ORIGINAL RESEARCH

Nocturnal Arrhythmias and Heart-Rate Swings in Patients With Obstructive Sleep Apnea Syndrome Treated With Beta Blockers

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BACKGROUND: The higher cardiovascular variability and the increased prevalence of arrhythmias in patients with obstructive sleep apneas may contribute to their higher rate of fatal events during sleep. In this regard, the use of beta blockers (BB) is debated because they may induce bradycardias and alter the pattern of heart rate changes induced by apneas. Thus, the aim of our study is to quantify peri-apneic heart-rate swings and prevalence of nocturnal bradycardias in BB-treated and BB-naive patients with obstructive sleep apnea.

METHODS AND RESULTS: Our real-life, retrospective, cohort study analyzed data from patients with obstructive sleep apnea after a basal cardiorespiratory polysomnography. Among 228 eligible participants, we enrolled 78 BB-treated and 88 BB-naive patients excluding those treated with antiarrhythmic drugs or pacemakers, or with uninterpretable ECG traces during polysomnography. In each patient, type and frequency of arrhythmias were identified and peri-apneic changes of RR intervals were evaluated for each apnea. BB-treated patients were older and with more comorbidities than BB-naive patients, but had similar obstructive sleep apnea severity, similar frequency of arrhythmic episodes, and similar prevalence of bradycardias. Apnea-induced heart-rate swings, unadjusted for age, showed lower RR interval changes in BB-treated (133.5±63.8 ms) than BB-naive patients (171.3±87.7 ms, \( P = 0.01 \)), lower RR interval increases during apneas (58.5±28.5 versus 74.6±40.2 ms, \( P = 0.01 \)), and lower RR interval decreases after apneas (75.0±42.4 versus 96.7±55.5 ms, \( P < 0.05 \)).

CONCLUSIONS: BB appear to be safe in patients with obstructive sleep apnea because they are not associated with worse episodes of nocturnal bradycardias and even seem protective in terms of apnea-induced changes of heart rate.

Key Words: arrhythmias ■ beta blockers ■ HRV ■ sleep apnea
could also induce bradyarrhythmias in such a condition. However, expanding previous observations in animal models, a recent study showed that BB prevalently affect heart rate (HR) accelerations, with scarce influence on decelerations, suggesting that the powerful vagal withdrawal associated with obstructive apneas obscures the bradycardic effect of beta-receptor blockade.

Available data on this issue are still scarce, and studies on BB influence on HR variability and on protection from cardiac arrhythmias and fatal events are needed to optimize treatment and cardiovascular protection in patients with OSA. Therefore, our study specifically explored peri-apneic HR changes, as well as the frequency of atrial and ventricular arrhythmias, in patients with OSA BB-treated or untreated (BB-naïve). In particular, we evaluated the types of arrhythmias during sleep and the HR variations induced by each apneic event in BB-naïve versus BB-treated patients with OSA.

METHODS
This retrospective study was approved by the Ethical Committee of Istituto Auxologico Italiano. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants
We considered 228 consecutive patients with a diagnosis of OSA who underwent a basal unattended polysomnography between 2013 and 2015 at Istituto Auxologico Italiano, San Luca Hospital, in Milan, Italy. We collected medical reports filled in at the time of polysomnography after signed consent to use anonymous data, including information on drugs taken.

We excluded patients under antiarrhythmic therapy with amiodarone (n=15), ivabradine (n=3), digoxin (n=1), BB with antiarrhythmic properties such as sotalol and propranolol (n=3), nondihydropyridine calcium channel blockers such as verapamil (n=1) and diltiazem (n=5), and sodium channel blockers such as propafenone (n=1) and flecainide (n=2). Moreover, we excluded patients with implanted pacemakers (n=3) and with ECG traces of so low quality that they could not be analyzed by the Holter software (n=28). The final study population for evaluating frequency and type of arrhythmias included 166 patients, divided into BB-treated (n=78) and BB-naïve (n=88) groups (Figure 1).
For the analysis of peri-apneic HR changes we additionally excluded RR-interval traces with ECG artifacts affecting >50% of the peri-event signal (n=41). We also excluded patients with pre-existing atrial fibrillation (n=9). In this way, we included 109 patients, divided into BB-treated (n=56) and BB-naïve (n=53) groups (Figure 1).

Data Collection
Cardiorespiratory Polysomnography and Holter Analysis

A basal unattended full-night cardiorespiratory polysomnography including ECG, body position, nasal airflow/snoring, thoracic and abdominal muscle effort, and oxygen saturation signal recordings (Embletta portable diagnostic system; PDS, Medcare, Reykjavik, Iceland) was obtained at home for every subject. Polysomnography-derived indices based on automatic scoring by a sleep diagnostic software (Embla RemLogic PSG Software, Natus Medical Incorporated) were manually reviewed by certified Experts in Sleep Medicine according to international guidelines of the American Academy of Sleep Medicine who were blinded regarding the patients’ drug therapy. Analysis of the nocturnal ECG trace was also performed by dedicated software (CustoMed GmbH, Germany) and manually reviewed by an expert cardiologist blinded regarding the patients’ drug therapy.

Peri-Apneic HR Changes

A custom software identified all QRS complexes, eliminated artifacts and premature beats, and extracted the beat-to-beat series of RR intervals (RRI) (the reciprocal of HR, expressed in ms) in sinus rhythm. Additionally, the software allowed manual editing of artifacts and premature beats by an ECG expert reader. The same software analyzed apnea-related changes of RRI linking obstructive apneic events, identified from the polysomnography, with the RRI series. The HR response to apneas has been quantified by evaluating RRI changes separately over the apneic phase and the postapneic phase. The latter was defined as the 8-s period after the resumption of breathing. This time window was selected taking into account the time interval required for a cardiac sympathetic activation and according to the typical duration of the HR response to apnea events. For each apneic event, we computed 3 indices describing the HR behavior in the apneic and in the postapneic phases, ie:

\[
RR_{mean} = \text{mean of all RRI during the apneic phase;}
\]
\[
RR_{max} = \text{mean of the 3 longer RRI during the apneic phase (bradycardic phase);}
\]
\[
RR_{min} = \text{mean of the 3 shorter RRI during the postapneic phase (tachycardic phase).}
\]

For homogeneity with other studies, the bradycardic and tachycardic phases of apneas are reported in terms of maximum and minimum HR, in beats per minute, as:

\[
HR_{brady} = \frac{60000}{RR_{max}}
\]
\[
HR_{tachy} = \frac{60000}{RR_{min}}
\]

Additionally, we described the peri-apneic RRI changes from the \(RR_{mean}\) as:

\[
RR_{dec} = RR_{max} - RR_{mean}
\]
“acceleration” occurring within the postapneic phase,

\[ RR_{acc} = RR_{mean} - RR_{min} \]

and the “swing,” i.e., the total peri-apneic changes in cardiac rhythm, as the difference in RRI between the bradycardic and the tachycardic apnea phases:

\[ RR_{swing} = RR_{max} - RR_{min} \]

Figure 2 illustrates graphically the RR indices defined above.

**Statistical Analysis**

Continuous variables, presented as median values (interquartile range), were compared between groups by Mann–Whitney U test. Discrete variables, reported as fraction or percentage of the entire population, were evaluated by \( \chi^2 \) test or Fisher Exact test, if needed.

All statistical tests were 2-tailed with significance set at \( P < 0.05 \). Statistical analysis was performed with “R: A language and environment for statistical computing. R Foundation for Statistical Computing”, R Core Team (2019).

**RESULTS**

General characteristics and polysomnography data are shown in Table 1. BB-treated patients were older, with a higher prevalence of ischemic cardiomyopathy, heart failure, diabetes mellitus, and arterial hypertension as compared with BB-naive patients. OSA severity and other polysomnography parameters were similar in the 2 groups.

The average HR during sleep tended to be lower in BB-treated compared with BB-naive patients (Table 2), and this was the case also for the highest HR value recorded overnight (88.2±13.7 versus 93.4±11.4 bpm, mean±SD, respectively, \( P < 0.01 \)). By contrast, the lowest HR was similar in the 2 groups (47.3±8.3 versus 48.4±7.6 bpm, respectively, \( P = 0.52 \)).

Analysis of arrhythmias on nocturnal ECG Holter recordings (Table 2) showed a tendency towards the more frequent occurrence of atrial fibrillation in BB-treated patients, but no significant differences in the number of arrhythmic events were found between groups. The general characteristics of the patients considered for the subanalysis of HR swings and their traditional indices of HR variability, measured during a

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**Figure 2.** HR accelerations and decelerations during a sleep apneic event.

The figure shows the nasal airflow (upper) and the RR-interval series (lower) and the peri-apneic episode as composed of a bradycardic phase (blue area) followed by a tachycardic phase (orange area). \( RR_{mean} \) is the mean of all RR intervals during the apneic phase (dot-dash line); \( RR_{max} \) is the mean of the 3 longer RR intervals during the apneic phase (dotted line); \( RR_{dec} \) is the difference between \( RR_{max} \) and \( RR_{mean} \) (double-headed arrow). \( RR_{min} \) is the mean of the 3 shorter RR intervals during the postapneic phase (dot line); \( RR_{acc} \) is the difference between the \( RR_{mean} \) and \( RR_{min} \) (double-headed arrow). \( RR_{swing} \) is the difference between \( RR_{max} \) and \( RR_{min} \) (double-headed arrow). For further details, see the Methods section. HR indicates heart rate; and RR, RR interval.
5-minute segment of RRI free from respiratory events at the onset of the sleep recording, are reported in Table S1. These data reflect the differences between BB-treated and BB-naïve patients in the general characteristics of the whole population (Table 1), and describe the expected reduction of HR variability compared with the general population,6-8 linking such prevalence of arrhythmias in patients with OSA as fact, while a number of studies have reported a higher risk in individuals affected by OSA,12,21 little is known about the rhythm acceleration during the postapnea period were less pronounced in BB-treated than in BB-naïve patients (RR_dec: 58.5±28.5 versus 74.6±40.2 ms, RR_acc: 75.0±42.4 versus 96.6±55.5 ms, respectively, P<0.05). Consequently, also the overall HR swings induced by apneas, RR_swing, were lower in BB-treated patients (BB-treated 133.5±63.8 ms versus BB-naïve 171.3±87.7 ms, P<0.01). No differences were found between BB-treated and BB-naïve patients in apnea duration (25.5±4.6 versus 24.8±4.6 s, respectively, P=0.37) and in the lowest value of oxygen saturation during the peri-apneic phase (89.9±3.9% versus 90.3±2.9%, respectively, P=0.96).

### DISCUSSION

Our article addresses a mostly unexplored field, as only a few studies have extensively considered the effect of BB on cardiac rhythm in patients with OSA. In fact, while a number of studies have reported a higher prevalence of arrhythmias in patients with OSA as compared with the general population,5-8 linking such a difference to the increased level of cardiovascular risk in individuals affected by OSA,12,21 little is known on the effects of different drugs on frequency and type of arrhythmias in patients with OSA.

In particular, to the best of our knowledge, there is only 1 relevant contribution to the effects of BB on

### Table 1. General Characteristics of BB-Naïve and BB-Treated Groups

| Anthropometric variables | BB-Naïve (N=88) | BB-Treated (N=78) | P Value |
|--------------------------|------------------|-------------------|---------|
| Male (%)                 | 64 (72.7%)       | 59 (75.6%)        | 0.80    |
| Age, y                   | 61.0 (19.5)      | 70.0 (13.0)       | <0.001  |
| Body mass index, kg/m²   | 29.4 (6.8)       | 28.9 (6.2)        | 0.36    |
| Comorbidities, n (%)     |                  |                   |         |
| Ischemic cardiomyopathy  | 4 (4.5)          | 34 (43.6%)        | <0.001  |
| Heart failure            | 0 (0)            | 11 (14.1%)        | <0.001  |
| Stroke/transient ischemic attack | 5 (5.7) | 7 (9) | 0.60 |
| Chronic kidney disease   | 2 (2.3)          | 7 (9)             | 0.08    |
| Chronic obstructive pulmonary disease | 3 (3.4) | 7 (9) | 0.19 |
| Diabetes mellitus        | 3 (3.4)          | 18 (23.1%)        | <0.001  |
| Hypertension             | 41 (48.6%)       | 61 (78.2%)        | <0.01   |
| AF/PAF (patients)        | 1 (1.1)          | 6 (7.7%)          | 0.52    |
| Polysomnographic indices |                  |                   |         |
| Average sleep time, min  | 439 (83)         | 462 (77)          | <0.05   |
| Mean SpO₂ (%)            | 93.4 (2.0)       | 93.1 (2.9)        | 0.60    |
| Minimum SpO₂ (%)         | 80.0 (10.0)      | 81.0 (7.0)        | 0.92    |
| Oxygen desaturation index, events/h | 20.2 (24.4) | 20.2 (18.6) | 0.93 |
| Apnea hypopnea index, events/h | 19.2 (221) | 20.0 (19.4) | 0.73 |
| Total                    | 18.7 (20.9)      | 18.0 (17.9)       | 0.87    |
| Obstructive              | 0.0 (0.3)        | 0.0 (0.4)         | 0.27    |
| Apnea hypopnea index distribution |          |                   |         |
| Mild                     | 30 (34.1%)       | 26 (33.3%)        | 0.92    |
| Moderate                 | 32 (36.4%)       | 32 (33.3%)        | 0.68    |
| Severe                   | 24 (27.3%)       | 23 (29.5%)        | 0.75    |

Data are shown as median (interquartile range) or as number of cases (percentage). Apnea Hypopnea Index (AHI) distribution: mild sleep apnea 5 ≤ AHI <15 events/h; moderate sleep apnea: 15 ≤ AHI <30 events/h; severe sleep apnea: AHI ≥30 events/h. AF indicates atrial fibrillation; BB, beta-blocker; P, statistical significance of the difference; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; SVEB, supraventricular ectopic beats; VEB, ventricular ectopic beats; and VT, ventricular tachycardia.

### Table 2. Holter-Derived Indices of Frequency and Type of Arrhythmias in BB-Naïve and BB-Treated Groups

|                  | BB-Naïve (N=88) | BB-Treated (N=78) | P Value |
|------------------|------------------|-------------------|---------|
| HR, bpm          | 61.4 (10.6)      | 59.7 (10.1)       | 0.054   |
| AF/PAF (patients)| 1 (1.1%)         | 6 (7.7%)          | 0.52    |
| SVEB (episodes)  | 7.5 (21.8)       | 9.5 (83.5)        | 0.41    |
| PSVT (episodes)  | 0.0 (0.3)        | 0.0 (0.0)         | 0.73    |
| PSVT duration, s | 1.90 (2.28)      | 2.35 (1.60)       | 0.60    |
| VEB              |                  |                   |         |
| Single           | 1.0 (17.3)       | 2.0 (28.0)        | 0.23    |
| Couples          | 1.0 (1.0)        | 2.0 (7.5)         | 0.18    |
| Triplets         | 0.0 (0.0)        | 0.0 (0.0)         | >0.99   |
| VT (patients)    | 2 (2.3%)         | 3 (2.6%)          | 0.67    |
| Sinus pauses duration, s | 3.15 (0.05) | 4.10 (1.50) | 0.16 |
| Sinus pauses (patients) | 19 (21.6%) | 16 (20.5%) | >0.99 |
| Sinus pauses (episodes) | 0.0 (0.0) | 0.0 (0.0) | 0.84 |
| AVB type II–III (patients) | 7 (8.0%) | 2 (2.6%) | 0.18 |

Data are shown as median (interquartile range) or as number of cases (percentage). P indicates the statistical significance of the difference. AF indicates atrial fibrillation; AVB, atrioventricular block; bpm, beats per minute; HR, heart rate; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; SVEB, supraventricular ectopic beats; VEB, ventricular ectopic beats; and VT, ventricular tachycardia.
Our study offers novel information along this line, regarding the prevalence of arrhythmias, inclusion criteria (enrolling patients with different OSA severity and comorbidities), and methodology for analysis of HR changes. Furthermore, it more deeply explores HR variations in relation to apneic events, because previous assessments of HR variability identified the greatest HR changes only, thus including a limited number of apnea/hypopnea events, and possibly introducing a bias in the results. Conversely, our study (1) considers the HR variations in all the events identified during the sleep study and (2) assesses the accelerations/decelerations of the cardiac rhythm, taking as reference level the mean RRI in each apneic phase to more precisely evaluate the actual amount of HR change induced by each event.

Starting from these elements of novelty, we showed that BB-naive and BB-treated patients do not differ concerning sinus rhythm pauses (number and duration) and atrioventricular block occurrence. This result can have important clinical implications, given that the
As discussed by Wolf et al, the lack of patients following rehabilitation programs. This could be particularly relevant in rehabilitation medicine when applied to comorbid patients with OSA. Our findings could be particularly relevant in real-life conditions, reinforcing the results about safety of BB use also in patients at higher risk of arrhythmias.

Additionally, we showed that the BB-treated group displayed lower apnea-related RR swings, less pronounced cardiac rhythm accelerations during the post-apneic phase, and less pronounced decelerations within the apnea phase compared with the BB-naive group. These data confirm and expand the previous observations suggesting that beta-adrenergic blockade probably has a role in reducing the HR changes associated with obstructive respiratory events. Reducing HR oscillations might be advantageous in patients with OSA, because the most important complications of sleep-disordered breathing are often related to the hyperactivation of the sympathetic nervous system, with the accompanying increase in cardiovascular variability. In fact, a reduction of cardiovascular variability and a reduction of sympathetic overactivity may lead to a decreased risk of sudden cardiac death and of cardiovascular complications. Thus, the demonstration that BB do not determine adverse effects in patients with OSA may open the way to their administration as an efficient strategy to control the sympathetic overactivity typical of these patients.

In terms of arrhythmias prevalence, the nocturnal ECG analysis is of high relevance because it also allows checking the safety of BB treatment in elderly patients with OSA. It should also be mentioned that BB, although considered safe for treating sympathetic overactivity in patients with OSA, and appears to reduce the amplitude of HR oscillations associated with the nocturnal apneas. Taking all these findings together, we can thus suggest that BB are safe for treating sympathetic overactivity in patients with OSA, and may also carry some specific advantages. Further longitudinal studies are needed to explore the mechanisms underlying the observed effects and additional clinical aspects such as the occurrence of a correlation between the severity of hypoxic exposure and the type and dose of the administered BB. Future intervention trials might clarify whether long-term use of BB in patients with OSA demonstrates a protective role in fatal events, thus paving the way to wider uses of BB as a preventive therapy to reduce the risk of cardiovascular events in OSA.

In conclusion, our findings suggest that BB therapy, when analyzing real-life data, does not determine an augmented risk of bradyarrhythmias in patients with OSA and appears to reduce the amplitude of HR swings associated with the nocturnal apneas. Taking all these findings together, we can thus suggest that BB are safe for treating sympathetic overactivity in patients with OSA, and may also carry some specific advantages. Further longitudinal studies are needed to explore the mechanisms underlying the observed effects and additional clinical aspects such as the occurrence of a correlation between the severity of hypoxic exposure and the type and dose of the administered BB. Future intervention trials might clarify whether long-term use of BB in patients with OSA demonstrates a protective role in fatal events, thus paving the way to wider uses of BB as a preventive therapy to reduce the risk of cardiovascular events in OSA.

ARTICLE INFORMATION
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Supplementary Material
Table S1

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Supplemental Material
|                                      | BB-NAÏVE (N=53) | BB-TREATED (N=56) | p-value |
|--------------------------------------|-----------------|-------------------|---------|
| **Anthropometric variables**          |                 |                   |         |
| Male (%)                             | 38 (71.7%)      | 40 (71.4%)        | 0.99    |
| Age (years)                          | 59.0 (16.0)     | 68.5 (13.0)       | <0.001  |
| Body Mass Index (kg/m^2)             | 30.0 (6.6)      | 29.0 (6.3)        | <0.05   |
| **Comorbidities n (%)**              |                 |                   |         |
| Ischemic Cardiomyopathy              | 3 (5.7%)        | 23 (41.1%)        | <0.001  |
| Heart Failure                        | 0 (0%)          | 7 (12.5%)         | <0.05   |
| Stroke/Transient Ischemic Attack     | 3 (5.7%)        | 5 (8.9%)          | 0.72    |
| Chronic Kidney Disease               | 1 (1.9%)        | 4 (7.1%)          | 0.36    |
| Chronic Obstructive Pulmonary Disease| 1 (1.9%)        | 3 (5.4%)          | 0.61    |
| Diabetes Mellitus                    | 2 (3.8%)        | 11 (19.6%)        | <0.05   |
| Hypertension                         | 25 (47.2%)      | 46 (82.1%)        | <0.001  |
| **Heart Rate Variability indices**   |                 |                   |         |
| mean RR (ms)                         | 858 (175)       | 941 (159)         | 0.010   |
| pNN50                                | 0.025 (0.199)   | 0.023 (0.054)     | 0.5     |
| RMSSD (ms)                           | 24.4 (20.3)     | 21.1 (12.2)       | 0.5     |
| Total Power (ms^2)                   | 1165.5 (2280.8) | 860.7 (1110.5)    | 0.07    |
| VLF Power (ms^2)                     | 547.5 (960.0)   | 382.1 (672.9)     | 0.10    |
| LF Power (ms^2)                      | 302.0 (584.3)   | 161.0 (308.1)     | 0.014   |
| HF Power (ms^2)                      | 98.9 (190.3)    | 79.8 (107.7)      | 0.2     |
| LF/HF Powers ratio                   | 3.57 (5.31)     | 2.34 (4.33)       | 0.2     |
| normalized LF power                  | 0.34 (0.30)     | 0.32 (0.19)       | 0.2     |
| **Polysomnographic indices**         |                 |                   |         |
| Average Sleep Time (min)             | 439 (85)        | 462 (69)          | 0.18    |
| Mean SpO2 (%)                        | 93.5 (2.1)      | 93.1 (3.2)        | 0.46    |
| Minimum SpO2 (%)                     | 80.0 (9.0)      | 81.0 (9.5)        | 0.93    |
| Oxygen Desaturation Index (events/h) | 19.2 (22.8)     | 16.8 (18.8)       | 0.54    |
| Apnea Hypopnea Index (events/h)      |                 |                   |         |
| Total                                | 18.3 (23.3)     | 17.1 (18.15)      | >0.99   |
| Obstructive                          | 18.3 (24.5)     | 16.5 (18.5)       | 0.69    |
| Central                              | 0.0 (0.3)       | 0.0 (0.3)         | 0.99    |
| Apnea Hypopnea Index distribution    |                 |                   |         |
| Mild                                 | 17 (32.1%)      | 23 (41.1%)        | 0.43    |
| Moderate                             | 20 (37.7%)      | 18 (32.1%)        | 0.55    |
| Severe                               | 16 (30.2%)      | 15 (26.8%)        | 0.83    |

*Heart Rate Variability assessed in lying position on a 5-minute segment of RR intervals at the onset of sleep monitoring without any respiratory event; pNN50= number of pairs of successive RR intervals that differs by more than 50 ms divided by the total number of RR intervals; RMSSD: Root mean square of the successive RR differences; VLF=Very-low frequency, from 0.0025 to 0.04 Hz; LF= Low frequency, from 0.04 to 0.15 Hz; HF= High frequency, from 0.15 to 0.4 Hz; Apnea Hypopnea Index (AHI): mild= 5≤AHI<15 events/h; moderate= 15≤AHI<30 events/h; severe= AHI≥30 events/h; p-value after Mann-Whitney U Test or Fisher’s Exact Test.