Electroencephalographic Correlates of Vasovagal Syncope Induced by Head-Up Tilt Testing

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Background and Purpose—We sought to determine whether the introduction of EEG monitoring during head-up tilt testing could significantly improve the understanding of the cerebral events occurring during tilt-induced vasovagal syncope and the potential danger to the patient of this diagnostic procedure.

Methods—EEG monitoring was performed during head-up tilt testing in a group of 63 consecutive patients (27 males and 36 females; mean age, 41.5 years) with a history of recurrent syncope of unknown origin despite extensive clinical and laboratory assessment.

Results—Syncope occurred in 27 of 63 patients (42.8%) during head-up tilt testing and was found to be cardioinhibitory in 11 of 27 (40.7%) and vasodepressor in 16 of 27 (59.3%). All patients with a negative response to head-up tilt testing showed no significant EEG modifications. In patients with vasodepressor syncope, a generalized high-amplitude, 4- to 5-Hz (theta range) slowing of EEG activity appeared at the onset of syncope, followed by an increase of brain-wave amplitude with the reduction of frequency at 1.5 to 3 Hz (delta range). The return to the supine position was associated with brain-wave amplitude reduction and frequency increase to 4 to 5 Hz, followed by restoration of a normal EEG pattern and arousal (mean total duration of syncope, 23.2 seconds.). In patients with cardioinhibitory syncope, a generalized high-amplitude EEG slowing in the theta range was noted at the onset of syncope, followed by a brain-wave amplitude increase and slowing in the delta range. A sudden reduction of brain-wave amplitude then ensued, leading to the disappearance of electrocerebral activity (“flat” EEG). The return to the supine position did not allow either the immediate resolution of EEG abnormalities or consciousness recovery, both of which occurred after a further time interval (mean total duration of syncope, 41.4 seconds.).

Conclusions—EEG monitoring during head-up tilt testing allowed recording and systematic description of electrocerebral abnormalities developing in the course of tilt-induced vasovagal syncope. (Stroke. 1998;29:2347-2351.)

Key Words: electroencephalography • syncope • tilt table test

Vasovagally mediated hypotension and bradycardia may severely impair cerebral blood flow and consequently induce a sudden and transient loss of consciousness and postural tone.1–3 The current pathophysiological hypothesis for such vasovagal episodes holds that a rapid preload reduction causes an abnormally elevated inotropic response, due to an exaggerated catecholamine release.1–3 The increase in myocardial contractility in the setting of a preload reduction activates cardiac mechanoreceptors, mediating via the brain stem an abnormal enhancement of parasympathetic activity, together with a sympathetic withdrawal.1–3 The resulting hypotension and bradycardia cause a reduction in cerebral blood flow and a consequent impairment of neurological function. However, the relevance of cerebral involvement and potential neurological damage related to vasovagal syncope is not completely understood yet.

EEG allows dynamic assessment of neurological function,4 while head-up tilt testing is currently used to induce a vasovagal syncope in susceptible individuals.5,6 Accordingly, the main hypothesis for the present clinical investigation was that the introduction of EEG monitoring during head-up tilt testing could significantly improve the understanding of the cerebral events occurring during tilt-induced vasovagal syncope and the potential danger that could be caused to the patient by this diagnostic procedure.

Subjects and Methods
The study population was composed of 63 consecutive patients (27 males and 36 females; mean age, 41.5 ± 11.4 years) with a history of recurrent syncope of unknown origin who were undergoing head-up tilt testing for further diagnostic assessment.

All patients were included if they had suffered at least 2 episodes of syncope during the preceding 6 months. In all cases the cause of syncope had not been established despite extensive clinical and laboratory evaluation, including history, physical examination, neurological assessment, full routine laboratory tests, 12-lead standard ECG, exercise ECG, Doppler echocardiography, 24-hour ECG monitoring, EEG, and duplex ultrasound scanning of the carotid
arteries. Carotid sinus massage was performed for 10 seconds on each side of the neck separately and was negative in all patients. Moreover, when clinically indicated, CT scans (in 47 patients) and MR imaging (9 patients) of the central nervous system and cardiac electrophysiological study (5 patients) had also been performed. Through such diagnostic workup, any cardiac, neurological, and metabolic diseases were ruled out in all cases.

The 63 patients and a control group of 10 asymptomatic, healthy subjects (6 females and 4 males; mean age, 35.5 ± 12.4 years) with no history of syncope in their lifetime provided informed consent and were submitted to the head-up tilt testing protocol currently used at our institution, which includes EEG monitoring during the whole procedure. Both patients and controls were free of any medication prior and during the whole study period.

The test was performed in the morning, in fasting state. A 20-g heparinized cannula was inserted in the antecubital vein in all patients before the diagnostic procedure. An electronically controlled tilt table (Ferrox VDE 0551, CIAR s.r.l.), with a foot-board for weight-bearing and restraining belts, was used for the procedure; such a device takes 10 to 18 seconds to reach the horizontal position from a 60° incline, depending on patient weight. Continuous ECG monitoring for heart rate and rhythm was performed, while a standard mercury sphygmomanometer was used to measure blood pressure at 5-minute intervals throughout the test. However, in case of symptom development blood pressure measurement was performed at 1-minute intervals. Continuous EEG monitoring was performed by a standard Esaote Biomedica Vega 24 device with electrodes placed according to the international 10-20 System with 18 channels of recording. Electrodes were held in place by collodion to avoid artifacts due to any kind of movement, and an experienced neurophysiologist coded the EEG using a conservative interpretation. In this study we used a previously described protocol for head-up tilt testing. First, the patients laid for 15 minutes in the supine position and subsequently were tilted at 60° for 45 minutes. The completion of the 2 test stages without symptoms indicated a negative response. The test was considered positive if syncope, defined as a sudden transient loss of consciousness with concomitant loss of postural tone and spontaneous recovery, occurred in association with hypotension, bradycardia, or both. As in previous studies, a gradual onset of minor symptoms, related to a progressive decrease in blood pressure, was regarded as a nonspecific result called “exaggerated response.” In case of syncope or exaggerated response, the procedure was terminated by rapidly lowering the tilt table to the supine position.

In accordance with previous reports, 2 main forms of positive response to head-up tilt test were identified: a pure vasodepressor form (syncope associated with a systolic blood pressure decrease to ≤60 mm Hg but without significant heart rate reduction) and a cardioinhibitory form (syncope associated with a systolic blood pressure decrease to ≤60 mm Hg and heart rate reduction to <40 bpm). All collected data are expressed as mean ± SD and analyzed by the unpaired Student t test for continuous variables and the χ² test for categorical variables.

### Results

A positive response occurred in 27 of 63 patients, giving an overall positive rate of 42.8%, whereas a negative response was noted in the remaining 36 patients (57.2%). Two of the 36 patients with a negative response actually showed an exaggerated response, as previously defined (prolonged symptoms without loss of consciousness). The mean time to symptom onset was 14.8 ± 6.8 minutes (range, 2 to 25 minutes).

Eleven of the 27 patients with a positive response during head-up tilt (40.7%) showed a significant bradycardia (mean duration of longest R-R interval on the ECG, 15.2 ± 11.7 seconds; range, 1.8 to 40 seconds) at the time of symptom onset, associated with or rapidly followed by hypotension (mean reduction of 68.6 ± 12.7 mm Hg for systolic and 40.9 ± 18.9 mm Hg for diastolic blood pressure), and were considered to have a cardioinhibitory response. The rest of the patients with a positive response (16 of 27, 59.3%)...
developed hypotension (mean reduction of blood pressure of 85.8±16.6 mm Hg for systolic and 57.6±17.8 mm Hg for diastolic), with minor variations of heart rate (mean reduction of 13.4±8.7 bpm), in association with the sudden loss of consciousness and were considered to have a vasodepressor response.10,13,14 This group included significantly more females than the cardioinhibitory group (14 of 16, 87.5% versus 4 of 11, 36.3%; \( P < 0.01 \)), but no significant difference was noted for age between the 2 groups.

Concomitant with the loss of consciousness, 10 of the 11 patients in the cardioinhibitory group (90.9%) showed a rigid flexed posture, followed by a rigid extended posture and bilateral myoclonic rhythmic jerks of brief duration (1 to 5 seconds). A similar pattern of convulsive syncope was noted in only 4 of 16 patients with vasodepressor syncope (25%; \( P < 0.01 \)). All subjects included in the control group had a negative response to head-up tilt testing.

**Electroencephalography**

All included subjects had a normal baseline EEG. Patients with a negative response to the head-up tilt, including the 2 subjects with the so-called exaggerated response, as well as all control subjects, showed no significant EEG abnormalities or modifications during the head-up tilt testing.

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**Figure 2.** EEG modifications in a patient with cardioinhibitory vasovagal syncope during head-up tilt testing. T indicates theta waves; D, delta waves; A, artifact; F, flat EEG; and BP, blood pressure.
The 16 patients with a positive vasodepressor response to the head-up tilt showed homogeneous behavior during EEG monitoring (Figure 1). Prodromal symptoms (nausea, vertigo, light-headedness) (mean duration 110.6±77.7 seconds; range, 30 to 300 seconds) preceded the loss of consciousness and were not associated with any significant EEG modification. Subsequently, the initially normal EEG pattern was followed by a diffuse generalized high-amplitude, 4- to 5-Hz (theta range) slowing of brain activity starting at the moment of syncope (mean duration, 4.0±2.1 seconds; range, 2 to 7 seconds). Such alterations were then followed by a further increase of brain wave amplitude and slowing at 1.5 to 3 Hz (delta range) (mean duration, 17.0±11.3 seconds; range, 6 to 47 seconds). However, no spike or spike-wave activity was recorded, even in patients with tonic-clonic jerks (4 of 16; 25%). When patients were returned to the supine position, the EEG showed a brief phase (mean duration, 2.1±1.2 seconds; range, 0 to 5 seconds) of brain wave amplitude reduction, with frequency increase to 4 to 5 Hz, followed by the restoration of a normal EEG pattern and arousal.

The mean total duration of the loss of consciousness in these patients was 23.1±12.3 seconds (range, 10 to 54 seconds).

A different but again homogeneous pattern of EEG modifications could be noted in the 11 patients with a positive cardioinhibitory response to head-up tilt (Figure 2). Prodromal symptoms had a significantly shorter duration in patients with a cardioinhibitory response than in those with a vasodepressor response (mean duration, 8.7±6.1 seconds; range, 5 to 22 seconds; \( P<0.01 \)) and were not correlated with any EEG modification. At the onset of syncope, the initially normal EEG pattern turned abruptly to a diffuse, generalized, high-amplitude, 4- to 5-Hz (theta range) brain-wave slowing, rapidly followed by a further brain-wave amplitude increase and slowing at 1.5 to 3 Hz (delta range) (overall mean duration, 7.6±2.9 seconds; range, 5 to 14 seconds). A sudden reduction in both amplitude and frequency of brain waves could then be noted, leading to the disappearance of electrocerebral activity ("flat" record, with a mean duration of 15.9±13.4 seconds; range, 1 to 46 seconds).

The return to the supine position allowed neither immediate resolution of the EEG abnormalities nor conscience recovery, but the complete normalization of the electrocerebral activity and the concomitant restoration of normal consciousness occurred after an additional time interval (mean duration, 15.1±6.0 seconds; range, 7 to 22 seconds). The prevalence of tonic-clonic jerks during loss of consciousness was significantly higher in patients with cardioinhibitory response (10 of 11; 90.9%) compared with patients with vasodepressor syncope (4 of 16; 25%, \( P<0.01 \)). In any event, no spike or spike-wave activity or lateralizing or focal abnormalities could be detected in any patient. In patients with cardioinhibitory response, the onset of bradycardia preceded the development of EEG abnormalities (mean time, 2.9±2.5 seconds; range, 0 to 8 seconds), while the restoration of a normal cardiac rhythm was not followed by the immediate recovery of electrocerebral activity (mean time of delay, 8.1±7.1 seconds; range, 0 to 24 seconds). The mean total duration of syncope in patients with cardioinhibitory syncope was significantly longer with respect to patients with vasodepressor syncope (41.4±16.7 seconds; range, 21 to 78 seconds; \( P<0.01 \)).

At the end of the test, the EEG was found to be normal in all cases and no neurological or cardiac abnormalities were noted in any patient, despite the occurrence of syncopal episodes.

**Discussion**

An abnormal vasovagal reflex is known to be the most common cause of syncope in the general population. In such a condition the development of hypotension and bradycardia is responsible for a sudden reduction of cerebral blood flow, with consequent hypoxia of those parts of the central nervous system controlling consciousness. Several studies have deployed head-up tilt testing to analyze both the pathophysiological mechanisms and the clinical implications of this complex syndrome. Conventional head-up tilt testing employs the concomitant assessment of cardiac rhythm and blood pressure behavior, allowing detection and distinction of a vasodepressor and a cardioinhibitory pattern for tilt-induced vasovagal syncope. Conventional EEG is currently used in the clinical evaluation of patients with unexplained recurrent syncope to exclude the presence of epilepsy or other significant neurological disorders. However, such a diagnostic method has a relevant potential for the dynamic assessment of cerebral electrophysiological modifications in different clinical settings. Actually, through several studies, Gastaut has shown the EEG correlates of syncope induced by eyeball compression. Such classic EEG studies have reported that after cardiac asystole, a stereotyped series of modifications take place, including the early appearance of slow, high-voltage activity in the theta range, followed by a further slowing in the delta range. The persistence of cardiac asystole determines the abrupt disappearance of electrocerebral activity with the development of a flat EEG recording. The restoration of cardiac rhythm induces the reappearance of brain-wave activity in a reverse manner from its disappearance. This pattern of EEG modifications is considered to be consistent with severe generalized ischemic anoxia of the central nervous system and is similar to the EEG picture we found in patients with vasovagal syncope of a cardioinhibitory nature. In our series the EEG alterations developed in a sequence similar to that already described by Gastaut, while showing a longer duration. This difference may be related to the longer period of asystole associated with tilt-induced vasovagal reflex when compared with the asystolic response determined by eyeball compression.

The only available data concerning EEG modifications during tilt-induced vasovagal syncope have been collected by Grubb and associates. In a recent study, these authors have performed head-up tilt testing with concurrent continuous EEG monitoring in patients with recurrent unexplained convulsive syncopal episodes. In these patients during tilt-induced convulsive syncope, the EEG showed diffuse generalized brain-wave slowing, but neither spike nor spike-wave activity were detected, thereby allowing differential diagnosis from epileptic seizures. Similar EEG modifications have been noted in our series in patients with tilt-induced vasodepressor
vasovagal syncope, who never showed periods of flat EEG recording during the loss of consciousness.

In this study the EEG monitoring performed during head-up tilt testing allowed the recording and the complete description of the sequence and relevance of electrocerebral abnormalities taking place during a tilt-induced vasovagal syncope. These EEG alterations represent the expression of cerebral function impairment due to the critical reduction of cerebral blood flow induced by the vasovagal hypotension and bradycardia. Actually, 2 different EEG pictures have been observed which correspond and are directly related to the 2 main hemodynamic patterns that distinguish tilt-induced vasovagal syncope. A diffuse, generalized brain-wave slowing was found in patients who developed hypotension alone (vasodepressor syncope), whereas periods of electrocerebral silence (flat EEG) were always recorded in subjects with hypotension and bradycardia (cardioinhibitory syncope). Furthermore, in accordance with previous reports, in our experience cardioinhibitory vasovagal syncope was found to be associated with a shorter duration of prodromes, with a higher incidence of tonic-clonic jerks and a longer overall duration of syncope. These findings support the idea that the persistence of cardiac activity during a tilt-induced vasovagal episode may be associated with a milder compromise of cerebral perfusion and therefore with less-severe clinical manifestations. Even if collected data cannot be considered as conclusive, such a hypothesis is somehow strengthened by the evidence that bradycardia support by cardiac pacing can, in some cases, ameliorate or resolve cardioinhibitory vasovagal episodes.

Limitations of the Study

The observations of this study have been collected in a controlled laboratory setting in which syncope has been induced with a standardized procedure. Therefore, recorded events may not fully correspond to spontaneous syncopal episodes, as already noted by several authors. In particular, spontaneous syncope determines a loss of postural tone with a consequent sudden fall; such an event allows immediate recovery of cerebral blood flow and is considered a protective mechanism. Because in head-up tilt testing patients are secured to the table, the return to the supine position may take a period of time, which depends on the technical characteristics of the different laboratory tables. This time interval may contribute to the relevance of symptoms and hemodynamic and EEG modifications. In this study, an electronically controlled tilt table has been used, taking up to 18 seconds to reach the horizontal plane; this time interval may be too long, possibly contributing to the dramatic picture of both hemodynamic and EEG modification in patients with syncope. Consequently, tilt tables with a short travel time to the horizontal plane should be preferred in order to reduce the overall duration of syncope. However, in some rare cases this situation might occur also spontaneously, as in patients whose body position at the beginning of the vasovagal reflex (eg, sitting, driving, or standing in small and restricted places) does not allow them to immediately reach the supine position. In addition, in this study blood pressure was discontinuously measured by a standard mercury sphygmomanometer during the head-up tilt testing. Such methodology may represent a limit, particularly in those patients showing brief prodromes or unheralded syncope, as a rapidly developing blood pressure fall could not be properly recorded.

References

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