CLINICAL STUDY

Variation of Electrocardiogram Features Across Sleep Stages in Healthy Controls and in Patients with Sleep Apnea Hypopnea Syndrome

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Summary
Sleep apnea hypopnea syndrome (SAHS) is an independent risk factor for various cardiovascular diseases. Electrocardiogram (ECG) features such as the RR, PR, QT, QTc, Tpe intervals and the Tpe/QT, Tpe/QTc ratios are used to predict and study cardiovascular diseases. It is not clear whether regular patterns of PR and Tpe-related features across sleep stages exist in SAHSs or healthy controls nor whether sleep stages affect the short- and long-range influences of respiratory events on ECG indices. We enrolled 36 healthy controls and 35 patients with SAHS in our study and analyzed the abovementioned ECG features. In the healthy controls, a significant regularity existed in these indices across sleep stages, which were weakened or disturbed in the patient group, especially the Tpe-related features. The differences between the patients and healthy controls were generally consistent across all sleep stages: patients had smaller RR, PR, QT and Tpe/QTc values, but larger QTc, Tpe and Tpe/QT values. After filtering the short-range influence of respiratory events, the differences in most features remained highly significant, except the QT interval. In the patient group, respiratory events decreased RR and PR intervals in most sleep stages and increased the Tpe-related features' values in deep sleep stages. These results may aid in the study of the relationships among SAHS, sleep disorders and cardiovascular diseases.

Key words: Pathological respiration, Cardiac electrical activity, Cardiovascular diseases, Ventricular arrhythmias, Autonomic nervous system

Sleep apnea hypopnea syndrome (SAHS) is characterized by repeated episodes of apnea or hypopnea lasting at least 10 s each and occurring at least 5 times an hour during sleep.1-3) SAHS is a typical clinical symptom of several chronic diseases, such as intermittent hypoxemia, insomnia, type 2 diabetes and metabolic dysfunction4 and an independent risk factor for cardiovascular diseases, most notably cardiac arrhythmias (e.g., ventricular arrhythmias as predictors of sudden cardiac death), coronary artery disease and myocardial infarction.5-7)

Electrocardiogram (ECG) features are used to predict and study cardiovascular diseases. A strong correlation exists between elevated heart rate and cardiovascular morbidity and mortality,8,9 and heart rate variability can be used to evaluate autonomic nervous system dysfunctions.9 The PR interval reflects atrial and atrioventricular nodal conduction.10 Additionally, the recognition of atrial fibrillation is essential to reduce the risk of death.11 Prolongation of the PR interval is a predictor of atrial fibrillation, which is the most common sustained arrhythmia and is independently associated with an increased risk of stroke, heart failure, dementia and death.12,13 Myocardial repolarization can be evaluated based on the QT and QTc intervals, and the inhomogeneity of ventricular repolarization is associated with ventricular arrhythmias.14 An abnormal QT/RR relationship may also be found during different sleep stages after myocardial infarction.15 The Tpe interval, a measurement of transmural dispersion of ventricular repolarization, when prolonged, represents a period of potential vulnerability to ventricular arrhythmias.16 Tpe/QT and Tpe/QTc ratios obtained from the ECG signal are also used as the indices of ventricular arrhythmogenesis.14

Previous studies have identified the impact of SAHS on ECG features. Prolong QTc intervals have been found in SAHS patients without hypertension and this prolongation may reflect the severity of SAHS.13 Baumert

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et al. suggested that the beat to beat variability of the QT interval is an indicator of the severity of obstructive sleep apnea. In addition, rising Tpe intervals, and Tpe/QT and Tpe/QTc ratios are seen in patients with moderate to severe SAHS. Smith et al. reported that RR and QT intervals were significantly decreased during respiratory event-related arousals phases. Compared with the ECG features in spontaneous arousals, RR interval shortening and PR interval prolongation were found to be greater during respiratory-induced arousals. Maier et al. found that the impact of sleep apnea was more uniform with respect to ECG morphology than heart rhythm. And we have studied the impact of respiratory events on cardiac autonomic nervous system by heart rate variability analysis. These results reveal that the sleep disturbances caused by respiratory events have an impact on ECG features.

There may be several reasons for regularity of changes in ECG features during the sleep process. Nobel Prize winners Rosbash, Michael and Hall have contributed information to the molecular mechanisms of circadian rhythms in organisms. The sleep state exhibits rhythms such as alternating non-rapid eye movements (NREM) and rapid eye movements (REM) during whole sleep. Therefore, cyclical fluctuations across the sleep stages may also be found in ECG features. Additionally, the wake stage and REM sleep are dominated by sympathetic nervous system activity, whereas during NREM sleep (N1, N2, N3), the parasympathetic system dominates. Changing the balance of sympathetic and parasympathetic activities may cause cardiac electrical disturbances potentially seen in ECG features. There have not been consistent conclusions by researchers on QT interval patterns during sleep. Lanfranchi et al. found sleep-related QT interval changes in pre- and post-menopausal women, but Baumert et al. found that the sleep stage had no significant effect on QT variability.

However, there are some questions that remain to be answered: firstly, whether regular patterns of PR and Tpe-related features across sleep stages exist in both healthy subjects and patients with SAHS? Secondly, do sleep stages affect the ECG indices’ differences between healthy controls and patients and after separating out the short-range influence of respiratory events, whether these differences remain? Thirdly, in the patients group, how sleep stages affect the impact of respiratory events on these ECG indices? Thus, we systematically investigated the effect of sleep on ECG features in healthy controls and in patients with SAHS, and evaluated the regularity of ECG features during sleep stages. We also analyzed the impact of respiratory events on ECG features in different sleep stages. These results may provide clues to the relationships among SAHS, sleep disorders and some cardiovascular diseases.

Methods

Participants: We recruited 90 subjects aged between 20 and 60 years, including 45 patients with confirmed SAHS (apnea-hypopnea index, AHI > 30) and 45 healthy, age-matched controls. Before polysomnography (PSG) examinations, every participant underwent a medical examination and had been asked about their medical history. None of the participants had any record of cardiac or vascular diseases, epilepsy, insomnia or other sleep disorders, except for SAHS. At the time of the study, none of them took medication known to affect ECG features (e.g., I and III class antiarrhythmic, antihistaminic, psychotropic or antibiotic drugs). All subjects were recruited and tested in the Sleep-Disordered Breathing Center of the 6th Affiliated Hospital of Sun Yat-Sen University. This study was approved by the ethics committee of the aforementioned hospital and informed consent was obtained from all study participants.

Measurement and definitions: Overnight polysomnography (PSG) examinations were recorded using an Alice® 5 Diagnostics Sleep System (Philips Respironics, Amsterdam, Netherlands). Respiratory events and sleep stages were strictly scored by registered PSG technologists according to the guidelines of the American Academy of Sleep Medicine (AASM).

In patients with SAHS, 2 types of ECG segments were selected from the PSG recordings: (1) the ECG segments during respiratory events (RE), including obstructive sleep apnea, central sleep apnea, or hypopnea; and (2) those occurring during pure normal breathing (NB). The interval time between NB segments and RE segments was at least 30 seconds. We did not classify the ECG segments in the control group. The duration of RE ranged from 20 seconds - 60 seconds, and those of NB and ECG segments in the controls, were 30 seconds (an epoch for sleep stage scoring according to AASM).

Segments with ECG artifacts and obvious interference were not included in the data for analysis. In addition, we did not analyze the RE segment that occurred in different sleep stages. In patients with SAHS, we chose almost all of the RE and NB segments that met the inclusion criteria in each sleep stage (REM, N1, N2, N3). To balance the sample size, for every healthy control, we randomly selected approximately 40 ECG segments from each sleep stage.

ECG feature extraction: The sampling rate of the ECG signal was set as 500 Hz in the Alice® 5 Diagnostics Sleep System (Philips Respironics, Amsterdam, Netherlands). The cut-off frequency of high-pass filtering was set at 0.3 Hz and for low-pass filtering was set at 70 Hz. We performed a continuous 1-D Mexican hat wavelet transformation to remove the baseline drift. A difference threshold algorithm was adopted to detect the QRS complex and the R peaks.

In this study, the following 5 important points were marked in each ECG cycle, as shown in Figure 1:

- point R-peak: The maximum amplitude point of each ECG cycle, representing the peak of the R wave in the ECG cycle.
- point QRS-start: The first baseline point before the Q-peak (the minimum amplitude point before R-peak), representing the start of QRS complex.
- point T-peak: The maximum amplitude point after the R-peak, representing the peak of the T wave in ECG cycle.
- point T-end: The first point returning to the baseline after the T-peak, representing the end of T wave.
- point P-start: The first point of return back to baseline
before the P-peak (the maximum amplitude point before R-peak), representing the start of the P wave in the ECG cycle.

Seven features, defined in Table I, were extracted by a MATLAB (Version 2014b, Natick, USA) program for each ECG cycle, and the mean values were calculated for each ECG segment. To ensure accuracy, the 5 points were visually checked in a program for each ECG cycle.

Statistical analysis: Analysis of variance was chosen to verify the significant differences in the ECG features of the following comparisons: (1) the ECG feature characterizations among the 4 sleep stages in the control group and the SAHS group; (2) the ECG feature differences between healthy controls and patients with SAHS, and the ECG differences between healthy controls and NB in patients with SAHS after eliminating the short-range impact of RE; and (3) an analysis of the short-range impact of RE as a function of the differences in ECG features between NB and RE in the SAHS group.

Each feature was normalized from 0 to 1 using equation (1), except for the second comparison, which was used to explore the differences between groups. Our experimental data satisfied the normal distribution and passed homogeneity testing. The significance level was $P < 0.05$. The Bonferroni correction was applied in the first comparison, so the significance level was $P < 0.05/C^2$. These analyses were run on the IBM SPSS statistics software version 22.0 (SPSS Inc.; New York, USA). Data in the tables and figures are expressed as the mean ± standard error of the mean.

$$x^* = \frac{(x - x_{\text{min}})}{(x_{\text{max}} - x_{\text{min}})}$$

where $x^*$ represents a normalized value.

Results

Subject characteristics: In our study, 10 patients with SAHS were excluded. Three of them had body mass indices (BMI) > 35 kg/m² and four others had poor data recorded from all of the electrodes due to frequent movement. The total sleep time of three patients was less than 6 h. Nine subjects in the control group were removed. Four of them had BMI > 35 kg/m² and five others were rejected because their AHI > 5. Ultimately, the data from 35 subjects with a clinical diagnosis of SAHS (30 < AHI < 55) and 36 controls (AHI < 5) were analyzed. The demographic and polysomnographic parameters are listed in Table II. In total, 5,097 and 6,379 ECG segments from the control and SAHS groups (NB and RE types), respectively, were selected. For the SAHS group, the number of RE segments was less in N3 (640 RE segments) than other sleep stages, especially in N2 (1,128 RE segments). A detailed data distribution in the 4 sleep stages is shown in Table III.

Comparison results among four sleep stages: In the control group, most of the ECG features showed a significant difference across the sleep stages, which is shown in Figure 2A. In general, except PR and Tpe/QTc, the differences of the other features between REM sleep and relative deep sleep (N2 and N3 stages) were greater than those between REM sleep and the N1 stage. The RR, QT and QTc intervals in REM sleep were significantly different from those in all of the N-REM stages. The PR interval and the Tpe/QTc ratio in REM sleep also had the largest and smallest values, respectively, but those in the N1 stage had the opposite extreme values. In addition, the RR, QT and Tpe intervals and the Tpe/QT ratio had the largest or smallest values in the N2 stage. The regularity of ECG features in patients with
SAHS were significantly less obvious than that of the normal controls, especially for the Tpe-related features, which is shown in Figure 2B. The RR and QT intervals still showed a similar trend and a significant difference across the sleep stages. The PR and QTc intervals and the Tpe/QTc ratio had certain significant differences which were similar between the SAHS and control groups.

### Healthy controls versus SAHS and healthy controls versus NB in SAHS:

We tested the differences between the healthy controls and SAHS groups in all sleep stages. From the results shown in Figure 3, sleep stages had little effect on these comparisons, and the results in all sleep stages were almost the same. Patients with SAHS had smaller RR, PR, QT and Tpe/QTc values, but larger QTc, Tpe and Tpe/QT values. Almost all of the comparisons showed significant differences. The PR in N1 stage, Tpe in REM sleep, Tpe/QT in N1 stage, Tpe/QTc in N1, and N2 and REM stages did not show significant differences.

### Discussion

From our results we made some general conclusions. First, a significant correlation between sleep stages and cardiac activity existed in healthy controls. In patients with SAHS, this correlation decreased to some extent. Second, the differences between healthy controls and patients with SAHS were consistent in all sleep stages, and the differences in most features remained highly significant in the comparison between healthy controls and NB segments in patients, except for the QT interval. Third, in the SAHS group, RE decreased RR and PR in most sleep stages, and increased Tpe, Tpe/QT, Tpe/QTc in the N2 and N3 stages. We also observed a decrease in Tpe/QT in the N1 stage, an increase in QT in N2 stage and a decrease in QTc in REM stage when RE happened.

### Comparison results between NB and RE type:

In the SAHS group, as shown in Figure 4, the comparisons that showed significant differences exhibited basically consistent results, except the Tpe/QT in N1 stage. In general, the occurrence of RE decreased RR and PR in most sleep stages, and increased Tpe, Tpe/QT, Tpe/QTc in the N2 and N3 stages. We also observed a decrease in Tpe/QT in the N1 stage, an increase in QT in N2 stage and a decrease in QTc in REM stage when RE happened.

### ECG features

<table>
<thead>
<tr>
<th>ECG features</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (ms)</td>
<td>The interval of two adjacent ECG cycles.</td>
</tr>
<tr>
<td>PR (ms)</td>
<td>The interval which is measured from the start of the P wave to the start of the QRS complex.</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>The interval which is measured from the start of the QRS complex to the end of the T wave.</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>The interval which is calculated using Bazett’s formula $QTc = QT\sqrt{RR}$.</td>
</tr>
<tr>
<td>Tpe (ms)</td>
<td>The interval between the peak and the end of the T wave.</td>
</tr>
<tr>
<td>Tpe/QT</td>
<td>The ratio of Tpe and QT.</td>
</tr>
<tr>
<td>Tpe/QTc</td>
<td>The ratio of Tpe and QTc.</td>
</tr>
</tbody>
</table>

### Table II. Anthropometric Data of Healthy Controls and Patients with SAHS in PSG

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n = 36)</th>
<th>SAHS (n = 35)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>37.2 ± 10.5</td>
<td>42.2 ± 13.8</td>
<td>0.138</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>23/11</td>
<td>21/12</td>
<td>/</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>24.82 ± 2.62</td>
<td>26.85 ± 3.18</td>
<td>0.052</td>
</tr>
<tr>
<td>AHI (events/hour), mean ± SD</td>
<td>1.68 ± 1.52</td>
<td>43.25 ± 9.72</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>TST (minutes), mean ± SD</td>
<td>466.24 ± 35.29</td>
<td>438.74 ± 31.56</td>
<td>0.018*</td>
</tr>
<tr>
<td>ODI (times/hour), mean ± SD</td>
<td>2.10 ± 1.53</td>
<td>45.23 ± 12.04</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>SpO2 minutes, %</td>
<td>91.16 ± 2.65</td>
<td>76.68 ± 7.24</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>SpO2 mean, %</td>
<td>96.67 ± 0.94</td>
<td>94.58 ± 1.91</td>
<td>&lt; 0.001***</td>
</tr>
</tbody>
</table>

PSG indicates polysomnography; SD, standard deviation; BMI, body mass index; AHI, apnea hypopnea index; ESS, Epworth sleepiness scale; TST, total sleep time; ODI, oxygen desaturation index ≥ 3%; SpO2 min and mean, minimum and mean arterial oxygen saturation; and #, using variance (ANOVA) analysis. ***P < 0.001, **P < 0.01, *P < 0.05.

### Table III. The Number of ECG Segments Analyzed across Sleep Stages in Healthy Controls and Patients with SAHS

<table>
<thead>
<tr>
<th>Sleep stage</th>
<th>Control (n = 36)</th>
<th>SAHS (n = 35)</th>
<th>RE</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM</td>
<td>1274</td>
<td>1508</td>
<td>687</td>
</tr>
<tr>
<td>N1</td>
<td>1285</td>
<td>1585</td>
<td>747</td>
</tr>
<tr>
<td>N2</td>
<td>1271</td>
<td>1884</td>
<td>756</td>
</tr>
<tr>
<td>N3</td>
<td>1267</td>
<td>1402</td>
<td>762</td>
</tr>
<tr>
<td>All stages</td>
<td>5097</td>
<td>6379</td>
<td>2952</td>
</tr>
</tbody>
</table>

SAHS indicates sleep apnea/hypopnea syndrome; NB, normal breathing; RE, respiratory event; and REM: rapid eye movement.

After separating out the short-range influence of RE, most features showed highly significant differences, except for QT interval which did not show a significant difference in any sleep stage. The typical values of ECG features are shown in Table IV.
Figure 2. The significant differences between ECG features in the control group and the SAHS group. A: The difference in control group. B: The difference in SAHS group. *P < 0.05/6; **P < 0.01/6; ***P < 0.001/6 (after Bonferroni correction).

nance mainly due to the enhancement of parasympathetic nervous system activity. This parasympathetic dominance may be important for cardiovascular health. The autonomic activity in REM sleep showed greater similarity to that during wakefulness and it was considerably variable. Shortening of the RR interval likely reflects parasympathetic withdrawal and/or increased sympathetic tone in the sinoatrial node, and a shortened PR interval may indicate the same ANS activity to the atrio-ventricular node. Shortening of the QT interval is likely a reflection of increased sympathetic outflow to the ventricular myocardium. It has been reported that altered cardiac autonomic activity and increased sympathetic activity are closely related to the heterogeneity of ventricular repolarization and an increased risk of ventricular arrhythmias.

The Tpe interval and the Tpe/QT ratio are good indicators of transmural dispersion of ventricular repolarization. Sicouri and Antzelevitch reported an association between ventricular arrhythmogenesis and Tpe prolongation, which has been associated with sudden cardiac death. Additionally, left ventricular diastolic dysfunction is considered the main cause of heart failure with preserved ejection fraction. The Tpe interval and the Tpe/QT ratio were greater during light sleep in our study, which showed that sleep inefficiency may be associated with ventricular arrhythmogenesis. In addition, increased N3 sleep reduces cardiac autonomic activity alterations and reduces the risk of cardiovascular diseases.

In patients with SAHS, the values for RR, PR, QT and QTc were still regular across the sleep stages, but there was a slight decrease in the significance. It is well known that patients with SAHS have increases in sympathetic activity and reduced baroreflex sensitivity, which precludes the timely enhancement of parasympathetic activity. Disorders of the parasympathetic/sympathetic balance may be responsible for this reduced significance. It is worth noting that Tpe, Tpe/QT and Tpe/QTc no longer showed regularity in patients with SAHS, which means that Tpe and Tpe/QT did not decrease during deep sleep like they did in healthy controls. This may increase the risk of ventricular arrhythmogenesis in patients with SAHS.

The comparisons between the healthy controls and patients with SAHS and between healthy controls and NB segments in patients indicated that the differences in most features, except the QT interval, exist, and are basically
Table IV. Values of ECG Features in Healthy Controls and SAHS Groups during the Whole Night

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 36)</th>
<th>SAHS (n = 35)</th>
<th>NB in SAHS (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (ms)</td>
<td>873.26 ± 122.70</td>
<td>835.53 ± 95.87***</td>
<td>828.13 ± 94.06***</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>413.14 ± 19.55</td>
<td>410.90 ± 31.85*</td>
<td>413.04 ± 30.48</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>428.55 ± 23.06</td>
<td>438.92 ± 22.94***</td>
<td>439.59 ± 21.56***</td>
</tr>
<tr>
<td>PR (ms)</td>
<td>176.28 ± 39.99</td>
<td>165.37 ± 25.10***</td>
<td>165.39 ± 27.58***</td>
</tr>
<tr>
<td>Tpe (ms)</td>
<td>88.86 ± 8.59</td>
<td>90.86 ± 14.93***</td>
<td>91.31 ± 14.99***</td>
</tr>
<tr>
<td>Tpe/QT</td>
<td>0.215 ± 0.025</td>
<td>0.220 ± 0.038***</td>
<td>0.220 ± 0.040***</td>
</tr>
<tr>
<td>Tpe/QTc</td>
<td>0.207 ± 0.024</td>
<td>0.205 ± 0.032*</td>
<td>0.206 ± 0.033</td>
</tr>
</tbody>
</table>

ECG indicates electrocardiogram; SAHS, sleep apnea/hypopnea syndrome; NB, normal breathing; REM, rapid eye movement. Data are described as mean ± SD. Differences were presented in values of Control group compared to SAHS group and Control group compared to NB in SAHS patients in the whole night. ***P < 0.001, **P < 0.01, *P < 0.05.

In the SAHS group, REM had greater impact on PR and Tpe-related features in the relatively deep sleep stages. The ECG features during REM also showed a tendency to light sleep. These results were consistent with the ANS regulation and sleep characteristics in patients with SAHS. It is well known that the apnea/hypopnea-related hypoxia induces elevations in sympathetic activity in patients with SAHS and that the cardiopulmonary consistent, in all sleep stages, which means the differences of most features are long-range rather than associated with a particular sleep stage. These results may support that fact that changes in the cardiac structures exist in patients with SAHS. It should be mentioned that although the results of Tpe and Tpe/QT ratio were the same as the research of Kilicaslan F, et al., the result of Tpe/QTc ratio is different. Many factors may affect on Tpe value, such as ethnic group, the position of the EEG lead, sex, age, or physiological condition. The results of the difference in Tpe/QTc ratio between groups requires further study.
Several studies have shown that SAHS is related to an increased risk of ventricular arrhythmias.\(^{40-42}\) The RR, PR, QT and QTc intervals are known to be affected by ANS modulation.\(^{46}\) QT, QTc, Tpe, Tpe/QT and Tpe/QTc are all related to ventricular repolarization.\(^{13}\) The results in this study show that there may be ventricular repolarization heterogeneity in patients with SAHS, which increases the risk of ventricular arrhythmias.\(^{13}\) We confirmed that the sleep state influenced ECG features, which may reveal a correlation between sleep disorders and cardiovascular diseases.

**Study limitations:** There are limitations to this study. Micro-arousal appears to exert a strong effect on sympathetic activity (e.g., heart rate and blood pressure) in patients with SAHS.\(^{43}\) In this study, respiratory event-related micro-arousal had been considered as part of the impact of RE. We were not able to distinguish between the respiratory event itself and the micro-arousal it caused. In addition, the parameters representing the severity of the RE, such as its duration or the level of associated SpO\(_2\) desaturation in each RE, were not included in this study.

**Conclusions**

The present study indicated that a significant regularity exists in ECG features across sleep stages. In patients with SAHS, this regularity is weakened or disturbed, which is predominantly observed in Tpe-related ECG features. The differences between the patients and healthy controls were basically consistent in every sleep stage; however, the PR in N1 stage; Tpe in REM sleep; Tpe/QT in N1 stage; and Tpe/QTc in N1, N2, REM stages did not show significant differences. REs had a more significant impact in deep sleep, which when coupled with the characteristics of patients with SAHS resulted in a tendency to light sleep during REs. Our results may provide evidence of the pathophysiological mechanisms between chronic sleep disturbances, such as SAHS, and cardiovascular diseases. From our results of ECG features, the increased prevalence of ventricular arrhythmias may be associated with increased ventricular repolarization heterogeneity and disturbed autonomic control of the cardiovascular system. These influences can evolve into structural changes in patients with SAHS.

**Disclosures**

**Conflicts of interest:** None.

**References**

et al