**Sleep-Disordered Breathing Increases Risk for Fatal Ventricular Arrhythmias in Patients With Chronic Heart Failure**

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**Background:** It has been shown that sleep-disordered breathing (SDB) is associated with adverse prognosis in patients with chronic heart failure (CHF), but little is known about the relationship between SDB and life-threatening arrhythmias.

**Methods and Results:** Fifty patients with CHF and SDB (33 male; mean age, 61 years) underwent Holter electrocardiogram and portable sleep monitoring simultaneously. The circadian variation in positive T-wave alternans (TWA; >65 μV) was determined during 6-hour intervals (0–6, 6–12, 12–18, and 18–24 h). In addition, power spectral analysis of heart rate variability (HRV) was evaluated across a 24-hour period. The subjects were divided into 2 groups based on whether respiratory disturbance index was ≥20 events/h (Group A, n=24) or not (Group B, n=26). The prevalence of positive TWA, parameters in HRV and the occurrence of ventricular tachycardia (>5 beats) were compared between the 2 groups. The prevalence of positive TWA in Group A was significantly higher than that in Group B in all 6-hour intervals. Low-frequency and high-frequency powers of HRV were significantly lower in Group A than in Group B across a 24-hour period. Importantly, the prevalence of ventricular tachycardia was significantly higher in Group A than in Group B (46% vs. 19%, P=0.04).

**Conclusions:** SDB may induce cardiac electrical instability associated with life-threatening arrhythmias across a 24-hour period in CHF. (Circ J 2013; 77: 1466–1473)

**Key Words:** Heart rate variability; Sleep-disordered breathing; T-wave alternans; Ventricular tachycardia
spectral method with an exercise stress protocol or the time-domain modified moving average (MMA) method on Holter ECG, the latter is useful during not only daytime but also at night.\textsuperscript{15-17}

The aim of the present study was to describe the influence of SDB on increased risk for life-threatening ventricular tachyarrhythmias in CHF patients. Therefore, we investigated the relationship between SDB with CHF and the risk for fatal ventricular tachyarrhythmias, using TWA with the time-domain method, HRV and ventricular ectopic beats analyzed on Holter ECG.

\section*{Methods}

\subsection*{Subjects and Study Protocol}

The subjects consisted of 50 patients with symptomatic heart failure, defined as New York Heart Association (NYHA) class II or III. The exclusion criteria were the presence of atrial fibrillation and receiving hemodialysis, implantable device therapy and SDB therapy. All patients underwent 24-h Holter ECG and portable sleep monitoring simultaneously. Blood sampling for B-type natriuretic peptide (BNP) measurements and echocardiography were performed on the same day as the sleep assessment. TWA was calculated using the time-domain MMA method, and positive TWA was defined as \(>65\,\mu\text{V}\). In addition, we carried out power spectral analysis and time-domain analysis of HRV, frequency of ventricular premature complexes (VPCs) and ventricular tachycardia (VT, >5 beats) on 24-h Holter ECG. The subjects were divided into 2 groups based on whether respiratory disturbance index (RDI) was \(\geq 20\) events/h (Group A, \(n=24\)) or not (Group B, \(n=26\)) on portable sleep monitoring. The parameters were compared between the 2 groups. Written informed consent was obtained from all subjects. The study protocol was approved by the ethics committee of Fukushima Medical University.

\subsection*{Portable Sleep Monitoring}

All subjects underwent overnight polygraphy with the use of standard techniques.\textsuperscript{18} Overnight polygraphy was performed using a type 3 polygraph system (LS-300; Fukuda Denshi, Tokyo, Japan), which consisted of the monitoring of ECG, thoracoabdominal motion, nasal airflow via airflow pressure transducer, and arterial oxymoglobin saturation (SpO\(_2\)) via pulse oximetry.\textsuperscript{18} Apnea was defined as absence of airflow for >10 s. Hypopnea was defined as a >30% reduction in monitored airflow accompanied by a decrease in SpO\(_2\) >4%.\textsuperscript{18} Standard definitions were used for OSA and CSA on the basis of the presence or absence of rib cage and abdominal excursions with an absence of airflow. RDI was defined as the number of apneas and hypopneas per hour during the time in bed. The major polygraphic parameters investigated were RDI, central apnea index, obstructive apnea index, lowest pulse oxygen saturation (lowest SpO\(_2\)), and mean pulse oxygen saturation (mean SpO\(_2\)).\textsuperscript{18} The data were visually inspected and scored by a single experienced laboratory technician who was blinded to the other results. Based on a median RDI (19.6 events/h) in the present study and previous reports,\textsuperscript{19,20} the present subjects were divided into 2 groups: RDI \(\geq 20\) events/h (Group A) or not (Group B).

\subsection*{Measurement of TWA}

All patients underwent 24-h Holter ECG at the same time as overnight portable sleep monitoring. In a manner similar to that used for routine Holter-based ST segment analysis, the greatest TWA magnitudes were separately examined for each of the 2 leads (the bipolar modified V\(_1\) and V\(_5\) leads). TWA was analyzed using the time-domain MMA method using MARS PC Holter Monitoring and Review System (version 7; GE Healthcare, Milwaukee, WI, USA). The MMA method has been described in a previous study by Nearing and Verrier.\textsuperscript{16} In brief, the MMA algorithm continuously streams odd and even beats into separate bins and creates average complexes for each bin. Average morphologies of both the odd and even beats were continuously updated by a weighting factor of one-eighth of the difference between the ongoing average and the new incoming beats. TWA was calculated as the maximum difference in amplitude between the odd and even median complexes from the J point to the end of the T-wave for each 15-s beat stream. TWA \(>65\,\mu\text{V}\) is useful for predicting fatal ventricular arrhythmia in various heart diseases.\textsuperscript{13} In the present study, we determined that positive TWA was \(>65\,\mu\text{V}\). TWA at heart rates \(>120\) beats/min or those with high noise levels \(>20\,\mu\text{V}\) were excluded from the analysis. Positive TWA in a single day was analyzed in the modified V\(_1\) and V\(_3\) leads; of these 2 leads the 1 with the higher TWA was termed the higher lead. Additionally, positive TWA during 6-h intervals (0–6, 6–12, 12–18, and 18–24 h) was determined.

\subsection*{Measurement of HRV}

Cardiac autonomic nervous system modulation was assessed by R-R interval in the power spectral analysis and the time-domain analysis. Recordings with >15% noise or ectopic beats during 24 h were excluded from the HRV analysis. Preliminary analysis allowed exclusion of noise, artifacts, premature beats, and postextrasystolic pauses from further analysis. HRV analysis was performed using the MARS PC Holter Monitoring and Review System.

In the power spectral analysis, low-frequency (LF) component, high-frequency (HF) component and LF to HF ratio were measured across a 24-h period. Spectral measures were computed using the fast-Fourier transform method. Spectral powers are expressed in ms\(^2\). A component in the frequency band from 0.03 to 0.15 Hz was considered an LF component. A component in the frequency band from 0.15 to 0.5 Hz was considered an HF component.\textsuperscript{21,22} In addition, standard deviation of all R-R intervals (SDNN) and standard deviation of the 5-min mean R-R intervals (SDANN) were calculated in the time-domain analysis.

\subsection*{Measurement of VPCs}

The total number of single VPCs was determined in a single day and during 6-h intervals (0–6, 6–12, 12–18, and 18–24 h). In this study, VT was defined as 5 repetitive VPCs with a heart rate >100 beats/min, and the appearance of VT in a single day was determined, because previous studies have reported that the presence of VT in 24-h Holter ECG is an independent marker for increased overall mortality rate and sudden death.\textsuperscript{23-25}

\subsection*{Statistical Analysis}

Statistical analysis was performed with SPSS (version 17; SPSS, Chicago, IL, USA). Data are presented as mean\(\pm\)SD. Number of VPCs is presented as mean\(\pm\)SE. BNP is presented as median and interquartile range. Differences between the 2 groups were assessed using the unpaired Student’s t-test for continuous variables and Fisher’s exact test for categorical variables. \(p<0.05\) was considered statistically significant. Circadian variation of the prevalence of positive TWA was analyzed using McNemar’s test. In HRV, analysis of variance with repeated measures was used to compare between-group and within-group measurements across 24-h periods.
Results

Subject Clinical Characteristics
Baseline patient characteristics are listed in Table 1. There were no significant differences in age, gender, body mass index, basal cardiac disease or NYHA functional class between the two groups. In addition, there were no significant differences in parameters in ECG, LVEF on echocardiography and BNP. Beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and diuretics were used as medical treatment for heart failure either alone or in various combinations in 76%, 90% and 50% of the study patients, respectively.

Portable Sleep Monitoring
The portable sleep monitor data are listed in Table 2. Min SpO₂ and mean SpO₂ were not different between the two groups.

Prevalence of Positive TWA
In a single day, the prevalence of positive TWA was significantly higher in Group A than in Group B (75% vs. 42%; Figure 1A). In addition, the prevalence of positive TWA in Group A was significantly higher than that in Group B in all 6-h intervals (0–6 h, 23% vs. 8%, P<0.05; 6–12 h, 50% vs. 25%, P<0.05; 12–18 h, 55% vs. 25%, P<0.05; and 18–24 h, 36% vs. 4%, P<0.05; Figure 1B). Circadian variation in the prevalence of positive TWA was not observed between the two groups (McNemar’s test).

There was no difference in the prevalence of positive TWA between patients with CSA- and OSA-dominant SDB (64% vs. 52%, P=0.39).

HRV
On power spectral analysis, LF and HF powers of HRV were significantly lower in Group A than in Group B across a 24-h period (LF, 50.9±44.6 ms² vs. 190.1±138.1 ms², P<0.05; HF, 39.5±27.2 ms² vs. 101.2±75.1 ms², P<0.05; Figures 2A, B). We also analyzed LF and HF powers of HRV during only the daytime. LF and HF powers of HRV were also significantly lower in Group A than in Group B during the daytime (LF,

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Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=50)</th>
<th>Group A (RDI ≥20events/h) (n=24)</th>
<th>Group B (RDI &lt;20events/h) (n=26)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.2±12.8</td>
<td>62.7±12.0</td>
<td>59.3±14.2</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>33 (66)</td>
<td>18 (75)</td>
<td>15 (58)</td>
<td>NS</td>
</tr>
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<td>BMI (kg/m²)</td>
<td>24.7±4.1</td>
<td>25.9±4.1</td>
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<tr>
<td>Basal cardiac disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ischemic heart disease</td>
<td>21 (42)</td>
<td>10 (42)</td>
<td>11 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>21 (42)</td>
<td>9 (38)</td>
<td>12 (46)</td>
<td>NS</td>
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<tr>
<td>Valvular heart disease</td>
<td>4 (8)</td>
<td>3 (12)</td>
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<tr>
<td>Others</td>
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<td>2 (8)</td>
<td>2 (8)</td>
<td>NS</td>
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<tr>
<td>NYHA functional class (II/III)</td>
<td>(31/19)</td>
<td>(15/9)</td>
<td>(16/10)</td>
<td>NS</td>
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<td>Electrocardiogram</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>70.3±12.0</td>
<td>70.6±13.9</td>
<td>70.1±10.1</td>
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<td>QRS duration (ms)</td>
<td>102.2±12.6</td>
<td>104.1±13.3</td>
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<tr>
<td>QTc interval (ms)</td>
<td>420.0±22.7</td>
<td>424.8±24.3</td>
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</tr>
<tr>
<td>LVEF (%)</td>
<td>42.8±14.5</td>
<td>41.1±13.6</td>
<td>44.5±15.4</td>
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<tr>
<td>BNP (pg/ml)†</td>
<td>217.2 (88.6–514.0)</td>
<td>242.7 (103.7–594.7)</td>
<td>194.6 (51.3–418.0)</td>
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<td>Medication</td>
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<td>β-blockers (%)</td>
<td>38 (76)</td>
<td>19 (79)</td>
<td>19 (73)</td>
<td>NS</td>
</tr>
<tr>
<td>ACEI/ARBs (%)</td>
<td>45 (90)</td>
<td>22 (89)</td>
<td>23 (88)</td>
<td>NS</td>
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<td>Diuretics (%)</td>
<td>25 (50)</td>
<td>10 (42)</td>
<td>15 (58)</td>
<td>NS</td>
</tr>
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</table>

Data given as mean±SD, n (%) or †median (interquartile range). ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RDI, respiratory disturbance index.

Table 2. Portable Sleep Monitor Data

<table>
<thead>
<tr>
<th></th>
<th>Group A (RDI ≥20events/h) (n=24)</th>
<th>Group B (RDI &lt;20events/h) (n=26)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>RDI (events/h)</td>
<td>31.1±11.2</td>
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<td>CAI (events/h)</td>
<td>10.2±9.1</td>
<td>2.5±2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OAI (events/h)</td>
<td>10.7±8.5</td>
<td>4.9±4.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CAI/OAI (%)</td>
<td>49.0±0.25</td>
<td>40.0±0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Min SpO₂ (%)</td>
<td>76.9±11.4</td>
<td>82.5±10.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean SpO₂ (%)</td>
<td>94.7±1.4</td>
<td>95.3±4.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data given as mean±SD. AI, apnea index; CAI, central apnea index; mean SpO₂, mean oxyhemoglobin saturation; min SpO₂, minimum oxyhemoglobin saturation; OAI, obstructive apnea index; RDI, respiratory disturbance index.
Specificity were 75% and 62%, respectively. The area under the curve was 0.63, and the sensitivity and the optimal RDI cut-off for prediction of VT was 19.1 events/h.

It has been shown that TWA is specifically exacerbated by conditions such as left ventricular dysfunction and congestive heart failure. Accordingly, TWA is considered to be an appropriate parameter to evaluate cardiac electrical instability in SDB with CHF. Previous studies have demonstrated that SDB is associated with poor prognosis, including SCD in CHF patients. The exact mechanisms of the increased risk of ventricular tachyarrhythmias, however, have not been elucidated in CHF patients with SDB. Gami et al found that patients with SDB had a significantly higher peak sudden death rate during sleep than patients without SDB.

Figure 1. Positive T-wave alternans (TWA) vs. respiratory disturbance index (RDI; Group A, RDI ≥20 events/h; Group B, RDI <20 events/h) for (A) a single 24-h period, and (B) 6-h intervals. (A) The prevalence of positive TWA was significantly higher in Group A than in Group B (P<0.05). (B) The prevalence of positive TWA was significantly higher in Group A than in Group B for all 6-h intervals (P<0.05).

Figure 2C. No circadian variation in LF and HF powers of HRV was observed in either of the 2 groups. On time-domain analysis, SDNN and SDANN were significantly lower in Group A than in Group B (SDNN, 76.5±26.5 ms vs. 100.3±27.9 ms, P<0.05; SDANN, 64.1±28.6 ms vs. 88.9±28.1 ms, P<0.05; Figure 3). There were no differences in SDNN and SDANN between patients with CSA- and OSA-dominant SDB (SDNN, 99.6±42.1 ms vs. 98.4±25.3 ms, P=0.90; SDANN, 83.5±35.3 ms vs. 81.1±24.1 ms, P=0.77).

Frequency of VPCs and VT
In a single day, the frequency of VPCs was significantly higher in Group A than in Group B (2,533.2±1,086.5 beats/day vs. 313.8±137.6 beats/day, P<0.05; Figure 4A). In addition, the frequency of VPCs in Group A was significantly higher than in Group B in all 6-h intervals (0–6 h, 767.2±320.6 beats/day vs. 80.8±41.1 beats/day, P<0.05; 6–12 h, 689.6±284.5 beats/day vs. 112.9±60.9 beats/day, P<0.05; 12–18 h, 564.2±228.2 beats/day vs. 51.1±16.6 beats/day, P<0.05; and 18–24 h, 942.5±374.7 beats/day vs. 60.6±25.1 beats/day, P<0.05; Figure 4B). Importantly, the occurrence proportion of patients with VT in a single day was significantly higher in Group A than in Group B (46% vs. 19%, P=0.04; Figure 5). The prevalence of VT in patients with CSA-dominant SDB tended to be higher than that in those with OSA-dominant SDB, but this was not statistically significant (44% vs. 20%, P=0.07).

Receiver operating characteristic curve analysis showed that the optimal RDI cut-off for prediction of VT was 19.1 events/h. The area under the curve was 0.63, and the sensitivity and specificity were 75% and 62%, respectively.

Discussion
In this study, we investigated the association between SDB with CHF and the risk for ventricular tachyarrhythmias using TWA with the time-domain method. HRV and ventricular ectopic beats analyzed on Holter ECG. As a result, SDB with CHF was associated with cardiac electrical instability and impaired autonomic nervous system modulation across a 24-h period. This is the first study to show that SDB with CHF influences the occurrence of fatal ventricular tachyarrhythmias not only during the night but also the day.

TWA and SDB
TWA is considered to present ventricular repolarization abnormalities. The measurement of TWA is useful for the appearance of fatal ventricular tachyarrhythmias and SCD in cardiovascular diseases. TWA is generally analyzed via the power spectral method, during the daytime with an exercise stress protocol. Therefore, it is difficult to investigate the relationship between SDB and the risk for ventricular tachyarrhythmias across a 24-h period. In addition, it is sometimes impossible for TWA to be analyzed using the power spectral method due to the impairment of exercise tolerance in CHF patients. In contrast, it is possible for TWA to be analyzed using the time-domain method during a 24-h period. In this study, TWA was analyzed via the time-domain method because the purpose of this study was to evaluate the risk for ventricular tachyarrhythmias across a 24-h period.

It has been shown that TWA is specifically exacerbated by conditions such as left ventricular dysfunction and congestive heart failure. Accordingly, TWA is considered to be an appropriate parameter to evaluate cardiac electrical instability in SDB with CHF. Previous studies have demonstrated that SDB is associated with poor prognosis, including SCD in CHF patients. The exact mechanisms of the increased risk of ventricular tachyarrhythmias, however, have not been elucidated in CHF patients with SDB. Gami et al found that patients with SDB had a significantly higher peak sudden death rate during sleep than patients without SDB. Similarly, Serizawa et al recently suggested that SDB-induced fatal ventricular tachyar-
Figure 2. Heart rate variability (HRV; power spectral analysis). (A, B) Low-frequency (LF) and high-frequency (HF) powers of HRV were significantly lower in Group A (respiratory disturbance index [RDI] ≥ 20 events/h) than in Group B (RDI < 20 events/h) across a 24-h period (P<0.05). (C) LF to HF ratio was not different between the 2 groups.

Figure 3. Heart rate variability (time-domain analysis). Standard deviation of all R-R intervals (SDNN) and standard deviation of the 5-min mean R-R intervals (SDANN) were significantly lower in Group A (respiratory disturbance index [RDI] ≥ 20 events/h) than in Group B (RDI < 20 events/h; P<0.05).
Mechanisms of Ventricular Tachyarrhythmias in CHF Patients With SDB

It is generally accepted that CHF patients are more likely to develop ventricular tachyarrhythmias and SCD because ventricular electrophysiological and structural remodeling occurs as a result of heart failure. The impairment of autonomic nervous control induced by SDB with CHF is thought to in-
creasingly promote cardiac electrical instability and increase the frequency of VPCs and VT across a 24-h period. The most likely explanation is that TWA is exacerbated by catecholamine excess, and ventricular ectopic beats are increased by the impaired oscillation of sympathetic or vagal activity in CHF patients. These abnormalities induced by SDB contribute to the formation of the arrhythmogenic substrates of ventricular tachyarrhythmias, and SDB with CHF leads to fatal ventricular arrhythmia and SCD.

Study Limitations

There were some limitations in the present study. First, the patients with atrial fibrillation were excluded because the association between manifestation of TWA and atrial fibrillation remains uncertain. Also, SDB has been shown to induce atrial fibrillation. Second, the frequency of VPCs and VT across a 24-h period. The most likely explanation is that TWA is exacerbated by catecholamine excess and ventricular ectopic beats are increased by the impaired oscillation of sympathetic or vagal activity.

Clinical Implications

If SDB with CHF is related to the appearance of ventricular tachyarrhythmias, SDB therapy may be effective against the appearance of ventricular tachyarrhythmias. The impairment of autonomic nervous control induced by SDB can be improved by oxygen therapy, continuous positive airway pressure and adaptive servo-ventilation. Thus, these therapies might be useful for the prevention of ventricular tachyarrhythmias. Further investigation of the association between CHF patients with SDB and the risk for ventricular tachyarrhythmias will lead to the development of effective therapeutic strategies.

Conclusion

SDB may impair ventricular repolarization and modulate the autonomic nervous system across a 24-h period, resulting in life-threatening ventricular tachyarrhythmias and SCD in CHF patients.

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Disclosures

None.

References


T-Wave Alternans and Sleep Apnea


