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New insights into the mechanism of neurally mediated syncope

M A Mercader, P J Varghese, S J Potolicchio, G K Venkatraman, S W Lee

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See end of article for authors' affiliations

Correspondence to:
Dr P J Varghese, The
George Washington
University Medical Center,
Department of Medicine,
Division of Cardiology,
2150 Pennsylvania
Avenue, NW, Suite
4-414, Washington DC
20037, USA;
domjxv@gwumc.edu

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Objective: To determine the role of the cerebral cortex in neurally mediated syncope, the electroencephalograms (EEG) of patients recorded during head up tilt table test were analysed.

Design: Retrospective study.

Setting: University hospital.

Patients: 18 patients with syncope or near syncope underwent head up tilt table test with simultaneous ECG and EEG monitoring.

Methods: Standard 70° tilt table test was done with simultaneous ECG and EEG monitoring. EEG waveforms were analysed by both visual inspection and spectral analysis.

Results: 6 of 18 patients (33%) had a positive tilt table test. Before syncope slow waves increased in patients with a positive test. In addition, five of six tilt positive patients (83%) had slow wave activity that lateralised to the left side of the brain (mean (SD) 822 (724) v 172 (215) μV^2 , $p < 0.05$), while none of the tilt negative patients exhibited lateralisation (24 (15) v 26 (19) μV^2 , NS). Spectral analysis showed that the lateralisation occurred in the δ frequency. The lateralisation preceded the event by 5–56 seconds (18 (21) seconds).

Conclusions: EEG activity lateralises to the left hemisphere of the brain before syncope. The lateralisation precedes syncope and is associated with the onset of bradycardia, hypotension, and clinical symptoms. These findings suggest that the central nervous system may have a role in neurally mediated syncope.

The exact pathophysiological mechanism of neurally mediated syncope (NMS) is not well understood. The most commonly held theory suggests that, before the onset of NMS, there is a significant increase in sympathetic tone caused by reduction in the preload of the ventricle with upright posture. This increased sympathetic tone results in increased ventricular contractility. The hypercontractile left ventricle in the setting of reduced ventricular preload stimulates mechanoreceptors in the left ventricle. Stimulation of these receptors triggers an inhibitory response similar to the Bezold-Jarisch reflex resulting in hypotension, bradycardia, and syncope.¹⁻³

Since this theory was proposed as a possible mechanism of NMS, there have been several studies challenging this hypothesis. Firstly, increased sympathetic activity before syncope has not been consistently observed. Secondly, recent studies indicate that there is no significant reduction in left ventricular volume during tilt and syncope in patients with NMS,⁴ and there was no echocardiographic evidence of hypercontractility of the left ventricle during positive tilt table test.⁵ Thirdly, NMS can occur in patients with functionally denervated hearts after orthotopic cardiac transplant,⁶⁻⁹ showing that mechanoreceptors in the left ventricle are not essential in triggering NMS. In addition, positron emission tomography of the left ventricle found no increase in sympathetic innervation in patients with NMS.¹⁰ These studies suggest that alternative mechanisms may explain NMS.

Many episodes of syncope occur after cortical stimulation such as smell or visual symptoms. There is evidence that the cerebral cortex has a major role in the autonomic control of the cardiovascular system.¹¹⁻¹⁴ The right hemisphere has a sympathetic predominance and the left hemisphere a significant parasympathetic effect. Recent observations suggest that ictal epileptiform activity in the left temporal lobe may result in bradycardia and asystole.¹⁵ Therefore, we postulated that the cerebral cortex may be the initiating site for NMS. We

studied the cortical activity by digitised electroencephalography (EEG) during the head up tilt table test in an attempt to characterise the role of the cerebral cortex in NMS.

METHODS

Patients

Eighteen patients who were undergoing prolonged EEG monitoring for unexplained blackout spells at the epilepsy unit in the neurology department at The George Washington University Medical Center underwent tilt table testing while 24 hour EEG recordings were being made. Medical records of these patients and the EEG recordings were examined. Our institutional review board approved this study.

Head up tilt table testing

Patients underwent head up tilt table testing in a postabsorptive state. Baseline recordings of ECG, heart rate, and blood pressure were obtained. The patient was then tilted to 70°. A continuous ECG was recorded while the non-invasive blood pressure was recorded every three minutes and with symptoms. Patients were observed for early symptoms. The tilt was continued for 40 minutes or until syncope or near syncope occurred. A positive tilt table test was defined as either syncope or near syncope associated with the sudden development of hypotension, bradycardia, or both. Positive tilt table tests were further classified into three types of responses.

- Type I, mixed response: heart rate rises initially and then falls but the ventricular rate does not fall to < 40 beats/min or falls to 40 beats/min for < 10 seconds with or without asystole for < 3 seconds. Blood pressure rises initially and then falls before heart rate falls.
- Type II, cardioinhibitory response: heart rate rises initially and then falls to a ventricular rate of < 40 beats/min for 10 seconds or asystole occurs for > 3 seconds. Blood pressure rises initially and then falls before or after heart rate falls.

Table 1 Response to tilt table testing

Patient	Age (years)	Response type	Symptoms	Time to symptoms (min)	Heart rate (beats/min)		Mean arterial pressure (mm Hg)	
					Initial	Onset of symptoms	Initial	Onset of symptoms
A	51	I	Warmth, nausea, near syncope	20	56	45	95	42
B	34	II	Warmth, nausea, near syncope	40	60	40	114	64
C	66	II	Dizziness, syncope	8	84	30	94	62
D	23	II	Warmth, nausea, diaphoresis, syncope	22	95	20	110	7
E	33	I	Dizziness, nausea, near syncope	25	72	56	84	51
F	20	III	Dizziness, near syncope	33	91	115	77	54
G	28		None		80	80	87	91
H	40		Shaking		108	120	113	128
I	33		Weakness, dizziness		84	84	101	90
J	27		None		92	74	87	99
K	30		Headache, numbness, nausea		80	65	96	102
L	17		Warmth, flushing		99	118	91	79
M	68		Warmth, drowsiness, near syncope		89	100	94	47
N	56		Dizziness		72	96	111	60
O	22		None		69	80	92	100
P	56		None		66	87	83	100
Q	86		None		52	53	113	96
R	38		Faked syncope		110	132	101	101

- Type III, pure vasodepressor response: heart rate rises progressively and does not fall > 10% from peak at time of syncope. Blood pressure falls to cause syncope.¹⁶

Negative tilt table test also included orthostatic hypotension, which was defined as a gradual decrease in systolic blood pressure of more than 20 mm Hg associated with symptoms such as dizziness or lightheadedness.

EEG

A standard 20 electrode montage was obtained from all patients. The electrode placement spanned the frontal, fronto-temporal, parietal, and occipital regions according to the 10–20 system for EEG recording. The EEG data were digitised and then analysed by both visual inspection and use of a computerised spectral analysis system (Insight, Persyst Development Corp, Prescott, Arizona, USA). The two minute interval before each syncopal or presyncopal event was analysed in detail by visual inspection first, then by spectral analysis in the α , β , θ , and δ wave frequency ranges. For patients with a negative test a similar analysis was obtained for two minutes during the test if the event button was pushed for minor symptoms or at the last two minutes of the tilt test.

Statistical analysis

Continuous variables are presented as mean (SD). Groups were compared by paired Student's *t* test. A probability value of $p < 0.05$ was considered significant.

RESULTS

Baseline characteristics

Of the 18 patients with EEG recordings, there were 7 men and 11 women ranging in age from 17–86 years. The average number of episodes of syncope or near syncope ranged from 1–24 a year. Most patients had a history of syncope for months or years; the longest was 13 years. One patient had congestive heart failure and one had left ventricular hypertrophy. No other patient had structural heart disease. Three patients had a history of hypertension. One patient was taking a β blocker at the time of the tilt test.

Response to tilt table testing

Six patients had a positive tilt table test (four patients had near syncope and two had syncope). Two patients had mixed responses (type I), three had cardioinhibitory responses (type

II), and one had a pure vasodepressor response (type III). The mean time to syncope was 25 (11) minutes. Of the 12 patients with a negative tilt table test, two had orthostatic hypotension with a gradual decline in blood pressure over time. Table 1 summarises the haemodynamic response to tilt table testing.

EEG results

The EEGs provided evidence of slow wave activity in patients with a tilt positive test who had syncope or near syncope. The slow wave activity lateralised to the left cerebral cortex in five of six patients with positive tilt table tests on visual inspection. The EEG data were then digitised and further analysed by spectral analysis. The results were plotted in topographic views, as fig 1¹ shows and table 2 summarises. In tilt positive patients, there were significant increases in peak δ waves from the baseline level, while there were no significant increase in δ waves in the tilt negative patients. The increase in the δ waves were seen predominantly in the left hemisphere ($822 (724) \nu 172 (215) \mu V^2$, $p = 0.029$) with the peak δ waves in the left hemisphere being approximately four times higher than in the right hemisphere (fig 2). Examination of topographs showed that the lateralisation appears to localise to the left temporal lobe area (fig 3). Furthermore, appearances of δ waves in the left temporal region appear to precede bradycardia and symptoms (fig 4). Two patients who developed orthostatic hypotension during the tilt table test did not develop slow waves despite significant hypotension. The tilt positive patient who did not have a significant increase in slow waves or lateralisation of δ activity developed near syncope with a junctional rhythm and hypotension only after 40 minutes of tilt. However, systolic blood pressure never fell below 80 mm Hg in this patient. This patient was taking a β blocker at the time of the tilt test. One patient developed psychogenic symptoms during the head up tilt test and no EEG changes were noted at the time.

DISCUSSION

The mechanism of NMS is poorly understood. Recent studies suggested that the central nervous system may have a role in the pathogenesis of NMS. We present further evidence from the present study that the central nervous system may have an important role in the pathogenesis of neurocardiogenic syncope.

Patients with positive tilt tests developed slow waves on EEG recordings before syncope. These slow waves on EEG

Figure 1 Typical electroencephalographic (EEG) findings in patients with neurocardiogenic syncope. Top: 15 selected EEG channels. A channels: left central temporal region; B channels, right central temporal region (B); C channels: left frontotemporal region; D channels: right frontotemporal area. Bottom: topographs of the δ frequency band. The front of the head is on top on each topograph. The amplitude of the δ wave is represented by a colour gradient with black being the lowest and white the highest. Increased δ activity appears first over the left hemisphere as denoted by the rectangle and the corresponding topograph (open arrow). The amplitude of the δ activity increases but remains lateralised to the left hemisphere as shown on the third topograph (solid arrow).

Table 2 Alterations in electroencephalographic δ waves						
Patient	Initial delta waves (μV^2)		Initial left to right ratio	Peak δ waves (μV^2)		Peak left to right ratio
	Left	Right		Left	Right	
A	54	17	3.2	1080	134	8.1
B	6	5	1.2	80	40	2.0
C	8	10	0.8	347	24	14.5
D	39	11	3.5	2010	570	3.5
E	10	4	2.4	293	10	29.3
F	5	16	0.3	1120	253	4.4
G	18	18	1	4	2	2.0
H	6	6	1	19	19	1.0
I	10	13	0.8	12	8	1.5
J	20	10	2	35	35	1.0
K	2	2	1	20	20	1.0
L	14	9	1.6	20	27	0.7
M	2	1	2	25	60	0.4
N	3	1	3	60	32	1.9
O	5	4	1.3	41	63	0.7
P	5	5	1	9	14	0.6
Q	7	4	1.8	14	20	0.7
R	3	9	0.3	26	11	2.4

Figure 2 Peak δ activities of left and right cerebral cortex in patients with tilt positive and negative results. Tilt positive patients have significant lateralisation of δ activity before syncope. The difference between left and right peak δ activity in tilt positive patients was significant ($p < 0.05$).

recordings appear to lateralise to the left cerebral cortex, particularly to the left temporal lobe region. Spectral analysis showed that this lateralisation occurred in the δ frequency range. Patients with a negative tilt table test including two patients with significant orthostatic hypotension did not develop slow waves on EEG recordings. Our finding is similar

to a previous case report in which an EEG in a patient with NMS showed higher amplitude δ waves in the left hemisphere than in the right.¹⁷

The role of the cerebral cortex in the control of the autonomic nervous system has been extensively studied. Cortical stimulation studies suggest a sympathetic predominance in the right hemisphere and parasympathetic effect in the left hemisphere.¹¹ Bradycardia and depressor responses were more frequently seen on stimulation of the left insular cortex. Studies following unilateral hemispheric inactivation by intracarotid amobarbital injection have shown differential left and right cerebral hemisphere effects on autonomic function.¹² Unilateral electroconvulsive treatment has a similar effect.¹⁴ In addition, power spectral analysis of heart rate variability before and after intracarotid amobarbital injections suggests that there is a right cerebral lateralisation of sympathetic activity.¹³ We also reported that ictal epileptiform activity involving the left temporal lobe resulted in bradycardia and asystole.¹⁵ These studies show that there are differential left and right cerebral hemisphere effects on autonomic function and that the left temporal lobe activity has a profound effect on parasympathetic activity of the heart resulting in bradycardia, asystole, and hypotension. Lateralisation and localisation of cortical activity in the left temporal lobe before

Figure 3 Topographic views of δ activity in tilt positive patients before syncope are shown. Peak δ activity is lateralised and localised to the left hemisphere (solid arrows). The areas of high amplitude seen in the frontal region and the occipital region are caused by artefacts from lead dislodgment and eye movements (open arrow).

Figure 4 The δ activity (Delta) in the left temporal lobe and heart rate changes (HR) over 30 seconds before syncope in a patient with typical cardioinhibitory response. Peak δ activity precedes the drop in heart rate.

tilt induced syncope or presyncope suggest that hypotension and bradycardia observed in patients with a positive tilt table test may be mediated through a localised activation of the left temporal lobe resulting in parasympathetic activation.

The presence of lateralised δ activity on EEG, which coincides with the initial presyncopal symptoms, is most likely indicative of a change in neuronal activity, possibly excitatory or inhibitory, or both. EEG lateralisation would argue against diffuse hypoxaemia secondary to a drop in blood pressure, since the changes in slow wave δ activity are lateralised more to the left hemisphere. EEG changes caused by decreased blood flow are usually a generalised slowing in the θ and δ frequency bands rather than lateralisation and localisation of δ activity to the left temporal lobe, as seen in our patients.¹⁸ Moreover, EEG changes in our patients occurred before the onset of syncope, and in two patients with significant orthostatic hypotension there were no changes in the EEG.

Grubb and colleagues¹⁹ and Rosendo and associates²⁰ found a paradoxical increase in cerebrovascular resistance secondary to arteriolar vasoconstriction in tilt positive patients and suggested that there was a derangement of cerebral autoregulation. We did not measure the blood flow pattern directly in the cerebral arteries. Therefore, we cannot rule out an alteration in the blood flow pattern leading to localised alteration in cortical activity. In addition, as we did not monitor arterial blood pressure continuously, we cannot eliminate the possibility that EEG changes were preceded by a fall in blood pressure.

Findings of the present study suggest that the cerebral cortex may have a role in the initiation of bradycardia associated with NMS. Simultaneous EEG recording with tilt testing and spectral analysis of the EEG may become an additional tool in delineating the mechanisms of NMS.

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Authors' affiliations

M A Mercader, P J Varghese, S W Lee, Division of Cardiology, Department of Medicine, The George Washington University, Washington DC, USA
S J Potolicchio, G K Venkatraman, Department of Neurology, The George Washington University

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