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# Predictors of Atrial Remodeling in Patients with Sleep Apnea: Analysis of Electrocardiographic and Echocardiographic Variables

**Tamer El Andere*, Luciana Vidal Armaganijan, Dalmo Antônio Ribeiro Moreira, Paulo Fernando Arruda João, Halsted Alarcão Gomes Pereira da Silva, Adriana Bertolami, and David Costa de Souza Le Bihan**

Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil

## Abstract

Background: Obstructive sleep apnea (OSA) is an important risk factor for the development and recurrence of atrial fibrillation (AF). Atrial remodeling (AR) plays a critical role in the genesis of AF. We evaluated electrocardiographic and echocardiographic variables (electrical, anatomic, and functional) associated with AR in patients with OSA.

Methods: Two hundred and three consecutive patients undergoing polysomnography were screened, by which 80 patients were included and divided into groups according to apnea-hypopnea index in OSA- (AHI < 15) or OSA+ (AHI ≥ 15). Minimum oxyhemoglobin saturation (>90%, 80-90%, and <80%) and total time <90% saturation [T90] (<1 min, 1-60 min, and >60 min) were correlated to electrocardiographic (12-lead and signal-averaged electrocardiogram - SAECG) and echocardiographic (2D strain and 3D volumetric and functional) variables.

Results: Patients with OSA+ presented lower left atrial passive emptying fraction (LAPEF) compared to OSA- patients. MinSat <80% was associated with increased P-wave duration on SAECG and lower conduit strain compared to those with MinSat >90%. T90 > 60min was associated with increased P-wave duration on SAECG and increased P-maximum, P-mean, and P-DII on 12-lead ECG, as well as shorter Tonset-Tpeak interval compared to <1min group. There were no differences between groups regarding atrial volumes and other functional and electrical features. T90 1-60min was associated with increased QT interval in lead V5 and increased Tpeak-Tend interval compared to <1min group. T90 > 60min was associated with increased P-wave duration in DII and increased P/PRi interval compared to <1min group.

Conclusions: The presence of OSA was not associated with significant electrical, functional, and structural atrial remodeling. With increasing evidence that a saturation-based analysis might be superior to AHI-based evaluation, we demonstrated the association of different non-invasive electrical and functional remodeling variables with hypoxemia, particularly by using a T90-based approach.

**Keywords:** Sleep Apnea; Atrial Remodeling; Atrial Fibrillation; Hypoxia Echocardiography; Electrocardiography

***Correspondence to:*** Tamer El Andere, Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil; E-mail: drtamerelandere@gmail.com

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## Introduction

There has been increasing evidence on the impact of obstructive sleep apnea (OSA) on the onset, recurrence, and persistency of atrial fibrillation (AF) [1]. Atrial remodeling (AR) plays a critical role in this scenario [2].

Guidelines have been emphasizing the importance of the diagnosis of OSA in AF patients [3]. The presence of OSA is associated with lower arrhythmia-free survival rates compared to patients without OSA. Therefore, screening is an important step when rhythm-control strategy is chosen [4].

The pathophysiological interrelationship is established by the multifactorial atrial arrhythmogenesis presented in OSA patients. Recurrent hypoxemia, reoxygenation, and associated inflammation chronically activates autonomic, inflammatory and tissue remodeling responses [5]. This promotes AR, which constitutes the arrhythmogenic substrate [6]. AR is divided into electrical [7], structural [8, 9], and functional AR [10].

The aim of the present study was to evaluate AR variables in patients with OSA using non-invasive electrocardiographic and echocardiographic methods, as well as the impact of the magnitude and duration of hypoxemia in these parameters.

## Methods

Two hundred and three consecutive patients undergoing polysomnography (PSG) in a tertiary hospital were screened, and 80 patients met eligibility for clinical, electrocardiographic, and echocardiographic evaluation.

Included patients were divided into groups based on Apnea-Hypopnea Index (AHI) established by the International Classification of Sleep Disorders (ICSD-3) [11]. The absence of OSA was defined by AHI <15 events/h (OSA-) and OSA was established by AHI ≥15 events/h (OSA+) [12]. Patients were also categorically divided into groups based on minimum oxyhemoglobin saturation (MinSat) (>90%, 80-90%, and <80%); and total time below 90% saturation (<1-minute, 1-60minutes, and >60minutes).

In-lab whole-night PSG was performed using digital ALICE-5 Respironics® device, under supervision of trained professionals. Patients were monitored by electroencephalogram, electrooculogram, electromyogram, electrocardiogram (ECG), pletismography, oxyhemoglobin saturation, airflow thermistor, microphone, and body positioning visualization.

## Electrocardiogram

All included patients underwent 12-lead ECG and signal average ECG (SAECG) analysis using the DMS model 300-6 device. SAECG was performed using Frank's leads.

Twelve-lead ECG was recorded at 25mm/s and 1mV/cm simultaneously in all leads. Electronic calipers were used for interval measurements using the TEB software. The following electrocardiographic variables were analyzed: SAECG P-wave duration; maximum (P-max), minimum (P-min), and mean P-wave (P-med) in 12-lead ECG [13]; P-wave dispersion (calculated by the difference between maximum and minimum P-wave in 12-lead ECG) (Pd); P-wave duration in lead II (P-DII); duration of PR interval in lead II; P/PR interval; QT duration in leads II and V5 and, its components (Q-Tpeak, J-Tpeak, Tonset-Tpeak, Tpeak-Tend) [14,15]; and corrected QT (QTc) using the Bazett's formula [16,17].

We sought to analyze different P-wave intervals as representatives of atrial depolarization and ventricular repolarization as an extrapolation of atrial repolarization by ECG evaluation.

## Echocardiogram

Echocardiogram was performed using the Vivid E9 GE HealthCare module. The three-dimensional full volume method was used for volumetric functional evaluation and the following left atrium (LA) volumes and indexes were calculated [18]:

- Maximum LA volume (MaxVol),
- LA volume preceding atrial contraction (PreA),
- Minimum LA volume (MinVol).
- Total LA emptying volume (TEV): MaxVol – MinVol;
- Total LA emptying fraction (TEF): (TEV/ MaxLAVol)x100,
- Passive LA emptying volume (PEV): MaxVol – PreA),
- Passive LA emptying fraction (PEF): (PEV / MaxVol)x100,
- Active LA emptying volume (AEV): PreA – MinVol),
- Active LA emptying fraction (AEF): (AEV/ PreA) x 100.

Atrial strain was obtained by speckle tracking evaluation in the reservoir (εR) and atrial contraction (εCT) phases. The conduit phase strain (εCD) was given by the difference between εR and εCT [8]. Diastolic function was graded according to current recommendations [19]. All echocardiographic data was analyzed offline using the EchoPac-PC software, and observers were blinded to patient's polysomnographic results.

By 2D- and 3D-echocardiographic analysis, we sought to evaluate the atrial structure by volumetric evaluation and its function by emptying volumes and fractions, as well as atrial strain in the different atrial cycle phases.

## Inclusion Criteria

Two hundred and three consecutive patients undergoing PSG at Instituto Dante Pazzanese de Cardiologia in Sao Paulo, Brazil, were summoned for initial evaluation.

## Exclusion Criteria

The following exclusion criteria were adopted: cardiomyopathy of any etiology, permanent pacemaker, moderate/severe valvopathy, chronic kidney disease on dialysis, angina, previous myocardial infarction or coronary revascularization, prior stroke, documented AF of any type, use of class I and/or III antiarrhythmic agents, CPAP usage at any time, central sleep apnea, untreated hypothyroidism, non-sinus rhythm at initial ECG evaluation, types II or III atrioventricular block and intraventricular conduction abnormalities, PR interval <120ms or >230ms, secondary ventricular repolarization abnormalities, heart rate <50bpm or >110bpm at basal ECG, moderate or severe pulmonary hypertension, restrictive diastolic dysfunction.

Local ethical committee approved the study and informed consent was provided to all included patients.

## Statistical Analysis

Initially, all variables were analyzed descriptively. Quantitative variables were presented as mean, standard deviation, and median when appropriate. Qualitative variables were presented as absolute and relative frequencies.

Linear regression models, with two progressive models, established the mean comparison between groups. On the first model, we considered the association of each of the IAH-based MinSat-based, and T90-based groups, regarding the following electrical, structural, and functional endpoints:

- Electrical Remodeling: P-SAECG, P-max, P-min, P-disp, P-med, QT-V5, QT-DII, QTc-DII, Q-Tpeak, Tpeak-Tend, J-Tpeak, P-DII, PRi-DII, and P/PRi-DII
- Structural remodeling: Max LA Volume, Min LA Volume, PreA LA Volume, and 2D-Indexed LA Volume.
- Functional remodeling: TEF, PEF, AEF, TEV, PEV, AEV, εR, εCT, and εCD.

On the second model, we adjusted by linear regression the initial model 1 results to age, sex, BMI, and the presence of diabetes, hypertension, and hyperlipidemia. Homogeneity between proportions was tested by the Chi-squared or Fisher's exact tests. For variable correlations we used the coefficients of Pearson and Spearman.

The software used for analysis was the R 3.6.0 (R Core Team, 2019). The adopted level of significance for tests was 5%.

# Results

Out of 203 screened patients, 123 were excluded in the table, resulting in a total of 80 included patients (60% females) (Table 1). Forty-one patients were classified as OSA- and 39 as OSA+.

**Table 1:** Exclusion criteria.

| Exclusion criteria | n | % |
|---|---|---|
| Ischemic cardiomyopathy/ AMI/ Myocardial Revascularization | 26 | 21,1% |
| Dilated cardiomyopathy | 10 | 8.1% |
| Chagasic cardiomyopathy | 6 | 4.9% |
| Hypertrophic cardiomyopathy | 5 | 4% |
| Hypertensive cardiomyopathy | 5 | 4% |
| Congenital cardiomyopathy | 2 | 1.6% |
| Atrial Fibrillation - Paroxistic | 12 | 9.7% |
| Persistent | 1 | 0.8% |
| Permanent | 6 | 4.9% |
| Stroke | 9 | 7.3% |
| Class I or III antiarrhythmics | 8 | 6.5% |
| CPAP | 7 | 5.7% |
| RBBB | 5 | 4% |
| Pacemaker | 4 | 3.2% |
| Moderate or severe valvopathy | 4 | 3.2% |
| Secondary ventricular repolarization abnormality | 4 | 3.2% |
| Angina | 4 | 3.2% |
| Dialytic nephropathy | 4 | 3.2% |
| Atrial Flutter | 2 | 1.6% |
| LBBB | 1 | 0.8% |
| Central apnea | 1 | 0.8% |
| Heart rate < 50bpm | 1 | 0.8% |
| TOTAL | 123 | 100% |

AMI: Acute myocardial infarction, CPAP: Continuous positive airway pressure, RBBB: Right bundle branch block, NYHA: New York Heart Association, LBBB: Left Bundle Branch Block.

Mean age was 60.8 ± 11.1 years and mean BMI was 31.95 ± 6.5kg/m². The majority of patients (91.2%) had hypertension and 61.3% were on three or more antihypertensive agents. Mean $CHA_2DS_2VASc$ score was 2.13. Demographic characteristics are presented in the below table (Table 2).

OSA+ patients were older and had higher prevalence of diabetes and hyperlipidemia as expected by the prevalence of these features in OSA patients and by the study's transversal design. Regarding medical therapy, a median of 3.05 and 2.63 antihypertensive agents were observed in the OSA+ and OSA- groups, respectively, with no significant statistical difference. Higher prevalence of statin use occurred in OSA+ patients. Polysomnographic, electrocardiographic and echocardiographic findings are shown in the table (Table 3).

Increased N1 stage, decreased slow-wave sleep, and increased arousals and desaturation indexes in the OSA+ group reinforce that patients were adequately stratified according to polysomnographic characteristics [20].

Heart rates and basic cycle length were similar in both groups, which made possible the analysis of the different ECG intervals. Likewise, patients with and without OSA exhibited similar and preserved left ventricular systolic function, with no significant differences in diastolic function.

## Atrial Remodeling Endpoints

Electrocardiographic findings are presented in the below tables (Table 4 and Table 5). No significant differences in all analyzed variables were seen between OSA- and OSA+ groups. Lower oxygen saturation (MinSat <80%) was associated with increased P wave duration on SAECG when compared to MinSat >90% (121.1 ± 5.5 *vs.* 109.83 ± 5.1, respectively; p = 0.042).

**Table 2:** Clinical demographic characteristics.

| Variable | OSA- (n = 41) | OSA+ (n = 39) | p value |
|---|---|---|---|
| Age (years) | 58 ± 11.63 | 63.77 ± 9.93 | 0.02 |
| Female | 28 (68.3%) | 20 (51.3%) | 0.12 |
| Weight (kg) | 83.5 ± 18.48 | 86.8 ± 18.92 | 0.42 |
| BMI (kg/m²) | 31.6 ± 6.2 | 32.3 ± 6.9 | 0.61 |
| Functional class: NYHA I | 36 (87.8%) | 28 (71.8%) | 0.22 |
| NYHA II | 3 (7.3%) | 6 (15.4%) | |
| NYHA III | 2 (4.9%) | 5 (12.8%) | |
| Hypertension | 36 (87.8%) | 37 (94.9%) | 0.43 |
| Systolic arterial pressure (mmHg) | 143.3 ± 24.5 | 135 ± 18.6 | 0.093 |
| Diastolic arterial pressure (mmHg) | 87.8 ± 13.7 | 82.3 ± 11.8 | 0.059 |
| Number of antihypertensive agents | 2.63 ± 1.7 | 3.05 ± 1.3 | 0.26 |
| Current Smoking | 1 (2.44%) | 2 (5.13%) | 0.61 |
| Previous smoking | 15(36.6%) | 17 (43.6%) | |
| Epworth sleepiness scale | 9.8 ± 5 | 10.3 ± 6.0 | 0.73 |
| Diabetes | 9 (22%) | 21 (53.9%) | 0.003 |
| Hypothyroidism | 5 (12.2%) | 3 (7.7%) | 0.71 |
| Obesity | 24 (58.5%) | 22 (56.4%) | 0.84 |
| Hyperlipidemia | 26 (63.4%) | 34 (87.2%) | 0.014 |
| Chronic kidney disease | 2 (4.9%) | 0 (0%) | 0.49 |
| Statin use | 23 (56.1%) | 32 (82%) | 0.012 |
| Oral antidiabetics/ Insulin | 15 (36.6%) | 21 (53.9%) | 0.12 |
| ASA | 19 (46.3%) | 19 (48.7%) | 0.83 |

AHI: Apnea-Hypopnea Index, OSA: Obstructive sleep apnea, BMI: Body Mass Index, NYHA: New York Heart Association scale, Asymp.: Asymptomatic, ASA: Acetylsalicylic Acid.

**Table 3:** Polysomnographic, electrocardiographic, and echocardiographic findings in patients with and without OSA.

| Variable | OSA- (n = 41) | OSA+ (n = 39) | p value |
|---|---|---|---|
| Polysomnography | | | |
| Total sleep time (min) | 319.8 ± 8 | 323.9 ± 11.5 | 0.72 |
| Sleep latency - NREM (min) | 27.7 ± 3.3 | 17.4 ± 4.7 | 0.032 |
| Sleep latency - REM (min) | 127.2 ± 13 | 120 ± 18.6 | 0.69 |
| Sleep efficiency (%) | 79.8 ± 1.8 | 79.6 ± 2.6 | 0.94 |
| Stage 1 | 9.35 ± 1.3 | 16.7 ± 1.9 | <0.001 |
| Stage 2 | 51.5 ± 1.4 | 46.9 ± 2 | 0.028 |
| Slow-wave sleep | 22.8 ± 1.3 | 18.7 ± 1.9 | 0.033 |
| Rapid eye movement sleep | 16.4 ± 1.1 | 17.2 ± 1.6 | 0.62 |
| Arousal index (events/h) | 13.6 ± 2.2 | 29.7 ± 3.1 | <0.001 |
| Desaturation index - NREM (events/h) | 22.8 ± 3.8 | 55 ± 5.5 | <0.001 |
| Desaturation index - REM (events/h) | 7.3 ± 3.4 | 44.3 ± 4.9 | <0.001 |
| Oxygen saturation - basal (%) | 95.9 ± 0.3 | 94.3 ± 0.4 | 0.001 |
| Oxygen saturation - mean (%) | 94.8 ± 0.3 | 92.8 ± 0.5 | <0.001 |
| Electrocardiographic | | | |
| Heart Rate (bpm) | 68.1 ± 10.2 | 66.2 ± 14.3 | 0.49 |
| Basic cycle length (ms) | 893 ± 131.7 | 936.9 ± 172.1 | 0.2 |
| Echocardiogram | | | |
| LVEF (%) | 65.4 ± 3.3 | 65.3 ± 4.2 | 0.91 |
| Indexed LAVol (2D) (ml/m²) | 34.6 ± 6.5 | 32.9 ± 8.6 | 0.39 |
| E/A | 1.09 ± 0.3 | 0.93 ± 0.3 | 0.026 |
| Diastolic Function: Normal | 32 (78.1%) | 26 (68.4%) | 0.66 |
| I Degree Diastolic Dysfunction | 2 (4.9%) | 3 (7.9%) | |
| II Degree Diastolic Dysfunction | 7 (17.1%) | 9 (23.7%) | |

OSA: Obstructive sleep apnea, NREM: Non-rapid eye movement sleep, REM: rapid eye movement sleep, LVEF: Left ventricular ejection fraction, LAVol: Left atrial volume, E/A: Mitral valve E velocity divided by A-wave velocity

**Table 4:** Electrocardiographic findings in patients with and without OSA.

| Variable | OSA- (n = 41) | OSA+ (n = 39) | p value |
|---|---|---|---|
| P-SAECG (ms) | 115.83 ± 1.9 | 119.69 ± 2.8 | 0.17 |
| P-Max (ms) | 123.05 ± 2.1 | 127.49 ± 3 | 0.15 |
| P-Min(ms) | 96.12 ± 1.9 | 96.69 ± 2.7 | 0.83 |
| P-Dispersion (ms) | 27.17 ± 1.9 | 30.79 ± 2.7 | 0.18 |
| P-Med (ms) | 112.51 ± 1.9 | 115.61 ± 2.7 | 0.25 |
| P-DII (ms) | 116.85 ± 2.4 | 122.74 ± 3.5 | 0.096 |
| PRi-DII (ms) | 169.2 ± 3.6 | 174.1 ± 5.2 | 0.34 |
| P/PRi | 0.7 ± 0.01 | 0.72 ± 0.02 | 0.39 |
| QT-DII (ms) | 405.9 ± 5.4 | 415.7 ± 7.7 | 0.2 |
| QT-V5 (ms) | 409.9 ± 5.4 | 416.5 ± 7.7 | 0.4 |
| QTc DII (ms) | 431.5 ± 3.9 | 432.1 ± 5.5 | 0.91 |
| Q-Tpeak (ms) | 318.3 ± 5.3 | 325.5 ± 7.5 | 0.34 |
| J-Tpeak (ms) | 228.9 ± 5.3 | 232.4 ± 7.6 | 0.64 |
| Tonset-Tpeak (ms) | 189.1 ± 6.3 | 187.5 ± 8.9 | 0.85 |
| Tpeak-Tend (ms) | 91.7 ± 3 | 90.9 ± 4.3 | 0.86 |

AHI: Apnea-Hypopnea Index, OSA: Obstructive sleep apnea, , SAECG: Signal-averaged electrocardiogram, P-Max: Maximum P-wave duration, P-min: Minimum P-wave duration, P-Med: Mean P-wave duration, P-DII: P-wave duration in lead DII, QT-DII: QT interval duration in lead DII, QT-V5: QT interval duration in V5, QTc: corrected QT interval, QT interval components: Q-Tpeak, J-Tpeak, Tpeak-Tend, and Tonset-Tpeak.

**Table 5:** Electrocardiographic findings according to minimal oxygen saturation and T90.

| MinSat | | | | | |
|---|---|---|---|---|---|
| **Variable** | **>90% (n = 12)** | **80-90% (n = 38)** | **p value** | **<80% (n = 30)** | **p value** |
| P-SAECG (ms) | 109.83 ± 5.1 | 115.47 ± 5.5 | 0.3 | 121.08 ± 5.5 | 0.042 |
| P-Max (ms) | 124.6 ± 6.6 | 121.1 ± 5.9 | 0.62 | 129.3 ± 5.9 | 0.36 |
| P-Min(ms) | 95.3 ± 4.9 | 96.2 ± 5.3 | 0.87 | 96.8 ± 5.3 | 0.78 |
| P-Dispersion (ms) | 28.7 ± 4.8 | 25.2 ± 5.2 | 0.49 | 32.6 ± 5.1 | 0.45 |
| P-Med (ms) | 110.7 ± 4.8 | 111.1 ± 5.2 | 0.94 | 117.4 ± 5.2 | 0.19 |
| P-DII (ms) | 114.83 ± 6.3 | 115.86 ± 6.8 | 0.88 | 124.1 ± 6.8 | 0.17 |
| PRi-DII (ms) | 162.8 ± 9.3 | 167.8 ± 10.1 | 0.62 | 176.4 ± 10 | 0.18 |
| P/PRi | 0.71 ± 0.03 | 0.69 ± 0.04 | 0.63 | 0.71 ± 0.04 | 0.91 |
| QT-DII (ms) | 405 ± 14.2 | 407.4 ± 15.4 | 0.87 | 414.7 ± 15.3 | 0.52 |
| QT-V5 (ms) | 408.6 ± 14.3 | 401.9 ± 7.7 | 0.78 | 414.1 ± 15.4 | 0.72 |
| QTc DII (ms) | 416 ± 10.7 | 428.1 ± 11.4 | 0.29 | 437.4 ± 11.4 | 0.064 |
| Q-Tpeak (ms) | 319.5 ± 13.9 | 323.4 ± 15.1 | 079 | 320.6 ± 15 | 0.94 |
| J-Tpeak (ms) | 232.5 ± 13.9 | 233.9 ± 15 | 0.92 | 227.2 ± 14.9 | 0.72 |
| Tonset-Tpeak (ms) | 190 ± 16.3 | 193.4 ± 17.6 | 0.84 | 183.2 ± 17.6 | 0.7 |
| Tpeak-Tend (ms) | 88.7 ± 7.8 | 88.2 ± 8.4 | 0.95 | 94.6 ± 8.4 | 0.48 |
| T90 | | | | | |
| Variable | <1minute (n = 10) | 1-60minutes (n = 57) | p value | >60minutes (n = 12) | p value |
| P-SAECG (ms) | 115.9 ± 2.7 | 117.17 ± 3.2 | 0.7 | 125.8 ± 4.3 | 0.026 |
| P-Max (ms) | 123.4 ± 3 | 123.3 ± 3.6 | 0.99 | 136.3 ± 4.9 | 0.009 |
| P-Min(ms) | 96.5 ± 2.7 | 94 ± 3.2 | 0.15 | 102.8 ± 4.3 | 0.32 |
| P-Dispersion (ms) | 24.8 ± 2.7 | 29.5 ± 3.2 | 0.15 | 33.6 ± 4.4 | 0.051 |
| P-Med (ms) | 113.1 ± 2.7 | 112.7 ± 3.1 | 0.81 | 123.2 ± 4.3 | 0.019 |
| P-DII (ms) | 116.3 ± 3.4 | 117.4 ± 13.7 | 0.78 | 135.3 ± 5.4 | 0.001 |
| PRi-DII (ms) | 165.7 ± 5.2 | 172.1 ± 6.2 | 0.3 | 180.8 ± 8.4 | 0.077 |
| P/PRi | 0.71 ± 0.02 | 0.69 ± 0.02 | 0.42 | 0.76 ± 0.03 | 0.11 |
| QT-DII (ms) | 399 ± 7.8 | 417.1 ± 9.2 | 0.053 | 400.8 ± 12.5 | 0.88 |
| QT-V5 (ms) | 401.9 ± 7.8 | 420.2 ± 9.1 | 0.049 | 399.7 ± 12.4 | 0.86 |
| QTc DII (ms) | 425.7 ± 5.7 | 431.8 ± 6.6 | 0.36 | 442.9 ± 9.0 | 0.06 |
| Q-Tpeak (ms) | 317.5 ± 7.7 | 326.8 ± 9.1 | 0,.31 | 306.8 ± 12.4 | 0.39 |
| J-Tpeak (ms) | 231.4 ± 7.7 | 233.5 ± 9.1 | 0.81 | 215.4 ± 12.4 | 0.2 |
| Tonset-Tpeak (ms) | 192.1 ± 8.8 | 194.6 ± 10.4 | 0.81 | 161 ± 14.2 | 0.031 |
| Tpeak-Tend (ms) | 81.7 ± 4.3 | 94.4 ± 5.1 | 0.015 | 92.9 ± 6.9 | 0.1 |

MinSat: Minimum saturation of oxyhemoglobin, SAECG: Signal-averaged electrocardiogram, P-Max: Maximum P-wave duration, P-min: Minimum P-wave duration, P-Med: Mean P-wave duration, P-DII: P-wave duration in lead DII, QT-DII: QT interval duration in lead DII, QT-V5: QT interval duration in V5, QTc: corrected QT interval, QT interval components: Q-Tpeak, J-Tpeak, Tpeak-Tend, and Tonset-Tpeak. T90: Total time below 90% of oxyhemoglobin saturation.

Patients in the group with T90 > 60 min presented longer P-SAECG, P-max, P-mean, and P-DII compared to T90 <1 minute group (125.8 ± 4.3 *vs.* 115.9 ± 2.7, p = 0.026; 136.3 ± 4.9 *vs.* 123.4 ± 3, p = 0.009; 123.2 ± 4.3 *vs.* 113.1 ± 2.7, p = 0.019; 135.3 ± 5.4 *vs.* 116.3 ± 3.4, p = 0.001, respectively. Although not statistically significant (p = 0.051), P-wave dispersion was numerically greater in the T90 > 60minutes compared to <1 min group.

With respect to repolarization parameters, the group represented by patients with T90, 1-60 min presented longer QT interval in lead V5 when compared those in T90 <1 min (420.2 ± 9.1 *vs.* 401.9 ± 7.8, respectively; p = 0.049). Although not statistically significant, similar results were observed with DII-lead QT and corrected QT intervals when T90 > 60 min and < 1 min groups were compared (p = 0.053 and p= 0.06, respectively). Finally, T 90 > 60 min group presented decreased Tonset-Tpeak interval when compared to the < 1 min group (161 ± 14.2 *vs.* 192.1 ± 8.8, respectively; p = 0.031).

Two- and three-dimensional echocardiographic parameters were not different between OSA+ and OSA- groups (Table 6). No differences were seen between groups when stratified according to saturation either (Table 7).

On the other hand, lower PEF was observed in OSA+ group (27.7 ± 1.8 *vs.* 32.4 ± 1.3, respectively; p = 0.012) and there was a trend towards decreased PEV and increased AEF in OSA+ patients compared to OSA- (p = 0.06 and 0.08, respectively) (Table 8).

Patients with MinSat between 80-90% and <80% presented lower conduit strain when compared to those with MinSat >90% (13.8 ± 2.8 and 13 ± 2.7 *vs.* 20.5 ± 2.4; p = 0.016 and p = 0.008, respectively). T90 >60minutes was associated with decreased PEF when compared to T90 <1 min (27.3 ± 3.1 *vs.* 33.6 ± 1.9, respectively; p = 0.045) (Table 9).

**Table 6:** Echocardiografic findings in patients with and without OSA.

| Variable | OSA- (n = 41) | OSA+ (n = 39) | p value |
|---|---|---|---|
| Indexed LAVol (2D) (ml/m²) | 33.4 ± 1,3 | 33.3 ± 1.8 | 0.97 |
| MaxLAVol (mL) | 58.1 ± 2,6 | 56.6 ± 3.7 | 0.69 |
| PreALAVol (mL) | 39.4 ± 2,1 | 41.1 ± 2.9 | 0.56 |
| MinLAVol (mL) | 27.2 ± 1,5 | 26.3 ± 2.1 | 0.66 |

AHI: Apnea-Hypopnea Index, OSA: Obstructive sleep apnea, LAVol: Left atrial volume, MaxLAVol: Maximum LAVol, PreALAVol: LAVol preceding atrial contraction, MinLAVol: Minimum LAVol.

**Table 7:** Echocardiographic findings according to minimal oxygen saturation and T90.

| MinSat | | | | | |
|---|---|---|---|---|---|
| **Variable** | **>90% (n = 12)** | **80-90% (n = 38)** | **p value** | **<80% (n = 30)** | **p value** |
| Indexed LAVol (2D) (ml/m²) | 35.8 ± 3.3 | 32.7 ± 3.6 | 0.38 | 33.5 ± 3.6 | 0.51 |
| MaxLAVol (mL) | 59.9 ± 6.9 | 56.7 ± 7.5 | 0.67 | 57.6 ± 7.4 | 0.75 |
| PreALAVol (mL) | 39.6 ± 5.4 | 39.1 ± 5.9 | 0.93 | 41.4 ± 5.8 | 0.75 |
| MinLAVol (mL) | 25.9 ± 3.9 | 26.3 ± 4.2 | 0.91 | 27.4 ± 4.2 | 0.72 |
| T90 | | | | | |
| Variable | <1minute (n = 10) | 1-60minutes (n = 57) | p value | >60minutes (n = 12) | p value |
| Indexed LAVol (2D) (ml/m²) | 32.3 ± 1.9 | 33.4 ± 2.2 | 0.61 | 34.5 ± 3 | 0.47 |
| MaxLAVol (mL) | 55.2 ± 3.9 | 57.2 ± 4.6 | 0.67 | 60.1 ± 6.2 | 0.34 |
| PreALAVol (mL) | 36.6 ± 3 | 40.3 ± 3.6 | 0.3 | 45.1 ± 4.9 | 0.086 |
| MinLAVol (mL) | 25.3 ± 2.2 | 26.9 ± 2.6 | 0.53 | 28.6 ± 3.3 | 0.35 |

MinSat: Minimum saturation of oxyhemoglobin, LAVol: Left atrial volume, MaxLAVol: Maximum LAVol, PreALAVol: LAVol preceding atrial contraction, MinLAVol: Minimum LAVol, T90: Total time below 90% of oxyhemoglobin saturation.

**Table 8:** Echocardiographic functional remodeling parameters in patients with and without OSA.

| Variable | OSA- (n = 41) | OSA+ (n = 39) | p value |
|---|---|---|---|
| TEF (%) | 52.8 ± 1.4 | 53.3 ± 2.1 | 0.83 |
| PEF (%) | 32.4 ± 1.3 | 27.7 ± 1.8 | 0.012 |
| AEF (%) | 47.5 ± 4.8 | 59.6 ± 6.9 | 0.083 |
| TEV (mL) | 30.9 ± 1.6 | 29.8 ± 2.3 | 0.64 |
| PEV (mL) | 18.9 ± 1.1 | 16 ± 1.5 | 0.06 |
| AEV (mL) | 12.2 ± 1.1 | 14.8 ± 1.6 | 0.11 |
| Reservoir strain (εR) (%) | 29.8 ± 1.4 | 30 ± 1.9 | 0.95 |
| Conduit strain (εCD) (%) | 14.4 ± 1 | 13.4 ± 1.4 | 0.5 |
| Contraction strain (εCT) (%) | 15.5 ± 0.8 | 16.4 ± 1.2 | 0.41 |

AHI: Apnea-Hypopnea Index, OSA: Obstructive sleep apnea, TEF: Total emptying fraction, PEF: Passive emptying fraction, AEF: Active emptying fraction, TEV: Total emptying volume, PEV: Passive emptying volume, AEV: Active emptying volume.

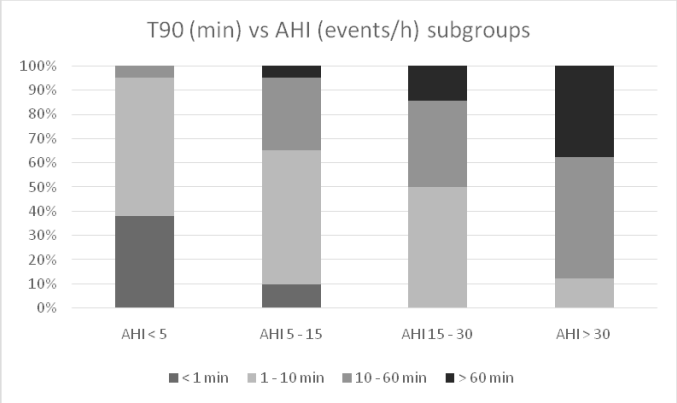
**Table 9:** Echocardiographic functional remodeling parameters according to minimal oxygen saturation and T90.

| MinSat | | | | | |
|---|---|---|---|---|---|
| **Variable** | **>90% (n = 12)** | **80-90% (n = 38)** | **p value** | **<80% (n = 30)** | **p value** |
| TEF (%) | 56.6 ± 3.7 | 53.3 ± 4 | 0.4 | 52.3 ± 4 | 0.28 |
| PEF (%) | 34.1 ± 3.4 | 31 ± 3.7 | 0.4 | 28.6 ± 3.7 | 0.14 |
| AEF (%) | 56.9 ± 12.9 | 51.2 ± 14 | 0.68 | 54.9 ± 13.9 | 0.88 |
| TEV (mL) | 34 ± 4.2 | 30.2 ± 4.5 | 0.39 | 30 ± 4.5 | 0.36 |
| PEV (mL) | 19.8 ± 2.8 | 17.9 ± 3 | 0.52 | 16.7 ± 3 | 0.31 |
| AEV (mL) | 14.2 ± 3.1 | 12.8 ± 3.3 | 0.66 | 14 ± 3.3 | 0.95 |
| Reservoir strain (εR) (%) | 34.6 ± 3.5 | 30 ± 3.8 | 0.22 | 29.1 ± 3.8 | 0.14 |
| Conduit strain (εCD) (%) | 20.5 ± 2.4 | 13.8 ± 2.8 | 0.016 | 13 ± 2.7 | 0.008 |
| Contraction strain (εCT) (%) | 14.5 ± 2.1 | 16.1 ± 2.3 | 0.46 | 15.9 ± 2.3 | 0.52 |
| T90 | | | | | |
| Variable | <1minute (n = 10) | 1-60minutes (n = 57) | p value | >60minutes (n = 12) | p value |
| TEF (%) | 53.9 ± 2.1 | 52.4 ± 2.5 | 0.56 | 53.8 ± 3.4 | 0.97 |
| PEF (%) | 33.6 ± 1.9 | 29.4 ± 2.3 | 0.074 | 27.3 ± 3.1 | 0.045 |
| AEF (%) | 47.4 ± 7.3 | 53.9 ± 8.6 | 0.45 | 59.3 ± 11.7 | 0.31 |
| TEV (mL) | 29.9 ± 2.4 | 29.8 ± 2.8 | 0.97 | 32.5 ± 3.8 | 0.49 |
| PEV (mL) | 18.4 ± 1.6 | 17.2 ± 1.9 | 0.51 | 17.8 ± 2.6 | 0.53 |
| AEV (mL) | 11.5 ± 1.7 | 13.4 ± 2 | 0.34 | 16.6 ± 2.7 | 0.06 |
| Reservoir strain (εR) (%) | 32 ± 2 | 29.1 ± 2.4 | 0.22 | 29.5 ± 3.2 | 0.44 |
| Conduit strain (εCD) (%) | 15.9 ± 1.5 | 13.1 ± 1.8 | 0.1 | 14.1 ± 2.4 | 0.45 |
| Contraction strain (εCT) (%) | 16 ± 1.2 | 15.9 ± 1.4 | 0.96 | 15.4 ± 1.9 | 0.76 |

MinSat: Minimum saturation of oxyhemoglobin, TEF: Total emptying fraction, PEF: Passive emptying fraction, AEF: Active emptying fraction, TEV: Total emptying volume, PEV: Passive emptying volume, AEV: Active emptying volume, T90: Total time below 90% of oxyhemoglobin saturation.

Finally, the exposure rates to desaturation varied between AHI subgroups (Figure 1).

**Figure 1:** T90 **vs.** AHI by different subgroups.




T90: Total time below 90% of oxyhemoglobin saturation, AHI: Apnea-Hypopnea Index.

## Discussion

In this transversal, hypothesis-generating study of the three main domains of atrial remodeling, we failed to demonstrate significant electrical differences between groups using an AHI cut off of 15 events/h. Increased P-SAECG, however, was observed in patients with MinSat <80%. Additionally, there was a significant association between abnormal P-wave-related variables, particularly P-SAECG, P-max, P-mean, and P-DII and T90 > 60 min.

Electrical remodeling was first demonstrated by the publication of Can I, et al. (2009) [13], in which P wave duration and its dispersion were significantly increased in patients with OSA compared to control. Significant reduction of P-wave duration was also reported after treatment with CPAP in small studies [16]. However, the only randomized study on the topic showed no relevant impact of CPAP on ECG variables during the follow up [17].

Intermittent hypoxemia reduces atrial velocity conduction and generates atrial tissue refractory heterogeneity. It also contributes to autonomic hyperactivation and inflammatory response [5]. Chronically, it results in longer atrial depolarization, represented by increased P-wave duration. As shown in 3452 patients by Gami AS, et al. (2007) [22], the decrease in oxyhemoglobin levels was the strongest risk factor for the occurrence of AF in patients <65 years.

Recently, there has been attributed an increasing value to T90-based evaluation. T90 assessment has shown to be superior to AHI as a prognostic factor regarding cardiovascular mortality in older men [23]. This reflects no correlation between T90 and AHI [24]. For an event to count by AHI evaluation, it does not necessarily have to have associated desaturation. Lower AHI values might include long apneas, with higher exposure to desaturation. In our study, the exposure rates to desaturation varied between AHI subgroups.

The longer the QT interval, the higher the risk of AF, as shown by the Nielsen JB, et al. (2013) [25], and different community prospective cohorts [26]. Although the association between T90 and the QT interval has not been demonstrated, this might be an important component involved with the genesis and recurrence of AF in OSA patients.

In the Bachmann TN, et al. (2016) [27], increased Tpeak-Tend was shown to be associated with increased mortality, cardiovascular death, and incident AF. In the study of Bilal N, et al. (2018) [28], OSA patients presented increased QT dispersion and reduction with CPAP use. The association between T90 and increased QT dispersion has not yet been shown. In the present study, T90 was associated with decreased Tonset-Tpeak, which reflects increased repolarization dispersion. This in turn when associated with intra e interatrial heterogeneous and slow conduction leads to atrial micro reentry, which, in part, result in AF.

In regards to echocardiographic parameters of structural remodeling, there were no differences between OSA– and OSA+ groups. It is well established that hypertension plays a critical role in the development of atrial remodeling in both OSA+ and OSA- patients. Studies have shown that OSA patients with hypertension present left ventricular remodeling [29,30]. Hypertension generates left ventricular hypertrophy, diastolic and/or systolic dysfunction, and activates the RAAS pathway, which subsequently lead to atrial remodeling [31]. Our

sample was composed by a high prevalence of resistant hypertension. This might have influenced the similar rates of diastolic dysfunction between OSA+ and OSA- groups.

Interestingly, all patients with no desaturation presented normal diastolic function. Diastole is an active, ATP-dependent process, and precedes systolic dysfunction in chronic exposure to hypoxemia [32].

Echocardiographic variables of atrial functional remodeling reflect the hypoxemia-associated diastolic dysfunction in atrial function. AHI-based and saturation-based evaluations both point towards conduit phase atrial dysfunction in OSA patients, intimately related to left ventricular myocardial relaxation, which is consistent with other studies evaluating atrial function in OSA patients [33,34].

## Conclusions

The presence of OSA was not associated with significant electrical, functional, and structural atrial remodeling. With increasing evidence that a saturation-based analysis might be superior to AHI-based evaluation, we demonstrated the association of different non-invasive electrical and functional remodeling variables with hypoxemia, particularly by using a T90 based approach.

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