Variable Cerebral Dysfunction During Tilt Induced Vasovagal Syncope

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AMMIRATI, F., ET AL.: Variable Cerebral Dysfunction During Tilt Induced Vasovagal Syncope. Electroencephalographic (EEG) monitoring was performed during head-up tilt testing (HUT) in a group of 63 consecutive patients (27 males, 36 females, mean age 41.5 years) with a history of recurrent syncope of unknown origin despite extensive clinical and laboratory evaluation. Syncope occurred in 27/63 patients (42.8%) during HUT and was cardioinhibitory in 11/27 (40.7%) and vasodepressor in 16/27 (59.3%). All patients with a negative response to HUT had no significant EEG modifications. In patients with vasodepressor syncope a generalized high amplitude 4-5 Hz (theta range) slowing of EEG activity appeared at the onset of syncope, followed by an increase in brain wave amplitude with a reduction of frequency at 1.5-3 Hz (delta range). The return to the supine position was associated with brain wave amplitude reduction and frequency increase to 4-5 Hz, followed by restoration of a normal EEG pattern and arousal (mean total duration of syncope 23.2 s). 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 ensued leading to the disappearance of electroencephalographic activity ("flat" EEG). The return to the supine position was not followed by immediate resolution of EEG abnormalities or consciousness recovery, both occurring after a longer time interval (mean total duration of syncope 41.4 s). EEG monitoring during HUT allowed the recording and systematic description of electroencephalographic abnormalities developing in the course of tilt induced vasovagal syncope. (PACE 1998; 21[Pt. II]:2420-2425)

Introduction

The current hypothetical pathophysiological mechanism of vasovagal syncope maintains that a rapid ventricular preload reduction causes an exaggerated inotropic response due to an overabundant cathecolamine release.1-3 This increased myocardial contractility in the setting of preload reduction activates cardiac mechanoreceptors, mediating via the brain stem an abnormal enhancement of parasympathetic activity, together with sympathetic withdrawal.1-3 The resulting hypotension and bradycardia cause a reduction in cerebral blood flow and secondary impairment of neurological function. Electroencephalography allows the dynamic assessment of neurological function,4 while head-up tilt testing is currently used to provoke vasovagal syncope in susceptible individuals.5,6 The hypothesis behind the present clinical investigation was that the inclusion of electroencephalographic monitoring during head-up tilt testing could significantly improve the understanding of the cerebral events occurring during tilt induced vasovagal syncope.

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 undergoing head-up tilt testing for further diagnostic evaluation. Patients were included if they had suffered at least two episodes of syncope during the preceding 6 months. In all cases a cardiac, neurological, or metabolic cause of syncope had been excluded.
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by extensive clinical and laboratory testing. 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, granted their informed consent and underwent head-up tilt testing according to a protocol, which, in our Institution, includes electroencephalographic (EEG) monitoring throughout the procedure.

The test was performed in the morning, in the fasting state, in the absence of pharmacological therapy. An electronically controlled tilt table (Ferrox VDE 0551; C.I.A.R. s.r.l.), with a weight-bearing foot board and restraining belts was used for the procedure. The table takes 10 to 18 seconds to reach the horizontal position from a 60° inclination, depending on patient weight. Continuous electrocardiographic (ECG) monitoring of heart rate and rhythm was performed, and a standard mercury sphygmomanometer was used to measure the blood pressure at 5-minute intervals throughout the test. At the time of symptom development, blood pressure measurements were 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 movement artifacts. An experienced neurophysiologist coded the EEG using a conservative interpretation. This study used the previously described "Westminster" protocol for head-up tilt testing. 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. If syncope developed during the test, the table immediately was lowered to the supine position and the procedure ended. In agreement with previous reports, two main forms of positive response to head-up tilt test were observed. A pure vasodepressor form (syncope associated with a systolic blood pressure decrease to 60 mmHg or less without significant heart rate reduction) and a cardioinhibitory form (syncope associated with a systolic blood pressure decrease to 60 mmHg or less and a decrease in heart rate to less than 40 beats/min). All data are expressed as mean ±SD and were analyzed by unpaired Student's t-test for continuous variables and $X^2$ for categorical variables.

**Results**

A positive response occurred in 27/63 patients, for an overall positive rate of 42.8%, and a negative response was noted in the remaining 36 patients (57.2%). The mean time to symptom onset was 14.8 ± 6.8 minutes (range 2 to 25 min). Eleven of the 27 patients with a positive response during head-up tilt (40.7%) developed significant bradycardia (mean duration of longest RR interval on the ECG 15.2 ± 11.7 s, range 1.8—40 s) at the time of symptoms onset that was associated with or rapidly followed by hypotension (mean reduction of 68.6 ± 12.7 mmHg for systolic and 40.9 ± 18.9 mmHg for diastolic blood pressure) and were considered to have had a cardioinhibitory response. The rest of the patients with a positive response (16/27, 59.3%) developed hypotension (mean reduction of blood pressure of 85.8 ± 16.6 mmHg systolic and 57.6 ± 17.8 mmHg diastolic) with minor changes in heart rate (mean reduction of 13.4 ± 8.7 beats/min) in association with sudden loss of consciousness and were considered to have had a vasodepressor response. This group included significantly more females than the cardioinhibitory group (14/16, 87.5% versus 4/11, 36.3%, $P < 0.01$), while no significant age difference was measured between the two groups. At the time of syncope, 10 of the 11 patients in the cardioinhibitory group (90.9%) had a flexed rigid posture, followed by a rigid extended posture and bilateral myoclonic rhythmic jerks of brief duration (1—5 s). 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 study participants had a normal baseline EEG. Patients with a negative response to the head-up tilt, as well as all control subjects, developed no significant EEG abnormalities during the test.

**EEG Findings in Patients with Vasodepressor Syncope (Fig. 1)**

The 16 patients with a vasodepressor response to the head-up tilt showed a homogeneous...
pattern during EEG monitoring. Prodromal symptoms, consisting of dizziness or light-headedness for a mean duration of 110.6 ± 77.7 s (range 30–300 s) preceded the loss of consciousness and were not associated with significant EEG changes. Subsequently, the initially normal EEG pattern was followed by a diffuse generalized high amplitude 4–5 Hz (theta range) slowing of brain activity starting at the moment of syncope (mean duration 4.0 ± 2.1 s, range 2–7 s). These alterations were then followed by a further increase in brain wave amplitude and slowing at 1.5–3 Hz (delta range) for a mean duration of 17.0 ± 11.3 s (range 6–47 s). However, no spike or spike wave activity was recorded, even in patients with tonic-clonic jerks (4/16, 25%). When patients were returned to the supine position, the EEG showed a brief phase (mean duration 2.1 ± 1.2 s, range 0–5 s) of brain wave amplitude reduction with frequency increase to 4–5 Hz followed by the return of a normal EEG pattern and arousal. The mean duration of unconsciousness in these patients was 23.1 ± 12.3 s (range 10–54 s).

**EEG Findings in Patients with Cardioinhibitory Syncope (Fig. 2)**

A different, but again homogeneous, pattern of EEG modifications was observed in the 11 patients with a cardioinhibitory response to head-up tilt. Their prodromal symptoms were significantly shorter in duration (mean duration 8.7 ± 6.1 s, range 5–22 s, P < 0.01) and were accompanied by no EEG changes. At the onset of syncope, the initially normal EEG changed abruptly to a diffuse, generalized high amplitude 4–5 Hz (theta range) brain wave slowing, rapidly followed by further brain wave amplitude increase and slowing at 1.5–3 Hz (delta range) for an overall mean duration of 7.6 ± 2.9 s (range 5–14 s). A sudden decrease in both amplitude and frequency of brain waves then was observed, leading to the disappearance of electroencephalographic activity ("flat" record) for a mean duration of 15.9 ± 13.4 s (range 1–46 s).

The return to the supine position coincided neither with the immediate resolution of the EEG.
abnormalities nor with recovery of consciousness; complete normalization of the electroencephalogram and the concomitant restoration of full consciousness occurred after an additional time interval of a mean duration of 15.1 ± 6.0 s. (range 7–22 s). The prevalence of tonic-clonic jerks during loss of consciousness was significantly higher in patients with cardioinhibitory response (10/11, 90.9%) than in patients with vasodepressor syncope (4/16, 25%, P < 0.01). No spike or spike
wave activity, lateralizing or focal abnormalities could be detected in any patient. In patients with a cardioinhibitory response, the onset of bradycardia preceded the development of EEG abnormalities by a mean time of $2.9 \pm 2.5$ s (range 0–8 s), and the restoration of a normal cardiac rhythm was not followed by the immediate recovery of electroencephalographic activity (mean duration of delay $8.1 \pm 7.1$ s, range 0–24 s). The mean duration of syncope in patients with cardioinhibitory syncope was significantly longer than in patients with vasodepressor syncope ($41.4 \pm 16.7$ s, range 21–78 s, $P < 0.01$). At the end of the test, the EEG had returned to normal in all cases and no residual neurological or cardiac abnormalities were noted in any patient.

**Discussion**

Several studies have used head-up tilt testing to analyze the pathophysiological mechanisms and the clinical manifestation of vasovagal syncope. Conventional head-up tilt testing uses the concomitant monitoring of cardiac rhythm and blood pressure to make a distinction between vasodepressor and cardioinhibitory patterns in tilt induced vasovagal syncope. Conventional electroencephalography is used in the evaluation of patients with recurrent unexplained syncope to exclude epilepsy or other significant neurological disorders. However, the method may also be relevant in the dynamic assessment of cerebral electrophysiological modifications in other clinical settings. In their studies, Gastaut and coworkers have examined the EEG correlates of syncope induced by eye-ball compression. These classic EEG studies have found that following cardiac asystole a stereotyped series of modifications take place, including the early appearance of slow high voltage activity in the theta range, followed by further slowing in the delta range. The persistence of cardiac asystole determines the abrupt disappearance of electroencephalographic activity with the development of a flat EEG recording. The restoration of cardiac rhythm induces the reappearance of brain wave activity in the reverse order. This pattern of EEG changes is consistent with severe generalized ischemic anoxia of the central nervous system and is similar to those recorded in our patients with cardioinhibitory vasovagal syncope. In our series, the EEG alterations appeared in a sequence similar to that described by Gastaut, although of longer duration. This difference may be related to the longer period of asystole associated with tilt induced vasovagal reflex compared with the asystolic response caused by ocular compression. Data pertaining to EEG changes 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 simultaneous continuous EEG monitoring in patients with recurrent unexplained convulsive syncopal episodes. During tilt induced convulsive syncope the EEG showed diffuse generalized brain wave slowing, but neither spike nor spike wave activity was observed, thus allowing the 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 loss of consciousness. In this study EEG monitoring allowed the recording and complete description of the sequence and relevance of electroencephalographic abnormalities taking place during tilt induced vasovagal syncope. These EEG changes are the expression of cerebral dysfunction during the critical decrease in cerebral blood flow induced by hypotension and bradycardia. Two different EEG pictures were observed, corresponding to the two hemodynamic patterns of tilt induced vasovagal syncope. Diffuse generalized brain wave slowing was seen in patients who developed hypotension alone (vasodepressor syncope), whereas periods of electroencephalographic silence (flat EEG) were consistently recorded in subjects with hypotension and bradycardia (cardioinhibitory syncope). Furthermore, in agreement with previous reports, cardioinhibitory syncope was associated with shorter prodromes with a higher incidence of tonic-clonic jerks and a longer overall duration of syncope. These findings support the belief that the persistence of some cardiac activity during tilt induced vasovagal episodes may be associated with less compromise of cerebral perfusion and, therefore, with less severe clinical manifestations. In absence of conclusive data this hypothesis is nevertheless strengthened by the observation of a clinical improvement or elimination of tilt induced syncope by pacing. Our observations of this study were made in a controlled laboratory setting.
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where syncope was provoked by a standardized procedure. Therefore, the events recorded may not fully reproduce the spontaneous syncopal episodes.\(^{20,21}\) In particular, spontaneous syncope causes a loss of postural tone with sudden fall; such a sequence allows the immediate recovery of cerebral blood flow and is considered a protective mechanism. With head-up tilt testing, patients are strapped to the table, thus, the return to the supine position may take some time, the length of which depends on the technical characteristics of the different laboratory equipment. This time interval may contribute to the severity of symptoms and hemodynamic and electroencephalographic changes. In this study, an electronically controlled tilt table was used, taking up to 18 seconds to reach the horizontal position; this time interval may be excessive, possibly contributing to the dramatic hemodynamic and electroencephalographic changes in our patients. Consequently, tilt tables with a faster return to the horizontal position are preferable to shorten the overall duration of syncope. However, in some cases, this situation also may occur spontaneously, e.g., in circumstances where in the beginning of the vasovagal reaction (sitting, driving, standing in a confined space, etc.) the patient cannot be immediately returned to the supine position.

References

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