The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes

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Syncope is defined as transient loss of consciousness as a result of cerebral hypoperfusion. Electroencephalography during syncope shows either a ‘slow-flat-slow’ or a ‘slow’ pattern. The first is believed to denote more severe hypoperfusion. Although the diagnosis of vasovagal syncope relies primarily on history taking, there is limited evidence regarding the relative importance of various clinical features, and none that relate them to the severity of electroencephalographic changes. The aim of this investigation was to study symptoms, signs and electroencephalographic changes with a 1 s resolution using electroencephalography and video data in 69 cases of tilt-induced vasovagal syncope. The main finding was that flattening of the electroencephalograph indicated more profound circulatory changes: the ‘slow-flat-slow’ group had a lower minimum blood pressure, longer maximum RR-interval, contained more cases with asystole and had a longer duration of loss of consciousness than the ‘slow’ group. Second, we describe a range of signs, including some that have rarely been reported in syncope, e.g. oral automatisms. Third, signs occurred at different rates depending on electroencephalographic flattening, suggesting a classification of syncopal signs. Type A signs (e.g. loss of consciousness, eye opening and general stiffening) develop during the first slow phase, stay present during flattening and stop in the second slow phase. Type B (particularly myoclonic jerks) occur when the electroencephalograph is slow but not flat: their abolition with electroencephalographic flattening suggests dependence on cortical activity. Type C signs (making sounds, roving eye movements and stertorous breathing) occur only in the flat phase, whereas type D (dropping the jaw and snoring) may occur either in slow or flat phases. In conclusion, our findings provide a detailed assessment of clinical symptoms in relation to electroencephalographic (EEG) changes during tilt-induced syncope.

Keywords: semiology; vasovagal reflex syncope; EEG

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Introduction

Transient loss of consciousness has many possible causes, of which epileptic seizures, syncope and head trauma are the most common (Moya et al., 2009). Vasovagal reflex syncope is by far the most common cause of non-traumatic transient loss of consciousness, with an estimated 30–40% of people experiencing one or more episodes in their lifetime (Moya et al., 2009). In this regard, syncope is defined as transient loss of consciousness due to cerebral hypoperfusion; in vasovagal syncope, activation of the autonomic nervous system results in low blood pressure and cerebral hypoperfusion through diminution of cardiac output, decreased vasoconstriction and bradycardia (van Dijk et al., 2009).

Diagnosing the cause of transient loss of consciousness relies primarily on history taking from patients and eyewitnesses (Moya et al., 2009). However, there is limited quantitative evidence regarding the relative importance of clinical features (Sheldon et al., 2002, 2006). In the case of syncope, symptoms and signs generally fall into two groups (van Dijk et al., 2009; Wieling et al., 2009): the first is related to the cause of syncope, such as palpitations in arrhythmia or pallor in reflex syncope. The second group comprises consequences of cerebral and retinal hypoperfusion. These include visual problems, diminished consciousness, loss of voluntary motor control and motor phenomena such as myoclonic jerks and stiffness (Wieling et al., 2009).

One of the few tools to study brain function during syncope is the electroencephalographic (EEG). The first EEG pattern of syncope to be described was the ‘slow-flat-slow’ pattern (Gastaut et al., 1956a; Gastaut and Fischer-Williams, 1957; Aminoff et al., 1988; Brenner, 1997; Ammirati et al., 1998; Martinez-Fernandez et al., 2008): in the first slow phase the alpha rhythm and other normal activity is lost and supplanted by slow activity, decreasing in frequency from theta to delta waves while wave amplitude increases. The second phase is marked by a fairly sudden flattening of the EEG. The third phase consists of slow activity, in which frequency and amplitude change in the reverse order as in the first slow phase. The second EEG pattern consists of increasing and decreasing slowing only (Karp et al., 1961; Aminoff et al., 1988; Brenner, 1997; Ammirati et al., 1998). The slow-flat-slow pattern is generally believed to denote more severe hypoperfusion; it was first described in asystolic syncope induced by eyeball pressure, and cardio-inhibitory reflex syncope has been associated with a slow-flat-slow pattern (Ammirati et al., 1998; Martinez-Fernandez et al., 2008). However, the slow-flat-slow pattern can occur without asystole (Brenner, 1997; Sheldon et al., 1998; Martinez-Fernandez et al., 2008).

Signs that indicate EEG flattening may help to identify severe hypoperfusion. However, there are few studies that correlate clinical signs and symptoms with EEG observations in syncope (Gastaut and Navarranne, et al., 1956b; Gastaut and Fischer-Williams, 1957; Aminoff et al., 1988; Martinez-Fernandez et al., 2008). We aimed to study symptoms and EEG changes with a 1 s resolution using EEG and video data in 69 tilt-induced cases of reflex syncope. Using these data, we studied (i) whether the slow-flat-slow pattern was associated with more severe circulatory changes; (ii) which signs were specifically associated with a particular EEG pattern; and (iii) whether this association shed light on the pathophysiology of these clinical syncopal events.

Materials and methods

Patients

Tilt-table test data performed at the Department of Neurology of the Leiden University Medical Centre were examined. For the present study records were eligible from 2006, when a video camera was attached to the tilt-table, to July 2011. The following physiological data were recorded and stored: continuous non-invasive finger blood pressure measurements, ECG, EEG and video.

Patients were referred from the tertiary outpatient syncope clinic at the Leiden University Medical Centre, and from the general neurology outpatient department. Inclusion required a clinical suspicion of vasovagal syncope and its provocation by tilt testing with or without sublingual nitroglycerin. Tilt-induced reflex syncope was defined using the triad of video, EEG and circulatory changes that characterize reflex syncope: (i) video data were compatible with loss of consciousness (see below); (ii) circulatory changes comprised an abrupt blood pressure decrease with an accelerating rate of drop, with or without bradycardia/asystole (van Dijk et al., 2009); and (iii) EEG changes consisted of either a slow or a slow-flat-slow pattern. Exclusion criteria included incomplete data and concomitant psychogenic pseudosyncope, non-vasovagal reflex syncope, or orthostatic hypotension. The hospital’s medical ethics committee approved the use of the data for the present study. Dutch law does not require individual informed consent for the publication of anonymous data gathered for purposes of patient care.

Clinical tilt protocol and data storage

A modification of the ‘Italian protocol’ was used to test for vasovagal syncope (Bartolletti et al., 2000). The test consisted of 10 min of supine rest followed by 20 min of head-up tilt to 70°, and, if no syncope occurred, by a further 20 min after a sublingual dose of 400 μg nitroglycerin. A technician and a neurology resident were present at all investigations. According to local guidelines, patients could be tilted back when reflex syncope was clinically likely and patients recognized symptoms during presyncope. In less clear cases patients were tilted back when syncope occurred or the EEG showed slowing or flattening. Tilting back to supine position required 12 s.

Non-invasive beat-to-beat blood pressure was recorded continuously with either a Finometer (Finapres Medical Systems) or a Nexfin® (BMEye) device. With both devices the analogue blood pressure was measured from the middle phalanx of the middle finger with the hand held at heart level in a sling. The analogue finger blood pressure signal was transferred to the EEG machine to ensure synchrony of all signals (note this is not the calculated brachial blood pressure signal).

A 16-channel EEG and one channel electrocardiogram were recorded. An EEG-machine (Nicolet 2100, Nihon Kohden) was used to store all signals using a sampling rate of 200 Hz.

Data analysis

Baseline data included age and gender. All recordings were inspected by an investigator (J.v.N.) and a neurologist experienced in EEG and syncope (R.D.T. or J.G.V.D.). Times of events were noted to the nearest integer second of ‘clock time’. Video records were reviewed by two
examiners repeatedly to achieve consensus regarding the occurrence and time of clinical events. EEG data were scored without additional recourse to the video after video data had been scored.

Clinical events

The list of clinical events was formalised after reviewing 10 tests and is shown in Tables 1–3. The clinical onset of loss of consciousness was defined as the first event to be recognised, usually indicating altered motor control, such as jaw dropping, head dropping or eye opening. The resumption of consciousness was defined as the resumption of purposeful movements, answering a question or a facial expression evidencing attention as well as awareness.

Electroencephalography

The beginning of EEG slowing was defined as the first delta wave of a consistent period of slowing, and the end of slowing as the last such delta wave. The beginning and end of a period of flat EEG was similarly noted. EEG times were noted by experienced electroencephalographers (J.G.v.D. or R.D.T.). An independent analysis of 20 EEGs (10 slow and 10 slow-flat-slow) by both investigators showed that the mean difference between observers of EEG events was 0.2 ± 2.6 s.

Heart rate and blood pressure

Continuous ECG and blood pressure data from 180 s before to 120 s after the clinically apparent onset of transient loss of consciousness were extracted. The following parameters were extracted from RR-intervals: a heart rate time series in beats/min; the longest RR-interval during syncope; the presence of asystole, here defined as an RR-interval ≥3 s. A 'smoothed mean arterial pressure' was calculated by smoothing the raw blood pressure signal using a 9 s window, including 4 s before a given point in time, that second itself, and 4 s afterwards. This approach allowed us to provide a value regardless of tachycardia or asystole. Shorter periods of smoothing were explored but resulted in a considerably noisier signal. When movement caused a loss of signal, data were considered missing. Heart rate and smooth mean arterial pressure curves were resampled at 1 s intervals to allow averaging across individuals. The minimum blood pressure at syncope was measured.

Statistics

Differences in rates of occurrence of events between the slow and slow-flat-slow groups were investigated with Fisher’s exact test. We studied whether events occurred at different rates in the slow-flat-slow group during slow and flat periods of the EEG with the following simulation procedure. First, the numbers of events in the slow-flat-slow group were

### Table 1 Occurrence of events

<table>
<thead>
<tr>
<th></th>
<th>All (n = 69)</th>
<th>Slow (n = 31)</th>
<th>SFS (n = 38)</th>
<th>P</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio %</td>
<td>Ratio %</td>
<td>Ratio %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating before</td>
<td>7/7 100.0</td>
<td>2/2 100.0</td>
<td>5/5 100.0</td>
<td>1.0</td>
<td>62</td>
</tr>
<tr>
<td>Pallor before</td>
<td>42/45 93.3</td>
<td>16/17 94.1</td>
<td>26/28 92.9</td>
<td>1.0</td>
<td>24</td>
</tr>
<tr>
<td>Yawning before</td>
<td>10/68 14.7</td>
<td>5/30 16.7</td>
<td>5/38 13.2</td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td>During syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes open during syncope</td>
<td>63/68 92.6</td>
<td>25/30 83.3</td>
<td>38/38 100.0</td>
<td>0.014</td>
<td>1</td>
</tr>
<tr>
<td>Dilated pupils</td>
<td>20/26 76.9</td>
<td>4/6 66.7</td>
<td>16/20 80.0</td>
<td>0.6</td>
<td>43</td>
</tr>
<tr>
<td>Making sounds</td>
<td>38/62 61.3</td>
<td>11/29 37.9</td>
<td>27/33 81.8</td>
<td>0.001</td>
<td>7</td>
</tr>
<tr>
<td>Jerks</td>
<td>41/68 60.3</td>
<td>17/30 56.7</td>
<td>24/38 63.2</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>Eyes upwards</td>
<td>34/57 59.6</td>
<td>5/22 22.7</td>
<td>29/35 82.9</td>
<td>&lt;0.001</td>
<td>12</td>
</tr>
<tr>
<td>Oral automatisms</td>
<td>33/65 50.8</td>
<td>13/28 46.4</td>
<td>20/37 54.1</td>
<td>0.6</td>
<td>4</td>
</tr>
<tr>
<td>Head turning</td>
<td>29/69 42.0</td>
<td>9/31 29.0</td>
<td>20/38 52.6</td>
<td>0.055</td>
<td>0</td>
</tr>
<tr>
<td>Jaw dropping</td>
<td>19/65 29.2</td>
<td>5/28 17.9</td>
<td>14/37 37.8</td>
<td>0.1</td>
<td>4</td>
</tr>
<tr>
<td>Head drooping</td>
<td>19/69 27.5</td>
<td>6/31 19.4</td>
<td>13/38 34.2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Roving eye movements</td>
<td>15/57 26.3</td>
<td>0/22 0.0</td>
<td>15/35 42.9</td>
<td>&lt;0.001</td>
<td>12</td>
</tr>
<tr>
<td>Snoring</td>
<td>12/69 17.4</td>
<td>0/31 0.0</td>
<td>12/38 31.6</td>
<td>&lt;0.001</td>
<td>0</td>
</tr>
<tr>
<td>Arm raising</td>
<td>13/65 20.0</td>
<td>7/29 24.1</td>
<td>6/36 16.7</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Nonsensical talking</td>
<td>4/69 5.8</td>
<td>3/31 9.7</td>
<td>1/38 2.6</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>2/54 3.7</td>
<td>0/21 0.0</td>
<td>2/33 6.1</td>
<td>0.5</td>
<td>15</td>
</tr>
<tr>
<td>After syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating after</td>
<td>28/30 93.3</td>
<td>13/14 92.9</td>
<td>15/16 93.8</td>
<td>1.0</td>
<td>39</td>
</tr>
<tr>
<td>Pallor after</td>
<td>45/53 84.9</td>
<td>19/23 82.6</td>
<td>26/30 86.7</td>
<td>0.7</td>
<td>16</td>
</tr>
<tr>
<td>Yawning after</td>
<td>3/69 4.3</td>
<td>0/31 0.0</td>
<td>3/38 7.9</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Dozing</td>
<td>3/68 4.4</td>
<td>1/30 3.3</td>
<td>2/38 5.2</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>Crying afterwards</td>
<td>3/69 4.3</td>
<td>0/31 0.0</td>
<td>3/38 7.9</td>
<td>0.2</td>
<td>0</td>
</tr>
</tbody>
</table>

For each event the number of occurrences is mentioned in relation to the number of cases in which its presence or absence could be determined (e.g. pupil dilation can only be observed when the eyes are open and well visible). The number of missing observations is indicated as ‘n’. Event ratios are presented for the entire group, for the ‘Slow’ and the ‘SFS’ groups. Data are ordered according to whether they occurred before, during and after syncope, and within each group by descending order of occurrence. P-values are determined with Fisher's exact test and compare findings between the two EEG groups; values <0.05 are indicated in bold. SFS = slow-fast-slow.
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Results

Patient group

A total of 720 tilt-table tests were performed during the study period, with the following circulatory events: reflex syncope in 92 cases (12.8%); presyncope in 101 (14.1%) and orthostatic hypotension in 84 (11.7%). Of 92 cases of reflex syncope, 18 were excluded because of insufficient video data, excessive missing data in three, young age (7 years) in one, and no clinical signs in one. Mean age of the resulting 69 cases was 46.0 ± 19.8 years (range 12–84 years). There were 35 males and 34 females. Nitroglycerin was used 48 times.

Figure 1 summarizes clinical, EEG and circulatory data. The average duration of loss of consciousness was 22.4 ± 10.7 s (median 20, range 4–55). The EEG histogram is shifted towards the left compared to the loss of consciousness histogram, showing that EEG slowing preceded the onset of loss of consciousness. The return of responsiveness followed the end of EEG slowing.

Table 2 Times of events in seconds relative to the start of EEG slowing

<table>
<thead>
<tr>
<th>All</th>
<th>Slow group</th>
<th>SFS group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Time</td>
<td>n</td>
<td>Time</td>
</tr>
<tr>
<td>Head dropping</td>
<td>1.7 + 4.5 (2)</td>
<td>6</td>
<td>3 (−11,6)</td>
</tr>
<tr>
<td>TLOC begin</td>
<td>3.2 + 4.3 (3)</td>
<td>31</td>
<td>2 (−5,9)</td>
</tr>
<tr>
<td>Arm raising</td>
<td>5.2 + 4.5 (5)</td>
<td>7</td>
<td>5 (−2,8)</td>
</tr>
<tr>
<td>Head turning</td>
<td>5.6 + 5.5 (5)</td>
<td>10</td>
<td>5.5 (−2,36)</td>
</tr>
<tr>
<td>Eye open</td>
<td>5.7 + 4.4 (5.5)</td>
<td>22</td>
<td>6.5 (2,24)</td>
</tr>
<tr>
<td>Eye turning</td>
<td>5.8 + 4.6 (6)</td>
<td>2</td>
<td>9.5 (5,14)</td>
</tr>
<tr>
<td>Start jerk</td>
<td>6.5 + 4.7 (7)</td>
<td>17</td>
<td>7 (1,21)</td>
</tr>
<tr>
<td>Start sound</td>
<td>10.4 + 6.8 (8)</td>
<td>11</td>
<td>8 (3,18)</td>
</tr>
<tr>
<td>Jaw drop start</td>
<td>10.3 + 7.0 (8)</td>
<td>5</td>
<td>13 (5,30)</td>
</tr>
<tr>
<td>Start snoring</td>
<td>9.8 + 7.5(8.5)</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>End jerk</td>
<td>11.2 + 5.8 (10)</td>
<td>17</td>
<td>12 (2,27)</td>
</tr>
<tr>
<td>Oral automatism</td>
<td>12.7 + 8.7 (12)</td>
<td>13</td>
<td>7 (4,23)</td>
</tr>
<tr>
<td>Eyes roving</td>
<td>13.9 + 3.9 (13)</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>End sound</td>
<td>14.9 + 6.5 (15)</td>
<td>11</td>
<td>13 (4,18)</td>
</tr>
<tr>
<td>Start jerk B*</td>
<td>20.7 + 6.6 (18)</td>
<td>3</td>
<td>17 (15,18)</td>
</tr>
<tr>
<td>End snoring</td>
<td>18.3 + 5.5 (19)</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>End jaw drop</td>
<td>21.3 + 12.2 (21)</td>
<td>5</td>
<td>25 (14,45)</td>
</tr>
<tr>
<td>End jerk B*</td>
<td>22.5 + 6.7 (22)</td>
<td>3</td>
<td>17 (16,22)</td>
</tr>
<tr>
<td>TLOC end</td>
<td>25.6 + 10.4 (23)</td>
<td>31</td>
<td>18 (10,44)</td>
</tr>
</tbody>
</table>

For each event the time of occurrence is stated relative to the start of EEG slowing. Numbers for the entire group (All) concern the mean and standard deviation, with the median in parentheses. Events are shown in the order of appearance according to median values. For the slow (S) and slow-flat-slow (SFS) groups, medians are given with the minimum and maximum values between parentheses. The P-value is determined with Mann-Whitney U test; P-values < 0.05 are shown in bold. na = not applicable, because there were no values in one group; TLOC = transient loss of consciousness.

*Some patients exhibited two bouts of myoclonic jerks. ‘Jerk B’ comprises the second bout in these patients.

counted separately for slow and flat EEG periods: the observed count. For each individual with the event in question the duration of slow and flat EEG periods was noted. In the simulation, an event was allocated to an individual’s slow or flat period with a chance weighted for relative duration of these phases. Simulated events were allotted to phases for all subjects with that event. Thereafter, the numbers of simulated events occurring during a slow phase were counted for the group. This simulation was run 105 times, resulting in a distribution of how often events occurring during a slow phase occurred by chance during a slow phase. The observed count was then compared to this distribution: if the observed count occurred in <5% of the 105 simulation runs, the P-value of this observation is <0.05. This simulation was used to determine if events were significantly over-represented in either the slow or the flat phase.

Differences between other quantitative data were investigated with Student’s t-test or the Mann-Whitney U test depending on data distribution. Correlations were investigated with Spearman or Pearson’s tests depending on distribution. Statistical tests were performed with SPSS version 17.
Main EEG findings are illustrated in Fig. 2. EEG changes were of shorter duration in the slow group (16.5±5.9 s) than in the slow-flat-slow group (26.2±8.5 s; combined slow and flat phases; Student’s t-test \( P < 0.0001 \)).

The slow group comprised 31 patients; there were 15 males; mean age was 44.8±18.9 years and nitroglycerin had been used in 21 cases. The slow-flat-slow group consisted of 38 cases with 20 males; mean age was of 46.9±18.9 years and nitroglycerin was used in 27 cases. The first slow phase lasted 7.7±4.7 s (median 7 s, range 1–25 s), flattening lasted for 11.6±8.3 s (median 10 s, range 1–34 s) and the second slow phase lasted 6.9±3.9 s (median 6 s, range 1–22 s). Within the slow-flat-slow group, the durations of the flat phase and the preceding slow phase were strongly inversely correlated (Fig. 2, Spearman’s test \( P < 0.0001 \)). There was no relation between the durations of the flat phase and the succeeding slow phase (Spearman’s test \( P = 0.86 \)), nor between that of the two slow phases (Spearman’s test \( P = 0.097 \)).

Gender ratios (chi square: \( P = 0.72 \)), use of nitroglycerin (chi square: \( P = 0.77 \)) and age (t-test \( P = 0.66 \)) did not differ significantly between the slow and slow-flat-slow groups.
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Occurrence of events in the two groups

Table 1 shows rates of occurrences of the various observed clinical events. With respect to events before and after syncope, sweating and pallor occurred frequently; the frequency of sweating may have been underestimated as it was often not clearly visible.

The eyes were open during transient loss of consciousness in 93% of all cases. When they were visible, they were directed upwards in 60%. They were closed before syncope in 55 cases, and then opened during it in 50; the five cases in whom the eyes remained closed were all in the slow group. Of the 14 cases in whom the eyes were open before syncope, closure occurred only once, in the slow-flat-slow group. Pupil dilation was common, but may have been underestimated as pupils were sometimes hard to discern. Myoclonic jerks were seen in 60% of patients, more often involving the shoulders and arms rather than the head and facial muscles. This rate may be an underestimation as the hands were rarely in view. This also holds for ‘arm raising’, consisting of one or two arms being raised in the air and staying in that position.

Sounds were very diverse, including short grunting sounds, moaning, short snorts and heavy or stertorous breathing. Stertorous breathing only occurred in the slow-flat-slow group. Oral automatisms were seen in half of the subjects, and were diverse in nature; they consisted of movements of the lips, cheeks or tongue.

Rates of occurrence differed significantly between groups for five events: eyes open, eyes upwards, making sounds, roving eye movements and snoring. All five events occurred more often in the slow-flat-slow group, and the last three events only occurred in the slow-flat-slow group.

Events as a function of slow and flat electroencephalographic periods

Table 2 shows the mean times of occurrence of the main events and whether these times differed between the groups. Head dropping, arm raising and head turning appeared to begin very early, sometimes before EEG slowing. Only three events occurred at significantly different times in the two groups: eye opening occurred later in the slow group, at a median of 6.5 s, than in the slow-flat-slow group, at 3 s. Likewise, myoclonic jerks ended later in the slow group, and transient loss of consciousness lasted longer in the slow-flat-slow group.

Table 3 summarizes which clinical observations occurred at significantly different frequencies during the first slow phase and the flat phase in the slow-flat-slow group. Events that started or occurred during the first slow phase were the onset of transient loss of consciousness and eye opening, and there was a non-significant trend for head turning. Events that occurred during the flat phase were the onset of roving eye movements, the end of the first bout of myoclonic jerks, the start of making sounds, the end of jaw dropping, the start of apnoea and the start of stertorous breathing.

Patterns of selected events

Start and end of transient loss of consciousness

Transient loss of consciousness started 3.3 ± 4.3 s after the onset of EEG slowing and responsiveness was delayed until 3.7 ± 3.7 s after the end of slowing (Fig. 2). At the end of transient loss of consciousness patients generally first looked around or turned their heads with an astonished expression, without responding to questions. After that, facial expressions changed abruptly, implying a sudden awareness of the situation.

Eye opening

The time of eye opening could only be established in those cases in which the eyes had been closed beforehand. Eyes tended to open during the first slow phase in the slow-flat-slow group, 3 s after the onset of EEG slowing (Table 2 and Supplementary Fig. 1). This was significantly earlier than in the slow group (6.5 s; Mann-Whitney U test: \( P < 0.007 \); Table 2). In five patients the eyes opened in the first seconds of the flat phase (Supplementary Fig. 1). The four cases in which the eyes remained shut were all in the slow group, and three of these cases had the shortest EEG slowing of the entire group. This suggests that eye opening need not occur if EEG alteration is mild; that it universally occurs during more severe EEG slowing; and that EEG flattening does not change the status of eye opening.

Myoclonic jerks

Myoclonic jerks occurred in two bouts. The onset of jerks occurred ~10× more often during the first slow phase than in the flat phase in the slow-flat-slow group, but the difference was not statistically significant (Fig. 3 and Table 3). Jerks were distributed evenly during slowing in the slow group, whereas they started in the slow-flat-slow group during the first period of slowing but ended at the onset of EEG flattening or a few seconds later. The second bout concerned fewer myoclonic jerks (Supplementary Fig. 2); these started in the second period of EEG slowing or after slowing had ended.

Stertorous breathing

Table 3 shows that this event started significantly more often during flat EEG periods than during slow EEG periods. Figure 4 shows that when this pattern started during EEG slowing, this was very near the onset of flattening, and also suggests that its occurrence points to prolonged flattening.

Discussion

In this study we present a detailed semiology of tilt-table induced vasovagal reflex syncope in a sizable group of syncope subjects. The analysis yields three main findings. First, we confirm in a large sample that flattening of the EEG indicates more profound circulatory changes. Second, we describe a wide range of clinical symptoms, including signs that have not or rarely been reported previously, such as oral automatisms. Third, we show that the occurrence of specific clinical signs depends on whether the EEG shows flattening.
Flattening of the electroencephalogram as a sign of severe cerebral hypoperfusion

The sensitivity of the EEG to ischaemia is well known: the EEG flattens when hemispheric blood flow falls below 0.16–0.17 ml/g/min (Astrup et al., 1981). The waves of the EEG are formed by inhibitory and excitatory postsynaptic potentials, and their amplitude reflects not only the number of potentials but also their synchrony of connected firing in a network. Ischaemia abolishes synaptic function well before permanent cell damage occurs (Hofmeijer and van Putten, 2012). The increasing amplitude and duration of slow waves in the slow phases thus likely reflects an increasing failure of network activity as synaptic connectivity decreases. In this view, flattening of the EEG denotes a complete network failure because there are too few functioning neurons to maintain network activity. Previous studies also showed that the slow-flat-slow pattern was associated with asystolic syncope and cardioinhibitory reflex syncope (Ammirati et al., 1998; Martinez-Fernandez et al., 2008).

Our study provides additional evidence that EEG flattening is indeed a sign of more severe cerebral hypoperfusion than EEG slowing alone: the slow-flat-slow group had a lower minimum blood pressure, longer maximum RR-intervals, contained more cases with asystole and had a significantly longer duration of transient loss of consciousness than the slow group. Furthermore, the inverse relationship between the duration of the first slow phase and the flat phase in the slow-flat-slow group suggests that the relative duration of the two phases is related to the rate of decrease of hypoperfusion (Fig. 5): a rapid perfusion decrease leads to a short first slow period and a long flat period. In rare cases, the EEG can flatten almost instantaneously. Note that smoothing the blood pressure data over 9 s may have caused the blood pressure drop during syncope to be underestimated slightly, but blood pressure data were only used in this study to prove systematic differences between the slow and slow-flat-slow groups, which worked satisfactorily.

Clinical signs and their relation to the electroencephalogram

We propose a classification of syncopal signs in four types based on their relation to the EEG (Fig. 6). Type A comprises signs that develop during the first slow phase, stay present during flattening and stop in the second slow phase. Type B signs are those that occur exclusively during EEG slowing, while type C signs are limited to the flat phase. Finally, type D signs may occur either during slow or flat phases. It should be noted that some events may not all have been observed and some occurred so rarely (nonsensical talking, nystagmus) that they could not be classified.

Type A signs

The most prominent sign of type A, starting and ending in slow phases, is loss of consciousness. The most likely cause is a loss of cortical activity, because this event starts during slow phases, represents an absence of normal activity and fits with the high susceptibility of the cortex to ischaemia. The recently recognized ‘consciousness system’ includes the cortex but also the upper brainstem, thalamus, hypothalamus and basal forebrain (Blumenfeld, 2012). Whether these additional regions are affected in syncope cannot be determined with our data.

Interestingly, patients generally first appeared awake before they began to respond verbally; in this phase they looked astonished but could direct their gaze at others speaking to them. It took ~4 s more for patients to become fully aware of their...
environment and interact with it in a coherent, meaningful way. The first phase of this typical sequence fulfils the ‘awake and attentive’ aspects of consciousness (Blumenfeld, 2012), whereas ‘awareness’ took several seconds more to emerge, and usually occurred abruptly. Note that we could not assess a similar sequence when subjects lost consciousness, as we did not continuously interact with them. However, literature data show that the first signs of evolving unconsciousness in syncope are fixation of the eyes and an inability to act. The latter is a state subjects later remembered, proving they were still aware of themselves and their surroundings at the time (Rossen et al., 1943; Luft and Noell, 1956; Karp et al., 1961). Taken together, these findings suggest differences in time of loss and recovery between the three aspects of consciousness, and that awareness of events depends critically on being attentive and awake.

Eye opening also belongs to type A, but requires a different explanation than transient loss of consciousness, because it cannot simply be the result of an absence of normal activity: the eyes in syncope are not half-closed as during neuromuscular blockade or death, but are wide open, requiring neural action. As the eyes remain opened during flattening, this action must be generated outside the cortex, possibly through disinhibition, as seen in decortication. General stiffening, including arm raising, is probably also explained in this manner.

**Type B signs**

Type B represents events that occur only during EEG slowing but not during flattening. Myoclonic jerks fit this pattern. Although some stated that myoclonic jerks only occurred during slow phases in syncope (Gastaut and Fischer-Williams, 1957; Stephenson, 1990) others wrote that they occurred during both flat and slow stages (Lempert and von Brevern, 1996). The present study strongly suggests that myoclonic jerks start during EEG slowing, but are abolished when the EEG flattens, in turn pointing towards an active cortical involvement. Gastaut and Fischer-Williams (1957) hypothesized that tonic contraction and myoclonic jerks in syncope were caused by a medullary-pontine mechanism, arguing, based on animal experiments, that ‘all the structures rostral to the brainstem are functionally dead’. We conclude in contrast that myoclonic jerks cannot be explained through loss of cortical inhibition, as they are only present when there is at least some cortical activity. How they are generated in the cortex remains unknown.

Other probable examples of type B are nonsensical talking and various sounds made by the subjects. Complex sensations such as an aura (Benke et al., 1997), near death experiences (Lempert and von Brevern, 1996), gestural automatisms (Gasparini et al., 2011), and complex movements such as lip-licking, sitting up right or rubbing the head (Lempert and von Brevern, 1996) can occur in syncope; their complexity suggests cortical involvement. This probably also holds for oral automatisms. Their subtlety probably explains why their presence has not been noted previously, even though they are common. As their duration was not noted uncertainty remains whether they fit type B.

**Type C signs**

Type C events only occur during flattening of the EEG. Examples are roving eye movements and stertorous breathing. Roving eye movements have been noted previously (Rossen et al., 1943).
These must be generated elsewhere than in the cortex. Brainstem action is possible, as the movement of the eyes proves that oculomotor motor nuclei are functional during EEG flattening. Not all brainstem functions remain intact, however, as the corneal reflex disappears in syncope (Rossen et al., 1943).

Snororing in syncope likely demands brainstem activity. It also occurs in the post-ictal phase of a generalized seizure, and then helps differentiate pseudoseizures from real ones (Sen et al., 2007). The respiratory network is situated in the brainstem, and responds to hypoxia in stages: the first response is an increase in the frequency and amplitude of ventilation, followed by a depression, finally followed by ‘gagging’ (Peña, 2009). In view of the short time involved, snorong in syncope probably corresponds to the first response. We therefore hypothesize that it is not so much caused by disinhibition of the cortex but represents a direct brainstem reflex to hypoxia.

**Type D signs**

The group of signs of type D events includes dropping the jaw and snoring. These signs can occur during slow as well as during flat phases and represent the majority of syncopal signs. Their lack of dependence on cortical activity suggests that they too are a result of disinhibition, but their variability remains unclear. Perhaps they reflect the degree of hypoperfusion of structures other than the cortex.

**Limitations**

The first limitation of this study is the precision of time measurements; this was probably better for clinical events, most of which were abrupt in nature, than for EEG changes. As EEG slowing begins and ends gradually, our delta wave threshold is subject to measurement uncertainty (attempts at automatic analysis were ineffective due to artefacts). An analysis on a subset of EEGs showed that there was no systematic bias between the reviewers, whereas the standard deviation of their times was 2.6 s. Note that this source of uncertainty can only affect results in one direction; it may have obscured some associations between signs and EEG patterns, but the reported associations remain valid.

Second, we did not formally study EEG and video data in blinded fashion, but the EEG was judged without simultaneously viewing the video recording. Third, we may have misidentified some cases of voluntary behaviour, particularly at the onset of syncope, as otherwise gross motor phenomena such as head dropping, head turning and arm-raising might occur before EEG delta activity. An unexpected observation was that myoclonic jerks could occur after the end of delta activity. The most likely explanation is that jerks can occur during mild slowing (theta waves).

Fourth, movements of the hands and legs may have been missed as they were not recorded on video. Finally, the circumstances under which our data were acquired must be taken into consideration. We used video data recorded with a camera fixed to a tilt-table test, interpreted after the fact and reviewed as often as necessary. This situation could hardly differ more from syncope in daily life, in which someone falls unexpectedly and may not be clearly visible to a distraught inexperienced observer, whose memory of the event is fraught with error during a later interview (Thijs et al., 2008). In such a setting only fairly spectacular events are likely to be remembered. A probable example of this effect is that myoclonic jerks are reported more often in tilt-table studies than in clinical studies (Wieling et al., 2009). The details of the tilt protocol and the administration of nitroglycerin may also have affected the results; in one laboratory, having one arm horizontal or not was enough to affect the rate of syncope (Kirbiş et al., 2010). The duration of syncope and the prevalence of slow and slow-flat-slow patterns may be different in spontaneous syncope depending on age and cause of syncope. However, the proportion of cases with asystole > 3 s and the duration of asystole in our study were similar to those in the ISSUE-2 and ISSUE-3 trials (Brignole et al., 2006, 2012). Furthermore, the study focused on the nature of relations of signs with EEG changes, and the wide range of findings ensured that the conclusions about those relations remain valid.

**Conclusion**

In the diagnosis of transient loss of consciousness a combination of clues is more helpful than any single one (Thijs et al., 2008; van Dijk et al., 2009; Wieling et al., 2009). Whether the eyes were open or not helps to recognize psychogenic attacks, as the eyes are commonly closed in psychogenic attacks, but open in syncope and seizures (Chung et al., 2006; Syed et al., 2008). The current study shows that the eyes can remain closed in syncope in rare cases, but, if so, that hypoperfusion was shallow and short-lasting. If witnesses report having seen the eyes move or report the patient making sounds during unconsciousness, in particular rhythmic noisy breathing, the presence of EEG flattening is almost certain, pointing to severe and prolonged hypoperfusion.

Our findings suggest that the pattern of signs indicates the time course of cerebral hypoperfusion, in particular its depth, speed of occurrence and duration. These parameters may depend on the cause of syncope, but based on our observations it is reasonable to anticipate that any cause of syncope resulting in short shallow hypoperfusion will elicit signs corresponding to the slow pattern, whereas any cause resulting in a quick circulatory standstill will result in another set of signs typical of the slow-flat-slow pattern. This rule may not apply to young children, as mechanisms of inhibition and disinhibition may differ from those in adults. As this could result in different clinical signs (for example, opisthotonus is described as common in asystolic syncope in young children but was not seen in our group), they were excluded from this study (Stephenson, 1990).

It remains to be established whether the pattern of signs described here can be used to infer the cause of syncope. This deduction requires a chain of relations linking signs to EEG changes, to the pattern of cerebral hypoperfusion, to the systemic circulation and finally to the cause of syncope. This paper only details the first two steps of this process.

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Supplementary material
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References


