## 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 bradyarrhythmias 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 bradyarrhythmias in BB-treated and BB-naïve 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-naïve 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-naïve patients, but had similar obstructive sleep apnea severity, similar frequency of arrhythmic episodes, and similar prevalence of bradyarrhythmias. Apnea-induced heart-rate swings, unadjusted for age, showed lower RR interval changes in BB-treated (133.5±63.8 ms) than BB-naïve 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 bradyarrhythmias and even seem protective in terms of apnea-induced changes of heart rate.

**Key Words:** arrhythmias ■ beta blockers ■ HRV ■ sleep apnea

The higher cardiovascular variability[1-5] and prevalence of arrhythmias in patients with obstructive sleep apneas (OSA)[6-8] may contribute to the increased rate of fatal events during sleep. In the general population, the risk of sudden cardiac death is augmented in morning hours,[9] reaching the nadir during night-time sleeping hours. Conversely, subjects with OSA, who represent patients at higher overall cardiovascular risk,[10-12] have an increased risk of sudden cardiac death, especially during sleeping hours.[13,14] These findings support the potential role of sleep-related breathing disorders in arrhythmogenesis[15,16] and highlight the importance of further exploring this issue.

Given this background, the use of beta blockers (BB) in treating the sympathetic activation of patients with OSA has been a matter of debate, because BB

## CLINICAL PERSPECTIVE

### What Is New?

- This study on 228 patients with obstructive sleep apnea describes for the first time the effects of beta-blocker (BB) treatment on peri-apneic heart rate changes and the frequency of atrial and ventricular arrhythmias in a real-life clinical setting.
- Nocturnal ECG Holter analysis showed no differences in the number of arrhythmias between BB-treated and BB-naïve patients.
- When considering the heart rate changes associated with each apnea episode, both the rhythm deceleration during the apnea and acceleration after the apnea were less pronounced in BB-treated than in BB-naïve patients.

### What Are the Clinical Implications?

- Our findings indicate that BB treatment does not increase the risk of bradyarrhythmias and reduces the amplitude of heart rate swings in patients with obstructive sleep apnea.
- Our results thus suggest that BBs are safe in patients with obstructive sleep apnea and that BBs also carry specific advantages to be confirmed in longitudinal studies.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **BB** | beta blockers |
| **HR** | heart rate |
| **HR$_{brady}$** | heart rate level in the bradycardic phase (=60 000/RR$_{max}$) |
| **HR$_{tachy}$** | heart rate level in the tachycardic phase (=60 000/RR$_{min}$) |
| **OSA** | obstructive sleep apneas |
| **RR$_{acc}$** | "acceleration" within the postapneic phase (=RR$_{mean}$−RR$_{min}$) |
| **RR$_{dec}$** | "deceleration" within the apnea (=RR$_{max}$−RR$_{mean}$) |
| **RRI** | RR intervals |
| **RR$_{max}$** | mean of the 3 longer RR intervals in the apneic phase (bradycardic phase) |
| **RR$_{mean}$** | mean of all RR intervals during the apneic phase |
| **RR$_{min}$** | mean of the 3 shorter RR intervals in the postapneic phase (tachycardic phase) |
| **RR$_{swing}$** | range of the peri-apneic changes of the cardiac rhythm (=RR$_{max}$−RR$_{min}$) |

could also induce bradyarrhythmias in such a condition.[17] However, expanding previous observations in animal models,[18] a recent study showed that BB prevalently affect heart rate (HR) accelerations, with scarce influence on decelerations,[19] 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 consensus 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).
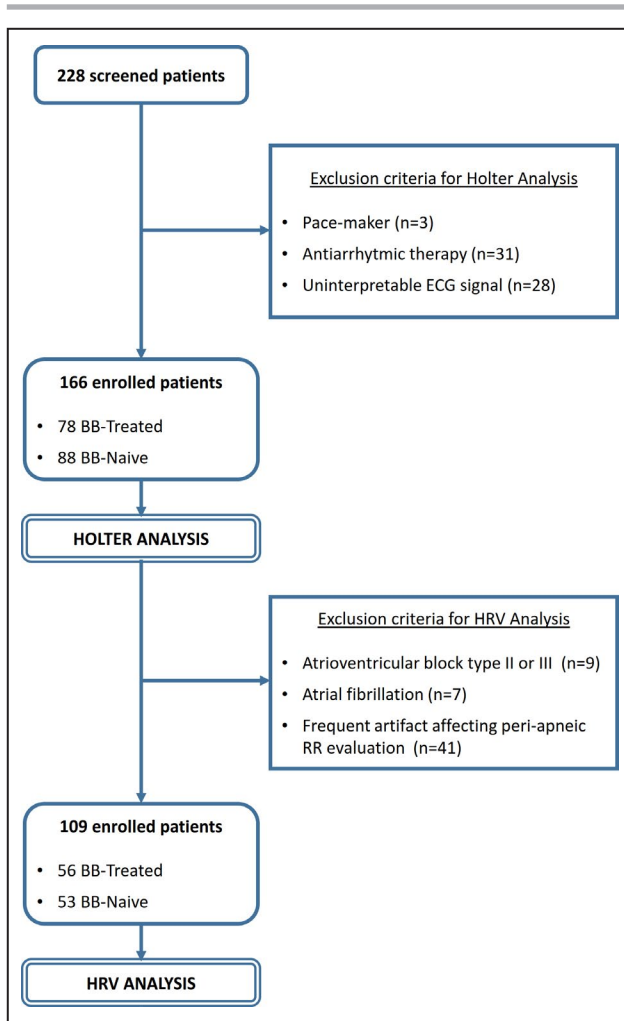
**Figure 1. Study flowchart.**
BB indicates beta blockers; HRV, heart rate variability; and RR RR interval.

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=7) and atrioventricular block type II or III (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,[20] 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:

$RR_{mean}$=mean of all RRI during the apneic phase;
$RR_{max}$=mean of the 3 longer RRI during the apneic phase (bradycardic phase);
$RR_{min}$=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:

$$HR_{brady} = 60000/RR_{max}$$

$$HR_{tachy} = 60000/RR_{min}$$

Additionally, we described the peri-apneic RRI changes from the $RR_{mean}$ as:
"deceleration" occurring within the apnea,

$$RR_{dec} = RR_{max} - RR_{mean}$$

"acceleration" occurring within the postapneic phase,

$$RR_{acc} = RR_{mean} - RR_{min}$$

and the "swing," ie, 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-naïve 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-naïve 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
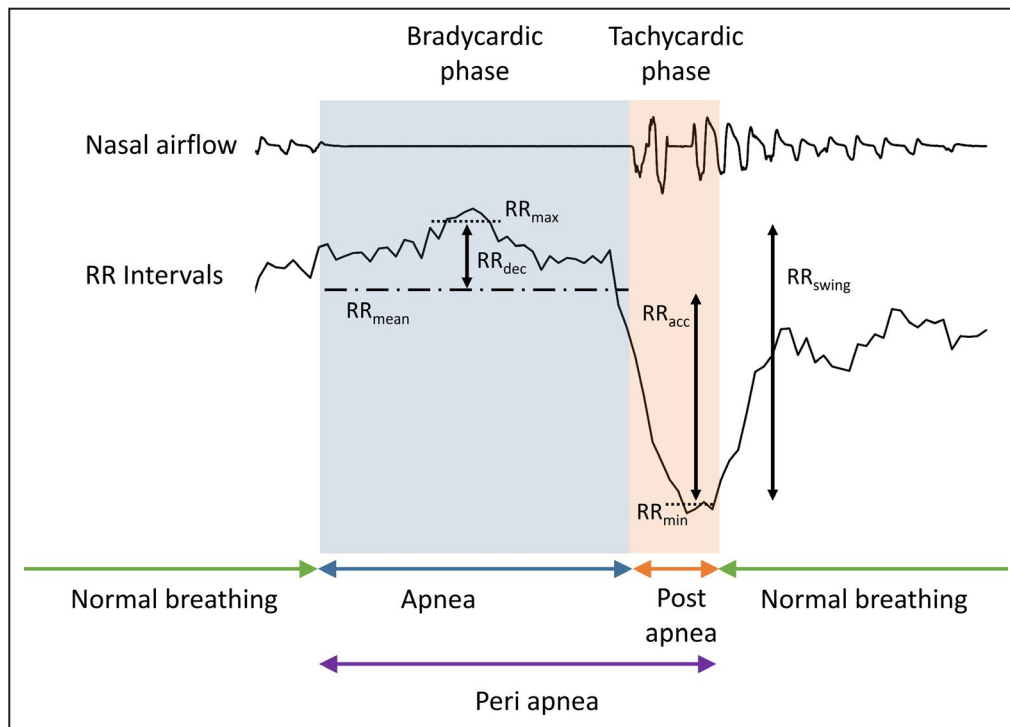
**Figure 2.  HR accelerations and decelerations during a sleep apneic event.**
The figure shows the nasal airflow (upper) and the RR-interval series (lower) and the peri-apneic episode as composed of a bradycardic phase (blue area) followed by a tachycardic phase (orange area). $RR_{mean}$ is the mean 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.

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

|  | BB-Naïve (N=88) | BB-Treated (N=78) | P Value |
|---|---|---|---|
| Anthropometric variables | | | |
| 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/m$^2$ | 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 (46.6) | 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 SpO$_2$ (%) | 93.4 (2.0) | 93.1 (2.9) | 0.60 |
| Minimum SpO$_2$ (%) | 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 | | | |
| Total | 19.2 (221) | 20.0 (19.4) | 0.73 |
| Obstructive | 18.7 (20.9) | 18.0 (17.9) | 0.87 |
| Central | 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%) | 26 (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; SpO$_2$, oxygen saturation by pulse oximeter.

**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 (53.5) | 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.

both the rhythm deceleration during apnea and 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 for both). 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<0.05).

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,[6-8] 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

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 components modulated by the cardiac sympathetic outflow in the BB-treated group. Regarding the peri-apneic HR changes (Figure 3, upper panels), HR$_{tachy}$ was higher in BB naïve (69.7±9.7 bpm) compared with BB-treated patients (66.3±9.5 bpm), while HR$_{brady}$ was similar in the 2 groups (57.0±7.1 versus 57.5±8.0 bpm, respectively). However, when we considered the changes from the mean RR value of each apnea (Figure 3, lower panels),
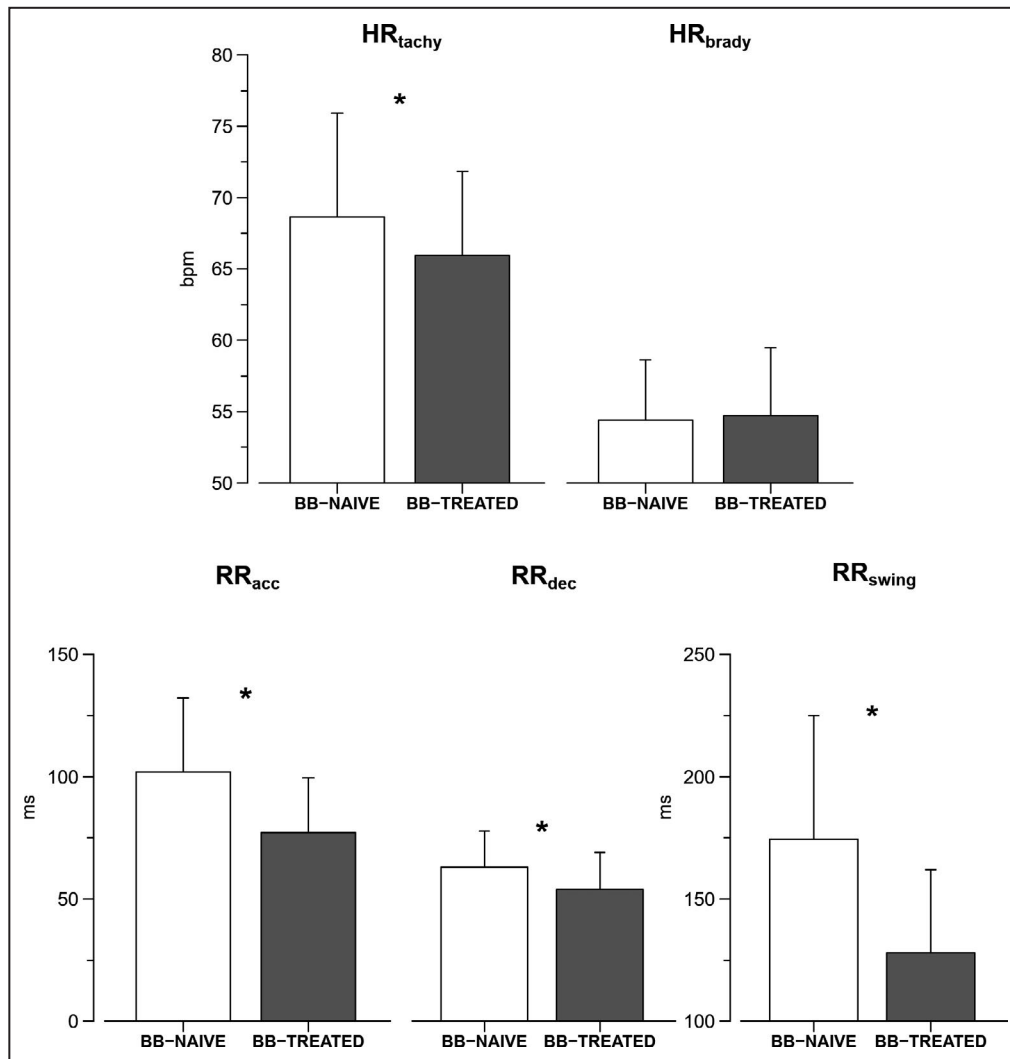
**Figure 3.   Peri-apneic HR values in BB-treated and BB-naïve patients with OSA (upper panels) and local RR changes induced by apnea in BB-treated and BB-naïve patients with OSA (lower panels).**

$HR_{tachy}$ is the mean of the 3 higher values of HR during the postapneic phase; $HR_{brady}$ is the mean of the 3 lower values of HR during the apnea; $RR_{acc}$ is the difference between the mean RR interval in the apneic phase and the mean of the 3 shorter RR intervals during the tachycardic postapneic phase; $RR_{dec}$ is the difference between the 3 longer RR intervals during the bradycardic apneic phase and the mean RR interval in the apneic phase; $RR_{swing}$ is the difference in RR intervals between the bradycardic and the tachycardic apnea phases. Data as median and median absolute deviation. Further details are provided in Figure 2 and the Methods section. The symbol * indicates differences between groups significant at $P<0.05$. BB indicates beta blockers; HR, heart rate; OSA, obstructive sleep apnea; and RR, RR interval.

HR variability and arrhythmias in patients with OSA.[19] 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-naïve 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

use of BB in patients with OSA has been limited in the past because of concerns on their possible excessive action on HR decelerations, with the possible risk of inducing excessive bradycardia and sinus pauses or blocks. In this context, it is important also to consider that in our study, the BB group showed a higher prevalence of comorbidities and a higher age, as expected 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 postapneic phase, and less pronounced decelerations within the apnea phase compared with the BB-naïve 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.[19] 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.[15,16,22-24] 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 treatment did not affect oxygen saturation during the night, and polysomnography indices of blood oxygen saturation were similar in BB-naïve and treated groups, notwithstanding the effects of nonselective BB on $\beta2$ adrenergic receptors expressed in bronchial smooth muscle cells and in lung alveolar cells[25] that could have had an unfavorable impact on airway obstruction and respiratory function in patients with OSA.[17] Given these results, our study suggests that there are no relevant contraindications to BB administration in patients with OSA. Our findings could be particularly relevant in rehabilitation medicine when applied to comorbid patients following rehabilitation programs.

Our study was not designed to identify the mechanisms underlying the observed effects of BB in patients with OSA. As discussed by Wolf et al,[19] the lack of excessive bradyarrhythmias might be because of a pronounced increase in vagal activity related to the apneic events, which prevented BB from having a further exacerbating effect on HR decelerations. This possibility was suggested by studies performed in animal models,[18] but no data are available in humans, where further studies are thus needed.

We acknowledge 2 limitations of this work because of the fact that we evaluated a population of patients in real-life conditions: (1) the BB-treated group had a higher prevalence of comorbidities, which may have affected the cardiac autonomic control contributing to lower peri-apneic HR swings in BB-treated patients. (2) BB-treated patients were older than BB-naïve patients. In spite of being unadjusted, the results of our study have an important clinical value because they demonstrate that BB+ patients (older and more frequently patients with diabetes mellitus, both conditions being potential determinants of autonomic dysregulations) appear to be even less exposed to the risk of arrhythmias and apnea-induced bradycardia than patients who do not receive this class of drugs. This strongly suggests that avoiding the use of BB in the fear of an increased risk of arrhythmic events is not justified. However, on the basis of unadjusted results, we cannot entirely attribute the differences we observed to the BB. Thus, to exclude that the observed reduction of HR variations is only because of the higher age of BB-treated patients, we considered the subgroup of participants in the narrower range between 60 and 85 years. The resulting BB-naïve and BB-treated groups have the same age, 66 (11) versus 71 (8) years as median (IQR), and sex composition (55% and 67% of males, respectively), but even if the samples are substantially smaller (N=22 for BB-naïve and N=39 for BB-treated), the BB-treated patients have a significantly lower $RR_{dec}$, 49 (25) ms versus 57 (22) ms with $P<0.05$, and a slightly lower $RR_{acc}$, 68 (35) ms versus 76 (68) ms, $P=0.39$.

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

## Supplementary Material

Table S1

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# Supplemental Material

**Table S1. Comparison between groups in the general characteristics of patients selected for HR swings analysis: data as mean (IQR) or number of cases (percentage).**

| | 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 SpO$_2$ (%) | 93.5 (2.1) | 93.1 (3.2) | 0.46 |
| Minimum SpO$_2$ (%) | 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.