Atrial Substrate and Triggers of Paroxysmal Atrial Fibrillation in Patients With Obstructive Sleep Apnea

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BACKGROUND: Obstructive sleep apnea (OSA) is associated with atrial remodeling, atrial fibrillation (AF), and increased incidence of arrhythmia recurrence after pulmonary vein (PV) isolation. We aimed to characterize the atrial substrate, including AF triggers in patients with paroxysmal AF and OSA.

METHODS AND RESULTS: In 86 patients with paroxysmal AF (43 with ≥moderate OSA [apnea–hypopnea index ≥15] and 43 without OSA [apnea–hypopnea index <5]), right atrial and left atrial voltage distribution, conduction velocities, and electrogram characteristics were analyzed during atrial pacing. AF triggers were examined before and after PV isolation and targeted for ablation. Patients with OSA had lower atrial voltage amplitude (right atrial, *P*=0.0005; left atrial, *P*=0.0001), slower conduction velocities (right atrial, *P*=0.02; left atrial, *P*=0.0002), and higher prevalence of electrogram fractionation (*P*=0.0001). The areas of atrial abnormality were consistent among patients, most commonly involving the left atrial septum (32/43; 74.4%). At baseline, the PVs were the most frequent triggers for AF in both groups; however, after PV isolation patients with OSA had increased incidence of additional extra-PV triggers (41.8% versus 11.6%; *P*=0.003). The 1-year arrhythmia-free survival was similar between patients with and without OSA (83.7% and 81.4%, respectively; *P*=0.59). In comparison, control patients with paroxysmal AF and OSA who underwent PV isolation alone without ablation on extra-PV triggers had increased risk of arrhythmia recurrence (83.7% versus 64.0%; *P*=0.003).

CONCLUSIONS: OSA is associated with structural and functional atrial remodeling and increased incidence of extra-PV triggers. Elimination of these triggers resulted in improved arrhythmia-free survival.

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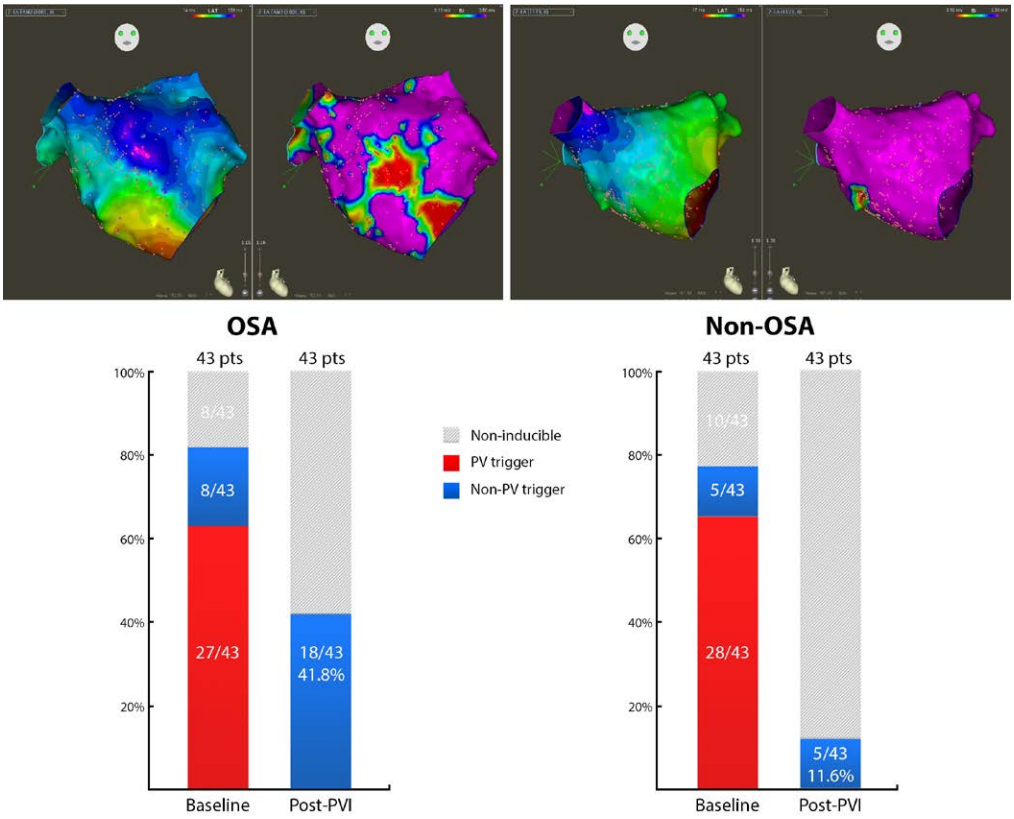
Key Words: atrial fibrillation ■ atrial remodeling ■ catheter ablation ■ incidence ■ prevalence



WHAT IS KNOWN?

- There is a strong association between atrial fibrillation (AF) and obstructive sleep apnea (OSA), and it is estimated that 50% of patients with AF also have OSA.
- The association between AF and OSA may be related to common risk factors and a mutually perpetuating pathophysiological relationship between these conditions.
- OSA promotes AF via electric and structural atrial remodeling.

WHAT THE STUDY ADDS?

- OSA in patients with paroxysmal AF is associated with biatrial structural remodeling presenting as patchy areas of low voltage and fractionated electrograms predominantly in the anterior septum.
- The pulmonary veins (PVs) are the major triggers for AF in patients with OSA; however, extra-PV triggers are highly common in this patient population.
- Ablation of extra-PV triggers in patients with paroxysmal AF and OSA is associated with improved clinical outcome compared with PV isolation alone.
- The high prevalence of OSA in patients with AF coupled with the increased incidence of extra-PV triggers calls for universal sleep study in all patients with AF and an ablation strategy incorporating targeting of extra-PV triggers.

Obstructive sleep apnea (OSA) is exceedingly prevalent in patients with atrial fibrillation (AF).[1,2] Individuals with OSA have 2 to 4× increased risk to develop AF when compared with those without OSA. Similarly, individuals with AF have an increased prevalence of OSA, ranging from 10% to 60%.[3] This wide range in the prevalence of OSA in patients with AF stems from differences in study design, patient population, and screening criteria. The coexistence of AF and OSA can be partially attributed to a common risk factor profile, including advanced age, hypertension, obesity, diabetes mellitus, and structural heart disease. Nonetheless, there may be a pathophysiologic, mutually perpetuating, relationship between AF and OSA that includes cardiac electric and structural remodeling.

OSA has been shown to promote AF via stretch-mediated shortening of atrial refractoriness and slow conduction mediated by collagen deposition and changes in gap junction content and function.[4,5] In particular, mechanical stretch of the thinned-walled atria shortens atrial refractoriness and promotes occurrence of spontaneous atrial premature depolarizations (APD), triggering episodes of AF in animal models of sleep apnea and in humans.[3,6]

In this study, we evaluated the occurrence and pattern of atrial remodeling in patients with AF and OSA. We specifically compared the voltage distribution, elec-

trogram characteristics, and conduction properties in patients with paroxysmal AF (PAF) with and without OSA. We also examined the frequency and distribution of AF triggers (pulmonary vein [PV] and extra-PV triggers) in patients with and without OSA. Last, we evaluated the role of extra-PV triggers in long-term arrhythmia control of patients with OSA.

METHODS

Study Population

The study groups consisted of patients with symptomatic PAF without prior diagnosis of sleep apnea referred for sleep study ≤90 days before index PV isolation (PVI) between August 2013 and March 2016 at 3 institutions: Beth Israel Deaconess Medical Center (Boston, MA), Texas Cardiac Arrhythmia Institute at St. David's Medical Center (Austin, TX), and University of Miami Miller School of Medicine (Miami, FL). Sleep apnea was evaluated using an in-laboratory overnight polysomnography or a home sleep apnea testing device (WatchPAT; Itamar Medical, Israel). Diagnosis of sleep apnea was determined according to the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine.[7] A normal sleep study was defined if the apnea–hypopnea index ≤5; mild sleep apnea by an apnea–hypopnea index range ≥5 and ≤15; and ≥moderate sleep apnea by apnea–hypopnea index ≥15. An episode was categorized as obstructive if apneic episodes occurred during respiratory effort. The 2 study groups included consecutive patients with a normal sleep study and consecutive patients with ≥moderate OSA. Patients with mild OSA were excluded because of potential overlap in atrial substrate and to decrease misclassification of cases and controls. The 2 study groups underwent a detailed mapping and ablation protocol as described in the section below that included PVI plus ablation of extra-PV triggers. The OSA study group is labeled [(+) OSA (+) PVI (+) triggers], and the non-OSA study group is labeled [(–) OSA (+) PVI (+) triggers].

To compare the effect of additional extra-PV trigger ablation on arrhythmia control in the study groups, control patients with normal sleep study and with ≥moderate OSA who underwent PVI alone without mapping and ablation of extra-PV triggers were identified from a prospectively collected cohort: [(–) OSA (+) PVI (–) triggers] and [(+) OSA (+) PVI (–) triggers], respectively.

To evaluate the atrial substrate specific for OSA, patients with heart failure (left ventricular ejection fraction ≤50%), significant valvular disease, previous myocardial infarction, untreated hypertension, and diabetes mellitus were excluded from the study. To examine the association between OSA and atrial substrate and AF triggers independently of the potential effect(s) of continuous positive airway pressure (CPAP) therapy, patients previously treated with CPAP were excluded (patients were allowed to start CPAP therapy after the ablation procedure). Last, we only included patients presenting in sinus rhythm to determine the baseline atrial substrate and avoid measurements related to acute electric remodeling. The institutional review board of each of the participating centers approved the study protocol.

Electrophysiology Study and Ablation

The procedures were performed in the postabsorptive state with conscious sedation or general anesthesia according to center and operator preference. Antiarrhythmic drugs (AADs) were discontinued for ≥5 half-lives before the ablation procedure (there were no patients on amiodarone). All patients were chronically anticoagulated for ≥4 weeks. The procedures were performed under uninterrupted warfarin (international normalized ratio range, 2–3) or rivaroxaban. In patients taking dabigatran or apixaban, a single dose was often held before the procedure. Unfractionated heparin was administered before the transseptal puncture to maintain an activated clotting time of 300 to 400 s for the duration of the procedure. An intracardiac echocardiography catheter (8F AcuNav; Biosense Webster) was advanced to the right atrium (RA). Electroanatomical mapping of the RA and left atrium (LA) was performed during proximal and distal coronary sinus (CS) pacing, respectively (cycle length of 600–800 ms). Electroanatomical mapping was performed using Carto3 (Biosense Webster, Johnson & Johnson) in 182 of 186 patients, whereas Rhythmia (Boston Scientific, Cambridge, MA) was used in 4 patients. Mapping was performed using multielectrode catheters, including circular (Lasso 10-pole, adjustable circumference; Biosense Webster), pentaray (Pentaray, interelectrode spacing 2-6-2 mm; Biosense Webster), or basket (Orion 64 electrodes; Boston Scientific) catheters. The mapping catheters were advanced into the atria over a long fixed curved or a steerable sheath. The mapping density was in accordance to the physician's practice, however, with an obligatory minimal cutoff point number of 250 and filling threshold ≤10 mm (allowing interpolation between points to be ≤10 mm). Ablation was performed using an open irrigation tip radiofrequency catheter (Thermocool ST or Thermocool SF; Biosense Webster) with energy of 20 to 40 W. PVI was performed by isolating the left and right pairs of veins en bloc using either a point-by-point or a continuous ablation approach, according to operator practice. Successful PVI was defined by the presence of entrance block (loss of PV ostia potentials) and exit block (failure to capture the LA during pacing from the PV ostia). Persistent isolation for each PV was reconfirmed after ≥15-minute waiting period. In cases of acute PV reconnection, additional radiofrequency applications were performed to reisolate the PV.

Identification and Ablation of AF Triggers

AF trigger was defined as an APD that initiated AF lasting ≥30 s. After completion of chamber mapping and before PVI, the ablation catheter was positioned in the right superior PV and the mapping catheter in the left superior PV. Two decapolar catheters were positioned in the CS and crista terminalis. An infusion of isoproterenol in increasing doses from 2 to 30 μg/min was given over 10 minutes until development of AF or junctional rhythm. As isoproterenol often results in transient hypotension, phenylephrine (50–200 mcg/min) was simultaneously infused to maintain a systolic pressure >90 mm Hg. If AF could not be initiated during the isoproterenol infusion or its wear-off period, isoproterenol infusion was restarted at the maximally achieved dose, and atrial pacing at progressively shorter cycle lengths down to effective refractory period was performed in an

attempt to induce AF. Once AF was induced, electric cardioversion was performed (during isoproterenol infusion) to lower the AF inducibility threshold and trigger initiation of AF as described previously.[8] If AF could not be induced with isoproterenol and cardioversion, adenosine was given at a dose sufficient to produce transient atrioventricular block, initially at 6 mg with incremental doses of ≤48 mg (Figure 1A). Trigger localization was estimated based on the earliest endocardial activation site and pattern of activation from the multiple LA and RA catheters. Once an AF trigger was identified, the catheters were repositioned around the zone of earliest activation and electric cardioversion was performed in an attempt to reinduce AF (Figure 1B). Repeat induction of AF was performed to examine the reproducibility of AF induction, the specificity of the initiating APD, and to better localize its origin.

After evaluation for AF triggers at baseline, PVI was performed as described above. Evaluation of AF triggers was repeated after PVI to identify extra-PV triggers. In addition to isoproterenol infusion, adenosine challenge was also performed in an attempt to identify dormant PV conduction and as an additional provocative test for identification of AF triggers. All extra-PV triggers were targeted for ablation. Ablation of extra-PV triggers was delivered as a cluster of radiofrequency ablation lesions (20–40 W; 20–40 s) at the site of the earliest activation as described above. After ablation, the provocative measure that resulted in APD-triggered AF was repeated to confirm elimination of the trigger. Additional ablation was performed in an attempt to eliminate all AF triggers.

Bipolar Voltage Distribution and Electrogram Measurement

Normal atrial bipolar voltage amplitude was defined as bipolar amplitude ≥0.5 mV as previously determined for multielectrode mapping catheters with 1 mm electrode size and 2 mm interelectrode spacing.[9] To minimize overestimation of the low-voltage area, we defined an area as low voltage only if the bipolar voltage amplitude was ≤0.5 mV in ≥3 adjacent points and the electrograms demonstrated fractionation and split potentials. Electrograms characteristics, including electrogram duration and presence of fractionations, were analyzed offline at uniform gain and paper speed of 200 mm/s. Normal electrograms were defined as (1) bipolar voltage amplitude ≥0.5 mV, (2) duration ≤50 ms, and (3) number fractionations crossing the isoelectric interval ≤5. Electrograms with double potentials at the crista terminalis or at both sides of the septum were considered normal if their individual component duration was ≤50 ms.

Atrial Conduction Time

Total atrial conduction time was determined by the P-wave duration before ablation as measured during ostial CS pacing at a constant rate of 600 ms. The P-wave duration was measured in lead II and averaged over 10 beats. Intra-atrial conduction time was determined separately for the RA and the LA after completion of the electroanatomical mapping. RA conduction time was determined during ostial CS pacing and measured from the site of pacing to the latest RA activation point. LA conduction time was determined during distal CS pacing and measured from the earliest to the latest LA activation point.

Follow-Up

Follow-up consisted of clinic visits at 1, 3, 6, and 12 months after the ablation procedure and at intervals of 6 months afterward. Holter monitoring of ≥1 week duration was performed at least twice during the first year after ablation.

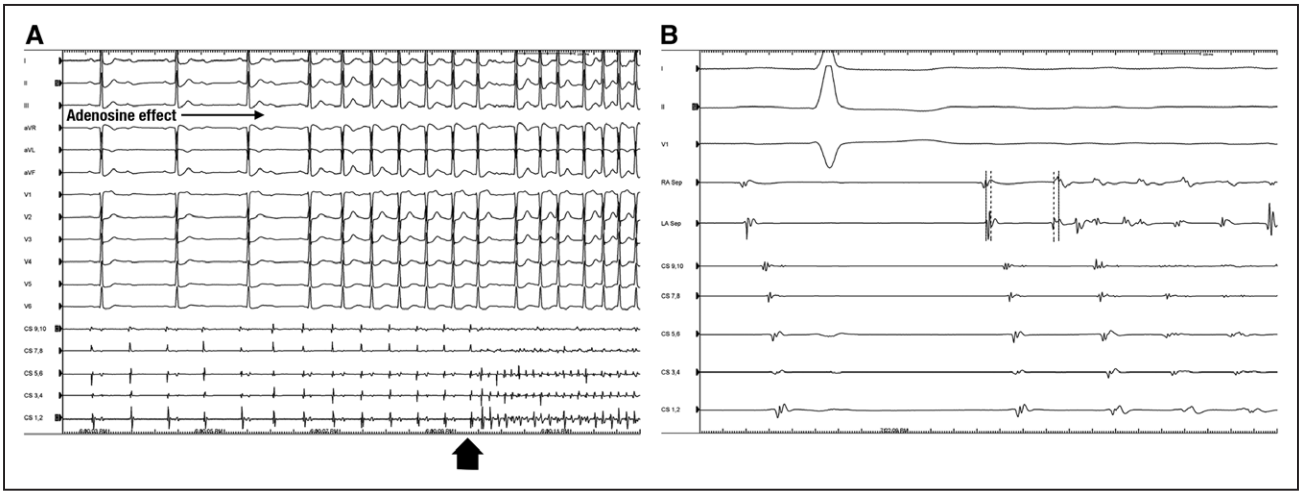


Figure 1. Identification of atrial fibrillation (AF) triggers.
A, Isoproterenol infusion (20 μg/min) did not induce AF. However, the concomitant administration of adenosine bolus (48 mg) resulted in increased atrioventricular block and initiation of AF (arrowhead). **B**, Initiation of AF from a left atrial premature depolarization (APD). In this case, the initial induction of AF appeared to originate from the interatrial septum. After restoration of sinus rhythm and preparation for a second induction of AF, the catheters were repositioned on the right (RA Sep) and left (LA Sep) interatrial septum. Note that during sinus rhythm, activation of the right septum (dotted line) precedes activation of the left septum (dashed line). The sinus beat is then followed by an APD-initiating AF originating from the left septum. Note the reversal of atrial activation with the left septum (dashed line) now preceding the right septum (dotted line).

Additional visits, electrocardiograms, and Holter monitoring were performed if patients reported arrhythmia symptoms between visits. All AADs were discontinued ≥5 half-lives before the ablation procedure and were not resumed after the procedure. Arrhythmia recurrence was defined as any documented atrial tachyarrhythmia episode lasting for ≥30 s that occurred after a 4-week blanking period after the ablation procedure. If arrhythmia recurred during the first 4-week period, electric cardioversion with or without initiation of AADs was considered. If AAD was initiated because of arrhythmia recurrence during the initial period, it was discontinued during the 3-month postablation clinic visit. Patients with documented recurrence after the blanking period were treated with AADs or repeat ablation. At each clinic appointment, patients were questioned about initiation of CPAP therapy and compliance with therapy.

Statistical Analysis

Continuous variables are reported as mean±SD (or median and interquartile range, as appropriate) and compared between groups using 1-way ANOVA (or Kruskal–Wallis) test. Categorical variables are reported as number and percentage and compared among groups using the Fisher exact test. Event-free survival was estimated by the Kaplan–Meier survival function. Pairwise comparisons of survival rates were made using Mantel–Cox log-rank test. The aim of the comparison was to evaluate the impact of extra-PV triggers ablation on arrhythmia-free survival. Therefore, each of the 2 study groups, with and without OSA, was compared with a respective control group who underwent PVI alone without ablation of extra-PV triggers. The impact of the following variables was assessed in a univariable Cox regression analysis: age, sex, body mass index, hypertension, diabetes mellitus, left ventricular ejection fraction, LA area indexed to body surface area (BSA), AF severity index (AF duration since diagnosis and frequency), AF duration, and ablation of extra-PV triggers. Variables demonstrating significant impact on arrhythmia-free survival were then evaluated in a multivariable model. A P value <0.05 was considered statistically significant. Analyses were conducted using SPSS Statistics 22.0 (SPSS, Inc, Chicago, IL).

RESULTS

Study Population

Baseline Characteristics

Forty-three patients with ≥moderate OSA completed the mapping and ablation study protocol, including ≥1-year follow-up duration [(+) OSA (+) PVI and (+) trigger]. Forty-five patients with normal sleep study completed the mapping and ablation protocol; however, 2 were lost to follow-up, and a total of 43 patients with normal sleep study [(–) OSA (+) PVI and (+) trigger] were analyzed. The control groups that underwent PVI alone without mapping and ablation of extra-PV triggers included 50 patients with OSA [(+) OSA (+) PVI and (–) trigger] and 48 patients without OSA [(–) OSA (+) PVI and (–) trigger]. Patient characteristics are summarized in Table 1. The 2 OSA groups had larger LA dimensions indexed to BSA (P=0.02). In patients with ≥moderate OSA, daytime somnolence was reported in 53 of 91 (58.2%; data were missing for 2 patients).

Characterization of Atrial Substrate

Atrial Voltage Abnormalities

The number of RA data points was 272±114 (median 282), and the number of LA data points was 556±320

Table 1. Baseline Clinical Characteristics in Each Study Group

	(+) OSA (+) PVI (+) Triggers (n=43)	(–) OSA (+) PVI (+) Triggers (n=43)	(–) OSA (+) PVI (–) Triggers (n=48)	(+) OSA (+) PVI (–) Triggers (n=50)	*P* Value*
Male sex	28 (65.1)	22 (51.1)	27 (56.2)	33 (66.0)	
Age, y	49±12	54±14	59±12	51±15	0.42
BMI, kg/m^2	31±6	29±7.5	26±9.0	32±5.5	0.23
Hypertension	21 (48.8)	18 (41.8)	18 (37.5)	27 (54.0)	0.62
AF duration, y	6.0 (2–8)	5.5 (1–14)	4.0 (1–14)	4.5 (2–7)	0.30
Frequency (episodes/mo)	3 (0–4)	2 (1–5)	2 (1–4)	3 (1–6)	
No. of failed AADs	0.8 (0–2)	0.7 (0–2)	0.5 (0–3)	0.4 (0–2)	0.41
Echocardiographic data					
LA area indexed BSA, cm^2/m^2	13.2±3.1	8.8±1.8	9.6±2.4	11.2±2.1	0.03
LVEF (%)	60±5	62±2	63±8	60±5	0.7
Polysomnography data					
Mean AHI	36±26	3±2	4±2	33±22	<0.0001
Desaturations ≥4%/h (no)	28±16	3±3	2±2	26±12	<0.0001

AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; AHI, apnea–hypopnea index; BMI, body mass index; BSA, body surface area; LA, left atrium; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; and PVI, pulmonary vein isolation.

*P value for 1-way ANOVA (Kruskal–Wallis) among all groups.

(median 560). Patients without OSA had normal atrial electrograms and bipolar voltage amplitude with a mean bipolar voltage amplitude of 2.4±1.6 mV (median, 2; range, 0.46–4.4 mV). In the RA, bipolar voltage amplitude and electrogram characteristics were normal in all. In the LA, bipolar voltage amplitude and electrogram characteristics were normal in 39 of 43 (90%). In 4 patients, areas of abnormal bipolar voltage with electrogram fractionation were observed in the anterior roof (2 patients), posterior wall (1 patient), and fossa ovalis (1 patient). In all 4 of these patients, the size of the low-voltage area was small (4.4±3.4 cm^2 [median, 4; range, 1.4–7.8]). Figure 2 shows a representative example of biatrial voltage map of a patient with a normal sleep study.

In the OSA group, the prevalence of low bipolar voltage amplitude and abnormal electrograms was significantly greater than the group without OSA (Figure 3). In the RA, areas of low bipolar voltage amplitude with abnormal electrograms were observed in 11 of 43 (25.5% RA; *P*=0.0005). The most common areas of abnormality were the septum (72.7%) and the posterolateral wall (36.4%). The area of RA bipolar voltage amplitude abnormality was small (4.1±3.6 cm^2 [range, 2.5–9.1]). In the LA, low bipolar voltage amplitude with abnormal electrograms was present in 32 of 43 (74.4%; *P*=0.0001), with the size of abnormality being relatively large (14.2±5.2 cm^2 [range, 8.6–19.4]). Importantly, the location of tissue abnormality was consistent in 29 of 32 (90%) patients, involving the anterior septum from the mitral annulus inferiorly, the base of the LA appendage superiorly, and the fossa ovalis posteriorly. Figure 4 shows an example of a patient with OSA demonstrating voltage abnormality at the RA and LA septum with electrograms showing delayed and fractionated signals.

Atrial Conduction Time

Total atrial conduction time was determined as the P-wave duration in sinus rhythm before the ablation procedure (heart rate, 72±36 beats per minute) and off AADs, β-blockers, or calcium channel blockers. The baseline P-wave duration was not statistically different between patients with and without OSA (128±62 versus 116±47 ms, respectively; *P*=0.09).

RA conduction time during proximal CS pacing was similar between patients with and without OSA

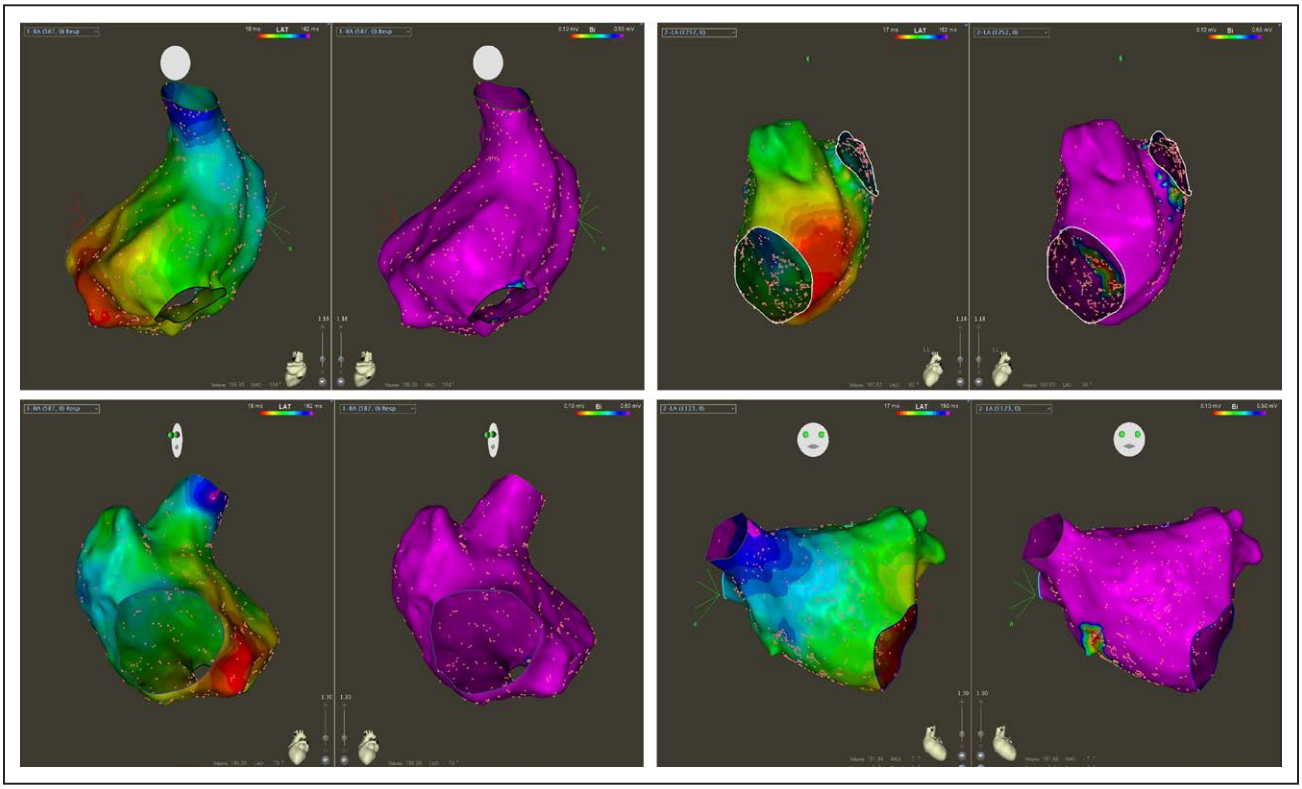


Figure 2. Voltage and conduction properties in non–obstructive sleep apnea (OSA).
Left, A bipolar voltage map (range, 0.1–0.5 mV) of the right atrium (RA) in posteroanterior (**top**) and left anterior oblique (**bottom**) projections during proximal coronary sinus pacing in a patient without OSA. The voltage amplitude is normal. Activation map is presented as isochronal steps of 10 ms, demonstrating early activation at the proximal coronary sinus pacing site with smooth and even propagation toward the zone of latest activation at the superior vena cava. **Right**, Bipolar voltage and activation maps of the left atrium at the left lateral (**top**) and right anterior oblique (**bottom**) projections during distal coronary sinus pacing. The voltage amplitude is normal (albeit the zone of the fossa ovalis) with normal wavefront propagation from the lateral mitral annulus to the zone of latest activation at the right superior pulmonary vein.

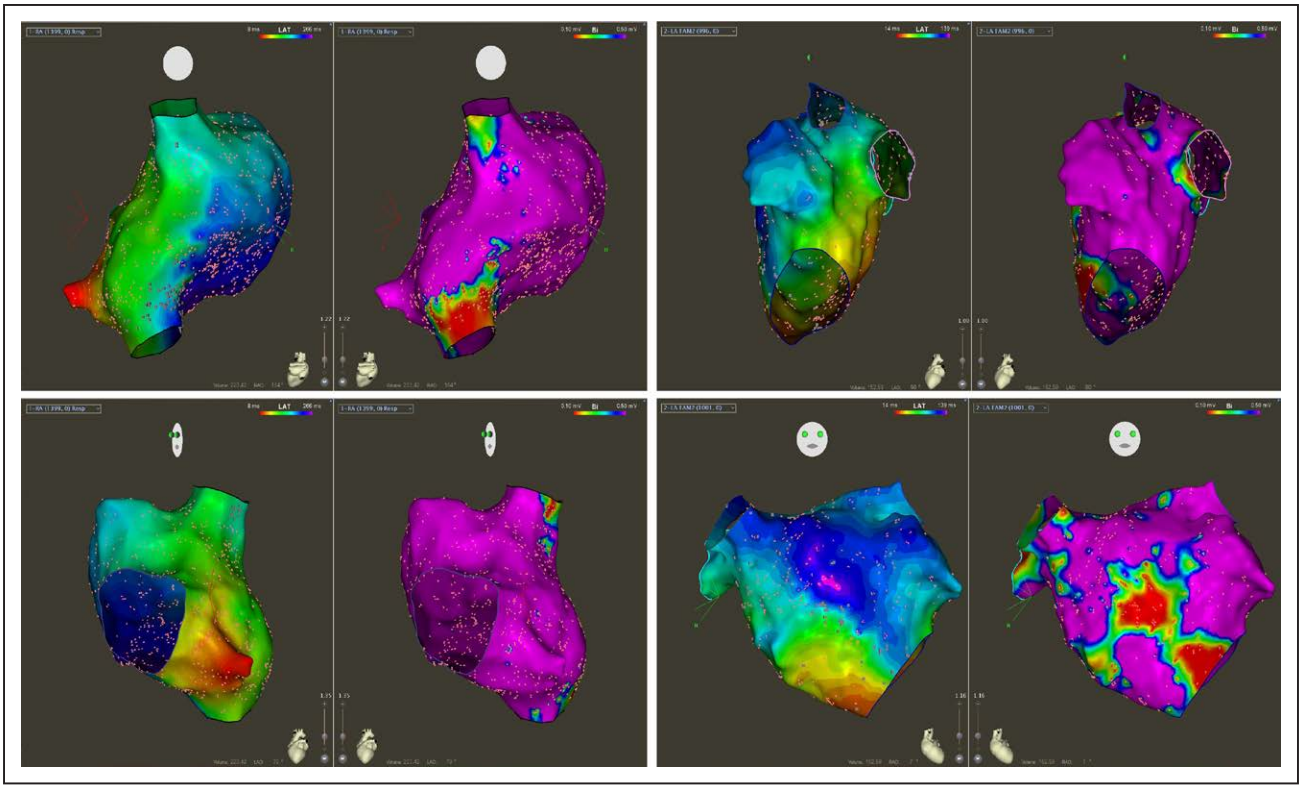


Figure 3. Voltage and conduction properties in obstructive sleep apnea (OSA).
Left, Bipolar voltage map (range, 0.1–0.5 mV) of the right atrium (RA) in posteroanterior (**top**) and left anterior oblique (**bottom**) projections during proximal coronary sinus pacing in a patient with OSA. This demonstrates an overall normal voltage amplitude, with small areas of lower voltage in the septum. The activation map, similarly presented as isochronal steps of 10 ms, demonstrates slow and abnormal conduction in the septum with the midposterior septum being activated 258 ms after the earliest activation of the proximal coronary sinus. **Right**, Bipolar voltage and activation maps of the left atrium at the left lateral (**top**) and right anterior oblique (**bottom**) projections during distal coronary sinus pacing. The voltage amplitude is abnormal with significant area of low voltage at the septum. The activation map during distal coronary sinus is abnormal, with slow conduction over the septum, at the zone of low voltage.

(142±64 versus 156±118 ms, respectively; *P*=0.12). However, the pattern of wavefront propagation differed between groups, such that in patients without OSA the area of latest activation was the right atrial appendage–superior vena cava junction, whereas in those with OSA the latest activation was the septal wall (Figures 2 and 3). Although the total RA activation time was similar between groups, RA conduction velocities were slower in patients with OSA (0.88 versus 1.22 mm/s; *P*=0.02).

LA conduction time during distal CS pacing was longer in patients with OSA (162±55 versus 108±26 ms, respectively; *P*=0.0008). Similarly, LA conduction velocities were significantly slower in patients with OSA (0.78 versus 1.32 mm/s; *P*=0.0002). The activation pattern was also different, such that the area of latest activation in patients with OSA was at the anterior septum, consistent with the area of low voltage (Figures 2 and 3).

Triggers of AF

Before PVI, APD-induced AF occurred in 33 of 43 (76.7%) patients without OSA and in 35 of 43 (81.3%) of patients with OSA. The most common technique for APD-induced AF initiation was isoproterenol infusion (44.1%), followed by a combination of adenosine bolus during maximal isoproterenol effect (30.9%), and electric cardioversion during isoproterenol infusion (25%). In 18 patients (20.9%; 10 from the non-OSA group and 8 from the OSA group), AF could not be induced spontaneously or during isoproterenol infusion with and without adenosine, or after cardioversion. The reproducibility of APD-induced AF initiation was examined in 62 of 68 patients. In these patients, AF was reinitiated in 56 of 62 (90%) using the same initial technique. The number of initiations per patient was 2.4 (median, 2 [1–4)]). In 50 of 56 (89.2%) patients with ≥1 initiation of AF, the initiating APD had similar activation pattern, suggesting a similar trigger site.

At baseline, the PVs were the most frequent triggers for AF in both the OSA (27/35; 77.1%) and non-OSA group (28/33; 84.8%). The left PVs were the dominant site in both groups (OSA, 66.6%, [18/27]; non-OSA, 71.4%, [20/28]). PVI was achieved in all patients. The protocol for identifying triggers of AF was then repeated. Patients with OSA had ≈3.5-fold increased frequen-

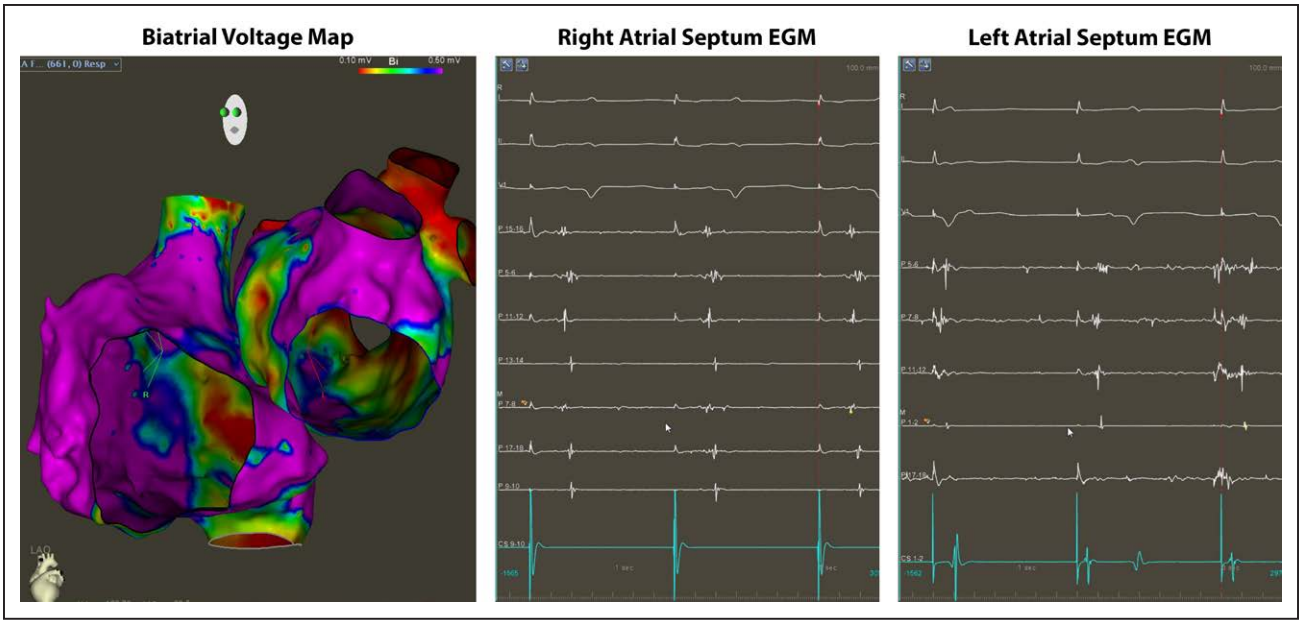


Figure 4. Biatrial voltage and conduction abnormalities in obstructive sleep apnea (OSA).
Left, Voltage map (0.1–0.5 mV) of the right and left atria from a patient with OSA. Note that the areas of low bipolar voltage primarily involve the interatrial septum. **Middle**, Electrogram (EGM) recorded on the right interatrial septum during proximal coronary sinus pacing (CS 9–10), whereas (**right**) electrograms recorded on the left interatrial septum during distal coronary sinus pacing (CS 1–2). Electrograms were recorded using a pentaray multielectrode mapping catheter and demonstrate abnormal low and fractionated signals.

cy of residual extra-PV triggers of AF. In patients without OSA, APD-triggered AF was present in 5 of 43 (11.6%) patients compared with 18 of 43 (41.8%) patients with OSA (*P*=0.003). Figure 5 shows the distribution of PV and extra-PV triggers in patients with and without OSA. In the 5 patients without OSA and extra-PV triggers post-PVI, the location was variable and occurred in sites of normal bipolar voltage and electrograms (eustachian ridge, crista terminalis, fossa ovalis, low anterior septum, and CS). In contrast, in 15 of 18 (83.3%) patients with OSA and extra-PV triggers, trigger sites were more commonly located within or adjacent to zones of low bipolar voltage and abnormal electrograms, most commonly the left anterior septum (12/15; 80%).

During AF, these trigger zones often demonstrated spatiotemporal electrogram dispersion with organized electric activity. Figure 6 shows a representative example from a patient with OSA and AF that was initiated

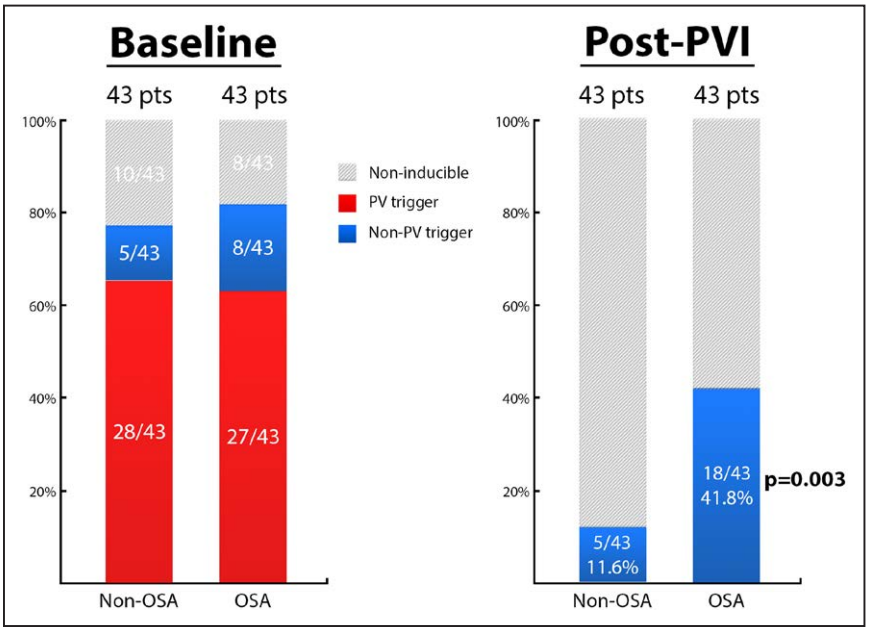


Figure 5. Distribution of atrial fibrillation (AF) triggers in patients with and without obstructive sleep apnea (OSA).
PVI indicates pulmonary vein isolation.

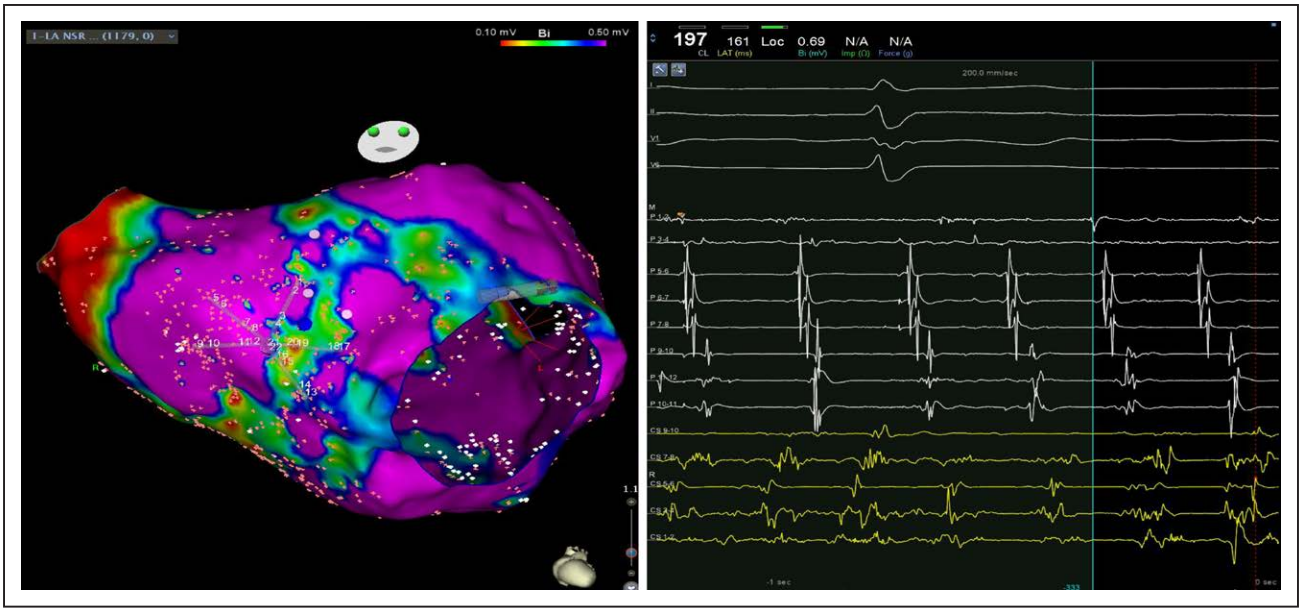


Figure 6. Stabilization of electric activity around zones of low voltage.
In this example of a patient with obstructive sleep apnea (OSA), a pentaray multielectrode mapping catheter was used to map the left atrium during atrial fibrillation (AF). A relatively stable beat-to-beat electric activity was recoded around the zone of low voltage over the septum. Ablation at this location resulted in termination of AF.

after PVI from an extra-PV trigger in the left anterior septum. Electrogram recorded in the area of the initiating trigger at the zone demonstrated a relatively organized and stable electric activity. This pattern of organized spatiotemporal electrogram dispersion during AF was present in 10 of 15 (66.7%) patients with OSA. Furthermore, ablation at these sites on the left anterior septum during AF resulted in termination of AF in 11 of 15 patients (73.3%).

After ablation of the extra-PV trigger(s), 15 of 23 (65.2%) patients were rendered noninducible using a similar induction protocol. In the remainder, APD-triggered AF was still present. Similar or additional triggers were identified and ablated in 4 additional patients. Overall, elimination of APD-triggered AF was achieved in 19 of 23 (82.6%), whereas in 4 of 23 (17.4%) elimination of APD-induced AF could not be achieved. The additional ablation time required for elimination of extra-PV triggers was 11 minutes [median, 12 minutes; range, 3–18 minutes]. Ablation of extra-PV triggers was not associated with additional complications. There were overall 3 complications: 1 groin hematoma in each group, and a single event of intubation-related pharyngeal hematoma in the OSA group. There was no cardiac tamponade, stroke, significant esophageal injury, or heart block. Evaluation of extra-PV triggers after PVI required 12±6 minutes. The potential increase in radiation exposure was evaluated by comparing the x-ray time between the 2 study groups in whom evaluation and ablation on extra-PV triggers were performed to the 2 control groups who underwent PVI alone. The x-ray time was similar between the groups. There was no difference in x-ray time (19±11 versus 17±22 min; *P*=0.21).

Clinical Outcome

During a follow-up period of 1 year, 35 of the 43 (81.4%) non-OSA patients and 36 of the 43 (83.7%) OSA patients maintained sinus rhythm after the first PVI. The arrhythmia-free survival rate was similar between the OSA and non-OSA groups (83.7% versus 79.1%; *P*=0.53). Two patients from the non-OSA group and 3 patients from the OSA group were on AADs therapy at 1 year after the index PVI (all on class Ic agents).

To examine the role of extra-PV trigger ablation on long-term arrhythmia control in patients with and without OSA, we compared arrhythmia-free survival between the OSA study group in whom extra-PV triggers were mapped and ablated [(+) OSA (+) PVI and (+) trigger] and the control group of patients with OSA who underwent PVI alone without mapping and ablation of extra-PV triggers [(+) OSA (+) PVI and (–) trigger]. Similarly, patients without OSA who underwent ablation of extra-PV triggers [(–) OSA (+) PVI and (+) trigger] were compared with a control group of patients without OSA who underwent PVI alone [(–) OSA (+) PVI and (–) trigger]. In patients with OSA, ablation of extra-PV triggers in addition to PVI resulted in a significantly improved clinical outcome (83.7% versus 64%; *P*=0.03, Figure 7). In contrast, in patients without OSA, ablation of extra-PV triggers in addition to PVI had no effect on arrhythmia-free survival (79.1% versus 83.3%; *P*=0.64).

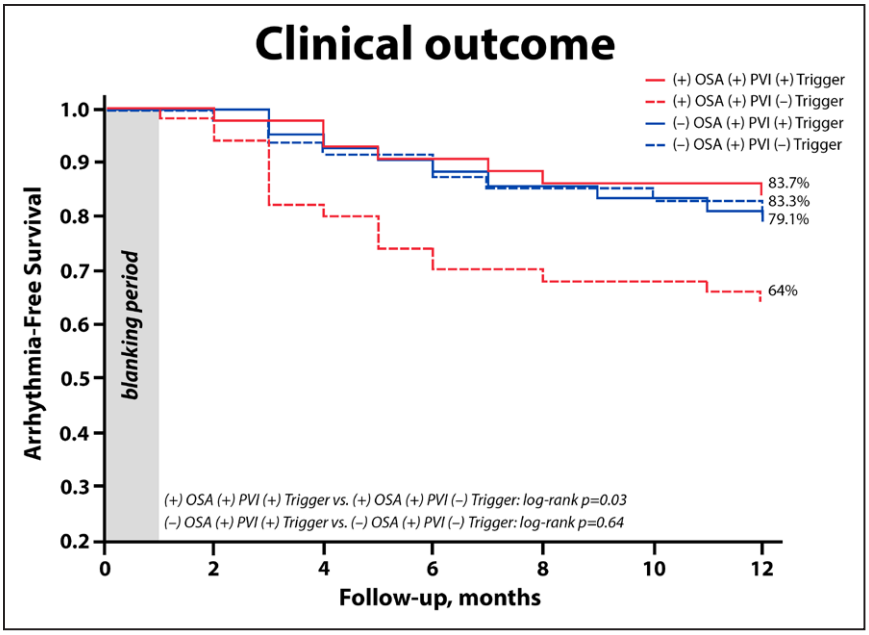


Figure 7. Kaplan–Meier survival curves according to treatment groups.
OSA indicates obstructive sleep apnea; and PVI, pulmonary vein isolation.

Clinical Variables Associated With AF Recurrence

The effect of baseline characteristics on arrhythmia recurrence was assessed using a stepwise Cox proportional hazards regression model. The [(+) OSA (+) PVI (+) triggers] was compared with the OSA [(+) OSA (+) PVI (–) triggers] group. In univariable analysis (Table 2), LA area indexed to BSA was associated with increased arrhythmia recurrence (hazard ratio [HR], 1.56; 95% confidence interval, 1.06–1.98; *P*=0.002), whereas ablation of extra-PV triggers was associated with reduced arrhythmia recurrence (HR, 0.42; 95% confidence interval, 0.22–0.78; *P*=0.005). The LA area indexed to BSA and ablation of extra-PV triggers were tested in a multivariable model (Table 2). Ablation of extra-PV triggers remained an independent predictor of reduced arrhythmia recurrence (HR, 0.45; 95% confidence interval, 0.21–0.86; *P*=0.02). The LA area indexed to BSA also remained associated with increased arrhythmia AF recurrence risk (HR, 1.32; 95% confidence interval, 1.15–3.70; *P*=0.01). During the follow-up period, 1 patient from the [(+) OSA (+) PVI and (+) trigger] and 2 patients from the [(+) OSA (+) PVI and (–) trigger] initiated CPAP therapy. Statistical analysis excluding these patients on CPAP therapy demonstrated a similarly significant difference between the groups (*P*=0.03).

DISCUSSION

In this study, we evaluated the anatomic and functional atrial substrate of patients with PAF and moderate-to-severe OSA. The major findings are as follows: (1) PAF in patients with OSA is often associated with patchy areas of low bipolar voltage and slow conduction, predominantly affecting the left anterior septum; (2) these zones are a common source of extra-PV triggers and localized circuits of AF; and (3) ablation of extra-PV triggers of AF

Table 2. Clinical Variables Associated With AF Recurrence

	Univariate			Multivariate		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age	1.32	0.8–1.76	0.39			
Sex	0.92	0.6–1.59	0.45			
BMI	1.41	0.9–1.78	0.07			
Hypertension	1.21	0.7–1.62				
Diabetes mellitus	1.4	0.8–1.91	0.10			
LVEF						
LA area indexed BSA	1.56	1.06–1.98	0.002	1.32	1.15–3.70	0.01
AF severity index						
Ablation of extra-PV triggers	0.42	0.22–0.78	0.005	0.45	0.21–0.86	0.02

AF indicates atrial fibrillation; BMI, body mass index; BSA, body surface area; CI, confidence interval; LA, left atrium; LVEF, left ventricular ejection fraction; and PV, pulmonary veins.

is associated with improved clinical outcome in patients with PAF and OSA undergoing catheter ablation.

Repetitive episodes of OSA have been associated with cardiac structural and electric remodeling. In animal models, repetitive episodes of OSA produce atrial fibrosis and important changes in connexin-43 expression and distribution, resulting in atrial conduction slowing and vulnerability for arrhythmias, including AF.[4] In addition, repetitive episodes of OSA also result in ventricular remodeling, including LV dilatation, hypertrophy, diastolic dysfunction, along with RV hypertrophy. The natural progression of OSA-mediated atrial remodeling in human is not entirely understood and may well depend on the frequency and severity of OSA, as well as natural compensatory mechanisms, including the genetic makeup; such that some patients with OSA do not have AF, whereas others have short PAF, with the majority progressing to persistent AF.

Our study found that patients with PAF and OSA have increased incidence of voltage abnormality, primarily involving the LA septum. This finding is consistent with a recent report by Dimitri et al,[10] showing reduced biatrial voltage in patients with PAF and OSA. Although atrial scar is common in patients with persistent AF, it is fairly uncommon in patients with PAF. The increased incidence of atrial scar in these patients may be the result of cardiac remodeling in patients with sleep apnea; however, the cause-and-effect relationship cannot be inferred from this study and requires a separate investigation. Nonetheless, the presence of atrial scar was associated with increased frequency of APDs (likely because of triggered activity) and initiation of AF from areas in and around the scar. This presence of atrial fibrosis has been strongly linked to AF, as fibrosis levels measured by cardiac magnetic resonance imaging are higher in AF patients compared with healthy subjects and correlate positively with AF recurrence.[11] Moreover, ablation around fibrotic areas identified either by late gadolinium enhancement or electroanatomical mapping has shown to improve ablation success rates.[11,12] Mechanistically, structural and functional tissue heterogeneity associated with fibrosis have generally been linked to arrhythmogenesis, for example, in ventricular infarction border zone.[13] Such border heterogeneity can be present as large collagen deposits within the functional myocardium, which can slow down or block the propagation of electric excitation waves, creating conditions for generation and sustenance of reentrant drivers. A recent study demonstrated that atrial areas adjacent to dense fibrosis have high levels of arrhythmogenic activity. Morgan et al[14] created a 3D model of the human atria with varying degree of fibrosis and myocyte–fibroblast coupling. They demonstrated that in models of diffuse fibrosis (such as in elderly patients or patients with hypertension), waves randomly meandered through the atria, whereas in models of patchy and localized fibrosis, such as in patients with OSA, rotors stabilized in the border zones of this patchy fibrosis, where slow conduction enabled the development of localized circuits (rotors) within these relatively small regions. This may explain the relatively high incidence of AF termination we observed with ablation in and around the localized scar area.

Ablation of AF triggers in abnormal atrial tissue resulted in improved clinical outcome with reduced arrhythmia recurrence. Whether this is because of elimination of the extra-PV triggers or because of ablation of the arrhythmogenic substrate supporting the circuit is unclear. These data are consistent with a recent report by Kottkamp et al[12] who studied the atrial substrate in patients with PAF and recurrent AF despite durable PVI. They found that this subset of patients commonly had confluent low-voltage areas (<0.5 mV); empirical ablation resulted in an improved clinical outcome with a reduced AF recurrence rate. The study did not include a systematic evaluation for the presence of sleep apnea, and therefore the relative specificity of OSA to atrial scar cannot be validated in this cohort. However, the presence of LA septal anterior scar was also found in 2 patients from the non-OSA group and is commonly observed in patients with persistent AF. Therefore, OSA may not necessarily represent a unique pathophysiological substrate for AF, but be strongly associated with atrial fibrosis and perpetuation of the arrhythmogenic milieu.

The value of CPAP for arrhythmia control in patients with AF has been evaluated in several observational studies.[15–21] Most showed that the CPAP use is associated with reduction in recurrence of AF in patients with OSA. However, the generalizability of these findings is unclear in view of the data's observational nature. A recent large randomized study in patients with OSA found that therapy with CPAP plus usual care, when compared with usual care alone, did not prevent cardiovascular events, including new-onset AF or strokes in patients with OSA and established cardiovascular disease.[22] It is possible that CPAP, like other disease-modifying interventions, exerts their maximal benefit in early disease states, especially when complicated by end-organ effects (including atrial scaring). In this regard, Pathak et al[23] prospectively examined the impact of aggressive risk factor reduction, including weight, blood pressure, glycemic, and lipid control on the frequency of AF frequency and the response to ablation. They found that aggressive risk factor management improved the long-term success of AF ablation (P<0.001). As sleep apnea often accompanies other risk factors, such as obesity, hypertension, and diabetes mellitus, it may beneficial to include routine screening and treatment of OSA in patients with early onset of AF.

Data from this study advocate for screening newly diagnosed AF patients for the presence of OSA. This

may help identify patients in whom PVI alone may not be insufficient. It may also facilitate earlier diagnosis and treatment of OSA. This strategy may improve the outcomes of patients with AF where conventional therapies seem to have reached their limits. However, there is an urgent need for high-quality data in the form of a large randomized trial to clarify the benefit of screening and treatment of sleep apnea in patients with AF.

Limitations

The major limitations of this study are its relatively small size and lack of randomization. However, the differences in atrial substrate noted between patients with and without OSA may serve as a strong signal toward a larger randomized trial. We did not perform cardiac magnetic resonance imaging in these patients and therefore cannot correlate the magnitude of voltage and electrogram abnormality with late gadolinium enhancement, presence of OSA, and extra-PV substrate for AF. Ablation of extra-PV triggers had positive clinical impact in patients with OSA but not in patients without OSA. The low occurrence of extra-PV triggers in the group with a normal sleep study and the overall small cohort cautions interpretation of this finding. In addition, follow-up monitoring of arrhythmia recurrence was limited to 2 weeks of continuous monitoring plus additional monitoring because of symptoms.

Conclusions

Patients with PAF and OSA demonstrate significant atrial remodeling characterized by structural and functional abnormalities with reduction of bipolar voltage amplitude and slowing of conduction, particularly in the LA anterior septum. These changes are associated with an increased incidence of extra-PV triggers for AF. Ablation of this substrate was associated with improved arrhythmia-free survival when compared with OSA patients undergoing PVI alone.

AFFILIATIONS

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FOOTNOTES

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Atrial Substrate and Triggers of Paroxysmal Atrial Fibrillation in Patients With Obstructive Sleep Apnea

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