Sleep related bradyarrhythmic events and heart rate variability in apparently healthy individuals

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ABSTRACT

Objective: It is thought that abnormal cardiac impulses of the autonomic nervous system during sleep are responsible for sleep-related bradyarrhythmias. Despite a proposed common etiopathogenesis and having common name of "sleep-related bradyarrhythmias," precise importance of sinoatrial or atrioventricular (AV) node involvement remains elusive. This study aimed to determine whether there is a difference in sleep-related bradyarrhythmias from the point of view of heart rate variability (HRV).

Methods: Patients were evaluated using 24-hour Holter electrocardiogram monitor. After careful medical evaluation, apparently healthy individuals with sleep-related sinus pauses ≥ 2 seconds on at least 1 occasion or those in whom Mobitz type I AV block occurred were included. Frequency and time domain analyses were conducted for daytime, nighttime, and 24-hour period.

Results: Total of 37 patients with sinus pause(s), 40 patients with Mobitz type I AV block(s), and 40 healthy controls were included. On HRV analyses, all time and frequency domain parameters were better in sinus pause group for daytime, nighttime, and 24-hour average (p<0.05 for all). Results of heart rate-corrected HRV analyses still showed significantly better total power (TP) and very low frequency (VLF) in the sinus pause group compared with AV block group (TP: 7.1×10^{-3} vs. 5.4×10^{-3}, p=0.011; VLF: 4.9×10^{-3} vs. 3.7×10^{-3}, p=0.007).

Conclusion: Despite proposed common autonomic mechanisms, sleep-related sinus pause cases demonstrated better HRV profile in comparison with Mobitz type I AV block. *(Anatol J Cardiol 2017; 17: 235-40)*

Keywords: atrioventricular block, heart rate variability, REM sleep-related sinus arrest, vagal syndromes

Introduction

There is an association between development of cardiac autonomic wave activity and development of sleep-related bradyarrhythmic events. These bradyarrhythmic events are sinoatrial (SA) and atrioventricular (AV) node-based and represent a broad spectrum of conditions seen in healthy individuals, mostly during rapid eye movement (REM) sleep. While imprecise, previous studies have reported such conditions to be a common occurrence. It is thought that pauses lasting >2 seconds are seen at an incidence of 26.6%, at a ratio of 5.1% in Mobitz type I, and at a ratio of 0.8% in Mobitz type II AV block (1). Despite obscure pathogenic nature of these bradyarrhythmias, abnormal cardiac impulses of the autonomic nervous system (ANS) during REM sleep are thought to be responsible for these arrhythmias. Increased nocturnal parasympathetic activity and withdrawal of sympathetic activity in various sleep state cycles can result in abnormal response from the SA and AV nodes (2). REM sleep-related sinus ar-

rests may last from 2 to 15 seconds (3). Similarly, even in its mildest form, it can last up to 11 seconds in cases with REM-related complete AV block (4). Despite the alarming level these bradyarrhythmia episodes can reach, they are often benign in character (5). Though referred to with a common name, "REM-related bradyarrhythmias," and thought to perhaps have a common mechanism, precise reasons and roles of SA and AV node involvement remain elusive. Innervation to both nodes overlaps substantially and each comprises specific neural connectivity. Right stellate ganglion and right cervical vagus nerve predominate in SA node, while AV node conduction is primarily controlled by left stellate ganglion and left cervical vagus nerve (6). Central nervous system interaction of these innervations, individual differences in autonomic balance, and unknown local or neuro-endocrine factors may certainly play a role and account for REM-related bradyarrhythmias.

Heart rate variability (HRV) is used to stratify risk in conditions such as myocardial infarction, heart failure, malignant arrhythmias, diabetic neuropathy, and many other illnesses (7). It is

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defined as variation of beat-to-beat intervals also known as RR intervals. The main structure that determines HRV is SA node. No matter how much influence non-autonomic factors exert on SA node, ANS is the main determinant (8).

To the best of our knowledge, there is not enough information presently in the literature regarding different sleep-related bradyarrhythmias and ANS activity. To address this, the present study was conducted to evaluate ANS activity in different types of sleep-related bradyarrhythmia from point of view of HRV.

Methods

Participants

Our study was designed as a cross-sectional, observational study that was conducted between January 2014 and January 2016. The plan for the study was to include patients aged between 18 and 65 years from cardiology outpatient clinic of Dışkapı Yıldırım Beyazıt Training and Research Hospital who were evaluated with 24-hour Holter electrocardiogram (ECG) monitor. Cases with sinus pauses of greater than or equal to 2 seconds on at least 1 occasion and those in whom Mobitz type I AV block was seen were evaluated in detail by an experienced cardiologist. Those with known arrhythmic disease, any conduction abnormality seen on surface ECG, permanent cardiac pacemakers, abnormal heart rhythms, syncope history, inappropriate sinus tachycardia, use of any medication that could potentially affect autonomic function (e.g., beta-blocker, calcium channel blocker, or similar), any structural heart disease (coronary heart disease history or echocardiographic evidence of valvular or muscular abnormalities), anemia, diabetes mellitus, electrolyte imbalance, history of stroke, hypertension, renal failure, thyroid function anomaly, pregnancy at time of study, systemic inflammatory illness or obstructive sleep apnea syndrome (OSAS) were all excluded from the study, as we wanted to analyze an apparently healthy population. Clinical history details and blood analyses were obtained from all participants. Age, gender, height, and weight information were recorded, as were presence or absence of hypertension, hyperlipidemia, and smoking habit, as all are risk factors for cardiovascular disease. Detailed questions assessing OSAS were asked; those who had pre-existing diagnosis of OSAS, history of loud or frequent snoring, choking or gasping during sleep, and excessive daytime sleepiness were also excluded from the study on grounds of suspicion of OSAS. Patients with daytime SA or AV-related bradyarrhythmic events, advanced AV block during the night, overlapping AV and SA node-related bradyarrhythmic events, extra systoles occurring at frequency exceeding 2 or more events per hour, or any sustained or non-sustained tachyarrhythmias were also excluded. Eventually, 37 subjects with sinus pause(s), 40 subjects with Mobitz type I AV block(s) and 40 age matched controls without any sleep related bradyarrhythmic events were included.

Every patient provided written, informed consent and the study was approved by the Local Ethics Committee. Cardiac func-

tion of participants was evaluated with echocardiography (Philips Healthcare, Andover, MA, USA) equipped with S5-1 probe.

24-Hour ECG (Holter) monitor analysis

We evaluated 24-hour Holter monitor recordings to assess HRV parameters in cases with sleep-related bradyarrhythmic events. HRV evaluations were performed by an experienced physician who was totally blind to study population. Holter ECG test was performed using 3-channel digitized recorder (DMS CardioScan Holter System 300-3A; DM Software, Stateline, NV, USA). Before data analysis, recordings obtained were manually preprocessed. Data with noise was excluded. HRV measurements were obtained using commercially available Holter software program (DMS CardioScan 12.0; DM Software, Stateline, NV, USA). For analysis of data, daytime was period between 6:00 a.m. and 11:00 p.m. and nighttime period was defined as 11:00 p.m. through 6:00 a.m. Patients confirmed that they were asleep during pause or block episode(s) recorded that occurred during the night.

Time domain HRV indices were statistically analyzed. Root mean square of successive differences (RMSSD), standard deviation of normal-to-normal (NN) intervals (SDNN), SDNN index (mean of deviation of the 5-minute NN intervals over the entire recording), standard deviation of averages of NN (SDANN) intervals calculated over 5-minute periods of the entire recording, and proportion of adjacent RR intervals differing by more than 50 milliseconds in the 24-hour recording (pNN50) were measured. Mean RR interval was also calculated. All data were measured according to Task Force of The European Society of Cardiology and the North American Society of Pacing and Electrophysiology (7). Frequency domain analysis of HR variability included total power (TP), high frequency (HF) component (0.15–0.40 Hz), low frequency (LF) component (0.04–0.15 Hz), and very low frequency (VLF) component (0–0.04 Hz). In order to off-set mathematical influencers on HRV parameters, VLF, LF and TP were divided by square of averaged RR interval, while HF was divided by the power of 5 of the averaged RR interval as previously described (9).

Asystole of at least 2 seconds in duration without evident P-wave was classified as sinus pause. Second-degree Mobitz type I AV block with narrow QRS complexes (increasing P-R interval on ECG until 1 impulse is not conducted) was accepted as Mobitz type I AV block.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences for Windows software, version 21.0 (SPSS, Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed or not. Continuous variables were expressed as mean±SD or median (interquartile range) values, whereas categorical variables were presented as percentages. To analyze statistical differences between categorical variables, chi-square test was used. Where appropriate, one-way analysis of variance

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Table 1. Comparison of demographic data and heart rate variability measures of patients

Variables	Control group (n=40)	Mobitz type I AV block (n=40)	Sinus pause (n=37)	P	P*	P#	P^
Minimum HR (min⁻¹)	48±7.3	45±6.3	36±5.6	<0.001	0.043	<0.001	<0.001
BMI, kg/m²	21.2 (19.2–22.9)	21.5 (19.2–22.8)	20.8 (19.5–23.1)	0.977	–	–	–
Age, years	28.5 (25.2–34)	30.0 (25–35)	29 (26–33.5)	0.938	–	–	–
Average HR (min⁻¹)	79 (73–85)	75 (71–84)	63 (57–74)	<0.001	0.518	<0.001	<0.001
Maximum HR (min⁻¹)	142 (134–152)	138 (124–153)	124 (101–151)	0.006	0.539	0.004	0.186
Sex, female, n (%)	22 (55)	26 (65)	18 (48)	0.343	–	–	–
Smoking, n (%)	5 (12.5)	4 (10)	6 (16)	0.715	–	–	–
Time domain parameters, ms							
SDNN	146±42.2	135±39.4	170±36.7	0.001	0.711	0.023	0.001
Mean RR	768 (711–828)	790 (714–831)	928 (851–1068)	<0.001	1.000	<0.001	<0.001
SDNN-i	56 (46–73)	54 (47–66)	77 (60–99)	<0.001	1.000	<0.001	<0.001
SDANN-i	132 (105–154)	114 (95–150)	148 (116–184)	0.007	0.949	0.101	0.006
rMSSD	31 (24–44)	30 (25–39)	54 (37–70)	<0.001	1.000	<0.001	<0.001
pNN50 (%)	8.5 (4–20)	7 (5–15)	21 (14–36)	<0.001	1.000	<0.001	<0.001
Frequency domain parameters, ms²							
TP	3077 (2089–5102)	2789 (2088–4204)	5779 (3803–8512)	<0.001	1.000	<0.001	<0.001
VLF	2166 (1467–3192)	1941 (1400–2925)	3592 (2560–5960)	<0.001	1.000	<0.001	<0.001
LF	704 (415–1220)	656 (421–954)	1368 (664–1680)	<0.001	0.951	0.008	<0.001
HF	233 (128–606)	219 (139–353)	551 (302–727)	<0.001	1.000	0.004	<0.001
LF/HF	2.8 (1.9–3.5)	2.5 (1.8–3.8)	2.2 (1.8–3.2)	0.289	–	–	–

P*= pairwise comparison between control and Mobitz type I AV block; P#= pairwise comparison between control and sinus pause; P^= pairwise comparison between Mobitz type I AV block and sinus pause. AV - atrioventricular; BMI - body mass index, HF - high frequency (0.15–0.4 Hz); HR - heart rate; LF - low frequency (0.04–0.15 Hz); LF/HF - low to high frequency ratio; pNN50 - percentage of RR intervals that are at least 50 ms different from previous interval; rMSSD - square root of mean of squared successive differences in RR intervals; SDANN-i - standard deviation of 5-minute means of RR intervals; SDNN - standard deviation of all normal RR intervals; SDNN-i - mean of 5-minute standard deviations of RR intervals; TP - total power (0.0–0.5 Hz); VLF - very low frequency (0.003–0.04 Hz). All values are mean±SD, median value (interquartile range), or n (%)

or Kruskal-Wallis test was used to compare the 3 groups with continuous variables.

Bonferroni multiple comparison post hoc test (for data with normal distribution) and Dunn's test (for data without normal distribution) were used to perform pair-wise comparison. All p-values were 2-sided and p-value of <0.05 was considered significant.

Results

Total of 37 people were identified as having sinus pause and 40 had Mobitz type I AV block. These were matched with 40 control participants of similar age and sex without any sleep related-bradyrhythmic evets. Mean age for entire group of 117 participants was 29.7±6.3 years. Groups were comparable in baseline characteristics including age, gender, body mass index (BMI), and cigarette use (Table 1).

On average, the group of sinus pause cases had higher values for maximal and minimal heart rate. Average and maximum heart rates were similar in control and Mobitz type I AV block groups (p=0.115, p=0.151, respectively); minimum heart rate was higher in the block group (p=0.043). Average number of events

was 1.58±0.4 in Mobitz type I AV block group and 1.69±0.5 in sinus pause group (p>0.05).

All time and frequency domain parameters in 24-hour Holter ECG HRV analyses (with exception of LF/HF) were better and statistically significant in sinus pause group (Fig. 1). There was no significant difference in any of HRV parameters between control and Mobitz type I AV block groups (p>0.05). In circadian HRV analysis, both daytime and nighttime HRV parameters were significantly better in sinus pause group (Table 2). Pairwise comparison of control and block groups did not yield any results that reached statistical significance (p>0.05).

Results of corrected HRV analyses still showed significantly better TP and VLF in sinus pause group compared with Mobitz type I AV block group (TP: 7.1×10^{-3} vs. 5.4×10^{-3}, p=0.011; VLF: 4.9×10^{-3} vs. 3.7×10^{-3}, p=0.007).

Discussion

In the current study, for the first time, it was demonstrated that sleep-related sinus pauses have more favorable HRV indices in comparison with Mobitz type I AV block and healthy controls.
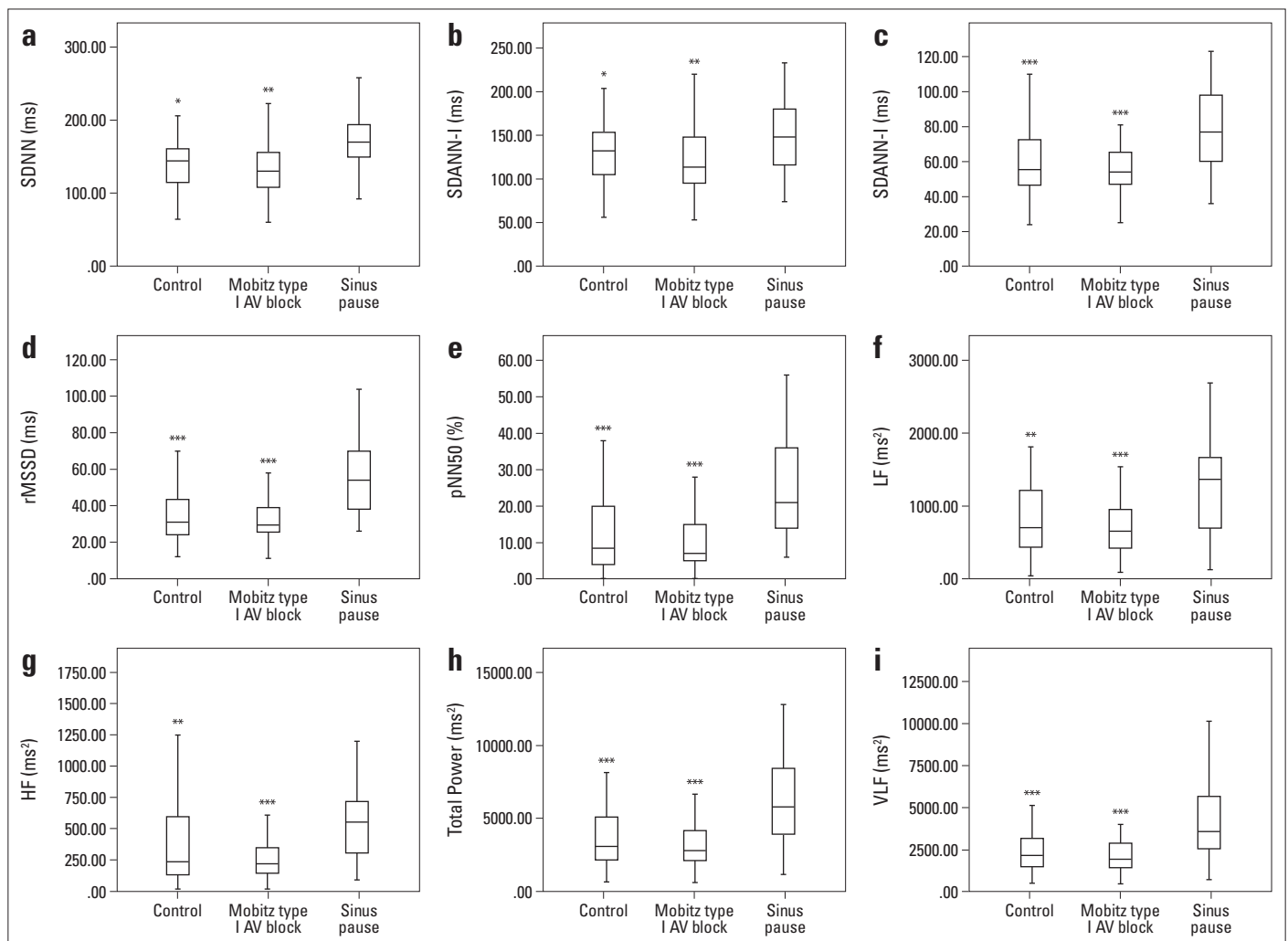
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Figure 1. Comparison of frequency and time domain heart rate variability indices between groups. (a) SDNN, (b) SDANN-i, (c) SDNN-i, (d) rMSSD, (e) pNN50, (f) LF, (g) HF, (h) TP, and (i) VLF analysis of patients with sleep-related Mobitz type I AV block, sleep-related sinus pause, and controls

AV - atrioventricular; HF - high frequency (0.15–0.4 Hz); LF - low frequency (0.04–0.15 Hz); pNN50 - percentage of intervals that are at least 50 ms different from previous interval; rMSSD - square root of mean of squared successive differences in RR intervals; SDANN-i - standard deviation of 5-minute means of RR intervals; SDNN - standard deviation of all normal RR intervals; SDNN-i - mean of 5-minute standard deviations of RR intervals; TP - total power (0.0–0.5 Hz); VLF - very low frequency (0.003–0.04 Hz). *$P<0.05$ compared with sinus pause group; **$P<0.01$ compared with sinus pause group; ***$P<0.001$ compared with sinus pause group

Furthermore, favorable HRV profile in sinus pause group was maintained during day and night periods. These findings suggest that there may be some independent and undefined neurophysiological mechanisms in development of different kinds of sleep-related bradyarrhythmias.

Sleep-associated bradyarrhythmias were reported for the first time in 1984 by Guilleminault et al. (3) as sinus arrest observed during REM sleep. Report of REM-associated AV blocks as well suggested that ANS imbalance observed during this period of sleep might be the etiological factor (10, 11). Effect of ANS on heart varies according to circadian rhythm and sleep state cycle (2). Actual etiology of these bradyarrhythmias, thought to be associated with vagal effect, is unknown. Moreover, in spite of common mechanism thought to be due to autonomic imbalance, it is not known if presence is associated with SA node in some people while AV node in others. The fact

that cardiac SA and AV nodes have different autonomic connections, the complex interactions of central cardio-inhibitory and cardio-accelerating centers, differences between SA and AV nodes, and many other undiscovered factors may have an effect in this matter (12).

Heart rate and HRV are identified as strong predictors of cardiovascular outcome (13). It was reported in a large-scale meta-analysis that low HRV is associated with a 32% to 45% increased risk of first cardiovascular event in populations without known cardiovascular disease, and increase in SDNN of 1% results in 1% lower risk of fatal or non-fatal cardiovascular disease (14). HR is known to have an important effect on HRV (15). Lower heart rate provided by higher parasympathetic activity and better HRV have positive effect on cardiovascular outcomes (7). In this study, cases with sinus pause during sleep under 24-hour Holter ECG are thought to have increased parasympathetic

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Table 2. Comparison of awake and sleep data

Awake							
	Control group (n=40)	Mobitz type I AV block (n=40)	Sinus pause (n=37)	P	P*	P#	P^
SDNN (ms)	125±40	120±31	148±34	0.002	1.000	0.017	0.003
rMSSD (ms)	28 (21-40)	28 (23-32)	49 (32-68)	<0.001	1.000	<0.001	<0.001
pNN50 (%)	7 (3-16)	6 (3-11)	18 (9-34)	<0.001	1.000	<0.001	<0.001
TP (ms²)	2829 (2108-4504)	2787 (1996-4118)	4985 (3145-8498)	<0.001	1.000	0.001	<0.001
VLF (ms²)	1981 (1546-2652)	2049 (1382-2969)	3248 (2201-6229)	<0.001	1.000	0.001	0.001
LF (ms²)	670 (380-1179)	567 (390-989)	1274 (603-1733)	<0.001	1.000	0.008	<0.001
HF (ms²)	185 (94-451)	185 (105-309)	444 (178-678)	0.001	1.000	0.008	0.001
Asleep							
	Control group (n=40)	Mobitz type I AV block (n=40)	Sinus pause (n=37)	P	P*	P#	P^
SDNN, ms	111 (80-140)	101 (77-124)	129 (102-172)	0.006	0.596	0.157	0.004
rMSSD, ms	34 (27-50)	32 (25-50)	70 (46-83)	<0.001	1.000	<0.001	<0.001
pNN50, %	13 (5-27)	11 (5-26)	31 (21-47)	<0.001	1.000	<0.001	<0.001
TP, ms²	3601 (2110-5730)	2906 (2176-4847)	6465 (4278-9463)	<0.001	0.861	0.001	<0.001
VLF, ms²	2378 (1382-3827)	1940 (1403-3045)	4183 (2745-6563)	<0.001	0.902	0.001	<0.001
LF, ms²	775 (439-1321)	612 (398-1032)	1183 (715-1737)	0.001	0.802	0.024	0.001
HF, ms²	355 (160-781)	266 (134-530)	632 (336-1134)	0.001	1.000	0.024	0.001

P*= pairwise comparison between control and Mobitz type I AV block; P#= pairwise comparison between control and sinus pause; P^= pairwise comparison between Mobitz type I AV block and sinus pause. HF - high frequency (0.15–0.4 Hz); LF - low frequency (0.04–0.15 Hz); pNN50 - percentage of RR intervals that are at least 50 ms different from previous interval; rMSSD - square root of mean of squared successive differences in RR intervals; SDNN - standard deviation of all normal RR intervals; TP - total power (0.0–0.5 Hz); VLF - very low frequency (0.003–0.04 Hz). All values are mean±SD, median value (interquartile range), or n (%)

tonus not only in nighttime sleep, but also during the daytime. Heart rate parameters were lower and all HRV parameters were significantly better compared with control and Mobitz type I AV block groups. In addition, it was observed that better HRV profile in these cases continued during both sleep and awake periods. Although common autonomic mechanisms are considered, HRV parameters of cases with Mobitz type I AV block are similar to those of control group. Exact cause of this condition is not known. In spite of limited literature data on this subject, in sleep research where Viola et al. (16) compared a case of second-degree AV block to 9 healthy patients in terms of HRV, they observed that the patient with AV block did not achieve increase in HRV and sympathetic parameters during REM period as did healthy individuals. Our study results indicated that temporary autonomic imbalance in development of Mobitz type I AV block is not a reflection of total autonomic activity of cases, unlike sinus pause. Higher HRV values seen in subjects with sleep-related sinus pause(s) were not just a sleep-related effect. We found that higher HRV was continuous throughout both day and night in sinus pause group. In the present study, lower heart rates during sinus pauses might be due to increased vagal tone. While it is assumed that positive effect of this low heart rate on HRV comes from common autonomic mechanism, there may be a mathematical bias in standard HRV analyses depending on differences in average heart rates (17). Briefly, it can be said that same degree

of vagal activity causes higher RR interval prolongation at longer baseline RR intervals, resulting in higher HRV. However, in some studies, non-corrected HRV parameters have been thought to be better predictors due to dependence on heart rate for cardiovascular prognostic effect (15). Yet, in analyses it has been shown that HRV parameters, which were more favorable in sinus pause cases compared with AV block cases, remained the same for corrected TP and VLF values also. Further studies are needed to determine clinical significance of HRV normalization procedure conducted according to average RR interval.

Study limitations

The main limitation of the present study is the relatively small number of participants and cross-sectional design. Additional HRV analysis methods and/or additional Holter monitoring would enhance repeatability and comparability. Moreover, study does not include any prolonged follow-up to assess clinical results of the findings. Although study population was relatively young with normal BMI, functional capacities of the patients could also be evaluated with quantitative methods. In addition, study findings cannot be generalized to all age groups. Finally, although OSAS was among study exclusion criteria, we did not perform ambulatory home polysomnographic study to safely exclude OSAS. We think that it's very unlikely inclusion of OSAS patient

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in our study population would have affected study results since participants were low-risk, young, healthy individuals. Further studies are required to clarify exact mechanisms of enhanced autonomic functions in sleep-related sinus pause cases.

Conclusion

In conclusion, sleep-related sinus pause cases demonstrated lower HR and better HRV profile compared with healthy individuals. Despite proposed common autonomic mechanisms, similar HRV effect was not observed in participants with sleep-related Mobitz type I AV block. Further studies are required to address this issue.

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