyden and Liu, 2008). The present data demonstrated parallel changes in cardiac output and systemic vascular resistance among patients with prolonged hypotension without syncope. Additionally, the patterns of change in systolic blood pressure appeared similar among cohorts until a point of divergence where patients with syncope had further plummeting of blood pressures

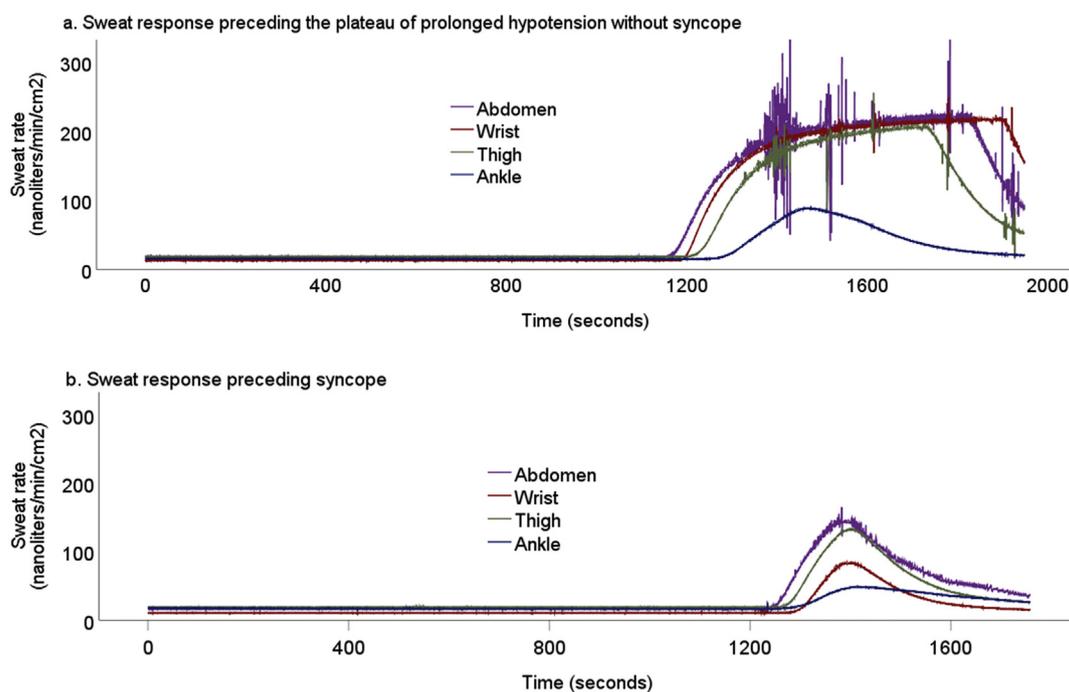


Fig. 5. a and b. All patients in both cohorts developed a sweat response associated with syncope or hypotension without syncope. Patients with hypotension without syncope (5a) had a robust sweat response that preceded the plateau in hypotension. The figure depicts elevated sweating measured at the abdomen, thigh, ankle, and wrist that continues well-after table lowering. The total duration of increased sweating lasts approximately 800 s. The sweat response with syncope (5b) began prior to loss of consciousness in this patient, but followed loss of consciousness in others.

and patients with hypotension without syncope developed a plateau that persisted until table lowering. The blood pressure plateau seemed to be counterbalanced by a substantial rise in systemic vascular resistance. The hemodynamic patterns with delayed orthostatic hypotension differ from those with vasovagal syncope, where hypotension progresses gradually and corresponds with a dropping systemic vascular resistance, but with little variation in cardiac output (Podoleanu et al., 2009). Although previous authors have included some young patients in their descriptions of delayed orthostatic hypotension (Streeten and Anderson Jr., 1992; Streeten and Anderson Jr., 1998), all patients with hypotension only in the present study had changes in hemodynamic parameters similar to the cohort with vasovagal syncope, albeit without the continued drop in blood pressure that ultimately caused syncope. Thus, the mechanism for hypotension only could be vasovagal. Considering that symptoms during tilt were identical to the symptoms that prompted clinical referral, it is possible that the phenomenon of prolonged hypotension without syncope during tilt-table testing represents the naturally occurring episodes of vasovagal near-syncope described by some individuals (Heyer et al., 2016a).

A diffuse sweat response occurs among young, otherwise-healthy individuals with tilt-induced syncope (Heyer et al., 2016b). It can precede or follow the clinical signs of loss of consciousness. The present data demonstrate that patients with hypotension only develop a diffuse sweat response that always precedes the plateau in hypotension. The sudomotor response is mediated by the sympathetic nervous system, so the robust increase in sweat rate represents a vigorous sympathetic response. The differences in sweating onset and degree between patients with hypotension only and those with syncope seem to suggest differences in the sympathetic output. Previous studies of muscle sympathetic nerve activity (MSNA) during the evolution of syncope have demonstrated withdrawal of sympathetic output to skeletal muscle in relation to vasodilatation and hypotension during the pre-syncope period (Jardine et al., 1998; Wallin and Sundlof, 1982), yet withdrawal of MSNA is not required for presyncope (Fu et al., 2012; Cooke et al., 2009; Vaddadi et al., 2010). It is not known how changes in sweat rate correlate with changes in MSNA.

There are several potential study limitations. First, patients who probably had hypotension without syncope, but requested early table lowering, were excluded. Some of these patients did not reach a point where the hypotension clearly plateaued or where high-amplitude EEG slowing occurred. The loss of these data serves as a study limitation, but the inclusion of only those patients who tolerated periods of hypotension well-beyond typical presyncope represents a study strength. Second, as it can be difficult to identify the moment of loss of consciousness, two clinical signs were used. This conservative approach might have overestimated the periods from onset of hypotension and EEG slowing to loss of consciousness, although the 1-s resolution in timing corrects for much of these potential errors. Third, MSNA was not used as a measure of sympathetic output, so the results cannot be compared across studies with measures of MSNA. Fourth, most patients had some degree of hyperventilation that preceded or coincided with hypotension (with or without syncope), which is normal. It is not clear how much of a role hyperventilation has on EEG slowing during hypotension (with or without syncope). Fifth, after 90 s of hypotension, patients determined when they could be lowered, biasing measures of overall duration. Finally, patients were highly selected based on their referral to a tertiary care, subspecialty clinic. Thus, a referral bias cannot be excluded.

In conclusion, a form of prolonged tilt-induced hypotension without rapid syncope can occur among young patients. Several parallels exist with the hemodynamic changes of tilt-induced vasovagal syncope, suggesting that hypotension without syncope could have a vasovagal mechanism. If true, understanding why some individuals develop a vasovagal response that does not culminate in rapid syncope may help to elucidate the physiologic underpinnings of the vasovagal reflex.

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Author contribution

GLH conducted all aspects of study, data analyses, and manuscript writing.

Conflict of interest statement

The author denies potential conflicts of interest to disclose.

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