Understanding syncope in the framework of transient loss of consciousness

Saal, D.P.

CHAPTER III

Temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope

Saal DP | Thijs RD | van Zwet EW | Bootsma M | Brignole M | Benditt DG | van Dijk JG

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Abstract

Background

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

Objectives

To **i**nvestigate the relation between the onset of asystole and of transient loss of consciousness (TLOC) in tilt-induced reflex syncope and estimate how often asystole was the principal cause of TLOC.

Methods

We evaluated electrocardiographic (ECG), electroencephalographic (EEG), blood pressure (BP) and clinical findings during tilt table tests. Inclusion required TLOC (video), EEG slowing, accelerating BP decrease and an RR-interval ≥3 seconds. We excluded cases with nitroglycerin provocation. Asystole after onset of TLOC (group A) or within 3 seconds 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; 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 mmHg, group C) than when it occurred late (32.0 mmHg, groups A and B), suggesting that vasodepression was not prominent at the start of asystole in early asystole, 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. Relying on ECG data only is likely to overestimate the importance of asystole.

Keywords: asystole, reflex syncope, tilt table testing, TLOC

Introduction

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 is by far the most common cause of reflex syncope. In many instances, susceptibility to vasovagal syncope may be unmasked by head-up tilt-table testing.[2]

Reflex syncope encompasses both vasodepressor and cardioinhibitory mechanisms. While either mechanism can cause syncope, in most cases both 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 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 seconds), which on its own causes blood pressure to fall precipitously. If asystole is sustained for a sufficiently long period of time, the resulting cerebral hypoperfusion causes unconsciousness about 6-8 seconds (s.) after the last heartbeat. [7,8]

The presence of asystole in VVS may prompt physicians to consider pacemaker therapy to prevent syncope recurrence. However, it is increasingly recognised [2] that the benefit of pacing is limited in VVS patients. In fact, recent observations from the ISSUE-3 and SUP-2[9,10] suggest that amongst 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 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 asystole and of TLOC during tilt-induced syncope. A second goal was to use the observed temporal relation 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 two tertiary syncope referral centres: 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, 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 centres. Part of the present patient group has been described before.[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 blood pressure (BP) showing the pattern of tilt-induced reflex syncope, i.e. an increasing rate of decline with or without bradycardia. We now incorporated one additional inclusion criterion: the ECG showed asystole, defined as an RR-interval of ≥ 3 s.; we also added one 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 one- or two-lead ECG. In the LUMC the video camera is attached to the tilt table and is aimed at the head and shoulders, while at SEIN a ceiling-mounted camera covers the entire tilt table.

Tilt table tests were performed using 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 degrees, after which, if syncope did not occur, sublingual nitroglycerin was used and patients were observed for another 20 minutes. However, as noted earlier, 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 of reflex syncope with clinical TLOC); presyncope (similar circulatory changes without clinical TLOC); slowing of the EEG, asystole, or a combination of these factors. Tilting back to the supine position required 12 s. at both centres.

Non-invasive 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 behaviour as a sign of syncope. All video records were reviewed by two of three examiners (DPS, RDT, JGvD), well acquainted with the semiology of syncope.

We searched for asystole (i.e., cardiac pause ≥3 s.) in a period beginning approximately 30 s. before and continuing during loss of consciousness. The ECG in syncope may show more than one RR-interval longer than three s.; we only analysed the first such episode. No attempts were made to quantify bradycardia preceding or following 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, resulting in missing values. MAP was calculated as the mean of the continuous BP signal over two 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 relation between asystole and TLOC

We set the start of TLOC as 'time zero' and expressed the start of asystole in integer s. relative to time zero. We divided patients into three groups based on the temporal relation of asystole to TLOC:

- Group A: asystole started after the onset of TLOC. In these cases asystole could with certainty not have been the principal cause of TLOC.
- Group B: asystole started at most three s. before the onset of TLOC. We postulate that asystole in this group was very unlikely to have been the principal cause of TLOC, based on prior observations indicating that pure asystole causes loss of consciousness seven to ten 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 four s. in standing subjects. Hence, we used a three s. threshold to increase confidence that asystole was not the cause of TLOC in this group.
- Group C: asystole started more than 3 s. before TLOC. In this group asystole may have been the major contributor causing TLOC.

Statistical analysis

The study was descriptive in nature. To analyse 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 which asystole may 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 1551 tilt-table tests with video-EEG were performed at the LUMC from 2006 to June 2015, and 412 tilt-table tests from 2009 to 2015 at SEIN. After excluding patients without syncope, 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) or those with incomplete video data, 35 cases remained. The median age of patients was 35 years (range 12-84); 21 were female, 14 male (Table 1).

Table 1. Characteristics of the groups according to onset of asystole related to TLOC.

	Group A Asystole starting after TLOC	**Group B** Asystole starting at most 3 seconds before TLOC	**Group C** Asystole starting more than 3 seconds before TLOC	**Total**
Subjects	9	3	23	35
Mean age (range)	46 (18-84)	34 (27-40)	32 (12-60)	35 (12-84)
Gender (M:F)	2:7	1:2	11:12	14:21
Mean duration asystole (s., mean ± SD)	8.9 ± 8.5	8.3 ± 4.9	14.6 ± 14.0	12.6 ± 12.4
Mean duration TLOC (s., mean ± SD)	27.8 ± 8.9	32.7 ± 10.4	33.0 ± 15.1	31.7 ± 13.3
Mean difference asystole -onset TLOC (s., mean ± SD)	4.4 ± 3.97	-2.3 ± 0.58	-7.5 ± 2.66	-4.1 ± 5.9

The groups were formed based on assumptions regarding the role of asystole in causing syncope: group A concerns those in whom asystole started after TLOC started, so asystole was certainly not the cause of syncope. In group B asystole started at most three seconds before the onset of TLOC, making a major role of asystole unlikely. In group C asystole started at least three seconds before syncope and may have played a major role.

Timing of asystole

Figure 1 and Table 1 show the relative timing of asystole and TLOC onset. In nine patients asystole started after onset of TLOC (Group A). MAP at the onset of asystole was missing in four cases, and for the remaining five cases median MAP was 32 mmHg (range 24-35).

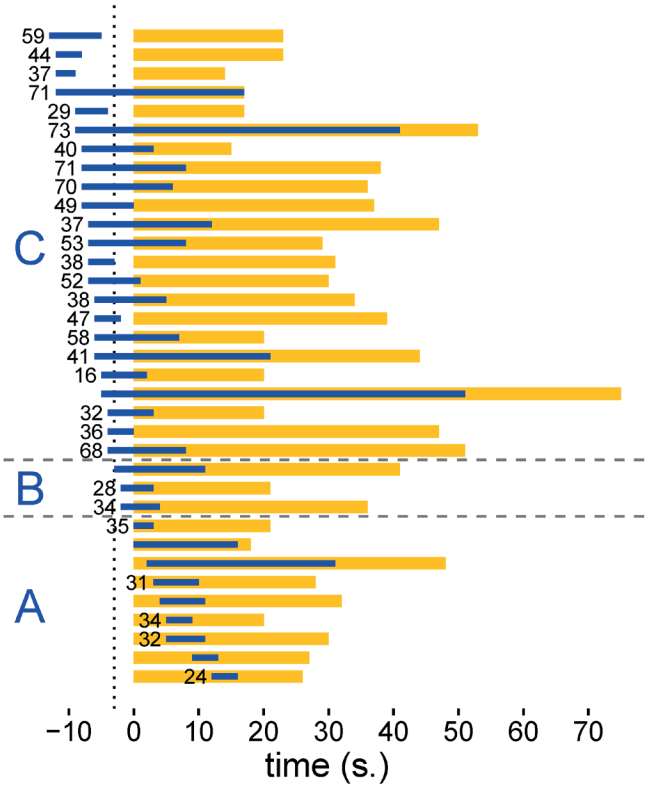

Figure 1. Relative time of asystole and transient loss of consciousness

Each line of horizontal bars concerns one subject. Orange bars denote the duration of clinically observed TLOC and blue bars denote the start and duration of asystole. Data are aligned to the start of TLOC, defined as occurring at zero seconds. The dotted line shows a period of 3 seconds before onset of TLOC. The numbers at the beginning of the asystole bars denote mean arterial pressure of the heart beat just before asystole; when MAP is not stated, it was too low to be measured at that point in time.

In three patients asystole coincided or preceded TLOC by at most three s. (Group B). The median MAP at the onset of asystole for two cases with measurable BP was 31 mmHg (range 28-34).

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

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 primarily caused syncope. In the remaining 23 cases (66%) asystole may have played a major role.

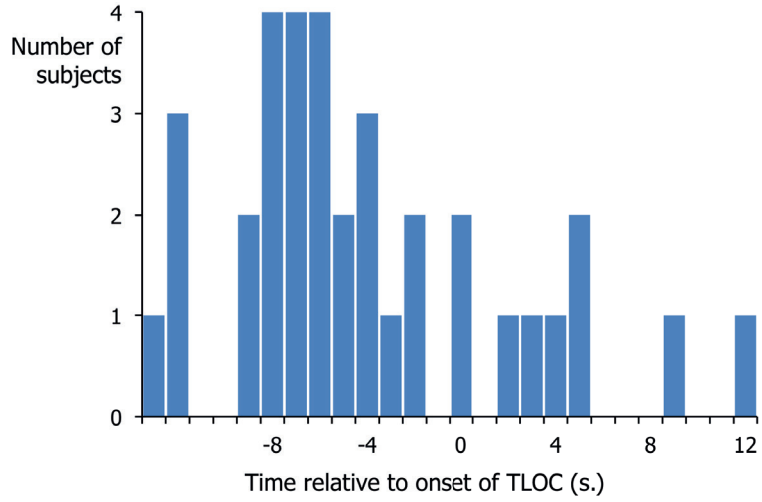

Figure 2. Histogram of the start of asystole in relation TLOC

On the horizontal axis the start of asystole is shown relative to the start of TLOC. The vertical axis shows the number of subjects. TLOC: transient loss of consciousness

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

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, blood pressure at the onset of TLOC is likely to represent the combined effects of vasodepression and

cardioinhibition. As noted earlier, there is no practicable way to disentangle the combined effects of vasodepression and cardioinhibition on blood pressure 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, i.e. > 3 s. before TLOC (group C, 45.5 mmHg) than when it started later (group A+B, 32 mmHg). 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.

Clinical implications

Figure 3 provides a schematic view illustrating how the magnitude as well as the timing of the vasodepressive and cardioinhibitory mechanisms may determine when syncope occurs. A key implication of these effects is that relying on heart rate data alone may overestimate the importance of asystole as the cause of TLOC. For instance, diagnostic studies based on ECG data only would show asystole in three of the four patterns of Figure 3 (patterns 2, 3 and 4), suggesting that pacemaker therapy might be efficacious in all three, whereas it may 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 may also conform to pattern 3.

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 sub-study, 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, suggesting 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, i.e. those with late asystole.[10] Potentially, some patients with VVS in whom asystole commences well before TLOC may benefit from pacing. If this concept proves valid, 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 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 as it reflects cardioinhibition in its most severe form.

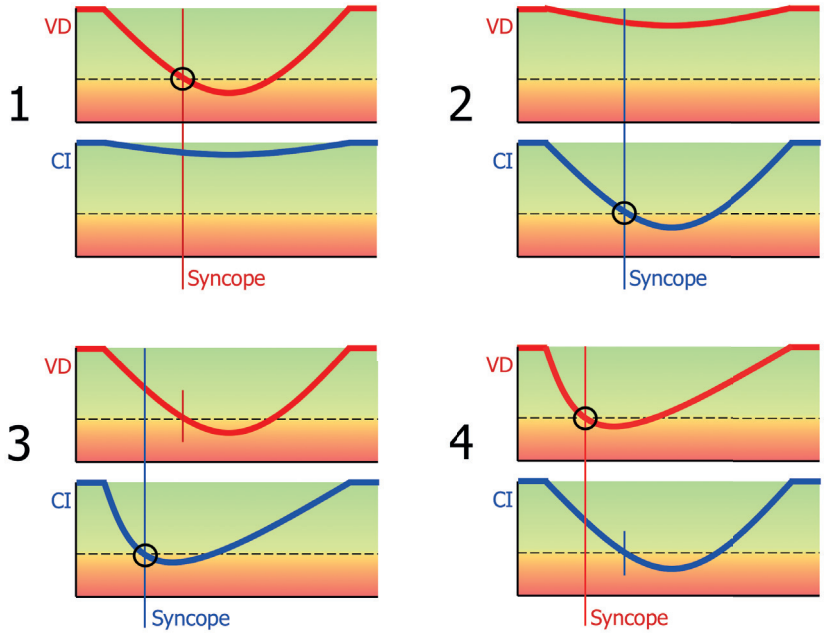

Figure 3. Schematic representation of possible relationships between strength and timing of vasodepressive and cardioinhibitory mechanisms in reflex syncope

Each of the four patterns 1-4 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 when at least one 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'. Patterns 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.

Limitations

The results reported here must be interpreted in the light of several important limitations. First, the number of patients was fairly low, due to 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 may 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 sub-study 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 realised 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 ILR 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 three second asystole threshold since previous studies show that TLOC is unlikely to occur with loss of cerebral blood flow of that duration or less. Consequently, asystole occurring three s. or less before TLOC could reasonably be argued to be non-contributory. However, it is recognized that in some patients, consciousness may 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 may thus be higher.

Conclusion

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 may 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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