

NOCTURNAL PHYSIOLOGICAL AND BIOCHEMICAL CHANGES IN SUDDEN UNEXPLAINED DEATH SYNDROME: A PRELIMINARY REPORT OF A CASE CONTROL STUDY

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Abstract. Sudden nocturnal deaths among "healthy" workers in Southeast Asia have been termed "sudden unexplained nocturnal death syndrome (SUNDS)" or "sudden unexplained death syndrome (SUDS)". The pathogenesis is still unknown. The paucity of publications on nocturnal monitoring and scientific data stimulated us to perform this study, which included biochemical tests and physiological monitoring during the night in 11 males north-eastern Thai workers. Group 1 (G1) consisted of 5 subjects with neither a previous history of near-SUDS (NSUDS) nor a familial history of SUDS (FHSUDS). Group 2 (G2) consisted of 6 subjects with a family history of either SUDS or NSUDS. Two subjects in G2 presented with NSUDS. Two-day nocturnal monitoring included blood sugar, electrolytes, and respiratory parameters. 24-hour Holter ECGs were monitored for 2 days. The subjects underwent exercise stress tests on the 2nd day of this study. Significant nocturnal hypoxia was more common in G2 than G1 and this abnormality was aggravated by exercise. There were no significant findings in sleep apnea (apnea indices) or in nocturnal biochemical changes, eg blood sugar, electrolytes, thiamine. The recordings of the Holter-ECGs were within normal limits in both groups. We conclude that nocturnal hypoxia might be the primary abnormality in SUDS, and this abnormality was aggravated by the day-time exercise. The cause of nocturnal hypoxia requires further studies.

INTRODUCTION

There have been many reported Southeast Asian mysterious nocturnal deaths and these have become known as the Sudden Unexplained Death Syndrome (SUDS) or Sudden Unexplained Nocturnal Death Syndrome (SUNDS) (CDC, 1988; Baron *et al*, 1983; Munger *et al*, 1986; Munger, 1987; Goh *et al*, 1990), which is termed lai-tai in Thailand. Although the pathogenesis of SUDS is still unknown, there are many proposed theories about the etiology, which include physical stress (Goh *et al*, 1990) and hypokalemia (Nimmannit *et al*, 1991), thiamine deficiency (Munger and Booton, 1990), cardiac conducting system anomalies (Gotoh, 1976; Ohada and Kawai, 1982; Kirschner *et al*, 1986), sinus arrest (Guilleminault, 1984) and ventricular fibrillation (Otto *et al*, 1984). Family

clustering of presumptive SUDS had been reported in northeastern Thai male adults (Tatsanavivat *et al*, 1991). Although nocturnal death is well established, night time monitoring (NTM) of such patients has been limited. Physiological and biochemical monitoring during the night in high risk populations might extend the knowledge of pathogenesis of SUDS. In this prospective study, 11 Thai workers, from the northeastern region of Thailand underwent NTM to determine nocturnal physiological and biochemical base line data and deviations.

Hypothesis

There may be nocturnal physiological and biochemical changes in northeastern Thai men and there may be different changes between those with a family history of SUDS (FHSUDS) and those without FHSUDS.

MATERIALS AND METHODS

11 male northeastern Thai workers, were ad-

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mitted for NTM to the Department of Medicine, Ramathibodi Hospital. They were divided into two groups. Group 1 (G1) consisted of 5 subjects with neither a previous history of near-SUDS (NSUDS) nor FHSUDS. Group 2 (G2) consisted of six subjects with either NSUDS (Case 7) or FHSUDS (4/6 were either sons or brothers of those with history of SUDS and 1/6 has a relative with SUDS), 2/6 in G2 had suffered cardiac arrest (NSUDS), had been admitted because of sudden unexplained cardiac arrest (SUCA) and had shown evidence of ventricular fibrillation on an electrocardiogram (ECG). NTM was performed one week after SUCA.

A detailed history and physical examination were obtained and the initial investigation included a complete blood count, electrolytes, blood urea, creatinine, liver function tests, glucose, cholesterol, triglycerides, calcium, phosphate, arterial blood gases, urine analysis, radiographs of the chest and lateral neck and paranasal sinuses, ECG, echocardiogram (ECHO), and waking electroencephalogram (WEEG) on the first day (D1). NTM was performed on the second day (D2) and the third day (D3). The following tests were done: fasting blood glucose, electrolytes, erythrocyte transketolase activity and thiamine pyrophosphate effect (TPPE). Nocturnal ambulatory monitoring consisted of many parameters; electro-oculogram to monitor rapid eye-movement (REM) and non-REM periods, thermistor as sensor for nasal and oral airflow, belts around the chest and abdomen for impedance pneumography to monitor respiratory efforts, and the use of a transcutaneous sensor for pulse oximetry to monitor the arterial oxygen saturation (SaO_2). In order to detect arrhythmias, a 48-hour Holter ECG monitor was also used. A venous cannula was inserted so that samples could be drawn at 18, 21, 24, 3 and 6 hours during the test period. All subjects were subjected to a standard exercise stress test up to level on D3.

The following calculations and indices have been used in this study. The apnea index (AI) is the sum of apneas during hours of the non-awake period (HNAP) divided by the HNAP. The maximal apneas (MXA) are the greatest number of apneas in any hour during the HNAP. The mean hypoxic time (MHT) during the HNAP is the sum of the periods of hypoxia (*ie*, $\text{SaO}_2 < 90\%$) divided by the HNAP and is expressed in seconds. The

maximal hypoxic time (MXHT) of any hour of the HNAP is the greatest sum of hypoxic episodes (*ie* $\text{SaO}_2 < 90\%$) in seconds. The longest hypoxic episode (LHE) is the longest period of hypoxia (seconds) anytime during the HNAP.

Statistical analysis

Data were collected and expressed as individual data and the mean \pm SD, with statistical comparison between G1 and G2. This was done with Student's unpaired *t*-test for parametric analysis and Fisher's exact test for non-parametric analysis.

RESULTS

Relevant clinical and laboratory data are shown in Table 1. Physical examination of the 11 subjects revealed a deviated nasal septum with bilateral tonsillar hypertrophy (case 6), and one case with signs compatible with peripheral neuropathy (case 9). The ECGs were normal in all except 2 cases in G2, one with incomplete right bundle branch block (IRBB) (case 6) another one with right axis deviation (case 9). The QT_c (QT intervals corrected for heart rate) were within normal limits ($\text{QT} < 0.44$ seconds) in both group except one in G2 was 0.445 seconds. ECHOs demonstrated mild mitral valve prolapse in two subjects (cases 2 and 10), and mild tricuspid regurgitation in another subject (cases 3): however, ejection fractions in these cases were within normal limits. The initial biochemical investigations, the daytime arterial oxygen saturations, spirometry, lateral neck x-rays, and the WEEGs were normal in all subjects with the exception of mild hypoalbuminemia (27.4 g/l) in case 6.

There was no evidence of hypokalemia (< 3.5 mg%) from any of the venous samples in D2 and D3 (table 2). There was no statistical evidence that the levels of potassium in G1 differed from those in G2, except for the samples drawn at 3 a.m. on D3 ($p < 0.05$) (Table 3). Even so, the lowest level of potassium was only 3.80 ± 0.17 mg%

The "Thiamine" status (THSS) of all 11 subjects on D2 and D3 is seen in Table 3. Thiamine deficiency, as assessed by morning erythrocyte transketolase activity and thiamine pyrophosphate effect (TPPE of $> 15\%$) was found 3/5 subjects of G1 and 4/6 subjects of G2. There were nocturnal variation of THSS. Of 11 determinants

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Table 1
Clinical data and initial laboratory data of 11 subjects.

	Case	Age	PE	CXR	ECG	Echo	Spirometry
Group 1	1	25	N	N	N	N	N
	2	26	N	N	N	N*	N
	3	26	N	N	N	N**	N
	4	30	N	N	N	N	N
	5	24	N	N	N	N	N
Group 2	6	25	A*	N	Incomplete RBBB	N	N
	7	57	N	Minimal TB	N	N	N
	8	30	N	N	N	N	N
	9	32	A**	N	R axis	N	N
	10	24	N	N	N	N*	N
	11	21	N	N	N	N	N

A* Bradypnea, deviated nasal septum, slight enlarged tonsil
 A** Peripheral neuropathy
 N* Normal ejection fraction, mild mitral valve prolapse
 N** Normal ejection fraction, mild tricuspid regurgitation
 Group 1 = without family history of SUDS
 Group 2 = with family history of SUDS

Table 2
Nocturnal potassium in 11 subjects on days 2 and 3.

	K D2		K D3	
	Gr 1 (n = 5) Mean ± SD	Gr 2 (n = 6) Mean ± SD	Gr 1 (n = 5) Mean ± SD	Gr 2 (n = 6) Mean ± SD
18.00	4.06 ± 0.23	4.28 ± 0.36	3.82 ± 0.23	4.08 ± 0.29
21.00	3.80 ± 0.27	3.97 ± 0.19	3.68 ± 0.16	3.85 ± 0.29
24.00	3.82 ± 0.24	3.98 ± 0.20	3.80 ± 0.29	4.17 ± 0.39
03.00	4.04 ± 0.47	4.30 ± 0.20	3.80 ± 0.17	4.28 ± 0.31*
06.00	4.22 ± 0.23	4.40 ± 0.24	4.18 ± 0.25	4.50 ± 0.75

*p < 0.05

on D2 and D3, some improvements in the THSS (lower TPPEs at least 5 of 11 determinants compared with those at initial 6 a.m. TPPE level) in 2/5 cases of G1 and 3/6 cases of G2.

48-hour Holter ECG recordings revealed neither prolonged pause (> 0.2 second) nor significant cardiac arrhythmia.

Nocturnal respiratory parameters recorded during D2 (Table 4) revealed abnormal apnea indices, ie > 5 (AIS), in 1/5 subjects of G1 and 3/6 subjects of G2, and MXAs were > 10 hour in 1/5 subjects of G1 and in 4/6 subjects of G2. There was no statistical difference between G1 and G2 for AIS and MXAs (p > 0.05), although MHTs > 30

Table 3
Thiamine (TPPE%) in 11 subjects.

Day	time	Cases										
		1	2	3	4	5	6	7	8	9	10	11
2	6	14.3	4.8	50.0	25.9	23.1	0	20.0	15.0	100	18.2	31.6
	18	13.3	25.7	31.2	22.6	27.3	2.6	0	33.3	35.7	0	18.2
	21	18.8	10.0	33.3	10.3	25.0	10.0	0	24.1	100.0	8.5	32.6
	24	30.2	9.6	26.3	3.4	14.8	2.3	0	0	45.8	7.3	0
	3	19.1	7.9	76.9	25.0	17.0	0	14.3	23.5	66.7	9.3	5.9
	6	18.8	9.8	46.7	11.7	14.3	7.1	16.7	11.8	23.1	6.4	11.9
3	18	11.9	10.0	44.8	19.2	30.9	6.2	0	23.1	30.0	4.3	55.0
	21	12.1	7.7	21.0	18.5	24.4	0	28.6	0	23.1	0	0
	24	10.3	9.6	36.4	15.5	23.8	0	12.5	25.9	16.7	0	31.6
	3	14.3	8.2	18.4	19.6	31.9	0	21.4	0	23.1	0	30.2
	6	13.0	0	32.3	10.0	25.0	8.7	50.0	0	0	6.7	34.3

seconds were found in 4/6 subjects of G2, this was not so in the subjects of G1 (statistically different $p < .$). In comparing the MXHTs > 30 seconds this was evident in only 1/5 of subjects of G1 compared with was evident in all subjects of G2 (statistically different, $p < 0.05$). Although none of the subjects in G1 developed LHE > 30 seconds, and 2/5 subjects in G2 had LHE > 30 seconds,

there was no statistical difference ($p > 0.05$).

During the nights of D3, NTM data were available on 5 subjects of G1 and only 5/6 subjects of G2 because of one technical failure (Table 5). AIS in G1 and G2 were found in 1/5 and 2/5 respectively, and this did not show any statistical difference ($p > 0.05$). The MXAs > 10 /hours in G1 and

Table 4
Respiratory parameters (non awake period).

		Day 2					
	Case	AI/hr	MXA/hr	MHT(sec)	MXHT(sec)	LHE(sec)	
Group 1	1	0.32	2	4.85	27	< 30	
	2	1.52	2	29.8	71	< 30	
	3	0.54	1	0.36	2	< 30	
	4	5.04	10	1.38	3	< 30	
	5	1.94	6	0.65	6	< 30	
Group 2	6	3.35	12	45.2	200	127 (70%)	
	7	13.2	24	30.2	146	< 30	
	8	0.83	4	16.83	86	< 30	
	9	25.8	49	42.3	91	< 30	
	10	6.07	11	9.5	56	< 30	
	11	0	0	256.2	1,295	499 (79%)	
p		0.34	0.17	0.04	0.01	0.22	

Table 5
Respiratory parameters (non awake period).

Day 3						
	Case	AI/hr	MXA/hr	MHT(sec)	MXHT(sec)	LHE(sec)
Group 1	1	8.1	25	0.86	3	< 30
	2	4.12	9	10.8	19	< 30
	3	3.78	7	15.6	58	< 30
	4	1.29	3	1.84	6	< 30
	5	1.18	3	2.37	10	< 30
Group 2	6	5.18	14	55.5	302	276 (70%)
	7	4.9	12	383.7	1,025	101 (51%)
	8	0.76	1	73.4	366	300 (84%)
	10	10.9	23	0.4	2	< 30
	11	0.8	4	502	1,116	1,041 (69%)
p		0.5	0.26	0.02	0.02	0.02

G2 occurred in 1/5 and 3/5 respectively, insignificantly different with $p > 0.05$. The MHTs > 30 seconds occurred in 4/5 of G2 but in 0/5 of G1. The MXHTs > 240 seconds occurred in 4/5 of G2 but in 0/5 of G1. The LHEs > 100 seconds were present in 4/5 of G2 but in 0/5 of G1. There was significant statistical difference ($p < 0.05$) in comparing the MHTs, MXHTs, and the LHEs between G1 and G2.

In scrutinizing cases 6, 7, 8, and 11, their hypoxic duration (MHTs and LHEs), recorded on D3, were all more prolonged than those recorded on D2, with the only exception being the MXHTs of case 11.

DISCUSSION

Other authors have suggested abnormal anatomy or function of the cardiac conduction system (Okada and Kawai, 1982; Gotoh, 1976; Kirschner *et al*, 1986) and Guilleminault *et al* (1984) have suggested that sinus arrest during REM sleep may be recorded as a plausible cause of SUDS. Our findings did not support such theories. Insignificant abnormal cardiac findings were found in both G1 and G2: 2 cases had mild mitral valve prolapse (cases 2, 10), and 1 case (case 3) had mild tricuspid regurgitation. However they all had normal ejection fraction, normal cardiac examinations and ECGs, 48-hours holter monitoring of these 3 cases were essentially normal. De-

spite the evidence of ventricular fibrillation in the ECGs during cardiac resuscitation of the 2 N-SUDS cases in G2 and the IRBB found in the post-resuscitation ECG in 1/2 N-SUDS cases, both of them had normal cardiac examination, normal ECHOs and 48-hours holter monitoring were also normal. Ventricular fibrillation (VF) in these 2 cases and in a previously report (Otto *et al*, 1984) might be the terminal events of SUDS.

Hypokalemia is considered by Nimmanmit *et al* (1991) to be a major factor is the etiology of SUDS, but we have not found any evidence to support the hypokalemic theory in this study, even though many blood samples were taken at intervals, particularly at night. In addition, the medical records of our two cases of NSUDS revealed that the potassium levels were never less than 3 mg%, even during admissions with cardiac arrest and cardiac resuscitation, and besides, they were successfully resuscitated without any potassium supplement. Although hypokalemia has been reported in north-eastern Thais, (Nimmannit *et al*, 1991) we are not convinced that hypokalemia is the primary cause in the possible chain of events leading to death (PCELD) in SUDS.

Thiamine deficiency (TD) was common in G1 and G2 subjects, but there was not a significant difference in levels between the two groups. In considering that 1/2 NSUDS cases did not show any TD, it seems unlikely that TD is the primary cause in the PCELD.

The results of NTM of G1 and G2 revealed longer duration of MHTs and MXHTs in G2 than G1. During D3, the durations of the LHEs in G2 were longer than those in G1. The levels of hypoxia varied from 51% to 89%. The greatest LHE (1041 seconds) was found in case 11 (D3).

Physical stress on D3 might have had an impact on our two near-SUDS subjects. Both developed longer MHT, MXHT and LHEs on D3. But the LHEs with the lowest SaO₂ of 70% and 51% respectively did not cause any cardiac arrhythmia. Nevertheless, if the LHEs were more prolonged and if the desaturations were more severe, we suspect that cardiac arrhythmias may have ensued.

The cause of nocturnal hypoxia (NH) was unknown. This abnormality may be genetic related, because NH found more common in G2 than G1. The mechanism of NH could not have been explained by a respiratory disease, for all cases had normal chest examination, chest x-ray, spirometry and daytime oxygen saturation. The cardiac dysfunction also could not have been the cause of NH, as all subjects had normal cardiac ejection fraction by ECHOs. There were no correlation between AIS and hypoxic parameters (MHT, MXHT, and LHEs both D2 and D3). There was insufficient evidence to suspect sleep apnea as the main cause for NH. However our airflow recording techniques might not have been sensitive enough to detect hypopnea or abnormal respiratory dysrhythmias, which may themselves be important causative factors in the NH and require further investigation.

In summary, NH was found to be the main physiologic abnormality in the northeastern Thai workers. Such an abnormality was found to be much more common in the group with FHSUDS and near SUDS than in the group without FHSUDS. This abnormality was aggravated by daytime physical stress. We speculate that this physiologic abnormality might be genetically determined and that hypoxia plays an important role in the PCELD.

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