Sleep and Breathing (2019) 23:1275–1281
https://doi.org/10.1007/s11325-019-01823-5

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Signal-averaged P wave area increases during respiratory events in patients with paroxysmal atrial fibrillation and obstructive sleep apnea

Ken Monahan[1] · Edward Hodges[1] · Arpit Agrawal[1] · Raghu Upender[2] · Robert L. Abraham[1]

Received: 29 November 2018 / Revised: 4 March 2019 / Accepted: 6 March 2019 / Published online: 18 March 2019

Abstract

Purpose P wave characteristics change during simulated apneic events in individuals with atrial fibrillation (AF). This study sought to assess whether similar changes occur during nocturnal respiratory events in patients with AF and obstructive sleep apnea (OSA).

Methods Thirty-five individuals with severe OSA who underwent formal polysomnography and subsequent AF ablation were compared to a matched group without AF. Electrocardiographic segments from each polysomnogram corresponding to the following events were identified: period of wakefulness closest to the initial onset of sleep (baseline-awake), first respiratory event, respiratory event with the lowest nadir oxygen saturation, longest respiratory event, and last respiratory event. Signal-averaged P wave duration and signal-averaged positive P wave area (amplitude*duration for positive P wave amplitudes) were extracted using custom software. P wave characteristics during respiratory events and the baseline-awake condition were compared.

Results Compared to the baseline-awake condition, the signal-averaged positive P wave area was significantly greater during the longest event and the event with the lowest oxygen saturation in those with AF, but not in those without AF. There were no significant differences in signal-averaged P wave duration for any respiratory event compared to the baseline-awake condition, regardless of AF status.

Conclusion In patients with paroxysmal AF and obstructive sleep apnea, the signal-averaged positive P wave area is greater during certain respiratory events than during wakefulness. This finding may reflect the acute impact on right atrial volume of increased venous return associated with respiratory events and could be useful to assess AF risk in sleep apnea and to monitor response to treatment.

Keywords Obstructive sleep apnea · Atrial fibrillation · Electrocardiogram · P wave

Introduction

Knowledge of the relationship between obstructive sleep apnea (OSA) and atrial fibrillation (AF) continues to evolve. Epidemiologically, individuals with OSA have a higher prevalence of AF than unaffected individuals [1]. Physiologically, an episode of AF is much more likely to occur following a respiratory event than during normal breathing [2]. Mechanistically, OSA increases sympathetic nervous system activity, inflammation, atrial fibrosis, and enhances the inducibility of AF, potentially via increased atrial effective refractory period and decreased conduction velocity caused by contemporaneous hypercapnia [3, 4].

Development of parameters obtained from the surface electrocardiogram (EKG) that are capable of integrating these physiologic and mechanistic effects of OSA on the AF substrate could enhance clinical assessment of AF propensity both at a given time and longitudinally, as well as in response to OSA therapy. Signal-averaged P wave duration (SAPWD),

✉ Ken Monahan
ken.monahan@vumc.org

[1] Division of Cardiovascular Medicine, Vanderbilt Medical Center, Nashville, TN 37232, USA

[2] Department of Neurology, Division of Sleep Medicine, Vanderbilt Medical Center, Nashville, TN 37232, USA

which reflects intra-atrial and inter-atrial conduction characteristics and is derived from surface electrocardiography [5], is prolonged during wakefulness in those with OSA [6] and increases above baseline in response to simulated airway obstruction in awake individuals [7].

To expand upon this work done in awake subjects, we postulated that measuring changes in SAPW characteristics in response to respiratory events in real-time (i.e., during a polysomnogram [PSG]) could assist in refining risk estimates for AF and may also lend more detailed insight into the pathophysiologic relationship between OSA and AF. As an initial step in testing this hypothesis, we sought to apply signal-averaging techniques to EKG data from PSGs in a population with AF that would ultimately undergo AF ablation and in a group matched on OSA severity, but without AF. Specifically, we aimed to (1) compare SAPWD and SAPWArea (the product of P wave duration and amplitude) during respiratory events to periods of normal breathing and (2) assess changes in these parameters over the course of an entire PSG.

Methods

Study cohort

The AF cohort consisted of individuals that were part of the Vanderbilt Atrial Fibrillation Ablation Registry (VAFAR). The VAFAR is a prospective clinical and genetic biorepository that systematically enrolls patients undergoing AF ablation at our institution [8, 9]. To identify subjects in VAFAR who had undergone formal PSG in the Vanderbilt Medical Center's Sleep Lab, this registry was queried for all participants whose electronic chart contained a PSG report from our institution. PSGs dedicated to adjusting therapy (i.e., titration studies) were excluded, but the diagnostic portions of split-night studies were eligible for analysis. Only individuals who had a PSG prior to their index AF ablation were included. Subjects with AF throughout their PSG or with an atrial paced rhythm were excluded from the analysis. We reasoned that participants in the VAFAR, who by definition have a high propensity for paroxysms of AF, would have the greatest likelihood of manifesting changes in SAPW characteristics in response to respiratory events and thus would be the optimal group in which to conduct this feasibility/proof-of-concept analysis.

The pool of control group (no AF) candidates was assembled from our institution's Sleep Lab database and included individuals that were of similar age (± 1 year difference), the same gender, had a PSG in the same month within a 2-year window (i.e., if the case patient had a PSG in April 2015, controls needed to have had their study in April 2014, April 2015, or April 2016), and had a comparable apnea-hypopnea index (AHI) as one of the patients with AF. We defined comparable AHIs as being in the same qualitative category for non-severe OSA (i.e., none [AHI < 5 events/h], mild [5–15 events/h], moderate [16–30 events/h]) and within 10 events/h if the AHI was in the severe category (> 30 events/h). For each case, a control was randomly selected from the list of all individuals that met the above criteria.

Demographic and anthropomorphic data as well as medical history and basic PSG characteristics were abstracted from the electronic medical record.

Polysomnographic studies

Polysomnographic data were obtained from the formal PSG and the associated report. Standard protocols for data acquisition and scoring were used, as described previously [10, 11]. The EKG signal (lead II) was sampled at 200 Hz. Apnea-hypopnea index (AHI) was defined as the sum of apneic and hypopneic events divided by the total duration of sleep. All PSGs were formally interpreted by board-certified sleep physicians at our institution.

Using the annotated respiratory event-log, several key events were identified for each PSG: (1) the period of wakefulness closest to the initial onset of sleep ("baseline-awake"), (2) the first respiratory event of the study, (3) the longest respiratory event, (4) the respiratory event with the lowest nadir oxygen saturation, and (5) the last respiratory event of the study. The baseline-awake period serves as a reference to facilitate comparisons with the other events and is particularly useful for individuals with high AHI, when periods of normal breathing during the PSG may be infrequent.

Electrocardiographic data extraction

The annotated respiratory event log informed selection of digitized EKG data from the PSG. Portions of the EKG signal that corresponded to the events of interest were manually identified, checked for excessive artifact/ectopy, and extracted to ASCII files using a widely available European Data Format (EDF) viewer (https://www.teuniz.net/edfbrowser/; version 1.56). As pro-arrhythmic effects of respiratory events can persist after the event is over, EKG segments began at event onset and lasted for a total of 90 s [2]. The baseline-awake period was defined as the contiguous 90-s interval closest to sleep onset.

Signal-averaged EKG analysis

Based on established techniques [12], custom software (Matlab version R2017b; Natick MA) developed by one of the authors (RLA) performed the signal-averaging analysis using as input the raw EKG data extracted from PSGs. For the EKG segment associated with a given respiratory event, each PQRST complex was identified automatically, aligned, and averaged point-by-point. The P wave onset and

termination were identified preliminarily by the software and verified manually. The signal-averaged PQRST complex was automatically subdivided into P wave, QRS complex, and T-wave after manual evaluation of the tracings for artifact and after manual verification of the QRS detection threshold. To account for differences in signal level among events, the signal-averaged waveform was normalized such that the peak-to-peak amplitude of the QRS complex was equal to that of the baseline-awake signal-averaged QRS complex. This step assumes that the QRS complex amplitude is constant for the duration of the respiratory event of interest. The resulting normalized and signal-averaged P waves for each event were de-trended such that the beginning and end of the P wave were zero (i.e., the P wave emerged from and receded into the baseline).

Analysis of the de-trended, normalized, and signal-averaged P wave included examination of the P wave intervals and morphology. For each respiratory event (as well as the baseline-awake period) for each participant, output included SAPWD and signal-averaged positive P wave area (SAPPWArea), defined as the summed product of the sampling period and amplitude for each point in the P wave above the baseline:

$$\text{SAPPWArea} = \sum_{n=1}^{T} (A_n * \Delta t) * \left(\frac{sign(A_n) + 1}{2} \right)$$

T= SAPWD*f_s
A_n is the amplitude of the P wave at point "n"
f_s is the sampling frequency of the EKG signal
Δt= 1/fs

Restricting the SAPPWArea calculation to positive P wave amplitudes was done based on the hypothesized physiology of changes in atrial size during a respiratory event that we wished to capture. Namely, we suspected that positive deflections represented increased atrial volume due to increased venous return associated with the large changes in intra-thoracic pressure induced by an apnea or hypopnea.

Statistical analysis

Comparisons between continuous variables were made using the Mann-Whitney test, as the relevant covariates were non-normally distributed. Comparisons between categorical variables were made using Fisher's χ^2 test. Within each group (i.e., AF or no AF), data from the baseline-awake condition and from the respiratory event condition of interest were modeled as paired occurrences. Therefore, the Wilcoxon matched-pairs signed-rank test was used for comparisons of signal-averaged P wave characteristics between different conditions within the same group (i.e., baseline awake vs longest event in the AF group). Comparisons between groups (i.e., AF vs no AF) were not modeled as paired occurrences. All analyses were completed in GraphPad Prism 7.02 (GraphPad Inc.; La Jolla CA); $p < 0.05$ was considered statistically significant.

Results

Each group consisted of 35 individuals who were middle-aged, predominantly male, nearly all Caucasian, obese, and had severe OSA (Table 1), reflecting a referral population for PSG. At the time of the PSG, two thirds of the AF group was on atrioventricular nodal (AVN) blockers (non-dihyropyridine calcium channel blockers and/or beta-blockers) and two thirds were on dedicated anti-arrhythmic drugs (50% Vaughn-Williams [V-W] class IC, 25% V-W class III, 25% amiodarone). Slightly less than one-third of the no-AF group was on AVN blockers (predominantly for hypertension), and only one individual was on an anti-arrhythmic drug.

Respiratory event characteristics and the number of P waves analyzed are shown in Table 2. The vast majority of events lasted less than 1 min, and there were no differences in duration between the first, lowest saturation, and last events within or between groups. None of the first events occurred during REM sleep as they took place very early on in the

Table 1 Cohort characteristics

Characteristic	AF	No AF
Participants	35	35
Demographics		
Age (years)	61 ± 7	61 ± 8
Gender (% female)	20	20
Ethnicity (% Caucasian)	97	94
BMI (kg/m^2)	35 ± 8	33 ± 7
AF therapy		
AVN blockers (%)	69	31
AAD (%)	66	3
Polysomnography		
TST (min)	335 ± 70	316 ± 91
REM (%)	16 ± 10	15 ± 9
Nadir SpO2 (%)	81 ± 8	80 ± 8
AHI (events/h)	40 ± 33	41 ± 31
Echocardiography[a]		
LA A-P diameter (mm)	43 ± 6	42 ± 5
LVEF (%)	55 ± 6	52 ± 13

Values are mean ± standard deviation

AAD anti-arrhythmic drugs, *AF* atrial fibrillation, *AHI* apnea-hypopnea index, *A-P* anterior-posterior, *AVN* atrio-ventricular node, *BMI* body mass index, *LA* left atrium, *LVEF* left ventricular ejection fraction, *REM* rapid-eye movement sleep, *TST* total sleep time

[a] $n = 28$ for AF group and $n = 18$ for no-AF group

Table 2 Respiratory event characteristics and number of P waves analyzed

Condition	Respiratory event duration (sec)	REM at onset (%)	Time of onset	TST elapsed at onset (%)	No. of P waves analyzed
Baseline awake ($n = 35$)					
No AF	n/a	n/a	n/a	n/a	92 ± 20
AF	n/a	n/a	n/a	n/a	90 ± 15
First event ($n = 34$)					
No AF	18 ± 8	0	22:15 ± 3:43	12 ± 12	91 ± 29
AF	16 ± 5	0	22:32 ± 0:44	8 ± 6	95 ± 14
Longest event ($n = 35$)					
No AF	47 ± 13	31	0:42 ± 4:24	46 ± 28	84 ± 31
AF	42 ± 14	37	1:37 ± 2:13	50 ± 29	87 ± 17
Lowest SpO2 ($n = 34$)					
No AF	27 ± 13	46	0:22 ± 4:18	41 ± 26	87 ± 31
AF	24 ± 10	46	1:24 ± 2:01	46 ± 26	94 ± 14
Last event ($n = 29$)					
No AF	20 ± 7	23	3:56 ± 3:52	90 ± 16	87 ± 23
AF	18 ± 7	29	5:03 ± 0:49	95 ± 4	79 ± 23

Values are reported as mean ± standard deviation. Data for "Time of onset" represent the average absolute time of event onset ± standard deviation (i.e., in the AF group, the onset of the last event was 5:03 AM ± 49 min)

REM rapid-eye movement sleep, *SpO2* oxygen saturation by pulse oximetry, *TST* total sleep time

course of the PSG. There was no difference in prevalence of REM sleep between the remaining respiratory event conditions. The longest and lowest saturation events occurred at approximately the same time of night (although an hour earlier in the no-AF group compared to the AF group) and at the same percentage of sleep time elapsed.

A representative example of signal-averaging is provided in Fig. 1. All of the PQRST complexes that occurred during a single respiratory event from a single patient are displayed (royal blue). The signal-averaged P wave (green), QRS complex (magenta), and T-wave (cyan) are highlighted. For both the no-AF and the AF groups, the SAPWD (panel A) and SAPPWArea (panel B) for baseline-awake and each respiratory event condition are shown in Fig. 2. Within both groups, there were no significant differences in SAPWD between baseline-awake and any of the respiratory event conditions. However, the SAPWD was significantly longer in the AF group compared to the no-AF group for all respiratory event conditions with the exception of the last event. In the AF group, for the longest respiratory event and the respiratory

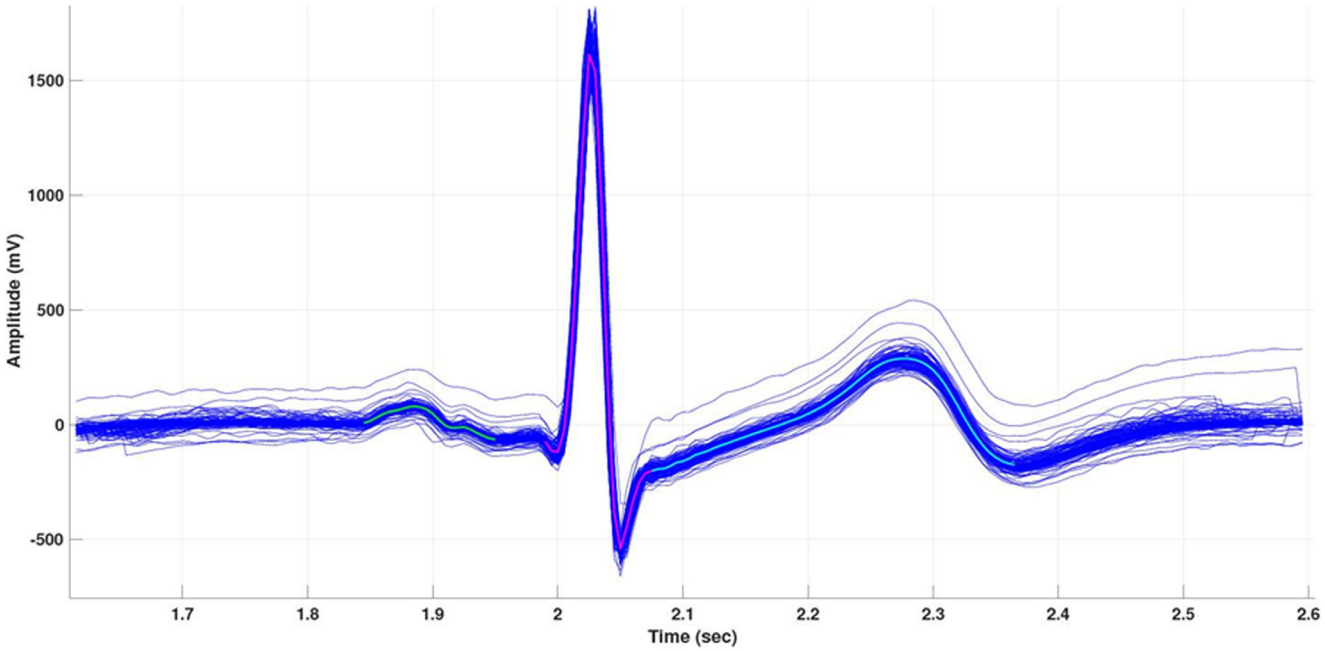

Fig. 1 Example of a signal-averaged P wave. For a single patient, all of the PQRST complexes that occurred during a single respiratory event are displayed (royal blue). These complexes are identified automatically, and each is temporally aligned on the QRS portion. Excessively noisy tracings are discarded, and the remaining complexes are averaged. The signal-averaged complex is automatically segmented into P wave (green), QRS (magenta), and T-wave (cyan). This segmentation is then verified manually

event with the lowest oxygen desaturation, the SAPPWArea was significantly higher compared to baseline-awake. The differences were not uniformly distributed around zero, indicating a non-random deviation from the null (Fig. 3). The differences from baseline-awake for the first respiratory events did not reach statistical significance but did show a trend in the same direction as the other conditions. There was no difference in SAPPWArea within the no-AF group nor was there a difference in this parameter between the AF and no-AF groups at any respiratory event condition.

Discussion

In patients with increased susceptibility to AF undergoing PSGs, we have demonstrated that signal-averaged positive P wave area increases during the longest and most hypoxia-inducing respiratory events relative to wakefulness. No such increase was found in a group of individuals with a similar burden of OSA, but without AF. In addition, consistent with prior work [13], we observed a longer SAPWD in those with AF compared to those without AF across all respiratory event conditions. These findings build on prior work in this field that evaluated SAPWD and P wave dispersion in awake individuals performing maneuvers that simulated apnea [7]. Expanding the study population to individuals undergoing standard sleep-laboratory PSGs extends the results to a more clinically applicable setting. In addition, the study suggests that SAPWD alone may not be the optimal indicator of acute changes to the atrial milieu in response to OSA events. It is plausible that transient alterations in atrial geometry, manifested by increased P wave amplitude, represent an important

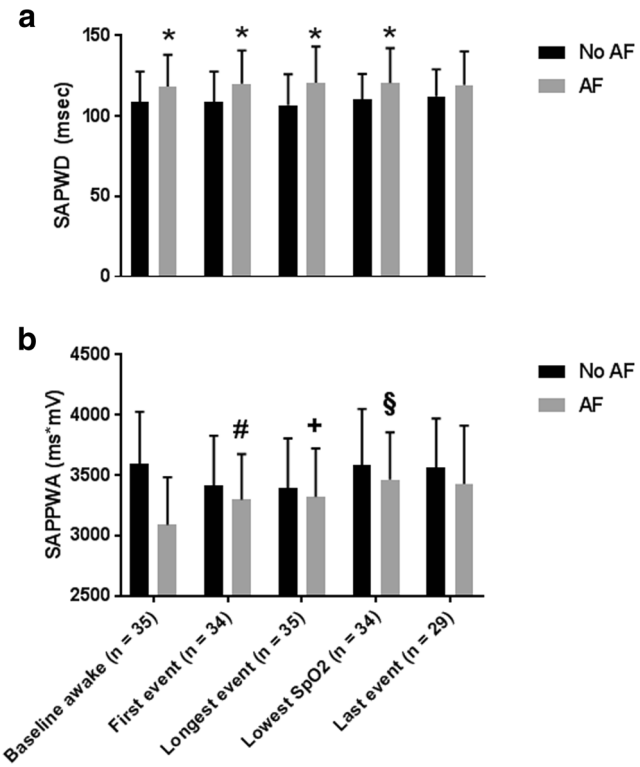

Fig. 2 Changes in signal-averaged P wave metrics with atrial fibrillation and respiratory events. **a** Signal-averaged P wave duration does not change during acute respiratory events but is longer in those with paroxysmal atrial fibrillation compared to those without atrial fibrillation. **b** Signal-averaged positive P wave area is greater during the longest respiratory event and the event with the lowest oxygen saturation compared to wakefulness, but only in those with paroxysmal atrial fibrillation. Data are displayed as mean (shaded bars) and standard deviation (thin lines); *$p < 0.05$ compared to no-AF for the same respiratory event. #$p = 0.05$ compared to baseline awake, +$p = 0.03$ compared to baseline awake. §$p = 0.005$ compared to baseline awake, AF atrial fibrillation. SAPWD signal-averaged P wave duration. SAPPWA signal-averaged positive P wave area, SpO2 oxygen saturation by pulse oximetry

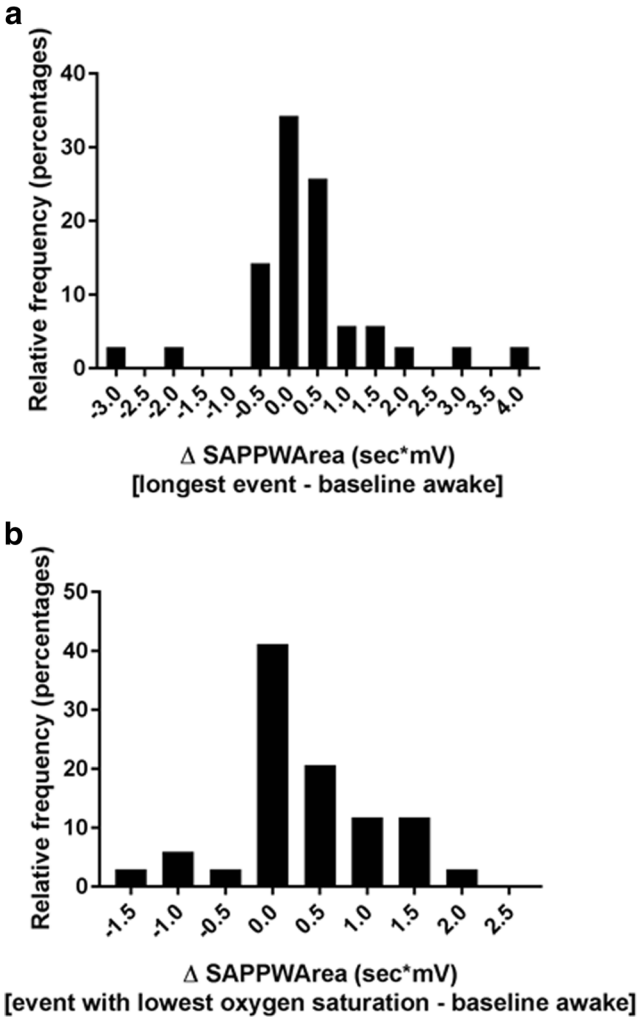

Fig. 3 Distribution of changes in signal-averaged positive P wave area relative to the baseline-awake condition For both the longest respiratory event (**a**; $p = 0.03$) and the respiratory event with the lowest oxygen saturation (**b**; $p = 0.005$), there was a significant difference in signal-averaged positive P wave area compared to the baseline-awake period (i.e., the distribution of the differences is not uniformly distributed around zero). SAPPWA signal-averaged positive P wave area

inducible change in the atrial substrate, perhaps reflecting increased atrial volume due to augmented venous return during OSA events. It is also possible that changes in body position during respiratory events may impact the electrical vector and lead to changes in P wave characteristics; assessing this possibility with 12-lead recordings or other techniques is beyond the scope of this study, which utilized clinically indicated PSGs. SAPWD and SAPPWArea may be complementary metrics, with the former serving as a longer-term gauge of the atrial response to chronic respiratory event exposure and the latter more indicative of the dynamic impact of respiratory events on electromechanical properties.

Prior work demonstrated more acute changes in SAPWD with respiratory events than was observed in our cohort [7]. The assessment of physiologic respiratory events in our study rather than simulated events, as in the prior study, may at least partially account for this difference. In addition, most of the respiratory events in our patients were hypopneas rather than full apneic events, which may have had a graded effect on SAWPD.

The difference in SAPPWArea between wakefulness and the first respiratory event during a PSG was of borderline statistical significance. This result could be due to type II error (i.e., too small of a sample size to detect the true effect) or the absence of the pro-arrhythmic influence of REM sleep. Alternatively, it may suggest that the impact of OSA events on atrial properties accumulates over repeated exposures during the course of a night's sleep, although SAPPWArea of the last respiratory event was not significantly different than baseline. Respiratory event duration is unlikely to be the sole determinant of meaningful changes to SAPPWArea as significant differences from baseline were seen in the lowest oxygen saturation group, despite those events being nearly 50% shorter than the longest respiratory events. REM sleep and associated increased sympathetic tone may play a role in the observed increase SAPPWArea, although REM sleep was present in less than half of individuals during the longest and lowest saturation events. A majority of the AF cohort was taking anti-arrhythmic drugs, which may have mitigated the impact of respiratory events on atrial depolarization and/or conduction and could contribute to the lack of change in SAWPD relative to the baseline-awake condition. As anti-arrhythmic drugs are prevalent in those treated for AF, development of alternative metrics to assess the impact of respiratory events on AF risk is reasonable.

The study has several limitations. The sample size is relatively small, and the results may not apply to segments of the population not well represented in this cohort (i.e., women and non-Caucasians). Although patients served as their own controls for the intra-PSG comparisons and there was a control group without AF used as a comparator, there was no "treatment" group (i.e., acute or chronic positive airway pressure use) to assess the response of signal-averaged metrics to OSA therapy. Evaluation of SAPPWArea in response to treatment is a target for further study. As the focus of this analysis was on signal-averaged P waves, we did not measure P wave dispersion, although this metric is associated with AF risk [14]. Even though we did not acquire the raw EKG data using the traditional methods for signal-averaged studies (i.e., with awake patients and using specialized equipment), we contend that the signal-averaging technique remains valid and has value as a means by which to increase the signal-to-noise ratio of the P wave signal in order to detect changes between baseline and respiratory event conditions. The relatively low sampling rate of the EKG channel has the potential to introduce low-pass filter effects into the data, although the P wave would not be expected to contain significant high-frequency components and thus the low-pass effect is unlikely to distort the signal substantially.

Conclusions

In summary, for individuals with an increased propensity for AF, this study provides signal-averaged EKG data suggestive of an acute mechanical response of the atria to OSA-related respiratory events that is not observed in those without AF. SAPPWA, if validated in more comprehensive studies, may be useful to assess AF risk in OSA and, potentially, to monitor the response to OSA treatment.

Acknowledgements The authors wish to thank Melissa Francis for expert assistance in obtaining the polysomnographic data.

Funding information This work was supported by CTSA award no. UL1TR000445 from the National Center for Advancing Translational Sciences.

Compliance with ethical standards

This study has been approved by the Vanderbilt Medical Center Institutional Review Board and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The manuscript does not contain clinical studies.

Disclaimer The contents for this work are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S, Sleep Heart Health Study (2006) Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. Am J Respir Crit Care Med 173:910–916
2. Monahan K, Storfer-Isser A, Mehra R, Shahar E, Mittleman M, Rottman J, Punjabi N, Sanders M, Quan SF, Resnick H, Redline S (2009) Triggering of nocturnal arrhythmias by sleep-disordered breathing events. J Am Coll Cardiol 54:1797–1804
3. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S (2017) Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. Circulation 136:1840–1850
4. Lau DH, Nattel S, Kalman JM, Sanders P (2017) Modifiable risk factors and atrial fibrillation. Circulation 136:583–596
5. Darbar D, Jahangir A, Hammill SC, Gersh BJ (2002) P wave signal-averaged electrocardiography to identify risk for atrial fibrillation. Pacing Clin Electrophysiol 25:1447–1453
6. Maeno K, Kasagi S, Ueda A, Kawana F, Ishiwata S, Ohno M, Yamaguchi T, Narui K, Kasai T (2013) Effects of obstructive sleep apnea and its treatment on signal-averaged P-wave duration in men. Circ Arrhythm Electrophysiol 6:287–293
7. Gaisl T, Wons AM, Rossi V, Bratton DJ, Schlatzer C, Schwarz EI, Camen G, Kohler M (2016) Simulated obstructive sleep apnea increases P-wave duration and P-wave dispersion. PLoS One 11: e0152994
8. Shoemaker MB, Muhammad R, Parvez B, White BW, Streur M, Song Y, Stubblefield T, Kucera G, Blair M, Rytlewski J, Parvathaneni S, Nagarakanti R, Saavedra P, Ellis CR, Patrick Whalen S, Roden DM, Darbar R. D (2013) Common atrial fibrillation risk alleles at 4q25 predict recurrence after catheter-based atrial fibrillation ablation. Heart Rhythm 10:394–400
9. Shoemaker MB, Muhammad R, Farrell M, Parvez B, White BW, Streur M, Stubblefield T, Rytlewski J, Parvathaneni S, Nagarakanti R, Roden DM, Saavedra P, Ellis C, Whalen SP, Darbar D (2013) Relation of morbid obesity and female gender to risk of procedural complications in patients undergoing atrial fibrillation ablation. Am J Cardiol 111:368–373
10. Goyal SK, Wang L, Upender R, Darbar D, Monahan K (2014) Severity of obstructive sleep apnea influences the effect of genotype on response to anti-arrhythmic drug therapy for atrial fibrillation. J Clin Sleep Med 10:503–507
11. Patel NJ, Wells QS, Huang S, Upender RP, Darbar D, Monahan K (2017) Relation of obstructive sleep apnea and a common variant at chromosome 4q25 to atrial fibrillation. Am J Cardiol 119:1387–1391
12. Ehlert FA, Steinberg JS (1995) The P wave signal-averaged ECG. J Electrocardiol 28:33–38
13. Conte G, Luca A, Yazdani S, Caputo ML, Regoli F, Moccetti T, Kappenberger L, Vesin JM, Auricchio A (2017) Usefulness of P-wave duration and morphologic variability to identify patients prone to paroxysmal atrial fibrillation. Am J Cardiol 119:275–279
14. Magnani JW, Williamson MA, Ellinor PT, Monahan KM, Benjamin EJ (2009) P wave indices: current status and future directions in epidemiology, clinical, and research applications. Circ Arrhythm Electrophysiol 2:72–79