Nocturnal heart rate variability in obstructive sleep apnea syndrome: effect of automatic positive airway pressure
Iman H. Galal

Background The cyclic hypoxemia and arousal characteristic of obstructive sleep apnea (OSA) causes dysregulation in the autonomic nervous system (ANS) resulting in cardiac rhythm disturbances. Positive airway pressure therapy in OSA results in ANS regulation. This study aimed at investigating the effects of automatic positive airway pressure (APAP) over nocturnal heart rate variability (HRV) in OSA and to further identify this effect in hypertensive versus normotensive OSA patients.

Patients and methods A total of 25 patients (four with moderate and 21 with severe OSA) were included (male/ female: 22/3; mean age 49.5±15.69 years). Patients were subdivided into two groups: 13 (52%) normotensive and 12 (48%) hypertensive patients. Two overnight sleep studies with polysomnographic-based nocturnal HRV were carried out: the first study was diagnostic, whereas the second one was an APAP titration study.

Results APAP results in significant reduction in most of time and frequency-domain indexes [except for standard deviation of average NN interval (SDANN, P=0.106), HRV triangular index (HRV_TI, P=0.057), and high-frequency power (HF, P=0.109)]; RR interval (P=0.024), standard deviation of all RR intervals (SDNN, P=0.012), mean of the standard deviation of all RR intervals for all 5-min segments (SDNN_Index, P=0.009), square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD, P=0.002), number of pairs of adjacent RR intervals differing by more than 50 ms in the entire analysis interval (NN50 count, P=0.004), NN50 count divided by the total number of all RR intervals (%NN50, P=0.001), total power (P=0.010), very low-frequency power (VLF, P=0.018), low-frequency power (LF, P=0.008), and low-frequency/high frequency (LF/HF, P=0.012). HRV did not differ significantly between the two groups either before or after APAP; however, most of the time-domain and frequency-domain HRV indexes decreased significantly with APAP in the hypertensive group.

Conclusion Nocturnal HRV improved with APAP in OSA. APAP was more beneficial in terms of ANS regulation in OSA patients with coexisting hypertension than normotensive OSA patients.

Keywords: automatic positive airway pressure, frequency domain, heart rate variability, obstructive sleep apnea syndrome, time domain

Introduction Positive airway pressure (PAP) is the standard treatment for patients with moderate-to-severe obstructive sleep apnea (OSA) – a sleep-related breathing disorder (SRBD) characterized by episodic complete or partial upper airway occlusion during sleep [1]. Over the past few years, the relationship between SRBD and cardiac arrhythmias have been thoroughly investigated [2–7]. Previous studies have shown that obstructive sleep apnea syndrome (OSAS) predisposes to clinically significant nocturnal impairment of the cardiac autonomic function, and such impairment correlated with the severity of OSAS [8–11]. The respiratory event-related cyclic hypoxemia and arousal characteristic of OSA causes dysregulation in the autonomic nervous system (ANS) in the form of enhanced sympathetic activity, and such impairment is thought to be the substrate necessary for heart rate variability (HRV) and consequently the development of cardiac arrhythmias [12–19]. HRV, the oscillation in the intervals separating consecutive heart beats, has gained importance as a noninvasive research and clinical tool for indirect quantitative and qualitative assessment of the cardiac autonomic function in both health and disease [20]. HRV is mediated by three main mechanisms including vagal feedback from pulmonary stretch receptors, central medullary coupling respiratory and cardiovagal neurons, as well as the arterial baroreflex [21].

It is well known that OSAS in an independent risk factor for the development of systemic hypertension [22]. Altered autonomic control in the form of sympathetic activation represents a possible mechanism linking OSAS and hypertension [23].

Nasal continuous positive airways pressure therapy in OSA results in ANS regulation with subsequent improvement in HRV and nocturnal arrhythmias [24,25].

In view of the above, this study was undertaken in an attempt to investigate the effect of automatic positive

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airway pressure (APAP) on nocturnal HRV in patients with OSA and to further identify this effect in hypertensive compared with normotensive OSA patients.

Patients and methods

Study population

This prospective study included 25 randomly selected patients with polysomnographically (PSG) confirmed OSA. Participants were selected from among patients referred to the sleep laboratory with symptoms suggestive of SRBD. All included patients were newly diagnosed with OSAS and were never treated previously with PAP therapy. Patients were further subdivided into two groups based on their blood pressure values: the first group comprised 13 (52%) normotensive patients, whereas the second group comprised 12 (48%) hypertensive patients. All patients underwent two consecutive overnight sleep studies (PSG): the first study was diagnostic for OSA, whereas the second was a titration sleep study using APAP. Exclusion criteria were as follows: patients with atrial fibrillation, frequent ventricular premature beats, congestive heart failure, coronary artery disease, and stroke. Verbal consent was obtained from patients, and the study was approved by the Local Ethics Committee of the Faculty of Medicine at Ain Shams University.

Polysomnography

Nocturnal, full-night PSG in the sleep laboratory starting from 10 p.m. to 6 a.m. was performed for all patients using a computerized system (N4000 Embla; Somnologica, Reykjavik, Iceland), including electroencephalogram, submental and anterior tibial electromyogram, oxygen saturation, ECG, inductance plethysmography of the chest and abdomen, nasal pressure sensor, and oronasal thermister monitoring. The recording was scored manually according to standard guidelines [26]. The apnea–hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of total sleep time (TST). The threshold for diagnosis of OSA was set at an AHI of at least 5, and the severity of OSA was arbitrarily defined by the cutoff levels of AHI: of at least 5 to less than 15 episodes/h of TST for mild, of at least 15 to less than 30 episodes/h of TST for moderate, and of at least 30 episodes/h of TST for severe OSA [27].

Automatic positive airway pressure titration study

The present study was performed during a standard, attended, overnight PSG in the sleep laboratory using an APAP device (AutoSet; ResMed, Sydney, Australia) according to the recommendations of the American Academy of Sleep Medicine [28]. The AutoSet device is a computer-based PAP system that automatically modulates mask pressure in response to snoring, airflow limitation, or the presence of either apneas or hypopneas. The minimum pressure was set at 4 cmH2O, whereas the maximum pressure was set at 20 cmH2O according to the sleep medicine Task Force guidelines [29]. Only patients with successful APAP titration were included in the present study. The criteria for unsuccessful titration were as follows: TST of less than 4 h; TST in the supine position of less than 1 h; rapid eye movement (REM) sleep duration of less than 10 min [30]; excessive overshoots of delivered pressure associated with sleep disruption [31]; insufficient correction of obstructive events, not allowing us to recognize a therapeutic pressure; and median nocturnal air leak of more than 0.4 l/s [32,33].

Heart rate variability analysis

Nocturnal ECG signals acquired by the PSG were digitalized. The analysis was carried out only for normal beats. HRV was evaluated using both time-domain and frequency-domain indexes. Time-domain indexes included the average length between each QRS complex (average RR interval), the standard deviation of all RR intervals (SDNN), the mean of the standard deviation of all RR intervals for all 5 min segments (SDNN index), the square root of the mean of the sum of squares of differences between adjacent RR intervals (RMSSD), the number of pairs of adjacent RR intervals differing by more than 50 ms in the entire analysis interval (NN50 count), the NN50 count divided by the total number of all RR intervals (NN50 of total heart rate (HR) (%)), standard deviation of average NN interval (SDANN), and the total number of RR intervals divided by the maximum height of the histogram excluding boundaries (HRV triangular index). In the frequency-domain analysis, the power was calculated for very low-frequency (VLF, 0.0033–0.04 Hz), low-frequency (LF, 0.04–0.15 Hz), and high-frequency bands (HF, 0.15–0.4 Hz) as well as the LF/HF ratio [20].

Statistical analysis

All statistical data analyses were carried out using the statistical package for social sciences software (SPSS for Windows, version 17.0; SPSS Inc, Chicago, Illinois, USA). Continuous numerical data are expressed as mean±SD, whereas categorical data are expressed as numbers and percentages. Normality distribution was tested using the Shapiro–Wilks test. Comparison between paired indexes was performed
using the paired \( t \)-test for parametric normally distributed data, and Wilcoxon's signed-rank test was used for nonparametric skewed data. Statistical significance was set at \( P \) values less than 0.05.

**Results**

A total of 25 (22 males and three females) patients with OSAS with a mean age of 49.52±15.69 years and mean BMI of 39.14±8.00 kg/m\(^2\) were included in this study; four patients had moderate OSAS, whereas the remaining 21 patients had severe OSAS. Patients with incomplete data were excluded. Table 1 shows the characteristics of all included patients as well as comparisons between different indexes before and during APAP. Several sleep indexes differed significantly during APAP: stages N1 and N2 nonrapid eye movement sleep (NREM, \( P=0.000 \)), stage N3 NREM sleep (\( P=0.000 \)), REM stage (\( P=0.002 \)), AHI (\( P=0.000 \)), oxygen desaturation index (\( P=0.000 \)), snoring index (\( P=0.000 \)), arousal index (\( P=0.000 \)), and REM latency (\( P=0.001 \)). Both baseline and maximum HR decreased significantly with APAP (\( P=0.011 \) and 0.024, respectively). All time-domain indexes [except for SDANN (\( P=0.106 \)) and HRV TI (\( P=0.057 \))] differed significantly during APAP: RR interval (\( P=0.024 \)), SDNN (\( P=0.012 \)), SDNN index (\( P=0.009 \)), RMSSD (\( P=0.002 \)), NN50 count (\( P=0.004 \)), and %NN50 of total HR (\( P=0.001 \)). All frequency-domain indexes [except for average HF power (\( P=0.109 \))] differed significantly during APAP: average total power (\( P=0.010 \)), average VLF power (\( P=0.018 \)), average LF power (\( P=0.008 \)), and LF/HF ratio (\( P=0.012 \)).
All time-domain and frequency-domain indexes were compared before and during APAP in both normotensive and hypertensive groups (Table 2). In the normotensive group, most of the time-domain and frequency-domain indexes did not differ significantly \((P>0.05)\) except for the RR interval \((P=0.015)\), average total power \((P=0.028)\), and average VLF power \((P=0.013)\). As for the hypertensive group, most of the time-domain and frequency-domain indexes differed significantly except for the RR interval \((P=0.643)\), SDANN \((P=0.695)\), and average VLF power \((P=0.109)\).

On comparing all time-domain and frequency-domain indexes before APAP in both groups, only SDNN index differed significantly \((P=0.04)\), whereas all other time-domain and frequency-domain indexes did not differ significantly \((P>0.05)\). The same comparison during APAP showed no significant difference \((P>0.05)\) between the two groups with regard to all time-domain and frequency-domain indexes (Table 3).

### Discussion

Spectral analysis for nocturnal HRV in OSA patients before APAP use showed an increase in all frequency-domain indices, demonstrating both sympathetic and vagal activation. In addition, time-domain indexes suggestive of parasympathetic activation (namely

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#### Table 2 Heart rate variability before and during automatic positive airway pressure in normotensive and hypertensive obstructive sleep apnea syndrome patients

| Variables                  | Normotensive OSAS \((N=13)\) | Hypertensive OSAS \((N=12)\) |
|----------------------------|-------------------------------|-------------------------------|
| Before APAP                | During APAP                   | Before APAP                   | During APAP                   |
| RR interval (ms)           | 825.08±111.88                 | 887.62±94.59                  | 898.67±94.59                  | 907.75±136.77                  | 0.643 |
| SDNN (ms)                  | 100.92±52.39                  | 84.62±23.78                   | 127.83±60.27                  | 106.50±70.25                   | 0.034 |
| SDNN index (ms)            | 72.46±52.69                   | 57.92±21.53                   | 110.08±65.53                  | 81.33±76.24                    | 0.012 |
| RMSSD (ms)                 | 60.00±32.34                   | 50.31±24.83                   | 116.00±112.60                 | 89.83±118.98                   | 0.005 |
| NN50 count                 | 4708.92±3855.97               | 3624.15±3226.32               | 6113.42±3814.18               | 2753.17±3568.50                | 0.008 |
| NN50 of total HR (%)       | 15.57±14.43                   | 11.89±10.39                   | 23.53±15.95                   | 10.19±14.07                    | 0.000 |
| SDANN (ms)                 | 88.46±40.17                   | 65.38±30.05                   | 161.50±280.14                 | 77.83±49.07                    | 0.695 |
| HRV TI                     | 17.77±8.55                    | 16.38±4.81                    | 19.58±4.60                    | 15.00±5.12                     | 0.002 |
| Average total power (ms²)  | 17311.54±15853.91             | 10043.85±3725.33              | 14147.17±7780.26              | 9446.58±3101.66                | 0.026 |
| Average VLF power (ms²)    | 11596.92±12409.25             | 5969.15±3056.24               | 8474.67±7628.13               | 5688.58±3409.62                | 0.109 |
| Average LF power (ms²)     | 4188.62±3773.69               | 2562.54±1009.77               | 3506.17±1454.63               | 2045.33±621.89                  | 0.005 |
| Average HF power (ms²)     | 1352.08±550.50                | 1354.54±720.15                | 1804.50±1058.98               | 1428.33±1250.37                | 0.034 |
| LF/HF ratio                | 3.23±2.08                     | 2.22±1.24                     | 2.51±1.46                     | 1.99±1.03                      | 0.043 |

APAP, automatic positive airway pressure; HF, high frequency; HR, heart rate; HRV TI, heart rate variability triangular index; LF, low frequency; NN50, the number of interval differences of successive NN intervals greater than 50 ms; OSAS, obstructive sleep apnea syndrome; RMSSD, square root of the mean squared differences of successive NN intervals; SDANN, standard deviation of average NN interval; SDNN, standard deviation of NN interval; VLF, very low frequency.

#### Table 3 Heart rate variability in normotensive versus hypertensive obstructive sleep apnea syndrome patients before and during automatic positive airway pressure

| Variables                  | Before APAP \((N=25)\) | During APAP \((N=25)\) |
|----------------------------|-------------------------|-------------------------|
|                           | Normotensive \((n=13)\) | Hypertensive \((n=12)\) |
|                           | Before APAP             | During APAP             | P             |
| RR interval (ms)           | 825.08±111.88           | 898.67±94.59            | 0.90          | 887.62±75.93 | 907.75±136.77 | 0.650 |
| SDNN (ms)                  | 100.92±52.39            | 84.62±23.78             | 0.077         | 127.83±60.27 | 106.50±70.25 | 0.574 |
| SDNN index (ms)            | 72.46±52.69             | 57.92±21.53             | 0.04          | 57.92±21.53 | 81.33±76.24 | 0.574 |
| RMSSD (ms)                 | 60.00±32.34             | 50.31±24.83             | 0.152         | 50.31±24.83 | 89.83±118.98 | 0.574 |
| NN50 count                 | 4708.92±3855.97         | 3624.15±3226.32         | 0.320         | 3624.15±3226.32 | 2753.17±3568.50 | 0.406 |
| NN50 of total HR (%)       | 15.57±14.43             | 11.89±10.39             | 0.168         | 11.89±10.39 | 10.19±14.07 | 0.347 |
| SDANN (ms)                 | 88.46±40.17             | 65.38±30.05             | 0.936         | 65.38±30.05 | 77.83±49.07 | 0.894 |
| HRV TI                     | 17.77±8.55              | 15.00±5.12              | 0.521         | 15.00±5.12 | 15.00±5.12 | 0.492 |
| Average total power (ms²)  | 17311.54±15853.91       | 10043.85±3725.33        | 0.936         | 10043.85±3725.33 | 9446.58±3101.66 | 0.669 |
| Average VLF power (ms²)    | 11596.92±12409.25       | 5969.15±3056.24         | 0.538         | 5969.15±3056.24 | 5688.58±3409.62 | 0.830 |
| Average LF power (ms²)     | 4188.62±3773.69         | 2562.54±1009.77         | 0.852         | 2562.54±1009.77 | 2045.33±621.89 | 0.141 |
| Average HF power (ms²)     | 1352.08±550.50          | 1354.54±720.15          | 0.320         | 1354.54±720.15 | 1428.33±1250.37 | 0.611 |
| LF/HF ratio                | 3.23±2.08               | 2.22±1.24               | 0.406         | 2.22±1.24 | 1.99±1.03 | 0.625 |

APAP, automatic positive airway pressure; HF, high frequency; HR, heart rate; HRV TI, heart rate variability triangular index; LF, low frequency; NN50, the number of interval differences of successive NN intervals greater than 50 ms; OSAS, obstructive sleep apnea syndrome; RMSSD, square root of the mean squared differences of successive NN intervals; SDANN, standard deviation of average NN interval; SDNN, standard deviation of NN interval; VLF, very low frequency.
RMSSD and %NN50 of total HR) were predominantly and significantly elevated before APAP, raising the assumption that OSAS can induce parasympathetic activation. Our findings of dual sympathetic and vagal activation in OSAS is not surprising, as other previous studies hypothesized that the repetitive upper airway collapse during sleep characteristic for OSAS causes initial vagal stimulation followed by abrupt sympathetic activation caused by hypoxemia and hypercapnia-related chemoreceptor stimulation [8,34].

On comparing all nocturnal HRV indexes before and during APAP, only SDANN and HRV TI time-domain indexes as well as HF power frequency-domain variables did not decrease significantly, suggesting that the reduction in sympathetic activity was more pronounced than that in vagal stimulation among OSAS patients in general, whether normotensive or hypertensive. A study by Karasulu et al. [35] using APAP reported that all time-domain indexes did not decrease significantly during APAP, whereas some frequency-domain indexes such as HF, LF, and VLF power decreased significantly on APAP, thus confirming the results of the present study regarding the reduction in both sympathetic and parasympathetic autonomic activities with APAP. The partial discrepancy between the results of both studies with regard to the time-domain indexes can be attributed to the difference in the type of APAP used in both studies; each APAP device has its own algorithm. The algorithm applied by the APAP device used in this study allows automatic increase or decrease in mask pressure in response to snoring, specific changes in inspiratory airflow contour morphology, or the presence of apnea or hypopnea in an attempt to restore complete airway patency. Patients with OSAS showed elevated nocturnal parasympathetic tone, as expressed by the higher values of %NN50 of total HR, RMSSD, and HF power, which reduced significantly with APAP, suggesting that APAP treatment in OSAS restores normal ANS activity. Chrysostomakis et al. [36] reported similar results following 2 months of treatment with CPAP. Moreover, a number of studies have also reported on the reduction in sympathetic activity in OSA patients on nasal continuous positive airways pressure [37–39].

A previous study conducted by the same author ([9]) on OSAS patients in an attempt to characterize the changes in nocturnal HRV and to further investigate the correlation between these changes and the severity of OSA results revealed clinically significant nocturnal impairment of the HRV mainly through spectral analysis and to a lesser extent through time-domain indexes, and such impairment correlated with the severity of the disease.

The findings of the present study showed no significant differences in both time-domain and frequency-domain indices of HRV between the hypertensive and normotensive groups either before or during APAP. Although only the SDNN time-domain index was significantly higher before APAP among the hypertensive group compared with the normotensive group, it is noteworthy that in this study spectral analysis of HRV was considered as a more sensitive indicator of ANS function than the time-domain variables; thus is simply because it is indicated to calculate the time-domain indexes over 24 h recordings, whereas spectral frequency-domain indexes can be calculated over a recording period of as short as 2–5 min [20]. Thus, based on the nature of the nocturnal recording in this study, the results of the frequency-domain indexes should be considered more seriously than those of the time-domain indexes. An interesting finding in this study was the elevated frequency-domain variables (except for HF power) in normotensive compared with hypertensive OSAS patients either before or during APAP titration, although not being significantly different. Thus, hypertensive OSAS patients exhibit increased parasympathetic activity (in terms of HF power) than normotensive OSAS patients. Cheng et al. [40] in his study demonstrated similar results with regard to nonsignificant differences in both time-domain and frequency-domain indexes of HRV between the two groups either before or during APAP treatment; however, their study reported lower HF power in hypertensive compared with normotensive OSAS patients. Accordingly, their study demonstrated decreased parasympathetic activity in hypertensive compared with normotensive OSAS patients either before or during APAP, and this was not in agreement with our results. A possible explanation for this discrepancy is the mismatch in BMI in both studies: OSA patients in the present study were far more obese, and it has been suggested that obesity affects autonomic activity.

When APAP was applied to normotensive patients, the frequency-domain indexes decreased but did not differ significantly. Although the VLF power increased significantly during APAP, the physiological explanation for the VLF index is not well established and seems to be related to the renin–angiotensin–aldosterone system, thermoregulation, and the peripheral vasomotor tone [41]. On the contrary, APAP application in hypertensive OSAS patients resulted in significant
changes in HRV: most of the HRV indexes decreased significantly with APAP. The increased sympathetic activity before APAP (as evidenced by increased LF power), the increased parasympathetic activity (as evidenced by increased HF power), as well as the increased sympathovagal activity of the heart (as evidenced by increased LF/HF ratio) significantly decreased with APAP, suggesting that hypertensive OSAS patients benefit from APAP treatment more than normotensive OSAS patients regarding ANS regulation. Moreover, it is worth mentioning that the elimination of airway collapse with APAP caused more significant reduction in LF compared with the HF and LF/HF ratio, suggesting that the degree of reduction in sympathetic activation with APAP was more than the reduction in vagal stimulation. Cheng et al. [40] and Heitmann et al. [42] revealed increased variability in autonomic activity during APAP titration in hypertensive versus normotensive OSAS patients. Moreover, the results of Cheng et al. [40] are in agreement with the present study regarding the predominance of LF changes of HRV among hypertensive patients during APAP titration.

There are several limitations to this study. First, only one APAP algorithm was investigated in this study. Second, HRV was investigated with one form of PAP therapy disregarding the effect of other forms of PAP therapy on HRV. Third, the immediate effect of APAP over HRV entails long-term follow-up to document such improvement with regular APAP usage.

It is worth mentioning that among the strengths in this study was the exclusion of OSAS patients with clinical conditions affecting autonomic activity and HRV. Moreover, the inclusion of normotensive OSAS patients for comparison with hypertensive patients clearly delineates the differences in HRV in normotensive versus hypertensive OSAS patients.

Conclusion
Nocturnal HRV improved with APAP in OSA patients. Furthermore, APAP was more beneficial in terms of ANS regulation in OSA patients with coexisting hypertension than normotensive OSA patients.

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Conflicts of interest
There are no conflicts of interest.

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