Blunted Nighttime Sympathetic Nervous System Response to Stress Among Thai Men with Positive Family History of Sudden Unexplained Nocturnal Death Syndrome

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Summary

Sudden unexplained nocturnal death syndrome (SUNDS) is prominent among northeast Thai men. This study tests the hypothesis that Thai men with positive family history of SUNDS display abnormal diurnal, autonomic nervous system responses to stress. Healthy northeast Thai men (20-49 years old) lived in the same rural area were divided into two groups based on their positive (PF) or negative family (NF1) history of SUNDS. A second control included Thai men with an NF history of SUNDS from a non-endemic area (NF2). All data were collected at 4:00-6:00 AM (nighttime) and 4:00-6:00 PM (daytime). All three groups displayed nighttime decreases in mean arterial pressure, heart rate, and blood glucose. Furthermore, all subjects displayed similar glucose tolerance and electrolyte balance. The tachycardic responses to a four-minute step test were similar among groups in the daytime, but the nighttime responses were significantly blunted in the PF group compared to either control group (about 20 bpm less). Tachycardic responses to a cold pressor test tended to decrease more during the nighttime in the PF compared to NF1 and NF2 groups, but the difference was not significant. Arterial pressure responses to the exercise were similar among the three groups during the nighttime, whereas in the NF2, daytime mean arterial pressures increased more than those in the other groups. The present data suggest that Thai men with a PF history of SUNDS display blunted sympathetic nervous system responses to stress during the nighttime, a potential factor that may trigger cardiac arrhythmias and contribute to SUNDS.

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Key words: Autonomic nervous system, Blood pressure, Cold pressor test, Diurnal heart rate, Electrolyte, Exercise, Glucose tolerance test, Oxygen consumption, Step test, Sudden cardiac death

Abnormal autonomic nervous system regulation underlies several cardiovascular diseases including hypertension, coronary ischemia, arrhythmias, sleep apnea, and sudden cardiac death.24-1 Sudden unexplained nocturnal death syndrome (SUNDS) is a nightmare disorder among healthy men, who have no chronic disease, are typically 20-49 years old, and live in Southeast Asia and South China.5 SUNDS is named “Lai Tai” in Thailand and Laos, “Bangungut” in Philippines, and “sudden manhood death syndrome” in mainland China.59 In fact, this abnormality has also been reported elsewhere, for example, “Pokkuri Death Syndrome” in Japan, “Dream Disease” in Hawaii, and “sudden adult death syndrome” in England.61 Although studies have intensively investigated the pathogenesis of SUNDS, its causes remain unclear. In most cases, cardiac arrhythmias are common before and during SUNDS,6-9 suggesting that cardiac electrical abnormalities may underlie SUNDS. Genetic investigation of postmortem victims and survivors indicates that some gene mutations in these individuals are related to cardiac ionic channels, particularly sodium, potassium, and calcium channels.5,9,10-13 Furthermore, using genetic transfection techniques, single-channel electrical activity recordings of cells from SUNDS victims indicate an abnormality in cardiac sodium channels that potentially contributes to arrhythmic genesis in these patients.16 However, studies have not tested other channels or the neurohormonal responses of these ionic channels. In addition, variations in cardiac ionic channels have been reported in SUNDS victims. Tester and coworkers investigated 173 sudden unexplained death cases and reported that in 45 cases (26.0%) of SUNDS, 45 putative pathogenic mutations existed (20 RYR2 [44.5%, 14 novel], 11 KCNQ1 [24.5%, 4 novel], 6 KCNH2 [13.3%, 5 novel], 6 SCN5A [13.3%, 2 novel], and 2 KCNE2 [4.4%]).17

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Under normal and stressful conditions, the autonomic nervous system plays a crucial role in adjusting cardiac electrical and mechanical activity, particularly at the level of cardiac ionic channel function. It is likely that some cardiac ionic channel mutations may contribute to SUNDS, but they likely require an appropriate stimulus to affect SUNDS, for example, sympathetic/parasympathetic imbalances. For example, Creighton et al. studied 14 cases of exercise-triggered sudden cardiac death and found three novel cardiac ryanodine receptor (RyR2) gene mutations in three unrelated patients. Furthermore, Skinner et al. reported rare missense variants in long QT syndrome genes in 5 (15%) of 33 sudden unexplained death cases. During a SUNDS attack, the victim frequently develops arrhythmias, muscular spasm, dyspnea, lack of wakening to stimuli, and sudden death. Thus, sympathovagal imbalance has been proposed as a contributor to SUNDS. A disease related to SUNDS, that is, Brugada syndrome, is not associated with altered baseline autonomic cardiovascular control during resting wakefulness and sleep; however, during REM sleep, it is associated with sleep-disordered breathing and decreased sympathetic and increased parasympathetic nerve activity. These disorders may contribute to cardiac arrhythmia in this syndrome. Furthermore, vagal-mediated ventricular arrhythmia is also reported in a case of Brugada syndrome. In contrast, Krittayaphong et al. reported lower resting vagal activity at night in Thai patients with Brugada syndrome compared to controls and suggested that this sympathovagal imbalance predisposes these individuals to cardiac arrhythmia and nocturnal death. However, Brugada syndrome is characterized by cardiac conduction abnormalities that can result in sudden death, whereas some SUNDS victims are previously healthy men without any known cardiac abnormality. These individuals likely have yet unidentified molecular abnormalities. Thus, the different pathologies in Brugada syndrome against other SUNDS patients may underlie the apparent differences reported in resting autonomic variability. The abnormal autonomic control of cardiac function in individuals with a PF history of SUNDS and related diseases has not been extensively studied, particularly during stress testing.

Recently, we showed that, in young healthy male, Thai university students, the locality in which they grew up directly related to their autonomic responses to stress. Individuals from rural (compared to central or urban) origin display decreased sympathetic and increased parasympathetic responses to cold and saline loading. These altered responses could predispose the rural individuals to increased incidence of SUNDS; however, diurnal differences in these responses have not been tested. Furthermore, perinatal and current environments, diets, life styles, work intensity, and genetics all contribute to cardiovascular disease and likely to SUNDS. The rate of SUNDS is initially high after at-risk individuals move to other countries, for example, studies of refugees from Southeast Asia living in the United States and Thai workers living in Singapore. In addition, there are no reports of autonomic control of cardiac function (particularly its diurnal variation) in healthy individuals who have a PF (compared to the negative) history of SUNDS and are living in the same location as their birthplace. The present study tests the hypothesis that Thai men with PF histories of SUNDS display abnormal autonomic nervous system responses to stress during nighttime. This study used standard, non-invasive techniques to explore the potential physiological precedents to SUNDS in the subjects who were living near their birthplace.

Methods

Subjects: Healthy northeast Thai men (20-49 years old) from a rural village with high incidence of SUNDS (Amphoe Wang Saphung, Loei Province, Thailand) were divided into two groups based on their PF history (PF, n = 15) or NF history (NF1, n = 12) of SUNDS. A second control group had an NF history and was from villages with negligible SUNDS rates (NF2, n = 11) (Amphoe Non Sa-at and Amphoe Nong Han, Udon Thani Province, Thailand; more than 100 km from Amphoe Wang Saphung). The PF subjects had a grandfather, grandmother, father, mother, sister, or brother who died and fit into at least three of the 10 criteria of presumed SUNDS. The final PF group included only sons or brothers of SUNDS decedents. These include death between 20 and 49 years of age, healthy without chronic diseases, normally working 24 hours prior to death, death during sleep, no abnormal symptoms before death, inability to be woken up before death, and no apparent forensic contributor to death. A physician took note of their clinical history and performed physical examinations. All voluntary subjects were consented, informed of all procedures, and allowed to quit the study at any time. The experiment was approved by the Institute Ethics Committee of Khon Kaen University and was under the control of a physician.

The villages were selected based on public survey data and questionnaire distribution. In the selected villages (about a square mile), selected families were interviewed to identify possible SUNDS subjects. PF was confirmed by official death reports and witness reports of the death. In addition, no subject was related to any other participants in the study, at least at the level of grandparents. All men were healthy and did not have any chronic or acute disease or were they on medical treatment. Their body mass indices were within a normal limit of 18.5-25 kg/m². This was confirmed by physical examination and blood tests. In addition, all volunteers were asked to try the cold pressor test and/or step test exercise before signing the informed consent. The volunteers that felt uncomfortable and/or exhibited any clinical abnormality during these tests were excluded from the study. The selected subjects were then allowed to live as usual in the same house and working place for at least a month before data collection.

Experimental protocol: A few days before starting the experiment, volunteers were asked to live as usual with adequate sleep (8 hours/night) and normal food intake, but to abstain from alcohol, smoking, and medications. On the day of experiment, subjects fasted after 12:30 PM. Baseline blood pressure and heart rate were measured (in the supine position) between 4:00 and 6:00 PM (daytime...
study), followed by venous blood samples (5 mL each). After 15-20 minutes rest, blood pressures and heart rates were measured before and during their right-hand immersion in cold water (2-4°C) for 2 minutes. Twenty minutes later, blood pressure and heart rate were recorded before, during, and after the six-minute step test.39) The subordinates later, blood pressure and heart rate were recorded between each experimental session.

Statistical analysis: Data are expressed as mean ± SEM. Statistical analyses were performed using one-way analysis of variance followed by the post hoc Duncan’s multiple range test and the paired Student’s t-test (SPSS PC+) with a significance criterion of $P < 0.05$.

Results

General characteristics: Age, body weight, maximal oxygen consumption, MAP, heart rate, serum sodium and potassium, serum creatinine, fasting blood sugar, and glucose tolerance were not significantly different among the three groups (Table). BUN significantly decreased in the NF2 group compared to the PF and NF1 groups. All groups displayed similar, significant decreases in nighttime (compared to daytime) fasting blood sugar, MAP, and heart rate, whereas nighttime serum creatinine significantly decreased in the NF1 and NF2 groups, but not in the PF group.

Responses to exercise stress test: During daytime, MAPs at rest and 4 minutes after exercise were not significantly different among the three groups, but during the 2- and 6-minute exercise, these indices significantly and markedly increased more in the NF2 group compared to the PF and NF1 groups (Figure 1A). During nighttime, although all groups significantly increased MAPs during the exercise stress test, their MAPs were not significantly different from each other throughout the experiment (Figure 1B). Furthermore, the increased MAPs during the test in the nighttime were sustained up to 2 minutes after the end of exercise; this response was not observed in the daytime study. The MAPs before, during, and after the exercise stress test were not significantly different between the PF and NF1 groups.

In the daytime, heart rates before, during, and after the exercise stress test were not significantly different among the three groups, but the values at 6-minute of exercise were slightly lower in PF than those in the other groups (Figure 1C). Nighttime heart rates significantly and markedly increased in all groups during the exercise stress test (about twice the resting heart rates), but the increased heart rate in response to the exercise was significantly less in PF (>20 bpm difference; ~25% reduction in the increase) than that in the NF1 and NF2 groups (Figure 1D). In addition, heart rates were not significantly different be-

### Table. General Characteristics among Groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PF (n = 15)</th>
<th>NF1 (n = 12)</th>
<th>NF2 (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>30.8 ± 1.9</td>
<td>32.8 ± 2.7</td>
<td>37.7 ± 2.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.4 ± 1.6</td>
<td>56.0 ± 1.4</td>
<td>59.8 ± 3.3</td>
</tr>
<tr>
<td>VO₂ max (L/minute)</td>
<td>3.6 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>91.4 ± 2.2</td>
<td>88.4 ± 2.8*</td>
<td>90.3 ± 2.1</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>73.5 ± 2.7</td>
<td>59.9 ± 2.3*</td>
<td>72.8 ± 2.8</td>
</tr>
<tr>
<td>Serum Na⁺ (mM)</td>
<td>151.4 ± 2.0</td>
<td>148.0 ± 1.2</td>
<td>150.1 ± 2.2</td>
</tr>
<tr>
<td>Serum K⁺ (mM)</td>
<td>4.1 ± 0.1</td>
<td>4.1 ± 0.0</td>
<td>4.0 ± 0.1</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>14.1 ± 0.6</td>
<td>13.8 ± 0.7</td>
<td>14.1 ± 0.6</td>
</tr>
<tr>
<td>Glucose tolerance (mg/dL)</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>Fasting (5-8 hours)</td>
<td>71.1 ± 2.2</td>
<td>63.7 ± 1.5*</td>
<td>68.9 ± 1.5</td>
</tr>
<tr>
<td>30 minutes</td>
<td>112.0 ± 3.8</td>
<td>106.9 ± 5.3</td>
<td>110.9 ± 3.8</td>
</tr>
<tr>
<td>60 minutes</td>
<td>110.9 ± 3.8</td>
<td>105.8 ± 7.8</td>
<td>107.9 ± 9.6</td>
</tr>
<tr>
<td>120 minutes</td>
<td>75.5 ± 5.6</td>
<td>75.3 ± 5.2</td>
<td>63.4 ± 6.3</td>
</tr>
</tbody>
</table>

Data are mean±SEM; * , # $P < 0.05$ between daytime and nighttime of the same group and to other two groups, respectively. PF indicates positive-family history group; NF1, negative-family history group living in the same village of PF; NF2, negative-family history group living in a different province from PF and NF1; VO₂ max, maximum oxygen consumption; MAP, mean arterial pressure; and HR, heart rate.
Figure 1. Daytime (A and C) and nighttime (B and D) MAP (A and B) and heart rate (C and D) before (0 minutes), during (2-6 minutes), and after step test exercise (8 minutes) in the PF history group, NF1 history group living in the same village of PF, and NF2 history group living in a different province from the PF and NF1 groups (*, #P < 0.05 compared to the other two groups and NF2, respectively).

Figure 2. Daytime and nighttime MAP (A and B) and heart rate (C and D) at baseline (A and C) and during cold response (B and D) in the PF history group, NF1 history group living in the same village of PF, and NF2 history group living in a different province from the PF and NF1 groups (*, #P < 0.05 compared to daytime of the same groups and PF and/or NF1, respectively).
Responses to cold pressor test: Resting MAPs were not significantly different among the three groups before either daytime or nighttime cold pressor test (Figure 2A and B). During the cold pressor test, MAPs significantly increased in all groups and those in the NF2 group were significantly higher than those of the other two groups. MAPs at baseline and in response to the cold pressor test were not significantly different between the PF and the NF1 groups in either daytime or nighttime. Baseline heart rates were not significantly different among the three groups in either daytime or nighttime, and all groups significantly decreased heart rate in nighttime compared to daytime (Figure 2C and D). Heart rates were not significantly different between groups during daytime or nighttime cold pressor tests; however, during the cold pressor test, only the PF group had nighttime heart rates significantly lower than daytime heart rates ($P < 0.05$; Figure 2D).

Cardiac oxygen consumption: Neither daytime nor nighttime estimated cardiac oxygen consumption was significantly different among the three groups before, during, or after the exercise stress test; however, the daytime value of the NF2 group at 6 minutes of exercise was slightly higher than that of the PF and NF1 groups (Figure 3). Furthermore, cardiac oxygen consumption at baseline and during exercise was significantly lower in the nighttime compared to that in the daytime in all three groups (Figure 4, left). During the cold pressor test, all groups displayed similar increases in cardiac oxygen consumption in both daytime and nighttime testing (Figure 4, right). Only the PF group displayed decreased cardiac oxygen consumption in the nighttime compared to the daytime responses. These changes in cardiac oxygen consumption during cold pressor test were consistent with changes in the heart rate (Figure 2C and D).

Discussion

The incidence of SUNDS is much higher in Southeast Asia and South China than that in other parts of the world, but the pathogenesis of this disorder remains unclear. Previous experiments indicate that compared to healthy, urban Thai men who lived in Khon Kaen (the Northeast part of Thailand) for at least 2-3 years, healthy, rural northeast Thai men display lower sympathetic and higher parasympathetic responses to stressors. This study examines subjects who lived in the rural Northeast Thailand, and the results demonstrate that compared to the two control groups, subjects with PF history of SUNDS responded to a physical stressor with markedly blunted sympathovagal increases during nighttime but not during daytime. These data support the hypothesis that inappropriate autonomic responses to stress during sleep or nighttime rest may predispose young healthy Thai men to SUNDS.

Increased sympathetic and decreased parasympathetic nerve activity during stress are crucial responses, since increased cardiac output acts to adequately supply the metabolic demands of the body, particularly for skeletal muscle contraction. Increased heart rate during steady exercise is directly proportional to the increased cardiac output and body oxygen consumption. Thus, increased sympathetic and decreased parasympathetic nerve activity maintain the heart rate at a higher-than-normal-level during continuous...
work. Decreased parasympathetic nerve activity appears to play an initial role at the beginning of the exercise, whereas the increased sympathetic nerve activity is primarily responsible for the increased heart rate during steady exercise. Furthermore, these autonomic responses are mainly driven by the central motor command and muscle proprioceptor feedback. The PF group’s blunted tachycardic response to continuous exercise may result from an inadequate sympathetic response or an inadequate cardiac sympathovagal response. An abnormal site of the autonomic nervous system regulation is likely to be in the central nervous system, since periodic sleep apnea or intermittent hypoxia increases risks of SUNDS, likely via chemoreceptor-mediated central neural function. The low tachycardic responsiveness to the nighttime cold pressor test displayed by the PF group compared to either NF group supports the proposal that abnormal central modulation of autonomic outflow during stress exists in the PF subjects. In contrast to the differential response of the PFs versus controls to physical stress, hand immersion in cold water for 2 minutes increased sympathetic and decreased parasympathetic drive to the heart and blood vessels followed by increases in the heart rate and blood pressure that were relatively equal in all the three groups. These autonomic responses were mediated by cold receptors and their connections to central autonomic neurons. However, an abnormal cardiac tissue response to catecholamine and acetylcholine release cannot be excluded in light of the discovery of a cardiac ionic channel mutation in some SUNDS survivors.

Although the present study cannot definitively identify the mechanism of the altered autonomic response to physical stress in the PF group, some potential factors are excluded by the present data. Abnormal insulin-glucose regulation can lead to early morning hypoglycemia followed by depressed neural function. Diurnal fasting blood glucose and glucose tolerance were not significantly different among the three groups, and average nighttime blood glucose levels were all below 70 mg/dL, thereby suggesting that mild hypoglycemia existed equally among all subjects. These fasting blood sugar levels were close to those reported in our previous study among young northeast Thai men. Blood glucose at these levels can trigger sympathetic activity that causes adrenergic symptoms, including tachycardia, wakefulness, and hunger. These signs are familiar among diabetic patients. It is possible that a combination of mild hypoglycemia and low sympathovagal responsiveness increases the risk of PF subjects experiencing SUNDS in early morning; that is, mild hypoglycemia without appropriate increased sympathetic drive may cause decreased blood pressure. These adverse responses might be exacerbated by sleep apnea-induced hypoxemia. The resulting mild hypotension (via baroreceptor-mediated responses) and hypoglycemia (via glucoreceptor-mediated responses) could synergistically trigger sympathetic overactivity, cardiac arrhythmias, and ultimately even death. Thus, arrhythmias are common among SUNDS before death, and wakening up patients during a SUNDS episode can increase survival.

Compared to sedentary or untrained subjects, well-trained athletes usually display decreased resting heart rate and tachycardic response to dynamic exercise. These changes relate to a decrease in sympathovagal activity to the heart. In this study, no difference in physical performance measures was observed. Furthermore, the three groups had similar maximum oxygen consumption and resting heart rate. The three groups’ cardiac oxygen consumption at rest and during exercise stress were similar.

Figure 4. Daytime and nighttime estimated cardiac oxygen consumption (systolic pressure × heart rate) at baseline (left) and during cold response (right) in the PF history group, NF1 history group living in the same village of PF, and NF2 history group living in a different province from the PF and NF1 groups (*P < 0.05 compared to daytime of the same group).
especially between the PF and NF1 groups. BUN was slightly and significantly lower in the NF2 group compared to the PF and NF1 groups, but was not significantly different between the PF and NF1 groups. All of these group values were within a normal range. Together with the similar plasma creatinine among groups, these data suggest normal renal excretory function in all groups. Furthermore, the three groups also had similar plasma electrolyte concentrations. Thus, the blunted nighttime tachycardic response to the step test in PF subjects is very unlikely to be due to higher physical performance of the PF group compared to the NF group.

Autonomic responses to stress in SUNDS appear dependent on previous areas in which a subject lived. This may explain why the incidence of SUNDS is high among Northeastern Thai men working in Singapore, among Laotian refugees in Thailand, and among Southeast Asian refugees in the United States. This study further indicates that a variation in autonomic responses to stress exists among normal subjects living in different rural areas of northeast Thailand, as indicated by the different arterial pressure responses to exercise and cold pressor test between the NF1 and NF2 groups during daytime. This may depend on many factors including the subject’s lifestyle, but does not appear related to physical performance. These data suggest that further study of the autonomic function of PF individuals should include a matched control that lives in the same area and has a similar lifestyle to the at-risk subjects, for example, the NF1 group in the present study.

In conclusion, SUNDS is a significant nightmare disorder among Southeast Asian men, including northeast Thai men. Although many possible causes have been reported, including genetic mutations, electrolyte imbalance, hormonal imbalance, and autonomic disorder, no single factor has defined the pathogenesis of SUNDS. Previously, we reported that the area in which a subject lived was critical to the abnormal autonomic response to the stress of a new environment. This study further indicates that, in subjects still living in their birthplace, the PF subject displayed blunted sympathetic nerve response to stress during the early morning, the time of when SUNDS deaths are most frequent.

Limitations in the interpretation of the current study: The interpretation of this study has some limitations that should be noted for further studies. This study did not include a direct index of malnutrition, which has been suggested as a risk factor for SUNDS. However, the data on body mass index and the physician’s examinations of the participants suggest that they were all in the normal body mass index range for their age (18.5-25 kg/m²), and all of them displayed no overt signs of malnutrition in their history and physical examinations. Future studies should also monitor serum magnesium (an important contributor to cardiac function), genetic profile, electrocardiography, and direct or indirect measure of autonomic nerve activity. Given the varied and rural locations of many of the subjects, these measures were beyond the scope of this study. Finally, direct measures of cardiac ionic function should be examined to understand their potential contribution to SUNDS.

Disclosures

Conflicts of interest: We have no conflicts of interest, and all authors participated actively in this study.

References