# OSAS Severity is Associated with Decreased Heart Rate Turbulence Slope

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## Abstract

*Obstructive sleep apnea syndrome (OSAS) has been associated to impaired baroreflex sensitivity (BRS) which has recently been shown to be non-invasively assessed by heart rate turbulence (HRT) analysis. Although HRT seems to be better suited than traditional heart rate variability indexes for autonomic assessment in presence of respiratory and arrhythmic disorders, very few papers addressed its evaluation in OSAS. Aim of the study is to find out whether and to which extend HRT is associated to OSAS severity. We studied HRT in polysomnographic recordings of 221 mild to severe OSAS pts. Results showed that, while HRT onset values did not significantly differ between mild (-0,78±1,50), moderate (-0,89±1,78) and severe (-0,70±1,28) pts., HRT slope significantly decreases (Kruskal-Wallis P value <0.05) from mild (3,27±2,7) to moderate (2,6±2,6) and severe (1,98±2,5) pts., with a significant Dunn's multiple comparisons post test only between mild vs. severe OSAS pts. Data indicate that the main BRS alterations do not appear in the early HRT phase triggered by transient vagal inhibition, but during the slow one, due to the sympathetic hyperactivity affecting the heart rate recovery. These findings support the conclusion that HRT assessment could have a prognostic value related to the development of cardiovascular disease in OSAS.*

## 1. Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated episodes of upper airway obstruction during sleep, leading to significant hypoxia. It is a highly prevalent disease in the population, affecting 1–4% of adults, mostly aging within 30 to 60 years old and just in 19% over 60 [1]. This pathology is usually diagnosed by polysomnographic studies, mainly consisting of nasal and oral breath flow measurements, snoring microphone recordings, thoracic and abdominal movements measurement by stress sensitive belts, and pulse oximetry, scoring OSAS severity by the number of apneas and hypopneas per hour during sleep, defined as apneas/hypopneas index (AHI). This index discriminates from mild (5≤AHI<15) to moderate (15≤AHI<30) and severe (AHI≥30) OSAS grade and has been associated to worse prognosis and mortality, mainly due to an increased rate of cardiovascular morbidity. Changes of the cardiac autonomic regulation are considered to be involved in the development of cardiovascular disease in patients with OSAS [2].

Sympatho-vagal balance is usually assessed by measuring heart rate variability [3-9] but some studies have questioned the validity of spectral heart rate variability measurements in the presence of sleep disordered breathing [10] mainly both for nonstationarity due to nonlinear heart period modulation caused by highly dynamic pathological respiratory patterns and for the elevated incidence of cardiac arrhythmias, including ventricular premature complexes (VPC) and sequences of tachycardia-brachycardia.

OSAS has been associated to impaired baroreflex sensitivity during sleep, which may contribute to the cardiovascular pathophysiology in these patients [11]. HRT has been recently shown as an attractive non-invasive way of baroreflex sensitivity assessment [12] and its impairments has been demostrated as the strongest electrocardiographic risk predictor in cardiac patients [13].

HRT consists on the analysis of short-term sinus cycle length fluctuations following spontaneous isolated VPC. The physiologic pattern of HRT is composed by a brief heart rate acceleration followed by a more gradual heart rate deceleration before the rate returns to a pre-ectopic level. Available physiologic investigations confirm that the initial heart rate acceleration is triggered by transient vagal inhibition in response to missed baroreflex afferent input caused by hemodynamically inefficient ventricular contraction. A sympathetically mediated overshoot of arterial pressure is responsible for the subsequent heart rate deceleration through vagal recruitment.

Although HRT seems to be better suited than traditional heart rate variability indexes for autonomic assessment in presence of respiratory and arrhythmic disorders, very few papers addressed its evaluation in OSAS. Aim of the study is to find out whether and to which extend HRT is associated to OSAS severity.

## 2. Methods

### 2.1. Study population

Only patients with newly diagnosed OSA defined by an apnea-hypopnea index (AHI) of at least 5 events per hour during polysomnography were taken into analysis. We studied HRT in polysomnographic recordings of 90 mild (5<AHI<15), 79 moderate (16<AHI<30) and 72 severe (AHI>30) OSAS pts. (age 62±14, 71% males). admitted in the Pneumological Rehabilitation Unit Institute of Maugeri Foundation of Telese Terme (BN, Italy). Exclusion criteria were defined as follows: treatment with betablocking agents or theophylline, history of cardiac disease, left ventricular dysfunction (ejection fraction < 50%), diabetes mellitus, and periodic breathing pattern.

### 2.2. Polysomnographic monitoring

Additionally to traditional polysomnographics signals of breath flow, snoring, thoracic and abdominal movements and pulse oximetry, all subject underwent to an holter ecg monitoring between 11 p.m. and 6 a.m, contemporary available by means of Somntè (Compumedics) polysomnograhic system.

Apneas has been defined as an airflow amplitude reduction of at least the 80% for more than 10 s and hypopneas were defined as an airflow amplitude reduction of at least the 50% for more than 10 s with a fall of at least the 4% in oxygen saturation and AHI of all recordings has been automatically calculated by the system with an algorithm for respiratory pattern recognition and manually verified by an expert technician. Each heart beat has been labeled as normal, VPC or aberrant according to recognition by the system with an algorithm for ecg holter analysis and after an investigator's verification.

### 2.3. HRT Analysis

All data has been imported from Somntè database and post-processed for HRT analysis by a customized Matlab software toolbox developed by the authors [14-16]. Accordingly to standards of measurements [13], HRT was estimated by two numerical descriptors: turbulence onset (TO), reflecting the initial phase of sinus rhythm acceleration and turbulence slope (TS), describing the late deceleration phase.

TO was calculated as a percentage difference between the mean of the first two RR intervals following the compensatory pause after a VPC and the last two sinus RR intervals before a VPC. TS was calculated as the maximum positive slope of a regression line assessed over any of 5 consecutive RR intervals within the first 15 sinus RR intervals after a VPC. Filtering algorithms were used to eliminate inappropriate RR intervals and VPC with overly long coupling intervals or overly short compensatory pauses. Filtering algorithms excluded from the HRT calculation RR intervals with the following characteristics: <300 ms, >2000 ms, >200 ms difference to the preceding sinus interval, and >20% difference to the reference interval (mean of the 5 last sinus intervals).

In addition, HRT calculation has been limited to VPC with a minimum prematurity of 20% and a post-extrasystole interval that is at least 20% longer than the reference interval (mean of last 5 sinus RR intervals). According to standard guidelines, for reliable construction of the VPC tachogram, all HRT values were then calculated from the averaged tachogram, selecting for the analysis only recordings with at least six isolated VPC, each followed by at least 15 sinus RR intervals (Fig. 1). Since it has recently been reported that TS is structurally related to the number of VPCs and its estimation method induces a mathematically determined increase inversely related to the square root of the VPCs number, a corrected TS (TSc) has been used as followed described[17].

$$TSc = TS - cTS$$

where $cTS = 0.02475 \times 13^{0.9499} \times RMMSD \div \sqrt{\#VPCs}$ and RMMSD is the square root of the mean squared difference of successive normal beat-to-beat differences.

### 2.4. Statistical analysis

Statistical analyses were performed by GraphPad Prism 5.0 software package (GraphPad Software, San Diego California USA). Due to the skewed distributions of all variables (D'Agostino & Pearson omnibus normality test p <0.05), analysis of variance in the three studied groups has been performed by Kruskal-Wallis test followed by Dunn's Multiple Comparison Test between each couple of groups (p=0.05). Descriptive statistics (Table 1) and data plot (Fig. 2 and 3) have therefore been expressed in medians and percentiles.

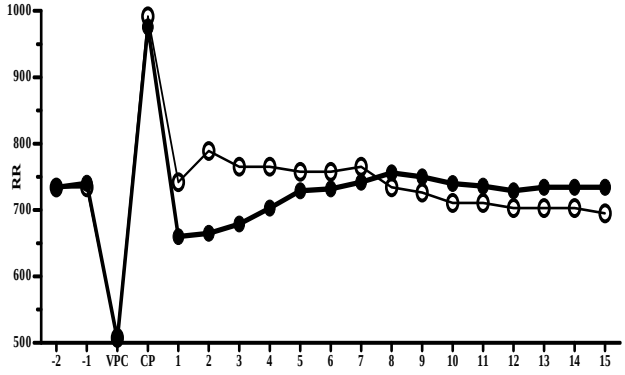


Figure 1. Examples of HRT curves in mild (black circles) and severe (white circles) OSAS patients.

## 3. Results

HRT analysis in OSAS patients' groups (see Table 1) was feasible according to all previous exposed criteria in 82 of 90 mild; 74 of 79 moderate and 65 of 72 severe OSAS patients. In the remaining patients, HRT analyses could not be performed, due to missing single VPCs during sleep. ANOVA of TO and TS in OSAS patients' groups (see Table 2) showed that, while TO values did not significantly differ between groups, TS significantly decreases from mild to severe patients, with a significant Dunn's multiple comparisons post-test only between mild vs. severe OSAS pts.

Table 1. HRT analysis in OSAS pts' groups.

| | Mild | Moderate | Severe |
|---|---|---|---|
| # Analysed Rec. | 82 | 74 | 65 |
| #VPC | 85±113 | 56±67 | 90±96 |
| TO (%) 25% perc. | -1.4 | -1.6 | -1.5 |
| TO (%) Median | -0.5 | -0.5 | -0.8 |
| TO (%) 75% perc. | 0 | 0.1 | 0.1 |
| TS (ms/RR) 25% perc. | 1.2 | 0.6 | 0.2 |
| TS (ms/RR) Median | 2.6 | 2.0 | 1.6 |
| TS (ms/RR) 75% perc. | 4.5 | 4.1 | 4.3 |

Table 2. ANOVA of TO and TS in OSAS pts' groups.

| TO (%) | | |
|---|---|---|
| Kruskal-Wallis test | p = 0.89 | |
| Dunn's Multiple Comp. Test | rank sum | Significance |
| Mild vs Moderate | 1,098 | Ns |
| Mild vs Severe | 5,313 | Ns |
| Moderate vs Severe | 4,215 | Ns |
| **TS (ms/RR)** | | |
| Kruskal-Wallis test | p = 0.02* | |
| Dunn's Multiple Comp. Test | rank sum | Significance |
| Mild vs Moderate | 16,86 | Ns |
| Mild vs Severe | 28,29 | * |
| Moderate vs Severe | 11,43 | Ns |

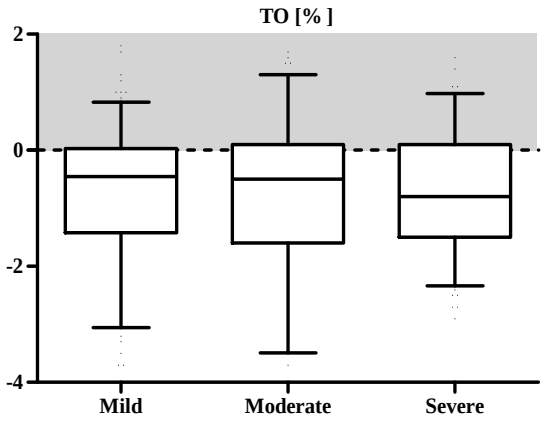


Figure 2. TO values in OSAS groups. Abnormal values over TO=0% cutoff dotted line in grey area.

## 4. Discussion

The study shows that OSAS severity is associated to decreased heart rate turbulence slope highlighting the following four novel findings.

The first one is that HRT analysis has been proved as an appropriate technique for the autonomic balance evaluation in OSAS, being suitable in over 90% of patients with disease of varying degrees.

The second is that VPC's number showed differences in means non statistically significant at ANOVA test between the three groups, confirming in some way that the only traditional ECG holter analysis of cardiac arrhythmias in OSAS doesn't allow to differently describe desease severity.

The third is that, considering that most clinical studies reported cutoff normal values of TO<0% and TS>2.5 ms/RR [14], data indicate that the main BRS alterations do not appear in the early HRT phase triggered by transient vagal inhibition, with TO<0 normal values in mild to severe pts., but during the slow one, due to the sympathetic hyperactivity affecting the heart rate recovery, with TS<2.5 abnormal values associated to increasing OSAS severity.

But the forth and most interesting clinical finding is that (see Box&Whiskers plot in Figure 3, lines from the bottom upwards respectively at $10^{th}$, $25^{th}$, median, $75^{th}$ and $90^{th}$ percentile of the distributions), while the simple polysomnographic analysis would have equally stratified the risk inside mild to severe groups, abnormal TS values allows to identify about a 70% of severe OSAS patients at higher risk of sudden cardiac death, about a 60% of moderate OSAS patients with greater probability to develop cardiovascular impairments, and also about a 50% of mild OSAS patients, normally not submitted to any medical treatment, with abnormalities in cardiac autonomic activity even in the absence of overt cardiac disease, suggesting, however, to start a therapy.

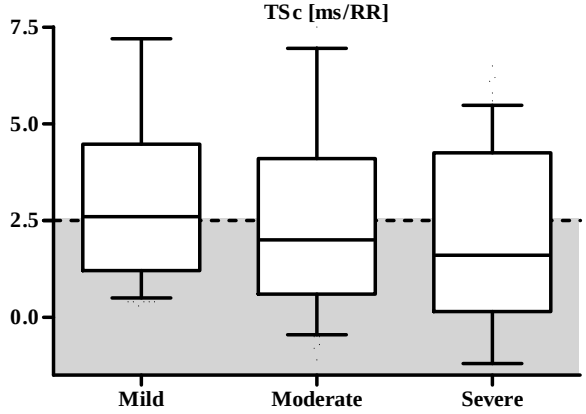


Figure 3. TS values in OSAS groups. Abnormal values below TS=2.5 ms/RR cutoff dotted line in grey area

## 5. Conclusion

Although there is a well-known evidence of sympathetic nervous system increasing activity in patients with sleep-disordered breathing, the pathophysiological mechanisms leading to cardiovascular disease in OSAS are complex and still not fully understood. HRT analysis appeared as a suitable tool for the autonomic control assessment in OSAS patients and further studies need to deeply investigate HRT alterations implicated in patients with mild-to-severe OSA.

Our study shows that nighttime heart rate turbulence slope decreasing is associated to rising OSAS severity. It may be therefore speculated that heart rate turbulence slope alterations may precede the development of cardiovascular disease in patients with OSAS. These findings support the conclusion that HRT assessment could have an in-time prognostic value related to the development of cardiovascular disease in OSAS [18,19], allowing to detect patients at greater probability of worsening, and stratifying their risk within the degree of OSAS severity.

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