

Overnight T-Wave Alternans in Sleep Apnea Patients

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Abstract

Sleep apnea (SA) is linked to cardiovascular complications and to an increased risk of sudden cardiac death. Microvolt T-wave alternans (TWA) is a non-invasive electrocardiographic (ECG) index of cardiovascular risk; its rate of occurrence in SA patients remains unknown. Thus, this study investigated the occurrence of TWA in SA patients during night. To this aim, overnight ECG recordings of 16 SA patients were analyzed for TWA identification by means of our heart rate adaptive match filter. Results indicate that overnight TWA was characterized by a low mean amplitude (mean TWA: 6 ± 3 μ V). However, higher-amplitude transient TWA episodes (max TWA: 29 ± 21 μ V) occurred overnight, sometimes when patients were awake (max TWA: 33 ± 18 μ V; 56% of cases) and sometimes when patients were sleeping (max TWA: 24 ± 23 μ V; 44% of cases with 13%, 19%, 6% and 6% during sleep stage 1, 2, 3 and 4, respectively). In only 3 subjects (19%) TWA peaks occurred during an SA episode: during obstructive apnea with arousal in two cases (max TWA of 7 μ V and 17 μ V, during stages 1 and 2, respectively) and during hypoapnea with arousal in one case (max TWA of 6 μ V while awake). Thus, SA patients show significant transient overnight TWA episodes, not necessarily occurring during a SA episode.

1. Introduction

Sleep is a periodic state of mind and body that differs from wakefulness because of a decreased ability to react to stimuli, a reduced consciousness, an almost complete inhibition of sensory and voluntary-muscles activities, and a drastic reduction of interactions with surroundings. By analyzing an electroencephalogram, sleep can be divided into two phases: non rapid eye movement (non-REM), also known as quiet sleep, and REM, also known as active sleep or paradoxical sleep. The non-REM phase can be further classified in stages 1 to 4. Stage 1 corresponds to drowsiness: eyes move slowly and muscle activity decreases. Stage 2 corresponds to light sleep: eyes do not move and heart rate (HR) and breathing

decrease. Stages 3 and 4 correspond to deep sleep: no eye movement and no muscle activity occur. Eventually, during the REM phase, rapid eye movements occur and HR and breathing increase. Sleep does not sequentially progress through the five stages and cycles every 90-120 minutes through them approximately four or five times per night.

Good sleep is necessary for optimal health and sleep disorders may affect hormone levels, mood and weight. Sleep apnea (SA) is one of the most common sleep disorders. It affects about 10% of adults in the general population and may overcome 50% in certain cardiovascular diseases involving sodium and water retention [1-4]. SA is a disorder in which breathing pauses of at least 10-15 s occur while sleeping. Breathing pauses can last as long as minutes and may reach an occurrence frequency of more than 30 times per hour. It can be classified in obstructive apnea (OA), the most common, when due to a collapse of the upper airway, or central apnea (CA), when due to a loss of ventilatory drive [2]. Hypopnea (HA) is less severe than SA and occurs when a shallow and slow breathing reduces the oxygen supply to lungs.

Although not yet used for cardiovascular risk assessment, there is a growing evidence that SA may cause or promote several cardiovascular diseases among which hypertension, coronary artery disease, heart failure and arrhythmias, and thus may be used as an index of risk for cardiovascular death [1,5,6,7,8]. Microvolt T-wave alternans (TWA), consisting in a subtle alternation of the electrocardiographic (ECG) T wave, is a promising non-invasive indicator of sudden cardiac death [9]. Although low-levels of TWA have been also observed in resting healthy subjects [10,11,12], TWA is more commonly found in patients affected by cardiovascular diseases [11,13,14,15,16] and its amplitude tends to increase with increasing heart rate (HR) [9,17,18]. As a consequence, since HR decrease during sleep and TWA is more hardly detectable, only few studies have investigated TWA incidence during sleep, especially when SA occurs [7,19]. Thus, aim of this study was to investigate the occurrence of TWA in SA patients during night to evaluate if TWA represents a potential tool to identify SA subjects at increased cardiovascular risk.

2. Methods

2.1. Clinical data

Clinical data consisted of sixteen 2h-to-7h long polysomnographic recordings all including several physiological signals (sampling rate: 250 Hz; resolution: 12 bit), among which a respiratory signal, a single channel ECG signal, an electroencephalographic signal, and an invasive blood pressure signal. Sleep stages and apnea were annotated every 30 s according to the Rechtschaffen and Kales's criteria [20]. Subjects were monitored in Boston's Beth Israel Hospital Sleep Laboratory for evaluation of chronic obstructive sleep apnea syndrome and to test the effects of continuous positive airway pressure, a standard intervention that generally prevents or reduce airway obstruction in pathological conditions. Data are available in the MIT-BIH Polysomnographic Database [21] by PhysioNet [22].

2.2. Automatic T-wave alternans identification

Automatic TWA identification was performed in four steps: windowing, preprocessing, suitability testing and adaptive filtering [23,24].

Windowing. From each recording, ECG windows containing 128 consecutive heart beats were recursively extracted with step of 30 s in order to match respiration windows used to annotate apnea.

Preprocessing. Each extracted ECG window was initially cleaned using a band-pass bidirectional 6th-order Butterworth filter (cut-off frequencies:0.5Hz and 45 Hz). Then, R peaks were detected and used to compute mean RR interval (RR), HR (as $1/RR$), and RR-interval standard deviation (RRSD) over the window. Baseline was estimated by a 3rd order spline interpolation of fiducial points located 70 ms before the R peaks and subtracted from the ECG window. Ectopic and corrupted beats were replaced by the median beat.

Suitability test. Once preprocessed, the ECG window was tested to evaluate its suitability for TWA identification. Specifically, if $RRSD \leq 0.1 \cdot RR$ and there were at most 10 replaced beats the window was considered suitable, otherwise it was rejected (i.e. considered not suitable for TWA identification).

Heart-rate adaptive match filter. TWA was automatically detected and quantified within each window using the heart-rate adaptive match filter (HRAMF) [23,24]. After having computed the TWA fundamental frequency (FTWA) as $1/(2 \cdot RR)$, HRAMF used FTWA to adaptively design a narrowband-pass filter with a 0.12 Hz wide passing band centred in FTWA. HRAMF was implemented as a 6th-order bidirectional Butterworth band-pass filter. After having processed the

ECG window, HRAMF provided a pseudo-sinusoidal signal that, in case of TWA, had maxima and minima occurring in correspondence of the ST segment or T wave. TWA amplitude was directly given by the pseudo-sinusoid amplitude.

2.3. Statistics

Each recording was characterized in terms of: mean HR, expressed as mean RR (MRR); HR variability (HRV), quantified as RR standard deviation; mean TWA; TWA variability (STD TWA), quantified as TWA standard deviation; and maximum TWA (max TWA). All statistics were quantified over the entire duration of the recording. Overnight association between HR and HRV and TWA was evaluated by computation of the correlation coefficient (ρ). Statistical significance (P) was set at 0.05.

3. Results

An example of overnight TWA and RR trends are represented in Fig. 1 that shows how TWA was generally low amplitude but, occasionally, it may show transient higher-amplitude episodes, usually close to regions with too high RRSD (dotted lines) for TWA to be detected.

Overall, overnight TWA was characterized by a low mean amplitude (mean TWA: $6 \pm 3 \mu V$; Table 1) and was associated to a quite low mean HR (71 ± 8 bpm corresponding to $MRR = 851 \pm 85$ ms; Table 1). However, higher-amplitude transient TWA episodes (max TWA: $29 \pm 21 \mu V$; Table 1) occurred overnight, sometimes when patients were awake (max TWA: $33 \pm 18 \mu V$; 56% of cases) and sometimes when patients were non-REM sleeping (max TWA: $24 \pm 23 \mu V$; 44% of cases with 13%, 19%, 6% and 6% during sleep stage 1, 2, 3 and 4, respectively; Table 1). No high amplitude TWA occurred during REM sleeping. Within the accepted HRV levels, TWA peaks increased with HRV ($\rho = 0.50$, $P < 0.05$). In only 3 subjects (19%) max TWA occurred during an apnea episode: during obstructive apnea with arousal in two cases (max TWA of $7 \mu V$ and $17 \mu V$, during stages 1 and 2, respectively; Table 1) and during hypopnea with arousal in one case (max TWA of $6 \mu V$ while awake; Table 1).

4. Discussion

This study investigated the occurrence of TWA in SA during night. Overnight TWA was automatically identified by using the HRAMF, a method particularly suitable for TWA identification in case of low HR (such as during sleeping) and relatively high HRV [10,23]. Still, in our SA patients, on average 55% of ECG windows were rejected because characterized by too high HRV

Table 1. Overnight HR and TWA features

Sbj	Overnight apnea	#suitable wnd	MRR (ms)	HRV (ms)	mean TWA (μ V)	STD TWA (μ V)	max TWA (μ V)	RR @max TWA (ms)	Sleep @max TWA	Apnea @max TWA
1	HA	537 (90%)	948	53	6	5	56	950	4	*
2	,HA,OA	294 (47%)	697	58	6	3	20	751	2	-
3	HA, OA, CA	42 (6%)	878	30	5	1	8	836	3	-
4	OA	254 (35%)	768	46	6	7	46	755	W	-
5	HA,OA	453 (63%)	971	46	5	4	29	921	W	-
6	HA,OA,CA	359 (50%)	801	77	14	6	43	846	W	-
7	OA	188 (30%)	917	57	8	3	22	860	W	-
8	OA	271 (39%)	669	27	6	2	17	635	2	OA*
9	none	470 (61%)	906	92	4	5	45	860	W	-
10	none	633 (84%)	830	59	10	6	58	759	1	-
11	HA,OA	334 (44%)	938	68	9	5	41	831	W	-
12	HA,OA,CA	285 (60%)	855	63	2	1	6	889	W	HA
13	HA,OA,CA	568 (80%)	845	54	3	1	7	944	1	OA*
14	HA,OA,CA	416 (57%)	902	66	5	5	59	809	W	-
15	HA, OA	244 (56%)	827	50	1	1	4	670	W	-
16	OA,CA	120 (80%)	866	35	2	1	4	875	2	-
tot		342 \pm 163 (55 \pm 22%)	851 \pm 85	55 \pm 17	6 \pm 3	3 \pm 2	29 \pm 21	824 \pm 91		

Sleep classification. 1-sleep stage 1; 2 sleep stage 2; 3: sleep stage 3; 4: sleep stage 4; W: awake.

Apnea classification. CA: central apnea; HA: hypopnea; OA: obstructive apnea with arousal; -: no apnea

*: arousal

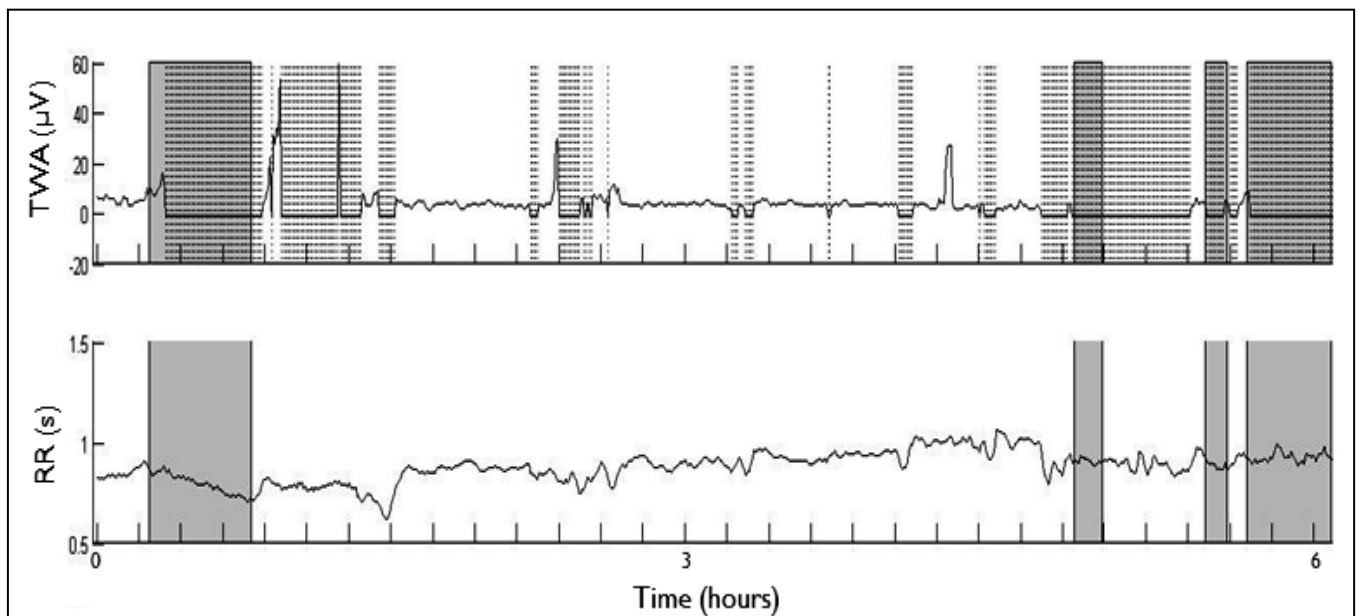


Figure 1. Overnight TWA and RR trends relative to patient number 14. Dotted lines are markers of not evaluable TWA (too high RRSD) whereas gray patches indicate occurrence of OA.

to allow TWA identification (Table 1). Yet, TWA was identified in all patients. Results indicate that, overnight, average TWA is low but short, transient, higher-amplitude TWA episodes usually occur. Moreover, they seem to occur in correspondence of regions characterized by higher HRV, often next to regions not suitable for TWA identification. Consequently, high-amplitude TWA episodes, and thus associated increment of cardiovascular risk, likely result underestimated. Future studies will evaluate the possibility of widening RRSD range for TWA identification in order to better assess high-amplitude TWA episodes in SA patients.

5. Conclusion

Average overnight TWA is negligible, but short, transient, higher-amplitude episodes of TWA may occur during night indicating an increment of cardiovascular risk. Such episodes not necessarily occur during an SA episode; rather they are concomitant with an increased HRV so that they result difficult to be reliably identified.

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