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ORIGINAL ARTICLE

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Obstructive sleep apnea and electrocardiographic P-wave morphology

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Abstract

Introduction: Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder with important cardiovascular implications. Left atrial abnormality can be identified by electrocardiographic P-wave morphology and is considered an important risk for atrial fibrillation (AF) and stroke, both of which have been associated with OSA. We hypothesized that severity of OSA would be associated with more abnormal electrocardiographic P-wave morphology as indicated by P-wave terminal force in V_1 ($PTFV_1$) and P-wave area in V_1 ($PWAV_1$).

Methods: Patients who underwent clinically indicated polysomnography and had 12-lead ECG were identified through medical record review. Logistic regression was used to determine the associations between the measures of OSA severity (apnea hypopnea index [AHI] and mean nocturnal oxygen [O_2] saturation) and abnormal $PTFV_1$ and $PWAV_1$ (defined by >75% percentile value of the studied cohort) adjusting for age, sex, body mass index, and hypertension.

Results: A total of 261 patients (mean age: 57 years old, male: 52%) were included in the study. Multivariate analysis showed that AHI was associated with abnormal $PTFV_1$ (>7,280 μV ms) and $PWAV_1$ (>1,000 μV ms; OR: 1.5; 95% CI [1.1, 2.0], $p = 0.008$; OR: 1.5 [1.1, 2.1], $p = 0.005$ per 1 *SD* increase in AHI, respectively). Mean O_2 saturation was associated with abnormal $PWAV_1$ (OR: 0.72 [0.54, 0.98], $p = 0.03$). Results remained unchanged after excluding patients taking AV nodal blocking agents.

Conclusion: In a sleep clinic cohort, there was significant association between OSA severity and ECG-defined left atrial abnormality.

KEYWORDS

atrial fibrillation, electrocardiography, obstructive sleep apnea, P-wave index

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder in the USA, and it has been noted to increase cardiovascular risk in addition to its known adverse effects on quality of life (Peppard et al., 2013). A growing body of evidence has linked OSA to the development atrial fibrillation (AF), which is the most common cardiac arrhythmia and associated with significant morbidity and mortality (Gami et al., 2007; Kwon et al., 2015; Kwon, Koene, Johnson, Lin, & Ferguson, 2018). Repetitive upper airway obstruction manifested in patients with OSA results in heightened sympathetic activity, intermittent hypoxemia, and left atrial (LA) stretch, which are strong triggers to nocturnal arrhythmias including AF. Moreover, chronic OSA can induce permanent atrial remodeling through the

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same mechanism, thereby creating a substrate for the development AF. This association between OSA and atrial remodeling has been demonstrated both by electrocardiographic and echocardiographic parameters (Kim, Cho, Kwon, Lee, & Kim, 2012; Maeno et al., 2013; Otto et al., 2007). While imaging modalities such as echocardiography directly assess LA measurements, electrocardiography assesses conduction abnormalities known to be associated with specific changes in cardiac chamber morphology that may precede appreciable structural changes on imaging. From a pathophysiologic perspective, delayed LA electromechanical activation as assessed by various P-wave morphologies obtained via electrocardiogram (ECG) has been suggested to play a significant role in the genesis of AF (Redline et al., 2010). In this light, certain P-wave indices have been proposed as a marker for LA remodeling. These indices have been demonstrated to correlate with structural changes by direct imaging assessments. Additionally, some indices have been identified as predictors of AF (Soliman, Prineas, Case, Zhang, & Goff, 2009; Weinsaft et al., 2014). Intriguingly, a number of recent studies have shown that P-wave terminal force in V_1 ($PTFV_1$]), one of the P-wave indices, is consistently predictive of ischemic stroke, independent of AF (Kamel, Hunter et al., 2015; Kamel et al., 2014). Given the known association of OSA and stroke, this association implies that $PTFV_1$ may be an important ECG marker of risk for both AF and stroke in patients with OSA. Our study focused on this particular index along with P-wave area in V_1 ($PWAV_1$) that has not been examined in association with OSA. We hypothesized that increasing severity of OSA would be associated with a higher likelihood of abnormal $PTFV_1$ and PWV_1.

2 | METHODS

2.1 | Subjects

Consecutive patients who were referred to the University of Virginia Sleep Disorders Center for diagnostic polysomnography (PSG; Charlottesville, VI, USA) from January 1, 2010 through December 31, 2016 were included in the study if the following criteria were met: (a) age ≥ 20 years, (b) normal sinus rhythm on 12-lead surface ECG, (c) ECG obtained within 1 year of PSG. Subjects with a documented history of AF or atrial flutter or chronic pulmonary disease requiring oxygen (O_2) supplement were excluded from the study.

2.2 | Sleep study data

Overnight PSG was performed employing the standard channels recommended by American Academy of Sleep Medicine (AASM), and data were processed with Embla Sandman Elite software (Natus Medical Incorporated, CA, USA). For this study, only those subjects who underwent full-night diagnostic PSG were included. The apnea hypopnea index (AHI) was defined as the number of apnea and hypopnea events divided by total sleep time and expressed as the number of events per hour. Apnea was defined as a reduction in airflow >90% of the preevent baseline and occurred for longer than 10 s using a thermocouple signal. Hypopnea events were recorded when the amplitude of the nasal pressure flow signal decreased by more than 30% of the preevent baseline for longer than 10 s; only hypopneas with 4% desaturation were included in the AHI reported here. Oxygen saturation (mean O_2 saturation) was also utilized as an alternative measure of OSA severity.

2.3 | Electrocardiography

Standard 12-lead ECGs (Philips PageWriter TC-70; GE, Eindhoven, the Netherlands) were digitally recorded at a speed of 25 mm/s with a 10 mm/mV. All ECGs were assessed visually for inadequate quality, processed digitally via an ECG software platform (TraceMaster-Philips Intellispace ECG; Philips Medical Systems, Andover, MA, USA), and confirmed visually by physicians. The same software program was used to automatically measure P-wave indices, including P-wave duration, P-wave amplitude, P-wave area, and PR interval (Figure 1). Each of these indices was recorded for both positive and negative deflections. The primary P-wave index outcome of interest was $PTFV_1$, which was defined as the duration in milliseconds (ms) of the terminal part [negative] of the P wave in lead V_1 multiplied by its depth in microvolts (μV). $PWAV_1$ was measured as the area under the both positive and negative deflection of the P wave (μV ms). To reduce interrater variability in transcribing ECG data, the data recorded by the ECG software were saved as an XML file and subsequently parsed and processed in a CSV file using the Python 3.5.2 software programming package and ElementTree standard library (Python Software Foundation; Wilmington, DE, USA). As a result, there was 100% reproducibility in transcription of ECG data, and any apparent outliers were manually surveyed and corrected as needed. Investigators extracting ECG measures were blinded to clinical and PSG data.

2.4 | Covariates

Demographic information (age, sex, and race), body mass index (BMI), medical history (hypertension and heart failure), and the use of AV nodal blocking agents including beta-blockers, calcium channel blockers, and digoxin were obtained from electronic medical records. BMI was categorized into normal (<25 kg/m^2), overweight (25–30), and obese (30≥).

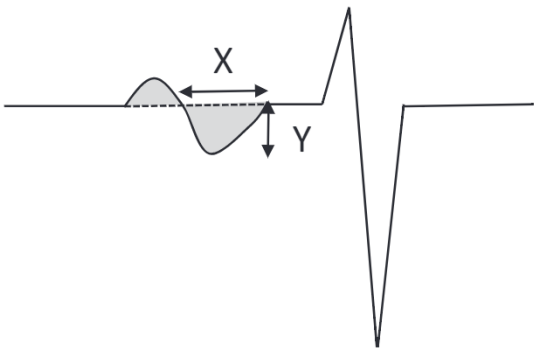

FIGURE 1 Depiction of key P-wave indices

TABLE 1 Patient characteristics by OSA severity

	All	AHI < 15	AHI 15–29	AHI ≥ 30	*p* Value
N	261	67	81	111	
Age	56.91 (12.35)	57.33 (12.79)	56.00 (12.07)	57.31 (12.39)	0.73
Male	131 (50.2)	21 (31.3)	38 (46.9)	71 (64.0)	<0.001
Race					
White	202 (77.4)	49 (73.1)	70 (86.4)	81 (73.0)	0.12
Black	52 (19.9)	17 (25.4)	10 (12.3)	25 (22.5)	
Asian	7 (2.7)	1 (1.5)	1 (1.2)	5 (4.5)	
BMI category (kg/m^2)					
<25	11 (4.2)	5 (7.5)	3 (3.7)	3 (2.7)	0.26
25–30	44 (17.0)	15 (22.4)	14 (17.3)	15 (13.5)	
30≥	204 (78.8)	47 (70.1)	64 (79.0)	93 (83.8)	
Hypertension	192 (73.6)	48 (71.6)	54 (66.7)	88 (79.3)	0.14
Heart failure	44 (16.9)	7 (10.4)	15 (18.5)	22 (19.8)	0.25
AV node blocker	126 (49.0)	28 (43.1)	35 (43.2)	63 (56.8)	0.1
$PTFV_1$ (μV ms)	5,400 (3,600)	4,999 (3,730)	5,030 (3,180)	5,870 (3,780)	0.17
$PAWV_1$ (μV ms)	820 (380)	730 (350)	790 (350)	890 (420)	0.02

Note. AHI: apnea hypopnea index; AV: atrioventricular; BMI: body mass index; $PTFV_1$: P-wave terminal force in V_1; $PWAV_1$: P-wave area in V_1.
Expressed as mean (*SD*) and *N* (%) for continuous and categorical variables, respectively.

2.5 | Statistical analysis

Baseline characteristics were described by OSA severity based on AHI (normal to mild [<15] vs. moderate [15–29] vs. severe [≥30]), and comparisons were made across the three groups using chi-square test for categorical variables and one-way ANOVA for continuous variables. We performed multivariable logistic regression to determine the association between measures of OSA including AHI and mean O_2 saturation (each OSA measure included separately) and the abnormal $PTFV_1$ (defined by >75% percentile value of the studied cohort) adjusting for age, sex, BMI, and hypertension status. Linear association between AHI and absolute value of $PTFV_1$ was also assessed. All outcome results were expressed per 1 *SD* of predictor values. Using the identical method, associations with $PWAV_1$ were examined. Finally, we repeated the analyses after excluding subjects who were on medications that can potentially influence P-wave indices. *p* Values <0.05 were considered significant. All analyses were performed using R Core Team 2013.

3 | RESULTS

Demographic and clinical data for the study population are detailed in Table 1. A total of 261 patients consisting of 50.2% men were included. Mean age (*SD*) of the cohort was 57 (12.4) years old with 22.6% being nonwhite. Patients with greater AHI tended to be men and more obese. Mean AHI was 35.6 (/hr) (29.1) and mean O_2 saturation 92.7 (%) (3.1). Median [IQR] values for $PTFV_1$ and $PWAV_1$ were 4,648 (μV ms) (3,024–7,280) and 800 (μV ms) (500–1,000), respectively. Based on this distribution, abnormal $PTFV_1$ and $PWAV_1$ were determined by 7,280 (μV ms) and 1,000 (μV ms), respectively.

3.1 | Sleep-disordered breathing and P-wave terminal force in VI

There was a trend toward higher $PTFV_1$ across all AHI categories (Figure 2a). However, in logistic regression analysis, AHI was found to be associated with abnormally high $PTFV_1$ after adjusting for other covariates. Each 1-*SD* AHI increase was associated with approximately 50% higher odds of abnormal $PTFV_1$ (odds ratio [OR] [95% CI]: 1.5 [1.1, 2.0], $p = 0.008$; Figure 3a). The logistic regression results indicated that mean O_2 saturation was not significantly associated with abnormal $PTFV_1$ (OR [95% CI]: 0.95 [0.86, 1.05], $p = 0.29$). In continuous-based analysis, both AHI and mean O_2 saturation showed linear relationships with $PTFV_1$ (Table 2). Each 1 *SD* increase in AHI was associated with 626.5 (μV ms) increase in $PTFV_1$, whereas each 1 *SD* decrease in mean O_2 saturation was associated with 525.9 (μV ms) increase in $PTFV_1$.

3.2 | Sleep-disordered breathing and P-wave area in V_1

There was a significant trend toward higher $PWAV_1$ across all AHI categories (Figure 2b). The logistic regression results showed that

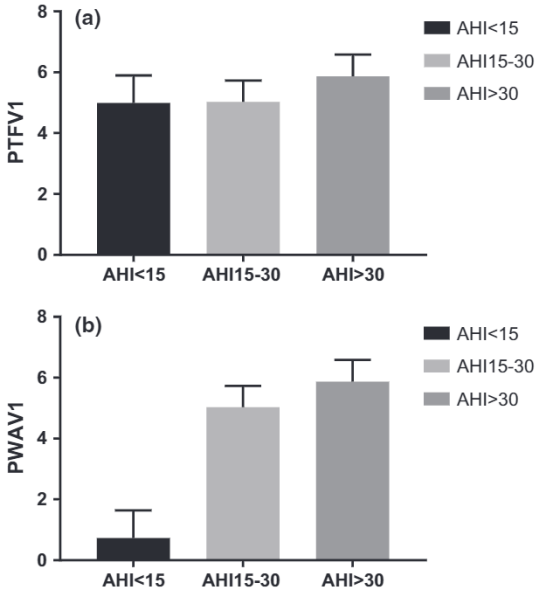

FIGURE 2 P-wave terminal force in V_1 across apnea hypopnea index categories

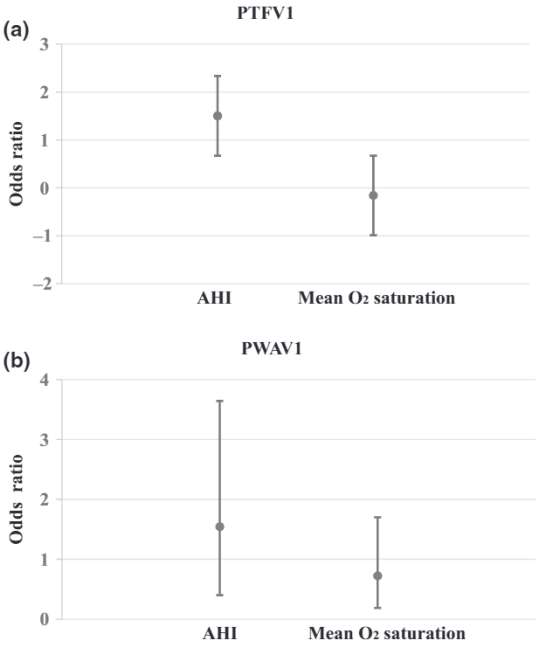

FIGURE 3 Odds ratio of abnormal P-wave indices by measures of obstructive sleep apnea

AHI was associated with abnormally high $PWAV_1$ after adjusting for covariates. Each 1-*SD* AHI increase was associated with approximately 50% higher odds of abnormal P area (OR [95% CI]: 1.5 [1.1, 2.1], $p = 0.005$; Figure 3b). In logistic regression analysis, mean O_2 saturation was also associated with abnormal $PWAV_1$ with each 1 *SD* increase associated with approximately 30% lower odds of abnormal $PWAV_1$ (OR [95% CI]: 0.72 [0.54, 0.98]), $p = 0.03$). In continuous-based analysis, AHI, but not mean O_2 saturation, showed a linear relationship with $PWAV_1$ (Table 2). Each 1 *SD* increase in AHI was associated with 72.4 (μV ms) increase in $PWAV_1$. Identical analysis for the component of $PTFV_1$ (i.e., P-wave duration [negative portion] in V_1 and P-wave amplitude [negative portion] in V_1) is shown in Table 3. The degree of contribution by each component was similar but the association between AHI and P-wave duration (negative portion) in V_1 did not reach statistical significance. Results remained unchanged when analyses were repeated after excluding patients taking AV nodal blocking agents except the linear association between mean O_2 saturation and $PAWV_1$ was lost (data not shown).

4 | DISCUSSION

In a sleep clinic cohort, we found a modest but significant association between OSA severity and ECG-defined LA abnormality. Severity of OSA as determined by AHI and mean O_2 saturation was associated with a higher likelihood of having abnormally high $PTFV_1$ and $PWAV_1$. These associations were independent of factors such as age, sex, BMI, and hypertension that are potential confounders (Baranchuk et al., 2011; Camsari et al., 2003; Robitaille & Phillips, 1967).

Abnormal P-wave morphology has been shown to indicate structural and electrical remodeling of the LA. Such LA abnormality provides substrate predisposing to AF. In this context, a growing number of studies have examined various P-wave indices in relation to OSA to better understand pathophysiologic link between OSA and AF, yielding varying results. The majority of the studies have focused on P-wave duration and dispersion which reflect atrial conduction delay and inhomogeneity of atrial conduction, respectively. Maeno et al showed that in patients referred to sleep clinics, the severity of SDB by AHI was significantly correlated with average P-wave duration in lead II from 12-lead ECG (Maeno et al., 2013). However, in a study from an ethnically diverse community cohort, the association between AHI and maximum P-wave duration was lost after multivariable adjustment (Kwon et al., 2017). Other studies have shown pronounced P-wave dispersion (difference between maximum and minimum P-wave duration) in patients with severe OSA (Cagirci et al., 2011; Can et al., 2009). Notably, these studies excluded patients with heart failure, ischemic heart disease, and valvular heart disease, which are all highly prevalent in patients with OSA. The clinical significance of these exclusions is exemplified by another study that demonstrated a more modest relationship between OSA and P-wave duration when patients with known cardiovascular disease were included (Baranchuk et al., 2011). Additionally, an analysis of long-term beta-blockade on P-wave duration demonstrated that this index can be affected by such therapy (Camsari et al., 2003). Therefore, the clinical usefulness of P-wave duration as potential prognostic tool in AF risk assessment is limited by both the lack of data in a representative sample of OSA patients and the effects of a medication that is commonly used in the OSA population.

TABLE 2 Linear associations between measures of OSA and P-wave indices

	$PTFV_1$		$PWAV_1$	
OSA measures	*β* coefficient	*p* Value	*β* coefficient	*p* Value
AHI	21.5 [5.4, 37.7]	0.01	2.5 [0.8, 4.2]	0.004
AHI (per 1 *SD*)	611.5 [148.9, 1,079.1]		73.0 [23.0, 122.9]	
Mean O_2 saturation	−171.2 [−317.8, −24.5]	0.02	−10.6 [−26.1, 4.9]	0.18
Mean O_2 saturation (per 1 *SD*)	−539.6 [−971.2, −72.0]		−34.6 [−80.6, 15.4]	

Note. AHI: apnea hypopnea index; OSA: obstructive sleep apnea; $PTFV_1$: P-wave terminal force in V_1; $PWAV_1$: P-wave area in V_1.

TABLE 3 Linear associations between measures of OSA and the components of $PTFV_1$

	P-wave duration (negative portion) in V_1		P-wave amplitude (negative portion) in V_1	
OSA measures	*β* coefficient	*p* Value	*β* coefficient	*p* Value
AHI	0.14 [0, 0.29]	0.06	0.17 [0.04, 0.30]	0.01
AHI (per 1 *SD*)	4.21 [−0.16, 8.42]		5.0 [1.2, 8.8]	
Mean O_2 saturation	−1.6 [−2.9, −0.3]	0.02	−1.3 [−2.5, −0.1]	0.03
Mean O_2 saturation (per 1 *SD*)	−4.9 [−9.1, −0.97]		−4.1 [−7.6, −0.29]	

Note. AHI: apnea hypopnea index; OSA: obstructive sleep apnea; $PTFV_1$: P-wave terminal force in V_1.

P-wave terminal force in V_1 is one of the P-wave morphology indices of abnormal interatrial conduction that has recently drawn significant attention because of its association with AF as well as multiple cardiovascular comorbidities. In an era prior to the development of advanced imaging modalities, increased $PTFV_1$ was demonstrated to be associated with AF even in the absence of known structural heart disease (Robitaille & Phillips, 1967). Decades later, modern electrophysiological studies have demonstrated that in the absence of structural heart disease, $PTFV_1$ is independently associated with an increased risk of recurrent AF even after a radiofrequency AF ablation (Martín García et al., 2012). Moreover, a number of studies have pointed to the utility of $PTFV_1$ in prediction of other major cardiovascular outcomes. Kohsaka et al reported $PTFV_1$ >4,000 μV ms was associated with ischemic stroke in patients with left ventricular hypertrophy (Kohsaka et al., 2005; Okin, Kamel, Kjeldsen, & Devereux, 2016). A series of subsequent studies from various community-based cohorts have consistently shown similar findings (Kamel, Bartz et al., 2015; Kamel, Hunter et al., 2015; Kamel, O'Neal et al., 2015). Interestingly, $PTFV_1$ has been shown to be predictive of incident ischemic stroke independent of AF highlighting the importance of LA abnormality alone in the pathogenesis of ischemic stroke (Kamel, Hunter et al., 2015; Kamel et al., 2014). In another recent study, the amplitude of the negative portion of a P wave, a component of $PTFV_1$, was associated with an increased risk of sudden cardiac death (Tereshchenko et al., 2014) and it is known that OSA has been linked to these cardiovascular outcomes (Gami et al., 2007, 2013; Redline et al., 2010). Thus, recognizing whether patients with OSA exhibit more abnormal $PTFV_1$ is important as it would provide further insight into the mechanism by which OSA exerts its effect on the aforementioned cardiovascular morbidities.

While AHI was associated with abnormal $PTFV_1$ (as defined by >75th percentile of $PTFV_1$), no significant association was found with mean O_2 saturation. However, in continuous-based analysis, an association was present for both measures of OSA. AHI and mean O_2 saturation measures are typically correlated, but the former assesses the quantity of obstructive respiratory events accompanying intermittent desaturations, whereas the latter assess the overall severity of hypoxemia, which can be influenced by factors other than OSA alone. This difference may be responsible for the discrepant results. Our finding is consistent with that of a previous study in which severity of SDB by AHI was associated with abnormally elevated $PTFV_1$ as defined by ≥4,000 μV ms from ethnically diverse community cohort (Kwon et al., 2017). It is notable that the mean $PTFV_1$ value of that study was much smaller than that of ours (2,245 vs. 5,400 μV ms). This difference may be due to the fact that subjects included in our study were clinic-based patients with a higher burden of cardiovascular comorbidities. This fact in turn suggests that the severity of OSA may be a valuable predictive tool in assessing LA abnormality even at an already high-risk group.

Although there is paucity of literature on $PWAV_1$ compared to other P-wave indices, a recent study by Weinsaft et al elegantly illuminated the potential utility of this particular index (Weinsaft et al., 2014). In this study, the investigators showed a high correlation between $PWAV_1$ and the LA chamber size measured by cardiac magnetic resonance imaging and demonstrated similar predictive value of $PAWV_1$ to imaging-quantified LA area for prediction for incident AF. To our knowledge, our study is the first to examine $PWAV_1$ in the context of OSA. Results of $PAWV_1$ closely mirrored those of $PTFV_1$, and similarly to $PTFV_1$ the results for AHI were more significant than for mean O_2 saturation. In the case of mean O_2 saturation, despite the lack of a significant linear relationship, a low mean O_2 saturation was predictive of higher odds of having abnormally high $PAWV_1$.

Our study has several strengths in investigating the relationship between $PFTV_1$ in a representative patient population without the exclusion of comorbidities and medications highly prevalent in this population, thus making it more clinically applicable. We utilized a commonly used software program for automated analysis and measurement of ECG parameters, including $PTFV_1$, and thus eliminated the need for the tedious manual measurement that is inherently vulnerable to interrater variability. Additionally, these measurements are readily available to any clinician with access to digitally processed ECGs, which in the era of electronic medical records represents the vast majority of practicing physicians (Jamoom, Yang, & Hing, 2016).

Several limitations of the study should be also noted. Our study included patients who were referred to sleep clinic for suspected OSA. Thus, the results of this study may not be applicable to the general population. The cross-sectional nature of our study does not allow us to infer a causal relationship. There was a maximum 1-year time interval between PSG and ECG during which time some patients included in the study may have received treatment for OSA at the time of ECG recording. Although no evidence currently exists as to whether treating OSA mitigates P-wave indices examined in our study, it is possible that the observed association could have been biased toward the null.

Despite this, the findings of this study bear potentially important clinical implications. Given the nonnegligible burden of the most commonly used OSA therapy with continuous positive airway pressure, there is a critical need for tools to enhance cardiovascular risk stratification. Both $PTFV_1$ and $PAWV_1$ are readily available ECG indices and so may represent convenient prognostic markers in predicting adverse cardiovascular outcomes in patients with OSA. Future studies should consider these findings as well as the effect of OSA treatment on these ECG markers of LA abnormality.

In conclusion, we found that in patients with OSA, the severity of OSA was associated with abnormal ECG signatures of LA abnormality as manifested by high $PTFV_1$ and $PAWV_1$. This may partly explain the pathophysiologic link between OSA and adverse cardiovascular outcomes such as AF and stroke.

CONFLICT OF INTEREST

None.

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