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Temporal Relationship of Asystole to Onset of Transient Loss of Consciousness in Tilt-Induced Reflex Syncope

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ABSTRACT

OBJECTIVES The purpose of this study was to investigate the relationship between the onset of asystole and transient loss of consciousness (TLOC) in tilt-induced reflex syncope and estimate how often asystole was the principal cause of TLOC.

BACKGROUND The presence of asystole in vasovagal syncope (VVS) may prompt physicians to consider pacemaker therapy for syncope prevention, but the benefit of pacing is limited in VVS.

METHODS We evaluated electrocardiography, electroencephalography, blood pressure, and clinical findings during tilt-table tests. Inclusion required TLOC (video), electroencephalographic slowing, accelerating blood pressure decrease, and an RR interval ≥3 s. We excluded cases with nitroglycerin provocation. Asystole after onset of TLOC (group A) or within 3 s before TLOC (group B) was unlikely to cause TLOC, but an earlier start of asystole (group C) could be the cause of TLOC.

RESULTS In one-third of 35 cases (groups A [n = 9] and B [n = 3]), asystole was unlikely to be the primary cause of TLOC. The median of the mean arterial pressure at the onset of asystole was higher when asystole occurred early (45.5 mm Hg, group C) than when it occurred late (32.0 mm Hg, groups A and B), which suggests that vasodepression was not prominent at the start of asystole in early asystole, further suggesting that early asystole was the prime mechanism of syncope.

CONCLUSIONS In one-third of cases of tilt-induced asystolic reflex syncope, asystole occurred too late to have been the primary cause of TLOC. Reliance on electrocardiography data only is likely to overestimate the importance of asystole. (J Am Coll Cardiol EP 2017;3:1592–8) © 2017 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Syncope is the form of transient loss of consciousness (TLOC) that is caused by brief and self-terminating diminution of global cerebral hypoperfusion (1). The term *reflex syncope* refers to those forms of syncope in which neural reflex responses play a key role in causing transient hypotension and consequent diminution of cerebral blood flow. Vasovagal syncope (VVS) is by far the most common cause of reflex syncope. In many instances, susceptibility to VVS can be unmasked by head-up tilt-table testing (2).

Reflex syncope encompasses both vasodepressor and cardioinhibitory mechanisms. Although either mechanism can cause syncope, in most cases both

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tend to occur together in reflex syncope (i.e., the mixed pattern). The basis by which the vasodepressor response contributes to syncope remains controversial, but it has been considered to be primarily due to venous pooling in the lower parts of the body, resulting in decreased cardiac venous return and a reduced cardiac output (3,4). The cardioinhibitory mechanism is effected primarily through an increase in vagal tone (5,6). Its most extreme expression is abrupt prolonged asystole (usually defined as a cardiac pause ≥3 s), which on its own causes blood pressure (BP) to fall precipitously. If asystole is sustained for a sufficiently long period of time, the resulting cerebral hypoperfusion causes unconsciousness about 6 to 8 s after the last heartbeat (7,8).

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The presence of asystole in VVS might prompt physicians to consider pacemaker therapy to prevent syncope recurrence; however, it is increasingly recognized (2) that the benefit of pacing is limited in VVS patients. In fact, recent observations from the ISSUE-3 (third International Study on Syncope of Uncertain Etiology) (9) and SUP-2 (Syncope Unit Project 2) (10) suggest that among patients with documented spontaneous asystole during VVS, pacing efficacy was primarily of value in those individuals without evident vasodepressor susceptibility (i.e., the latter observation implies that the VVS origin was truly due to cardioinhibition). Unfortunately, when vasodepression and cardioinhibition act at the same time, it is not usually feasible to quantify how much each contributes to cerebral hypoperfusion. However, during head-up tilt-induced syncope with continuous electroencephalographic (EEG) monitoring, it is possible to determine both when asystole starts and when onset of TLOC occurs; thus, if asystole starts after the onset of TLOC, it cannot have been the principal cause of TLOC. Similarly, if asystole starts within 3 s of TLOC, the bradycardia is unlikely to be the cause of syncope. On the other hand, if asystole begins >3 s before TLOC, there is a reasonable likelihood that the bradycardia did contribute to TLOC.

The objective of this study, using head-up tilt testing with continuous video-EEG recording, was to describe the temporal relation between the onset of asystole and of TLOC during tilt-induced syncope. A second goal was to use the observed temporal relationship to estimate how often asystole could be the prime cause of TLOC in tilt-induced syncope.

METHODS

PATIENTS. This report is based on all tilt-table tests performed between 2006 and 2015 for evaluation of TLOC at 2 tertiary syncope referral centers: the Department of Neurology of the Leiden University Medical Centre (LUMC), and the syncope clinic of Stichting Epilepsie Instellingen Nederland (SEIN). These institutions share expertise, use the same indications and protocols for tilt-table testing, use the same brand of tilt table, and have collaborated on studies assessing the semiology and pathophysiology of tilt-induced syncope and psychogenic pseudosyncope (11–15).

Suspected susceptibility to vasovagal syncope is the most common indication for tilt-table tests in both centers. Part of the present patient group has been described previously (14). In that study, tilt-induced reflex syncope was defined using the following triad: video records compatible with loss of consciousness, EEG changes showing a slow or slow-flat-slow pattern, and BP showing the pattern of tilt-induced reflex syncope, that is, an increasing rate of decline with or without bradycardia. We now incorporated 1 additional inclusion criterion: the electrocardiogram (ECG) showed asystole, defined as an RR interval of ≥3 s. We also added 1 exclusion criterion: tilt tests in which syncope developed after administration of sublingual nitroglycerin were excluded on the assumption that nitroglycerin administration might influence the relative contribution of vasodepression and cardioinhibition.

CLINICAL TILT PROTOCOL AND DATA EXTRACTION. We used EEG machines to store data sampled at 200 Hz. Recordings comprised continuous video, EEG, BP (derived from finger plethysmography), and a 1- or 2-lead ECG. In the LUMC, the video camera is attached to the tilt table and is aimed at the head and shoulders, whereas at SEIN, a ceiling-mounted camera covers the entire tilt table.

Tilt-table tests were performed with a modified Italian protocol (16). The usual test protocol consisted of 10 min of supine rest followed by 20 min of head-up tilt to 70°, after which, if syncope did not occur, sublingual nitroglycerin was used and patients were observed for another 20 min. However, as noted previously, the present study included only tests in which TLOC occurred in the drug-free first 20 min after head-up tilt. Reasons to tilt patients back before the expiration of the allotted protocol time included the presence of syncope (i.e., the circulatory pattern

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
ECG = electrocardiography
EEG = electroencephalography
LUMC = Leiden University Medical Centre
MAP = mean arterial pressure
SEIN = Stichting Epilepsy Instellingen Nederland
TLOC = transient loss of consciousness

TABLE 1 Characteristics of the Groups According to Onset of Asystole Related to TLOC

	Group A: Asystole Starting After TLOC (n = 9)	Group B: Asystole Starting ≤3 s Before TLOC (n = 3)	Group C: Asystole Starting >3 s Before TLOC (n = 23)	Total (n = 35)
Age, yrs	46 (18–84)	34 (27–40)	32 (12–60)	35 (12–84)
Male:female	2:7	1:2	11:12	14:21
Duration of asystole, s	8.9 ± 8.5	8.3 ± 4.9	14.6 ± 14.0	12.6 ± 12.4
Duration of TLOC, s	27.8 ± 8.9	32.7 ± 10.4	33.0 ± 15.1	31.7 ± 13.3
Difference in asystole to onset of TLOC, s	4.4 ± 3.97	−2.3 ± 0.58	−7.5 ± 2.66	−4.1 ± 5.9

Values are n, mean (range), or mean ± SD. The groups were formed based on assumptions regarding the role of asystole in causing syncope. Group A consists of those in whom asystole started after TLOC began, so asystole was certainly not the cause of syncope. In group B, asystole started at most 3 s before the onset of TLOC, which makes a major role of asystole unlikely. In group C, asystole started at least 3 seconds before syncope and might have played a major role.

TLOC = transient loss of consciousness.

of reflex syncope with clinical TLOC); presyncope (similar circulatory changes without clinical TLOC); and slowing of the EEG, asystole, or a combination of these factors. Tilting back to the supine position required 12 s at both centers.

Noninvasive beat-to-beat BP was recorded continuously with either a Finometer (Finapres Medical Systems, Amsterdam, the Netherlands) or a Nexfin (BMEye, The Hague, the Netherlands) device. We measured BP from the middle phalanx with the hand held at heart level in a sling to ensure immobility and reduce the need for height correction.

We assessed the time of onset of clinical TLOC and its duration using video records as described previously (14). In brief, the onset of TLOC was defined as the first event indicating a loss of motor control (e.g., head dropping, eye opening, jaw dropping). We used EEG slowing as an additional quality indicator; besides proving brain hypoperfusion, abnormal EEG findings reduced the possibility of misidentification of voluntary behavior as a sign of syncope. All video records were reviewed by 2 of 3 examiners (D.P.S., R.D.T., J.G.v.D.) well acquainted with the semiology of syncope.

We searched for asystole (i.e., cardiac pause ≥3 s) in a period beginning ≈30 s before and continuing during loss of consciousness. The ECG in syncope may show more than 1 RR interval longer than 3 s; we only analyzed the first such episode. No attempts were made to quantify bradycardia before or after periods of asystole.

To illustrate BP changes in relation to the start of asystole, we noted mean arterial pressure (MAP) at the heartbeat defining the onset of asystole. In some cases, BP could no longer be measured at that point in time, which resulted in missing values. MAP was calculated as the mean of the continuous BP signal over 2 s in LUMC cases and as one-third of the sum of systolic BP and double the diastolic BP in SEIN cases.

ANALYSIS OF THE TEMPORAL RELATIONSHIP BETWEEN ASYSTOLE AND TLOC. We set the start of TLOC as time zero and expressed the start of asystole in integer seconds relative to time zero. We divided patients into 3 groups based on the temporal relation of asystole to TLOC: 1) Group A: asystole started after the onset of TLOC. In these cases, asystole could not have been the principal cause of TLOC. 2) Group B: asystole started at most 3 s before the onset of TLOC. We postulate that asystole in this group was very unlikely to have been the principal cause of TLOC, on the basis of prior observations indicating that pure asystole causes loss of consciousness 7 to 10 s after the last heartbeat (7,8). In these studies, the shortest estimate of the interval between the last beat and the onset of TLOC was 4 s in standing subjects. Hence, we used a 3-s threshold to increase confidence that asystole was not the cause of TLOC in this group. 3) Group C: asystole started >3 s before TLOC. In this group, asystole could have been the major contributor causing TLOC.

STATISTICAL ANALYSIS. The study was descriptive in nature. To analyze the MAP at the onset of asystole between groups, we combined groups A and B to represent those with late asystole, unlikely to cause TLOC, and compared their MAP with that of group C, representing early asystole, in whom asystole might have caused TLOC. To do so, we estimated the standardized mean difference between groups by dividing the difference of the group MAP averages by their pooled standard deviation and calculated the 95% confidence interval.

RESULTS

PATIENT GROUP. A total of 1,551 tilt-table tests with video-EEG were performed at the LUMC from 2006 to June 2015, and 412 tilt-table tests were performed

from 2009 to 2015 at SEIN. After excluding patients without syncope, patients with syncope without asystole, syncope due to other mechanisms (e.g., carotid sinus syndrome, orthostatic hypotension, use of nitroglycerin), multiple causes of apparent but not true TLOC (such as additional psychogenic pseudosyncope), and those with incomplete video data, 35 cases remained. The median age of patients was 35 years (range 12 to 84 years); 21 were female, and 14 were male (Table 1).

TIMING OF ASYSTOLE. Figure 1 and Table 1 show the relative timing of asystole and TLOC onset. In 9 patients, asystole started after onset of TLOC (group A). MAP at the onset of asystole was missing in 4 cases, and for the remaining 5 cases, median MAP was 32 mm Hg (range 24 to 35 mm Hg).

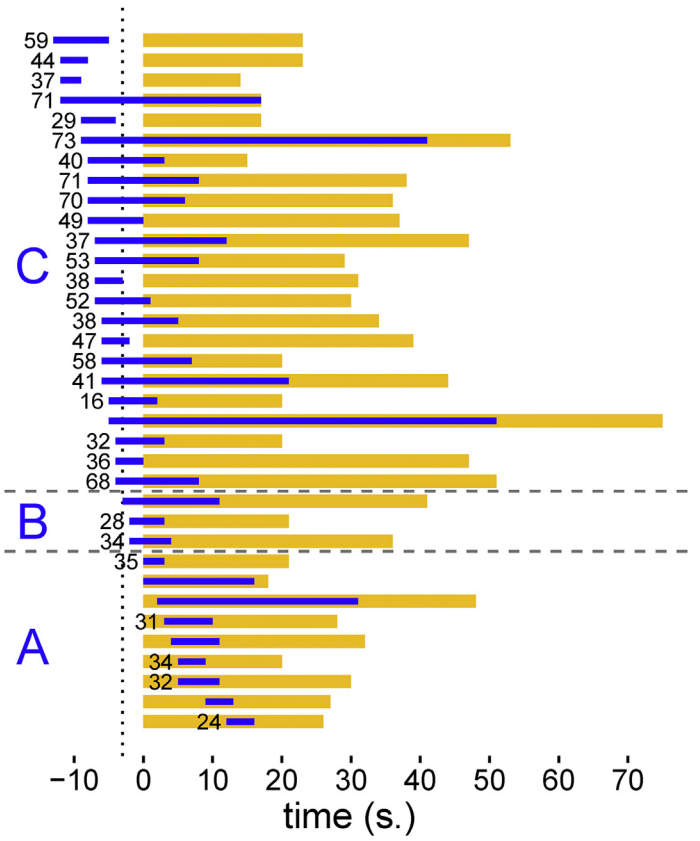
In 3 patients, asystole coincided with or preceded TLOC by at most 3 s (group B). The median MAP at the onset of asystole for 2 cases with measurable BP was 31 mm Hg (range 28 to 34 mm Hg).

Group C comprised 23 patients in whom asystole preceded TLOC by at least 3 s; the median MAP at the onset of asystole of 22 cases was 45.5 mm Hg (range 16 to 73 mm Hg).

Figure 2 summarizes the number of subjects with asystole, related to the beginning of TLOC. Groups A and B together comprised 12 of 35 cases (34%): in these subjects, asystole was considered unlikely to have been the primary cause of syncope. In the remaining 23 cases (66%), asystole might have played a major role.

The median MAP of groups A and B together (n = 7) was 32 mm Hg (range 24 to 35 mm Hg), and that of group C was 45.5 mm Hg (range 16 to 73 mm Hg). The standardized mean difference was −1.22 (95% confidence interval: −2.12 to −0.31).

FIGURE 1 Relative Time of Asystole and TLOC



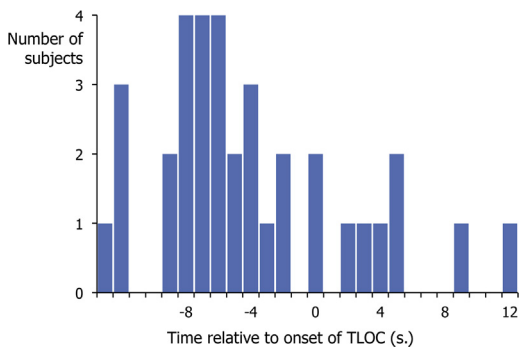
Each line of horizontal bars concerns 1 subject. **Yellow bars** denote the duration of clinically observed transient loss of consciousness (TLOC), and **blue bars** denote the start and duration of asystole. Data are aligned to the start of TLOC, defined as occurring at 0 s. The **dotted line** represents a period of 3 s before onset of TLOC. The numbers at the beginning of the asystole bars denote mean arterial pressure of the heartbeat just before asystole; when mean arterial pressure is not stated, it was too low to be measured at that point in time. A, B, and C denotes groups A, B, and C.

DISCUSSION

The main finding in this study was that in one-third of cases (34%), asystole as defined above started after the onset of TLOC, or within such a short time (≤3 s) before TLOC that in either case, it was very unlikely that the bradyarrhythmia would have been the prime cause of TLOC. On the other hand, in 23 of 35 cases (66%), asystole preceded TLOC by a sufficiently long time to allow asystole to have played a key role in triggering unconsciousness.

Our analysis was based solely on the time of onset of asystole relative to that of TLOC. At no point did we assume that vasodepression was absent. In fact, BP at the onset of TLOC is likely to represent the combined effects of vasodepression and cardioinhibition. As noted previously, there is no practical way to disentangle the combined effects of vasodepression and cardioinhibition on BP and hence on cerebral hypoperfusion. We chose to estimate vasodepression at the onset of asystole by measuring MAP at that point in time. Median MAP was higher when asystole occurred early, that is, >3 s before TLOC (group C, 45.5 mm Hg) than when it started later (group A + B, 32 mm Hg). The fact that MAP was higher for early than for late asystole suggests that vasodepression was less pronounced in early asystole and that early asystole was reasonably likely to be the prime cause of TLOC.

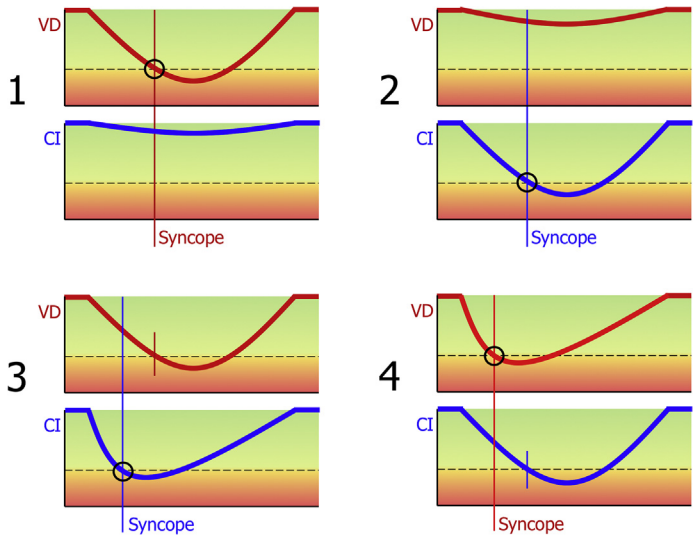
FIGURE 2 Start of Asystole in Relation to TLOC



On the horizontal axis, the start of asystole is shown relative to the start of transient loss of consciousness (TLOC).

CLINICAL IMPLICATIONS. Figure 3 provides a schematic that illustrates how the magnitude and the timing of the vasodepressive and cardioinhibitory mechanisms can determine when syncope occurs. A key implication of these effects is that relying on heart rate data alone can overestimate the importance of asystole as the cause of TLOC. For instance, diagnostic studies based on ECG data only would show asystole in 3 of the 4 patterns of Figure 3 (patterns 2, 3, and 4), suggesting that pacemaker therapy might be efficacious in all 3, whereas it might only be expected to do so in the absence of important vasodilation (pattern 2) (9). Note that we do not state that all those with early asystole (group C) conform to pattern 2; they might also conform to pattern 3.

FIGURE 3 Possible Relationships Between Strength and Timing of Vasodepressive and Cardioinhibitory Mechanisms in Reflex Syncope



Each of the 4 patterns 1 through 4 shows the time course of cerebral perfusion **(bold lines)** as affected by vasodepressor (VD) and cardioinhibitory (CI) mechanisms, as if these act independently. The **orange zone** in each panel denotes significant hypoperfusion: as soon as perfusion drops into this zone, syncope is thought to occur. This simplification is limited to situations in which at least 1 mechanism is strong enough to cause syncope on its own. Pattern 1 shows a strong VD effect and a negligible CI effect on cerebral perfusion: the VD mechanism decreases perfusion by itself to such a degree that syncope ensues. Pattern 2 shows the opposite situation, in which VD will not cause syncope on its own, but CI will. Patterns 3 and 4 show mixed forms. Pattern 3 shows early CI: here, VD and CI would each cause syncope if they were the only active mechanism, but CI acts earlier and is the prime cause of the beginning of syncope. Pattern 4 shows late CI, in which the beginning of syncope is due to VD.

Clinical experience illustrates that pacing does not always work in asystolic reflex syncope (2,17,18). Our findings provide a possible explanation for the lack of pacemaker efficacy in certain cases, specifically those in which asystole occurs after onset of TLOC or very soon before TLOC. Another important issue determining pacemaker response in asystolic reflex syncope concerns a possible additive vasodilatory component. Recent thinking concerning tilt-table testing stresses that a positive tilt test suggests an underlying clinically important vasodepressive tendency and consequently a low probability that pacing therapy will be effective (19). In Figure 3, that vasodepression tendency would result in an abnormal tilt test in patterns 1, 3, and 4. These considerations were inspired by the ISSUE III substudy, in which pacing was performed in patients in whom an implantable loop recorder had previously shown asystole (9). In that study, pacing usually did not prevent syncope if a previous tilt-table test had been positive, which suggests a vasodepressor contribution to the syncope. The SUP-2 study also showed more benefit from pacing in those with a negative tilt-table test. In that study, the group with asystole during TTT (n = 38) had a recurrence rate of 23% after 3 years. It is tempting to think that this group corresponds to our groups A and B (together 34%) in the present study, that is, those with late asystole (10). Potentially, some patients with VVS in whom asystole commences well before TLOC could benefit from pacing. If this concept proves valid, the next steps would include measuring the onset of asystole in relation to that of TLOC, determining whether the relative timing of asystole onset is reproducible, and finally determining whether pacing for early-onset asystole reduces syncope risk. In principle, the same reasoning also applies to bradycardia, but we chose to limit our study to asystole because it reflects cardioinhibition in its most severe form.

STUDY LIMITATIONS. The results reported here must be interpreted in the light of several important limitations. First, the number of patients was fairly low

because of the combined demands of syncope and asystole without the use of nitroglycerin. Second, the study focused on findings obtained during tilt-induced syncope. Heart rate might well behave differently between tilt-table tests and spontaneous events, so we do not know whether our findings apply to real life. Third, this study is unable to inform on the reproducibility of the findings.

Fourth, the impact of our observations on therapeutic interventions, particularly pacemaker therapy, is unclear. Specifically, the ISSUE-III substudy alluded to above suggests that pacing to prevent asystole and TLOC is less useful in those patients with an evident vasodepressor susceptibility based on prior tilt-table testing (9). In this regard, we stress that our study only comprised patients with positive tilt-table tests; we did not examine how these patients would have responded to pacing. Consequently, we cannot state whether pacing is more useful in patients in whom asystole occurs early with regard to TLOC versus late-onset asystole. However, it should be realized that the ISSUE-III investigators did not attempt to ascertain whether asystole occurred before, during, or after TLOC onset. Consequently, a useful next step would be to combine implantable loop recordings with comprehensive video-EEG analysis and TLOC onset assessment, as was used here.

Finally, our approach to assess the timing of asystole relative to onset of TLOC was robust, but not perfect. We used a 3-s asystole threshold because previous studies showed that TLOC is unlikely to occur with loss of cerebral blood flow of that duration or less. Consequently, asystole that occurred 3 s or less before TLOC could reasonably be argued to be noncontributory. However, it is recognized that in some patients, consciousness might be unaffected for 8 to 10 s (8). Because of this variation in the syncope threshold, the proportion of cases without a primary cardioinhibitory mechanism could be higher.

CONCLUSIONS

In one-third of cases with tilt-induced reflex syncope with asystole, asystole occurred too late to have been the primary cause of loss of consciousness. These results might help to explain the apparent ineffectiveness of pacemaker therapy in many cases of cardioinhibitory reflex syncope and suggest that efforts to prevent syncope by pacing intervention should focus on the timing of asystole in relation to that of TLOC.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Asystole during tilt-table testing occurs too late in at least one-third of cases to be the primary cause of TLOC.

TRANSLATIONAL OUTLOOK: Syncope prevention with pacemaker therapy should focus on timing of asystole in relation to TLOC.

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