

## ASSOCIATIONS BETWEEN CARDIOEMBOLIC STROKE AND OSA

## Associations between Cardioembolic Stroke and Obstructive Sleep Apnea

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**Study Objectives:** To assess etiology of ischemic stroke in patients with obstructive sleep apnea (OSA) compared with controls. This information may aid in determining how OSA increases stroke risk and facilitate recurrent stroke prevention in patients with OSA.

**Design:** Retrospective, case-control study.

**Setting:** Academic tertiary referral center.

**Patients:** Consecutive patients who underwent polysomnography and had an ischemic stroke within 1 year were identified. Stroke subtype was determined using two validated algorithms. Polysomnographic results were used to separate patients into OSA cases and controls. Information regarding cardiovascular risks, neuroimaging, and echocardiographic data were collected.

**Interventions:** N/A.

**Measurements and Results:** In 53 subjects, cardioembolic (CE) strokes were more common among OSA cases than controls (72% versus 33%,  $P = 0.01$ ). The majority of CE strokes occurred in those with moderate to severe OSA. Atrial fibrillation (AF) was more frequent in OSA cases (59% versus 24%,  $P = 0.01$ ). The association between OSA and CE stroke remained significant after controlling for AF ( $P = 0.03$ , odds ratio 4.5).

**Conclusions:** There appears to be a strong association between obstructive sleep apnea (OSA) and cardioembolic (CE) stroke. In patients with OSA presenting with cryptogenic stroke, high clinical suspicion for CE is warranted. This may lead to consideration of diagnostic studies to identify CE risk factors such as paroxysmal atrial fibrillation (AF). CE strokes are more common in patients with OSA even after adjusting for AF. This finding may reflect a high rate of occult paroxysmal AF in this population; alternatively, OSA may lead to CE strokes through mechanisms independent of AF.

**Keywords:** atrial fibrillation, cardioembolism, cryptogenic stroke, sleep disordered breathing, stroke prevention

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## INTRODUCTION

Each year in the United States, 795,000 strokes occur, most of which (87%) are ischemic.<sup>1</sup> Strokes may be associated with severe consequences, including loss of mobility and vision, speech dysfunction, inability to live independently, and death.<sup>2</sup> Stroke is the leading cause of adult disability in the United States.<sup>1</sup>

Nearly a quarter of strokes in the United States are recurrent events.<sup>1</sup> Determining the cause of stroke is a key element in developing specific management strategies to reduce a patient's risk of a subsequent event. However, 25% to 40% of ischemic strokes are cryptogenic, in which the stroke etiology remains unknown or there are multiple equally likely mechanisms.<sup>3–5</sup>

Obstructive sleep apnea (OSA) affects 24% of middle-aged men and 9% of women.<sup>6</sup> The Sleep Heart Health Study determined that OSA is 30% more common in people who have a stroke. This study, among others, found that OSA is an independent risk factor for ischemic stroke.<sup>7–9</sup> Men with moderate to severe OSA are at a threefold higher risk of stroke.<sup>8</sup> However, the causal mechanisms behind this relationship have remained

undetermined. The major risk factors for ischemic stroke include hypertension, atherosclerosis, and atrial arrhythmias.<sup>1</sup> Although untreated OSA is associated with each of these diagnoses, one of the strongest drivers of stroke risk may be the associations between OSA and atrial fibrillation (AF).<sup>10,11</sup>

AF affects at least 4% of persons older than 60 y and increases stroke risk fivefold.<sup>12,13</sup> Cardioembolism (CE) is responsible for 20% to 30% of all strokes, and the majority of these are due to AF. AF may remain undiagnosed in persons who are asymptomatic or with paroxysmal disease. Therefore, the stroke risk associated with AF may be underestimated.<sup>14</sup>

Our study used validated algorithms to determine the stroke subtype in a group of patients with OSA compared with controls without clinically significant sleep disordered breathing. We hypothesized CE strokes occur more commonly in patients with OSA because of the relationships between OSA and AF. Understanding the specific mechanisms by which OSA exerts its influence as a stroke risk factor may be helpful in tailoring diagnostic evaluations and management strategies for prevention of recurrent stroke. This understanding may be particularly important in the case of cryptogenic strokes in patients with OSA.

## METHODS

## Subjects

We performed a retrospective, case-control study using chart review. Eligibility criteria included adult male and female patients who underwent standard, attended, in-laboratory polysomnography at Mayo Clinic in Rochester, Minnesota, during an 11-y period. Each patient must have experienced an

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ischemic stroke within 1 y after polysomnography was performed. International Classification of Diseases, Ninth Revision, codes for cerebrovascular disease were used to identify potential subjects. Consecutive chart review was conducted to ensure inclusion criteria were accurately met and to obtain data on medical history, and neuroimaging, cardiac, and laboratory evaluations.

Subjects with transient ischemic attack, intracerebral hemorrhage, or other nonstroke event (i.e., indeterminate spell, migraine) were excluded, as were subjects in whom the ischemic stroke occurred outside the time frame of 1 y after polysomnography. Subjects were also excluded if the stroke was identified as an incidental finding on neuroimaging and the date of the stroke was not clear.

All clinical information potentially containing evidence of atrial arrhythmias, including resting electrocardiograms, Holter monitors, telemetric monitors, echocardiograms, and stress tests, were reviewed for the presence or absence of atrial arrhythmias in a blinded fashion by a cardiovascular specialist (A.D.C.).

After determination of stroke subtype, polysomnography data were evaluated. Potential relationships between central sleep apnea and cerebrovascular disease remain unclear on the basis of current literature; therefore, patients with predominantly central sleep apnea were excluded from the study. Subjects with obstructive disease and an apnea-hypopnea index more than 10/h were classified into the OSA group. Subjects with an apnea-hypopnea index of 10/h or less served as controls. We chose this distinction as a means to provide comparability with other studies on OSA and stroke that used the same parameters to define clinically significant OSA.<sup>15–19</sup>

All study subjects provided authorization for records to be used for purposes of medical research. This study was approved by the Mayo Clinic Institutional Review Board.

### Determination of Stroke Mechanism

The Causative Classification System (CCS) of ischemic stroke was used to determine stroke etiology.<sup>20</sup> This is a Web-based program in which data regarding clinical history, brain and vascular imaging, cardiac assessment (including transthoracic and transesophageal echocardiography), and laboratory information are entered. The most likely stroke cause is determined by the computerized algorithm. The investigator entering data into the CCS obtained certification in use of this tool and is a board-certified neurologist (M.C.L.). Stroke etiology was also reviewed by study team members who are cerebrovascular neurology subspecialists (K.D.F., R.D.B.).

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system was used as a secondary tool to determine stroke subtype.<sup>21</sup> The CCS algorithm tends to rely heavily on imaging data and may provide an indeterminate etiology for cases in which magnetic resonance imaging was not performed, even if the stroke phenotype can be established through other available data. Therefore, secondary analysis was performed on all strokes using the TOAST criteria.<sup>22</sup> For situations in which the CCS algorithm indicated indeterminate cause, but the TOAST algorithm specified a stroke subtype, the TOAST subtype was used for purposes of the study. If the TOAST

algorithm also provided indeterminate stroke cause, the stroke cause was classified as indeterminate.

Both CCS and TOAST are validated for research involving etiologic classification of ischemic stroke. The tools have excellent intrarater and interrater reliability.<sup>20,21,23</sup> The investigators entering data into the CCS or TOAST algorithms were blinded to whether subjects were in the control or the OSA group.

### Polysomnography

All subjects underwent attended, in-laboratory polysomnography at the Mayo Clinic Center for Sleep Medicine. The laboratory is accredited by the American Academy of Sleep Medicine. Polysomnographic data were scored in a standard fashion by registered polysomnographic technologists and board-certified sleep medicine specialists in compliance with rules, terminology, and technical specifications as specified by the American Academy of Sleep Medicine. Standard recording parameters include electroencephalogram, electromyogram of the limbs and submental area, electrooculogram, thermistor airflow measurements, inductance plethysmography, electrocardiogram, digit pulse oximetry, upper airway sound recording, and video monitoring. Apneas were defined as cessation of airflow for 10 sec or more; hypopneas were defined as a decrease in nasal pressure signal by 30% or more for 10 sec or more with a 4% or more oxygen desaturation from preevent baseline.<sup>24</sup> Respiratory events with associated inspiratory effort were scored as obstructive, whereas events with absent effort were scored as central. Central sleep apnea was defined as a central apnea index more than 5/h, with more than 50% of total events being central in nature. Subjects with predominantly central sleep apnea were excluded from the study.

### Statistical Analysis

Results are reported as frequencies and percentages for categorical variables and mean (standard deviation, SD) or median (minimum, maximum) for continuous variables of interest. Distribution of risk factors between the two groups was compared using  $\chi^2$  test or Fisher exact test for categorical variables and two-sample *t* test or Wilcoxon rank sum test for continuous variables. Further analysis was performed using univariable and multivariable logistic regression. Associations are summarized as odds ratio and 95% confidence intervals. Subgroup analysis comparing occurrence of CE strokes between both groups was performed using  $\chi^2$  test or Fisher exact test for categorical variables and two-sample *t* test or Wilcoxon rank sum test for continuous variables. Statistical significance was defined as  $P < 0.05$  using two-sided tests.

### RESULTS

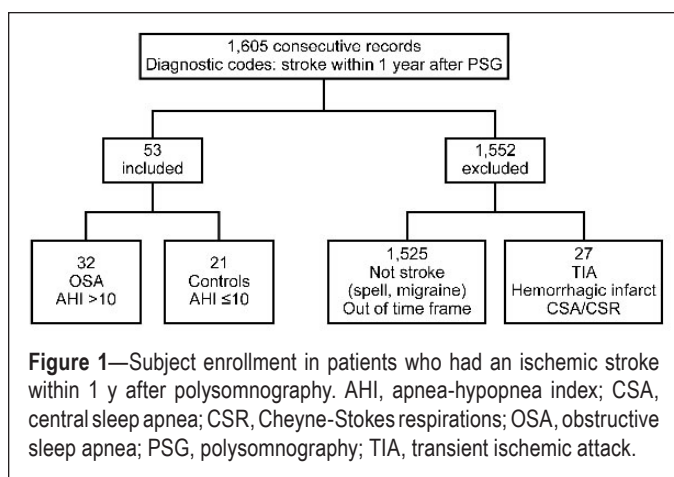
Initial database query yielded 1,605 possible subjects. After consecutive chart review, 1,552 subjects were excluded because the clinical event was not an ischemic stroke or the stroke did not occur within the specified time frame (Figure 1). Fifty-three subjects were included for analysis of stroke cause. After classification of stroke mechanism, polysomnography records were reviewed and subjects were classified into cases or controls.

Baseline information for the 32 OSA and 21 control subjects is outlined in Table 1. The vascular comorbidities between

**Table 1**—Baseline clinical characteristics for patients who had an ischemic stroke within 1 y after polysomnography.

Characteristic	All Patients	Group		P <sup>a</sup>
		OSA	Control	
Number of subjects	53	32	21	
Number of male/female patients (% male)	35/18 (66)	24/8 (75)	11/10 (52.4)	0.14
Mean age (SD), y	64.9 (11.69)	67.1 (9.32)	61.5 (14.17)	0.20
Smoking history, n (%)	9 (17)	5 (15.6)	4 (19)	0.99
BMI, mean (SD)	33.3 (6.68)	34.3 (6.75)	31.9 (6.45)	0.28
Median		32.8	31.0	
Range		22.5–52.3	18.5–45.7	
Diabetes mellitus, n (%)	17 (32.1)	11 (34.4)	6 (28.6)	0.77
Hypertension, n (%)	43 (81.1)	27 (84.4)	16 (76.2)	0.49
Hyperlipidemia, n (%)	33 (62.3)	20 (62.5)	13 (61.9)	0.99
CAD (or prior MI), n (%)	16 (30.2)	13 (40.6)	3 (14.3)	0.07
AHI, mean (SD)	21.9 (23.46)	32.6 (24.88)	5.6 (3.02)	< 0.01
Median		22.5	6	
Range		11–108	0–10	

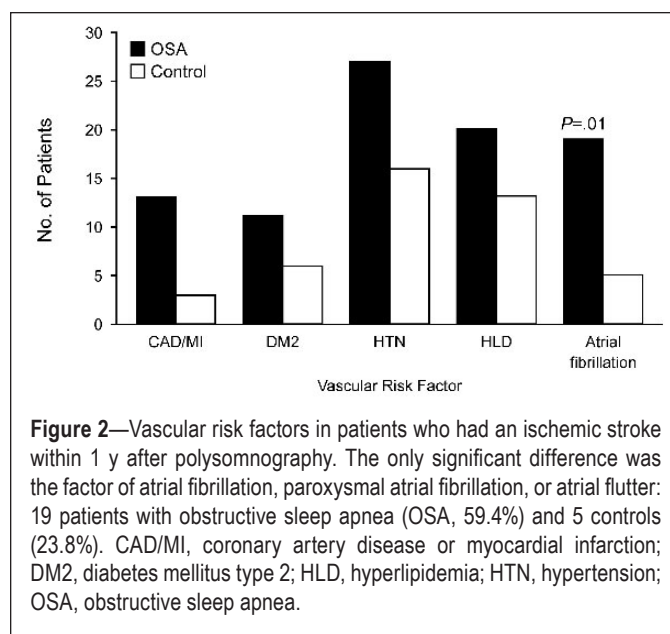
<sup>a</sup>All P values were determined with two-tailed Fisher exact test. AHI, apnea-hypopnea index; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; OSA, obstructive sleep apnea.



the groups were not significantly different, with the exception of AF (Figure 2). History of AF (including chronic and paroxysmal) and atrial flutter was significantly more common in the OSA group than in controls (19 versus 5,  $P = 0.01$ ). The mean apnea-hypopnea index among case patients in our study was 32.6/h (SD 24.88, median 22.5, range 11–108). Approximately 40% of case patients had an apnea-hypopnea index of 30/h or more.

Ischemic stroke subtype for the OSA and control groups are shown in Figure 3 and Table 2. With use of the CCS algorithm, eight patients initially had an indeterminate stroke phenotype. Through use of the TOAST criteria, a stroke phenotype was subsequently determined on seven of these patients.

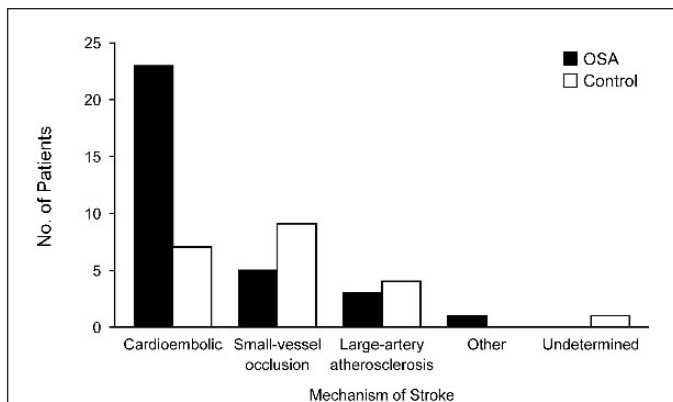
Strokes in patients with OSA were predominantly CE in etiology, and the majority of CE strokes occurred in subjects with moderate to severe OSA. The mean apnea-hypopnea index for CE strokes in patients with OSA was 28.32/h (SD 21.70). CE strokes were significantly more common in patients with OSA than controls (23/32 versus 7/21,  $P = 0.01$ ). Small-vessel occlusion strokes were most common in the control population.



We examined potential relationships between sleep related hypoxemia and the outcome of CE stroke. Mean percentage of time spent below 90% during polysomnography was 18.62 (SD 28.62) for subjects who had CE strokes and 13.26 (SD 23.10) for other stroke etiologies; however, the difference was not statistically significant ( $P = 0.24$ ).

Previous history of stroke was not a formal exclusion criterion. One patient in the OSA group had a history of a small-vessel occlusion (lacunar) infarction 17 y before undergoing polysomnography and had resolution of clinical deficits. The recurrent stroke subtype in this patient was also found to be from small-vessel occlusion.

Table 3 lists the frequencies of CE risk sources. AF was the only individual CE risk factor significantly different between cases and controls. In aggregate, CE risk factors occurred



**Figure 3**—Ischemic stroke etiology in patients who had a stroke within 1 y after polysomnography. Other etiologies were uncommon causes (dissection). Undetermined etiologies were two or more possible causes, negative evaluation, or incomplete evaluation. OSA indicates obstructive sleep apnea.

**Table 2**—Etiology of ischemic stroke for patients who had an ischemic stroke within 1 y after polysomnography.

Etiology	Group		P <sup>a</sup>
	OSA (n = 32)	Control (n = 21)	
Cardioembolic, n (%)	23 (71.9) <sup>b</sup>	7 (33.3)	0.01
Other, n (%)	9 (28.1)	14 (66.7)	

<sup>a</sup>Logistic regression: association between OSA and cardioembolic stroke remained significant after adjusting for atrial fibrillation (P = 0.03, odds ratio 4.5). <sup>b</sup>Frequency of cardioembolic stroke increased with OSA severity. OSA, obstructive sleep apnea.

more frequently in patients with OSA than controls (27/32, 84% versus 11/21, 52%, P = 0.02). Logistic regression analysis was performed to account for effects of each of the following potential confounders: age, sex, body mass index, hypertension, diabetes, hyperlipidemia, and coronary artery disease. The results of this analysis showed that, on controlling for each variable independently, there continued to remain a significantly increased risk for cardioembolic stroke in the OSA group compared with controls. The odds ratio for cardioembolic stroke among OSA cases remained between 4.3 and 6.1 (P values between 0.005 and 0.019). Analysis accounting for the aforementioned potential confounding variables in a single model was also performed. We acknowledge that with our sample size, the P value for this calculation is not significant. However, we continue to show a similar odds ratio (odds ratio 4.1, P = 0.08) for CE stroke among patients with OSA. We then controlled for known atrial fibrillation, and OSA remained strongly associated with CE stroke (odds ratio 4.5, P = 0.03).

There were no significant differences between groups for left ventricular ejection fraction, left atrial volume index, or right ventricular systolic pressure.

## DISCUSSION

To our knowledge, this study is the first to demonstrate two important findings about the relationships between OSA and ischemic stroke. First, OSA is strongly associated with cardioembolism compared with other stroke etiologies and, second, although AF is of higher frequency in ischemic stroke patients with OSA compared to controls, the association between OSA and CE stroke remains even after adjustment for the presence of known AF.

Current literature reports a strong association between OSA and AF. The Sleep Heart Health Study found that AF is more

**Table 3**—Cardioembolic risk factors for patients who had an ischemic stroke within 1 y after polysomnography.

Risk Factor	Group	
	OSA (n = 32) <sup>a</sup>	Control (n = 21) <sup>b</sup>
High-risk sources, n (%)		
Atrial fibrillation (includes chronic and paroxysmal AF and atrial flutter) <sup>b</sup>	19 (59)	5 (24)
Mitral stenosis	1 (3)	1 (4.8)
Bioprosthetic or mechanical valve	2 (6)	2 (9.5)
Dilated cardiomyopathy	2 (6)	0 (0)
Chronic MI and EF < 28%	1 (3)	0 (0)
Infective endocarditis	0 (0)	1 (4.8)
Low or uncertain risk sources, n (%)		
Mitral annular calcification	3 (9)	0 (0)
PFO	7 (21)	3 (14)
Atrial septal aneurysm and PFO	1 (3)	0 (0)
Hypertrophic cardiomyopathy	1 (3)	0 (0)
Wall motion abnormalities	2 (6)	1 (4.8)
LV hypertrophy	1 (3)	2 (9.5)
Left atrial smoke	1 (3)	0 (0)
Other (ASD, VSD, third-degree AV block)	11 (34)	6 (29)

<sup>a</sup>At least one cardioembolic risk factor was present in 84% of OSA subjects and in 52% of controls (P = 0.02). <sup>b</sup>Atrial fibrillation was the only individual cardioembolic risk factor that was significantly different between cases and controls. AF, atrial fibrillation; ASD, atrial septal defect; AV, atrioventricular; EF, ejection fraction; LV, left ventricular; MI, myocardial infarction; OSA, obstructive sleep apnea; PFO, patent foramen ovale; VSD, ventricular septal defect.



common in subjects with OSA (4.8% versus 0.9%,  $P = 0.003$ ).<sup>25</sup> Patients with AF are more likely to have OSA than controls (49% versus 32%,  $P = 0.001$ ).<sup>26</sup> In an analysis comparing patients who had OSA and history of stroke with those who had OSA and no stroke history, AF was significantly more common in the OSA patients with stroke (50.0% versus 10.8%,  $P < 0.01$ ).<sup>27</sup> Untreated OSA increases the risk of recurrence of AF after cardioversion.<sup>28</sup> It is theorized that OSA-induced cycles of hypoxemia, sympathetic activation, and transmural pressure gradients all lead to the eventual development of AF.<sup>10,29</sup> Untreated OSA is also associated with hypercoagulability, thus heightening eventual risk for cardioembolism.<sup>30</sup>

Strokes in patients with AF are severely disabling in 60% of patients and result in death in 20%.<sup>31</sup> The presence of known AF is a pivotal factor in developing management strategies for prevention of recurrent stroke. In patients who have had stroke but do not have documented AF, antiplatelet therapy is often used to reduce the risk of recurrence. In patients with known AF, anticoagulation is recommended. In patients with AF, anticoagulants result in a 40% to 70% reduction in stroke risk, compared with an approximate 20% risk reduction with antiplatelet therapy.<sup>32,33</sup>

Paroxysmal or intermittent AF makes up 25% to 62% of all AF.<sup>34</sup> This frequently undiagnosed condition is an important etiology of ischemic stroke that would have otherwise been called cryptogenic. Studies using extended cardiac rhythm monitoring in patients with cryptogenic strokes have detected paroxysmal AF in 12% to 20% of patients.<sup>35,36</sup>

Our results demonstrate that the majority of ischemic strokes in patients with OSA are CE in nature. High clinical suspicion for AF or paroxysmal AF is warranted in patients with OSA who have had a cryptogenic stroke. Cardiac monitoring should be considered in all patients with OSA who present with cryptogenic stroke. Detection of occult AF in these patients would likely result in the initiation of anticoagulation therapy, thereby serving an important role in stroke prevention.

On logistic regression analysis, the association between OSA and CE stroke remained significant even after adjusting for known AF ( $P = 0.03$ , odds ratio 4.5). Some of these CE strokes likely were due to undiagnosed paroxysmal AF. But, perhaps OSA leads to CE strokes through mechanisms other than AF. OSA may lead to morphologic and structural changes in the myocardium that could potentiate multiple CE risk factors beyond AF. Lower-risk potential sources of cardioembolism include left ventricular systolic dysfunction, mitral annular calcification, patent foramen ovale, and regional wall motion abnormalities.<sup>37</sup> Our results show that, in aggregate, both high- and low-risk factors leading to CE are more common in patients with OSA. Patent foramen ovale was the most common low-risk factor for CE stroke in patients with OSA (25%); however, the difference in patent foramen ovale between groups was not significant. Work from Konecny et al.<sup>38</sup> suggests OSA causes increased right-to-left pressure gradient across the atrial septum, which could lead to patent foramen ovale-mediated paradoxical embolus and CE stroke.

Left atrial volume is typically increased in patients with AF, and persistent AF leads to greater left atrial volume indices.<sup>39,40</sup> The finding in our study of left atrial volume index being statistically similar between OSA and control groups also supports

the hypothesis that CE strokes may occur in patients with OSA through mechanisms other than AF. Svatikova et al.<sup>41</sup> also found no significant differences between left atrial size in ischemic stroke subjects with or without OSA. Work by Kamel et al.<sup>42</sup> examined associations between markers of left atrial dysfunction and risk of ischemic stroke. The study found a significant association between p-wave morphology abnormalities on electrocardiography and risk of subsequent ischemic stroke in subjects without AF. The data suggest that conditions other than AF lead to a condition of atrial cardiopathy and may serve to increase risk of CE.

Given these findings, when a patient with OSA presents with cryptogenic stroke, transthoracic or transesophageal echocardiography may be considered to identify the presence of both high- and low-risk factors for CE. On the basis of our results, extended cardiac monitoring may also be a consideration. Although extended monitoring was not performed on the patients in this study, this is an emerging tool in the work-up of cryptogenic stroke. In the EMBRACE study,<sup>43</sup> 30-day non-invasive ambulatory electrocardiographic monitoring was performed on patients with cryptogenic stroke (with no evidence of AF during 24 h of standard-of-care poststroke electrocardiographic monitoring). AF was detected in 16.1% of patients who underwent extended monitoring and in 3.2% of controls who underwent conventional follow-up ( $P < 0.001$ ). Extended monitoring improved detection of paroxysmal AF by a factor of 5 and led to increased rates of initiation of anticoagulation therapy. The CRYSTAL AF study<sup>44</sup> similarly demonstrated detection of AF at 1 y in 12.4% of patients who received an insertable cardiac monitor for extended monitoring and in 2% of controls ( $P < 0.001$ ).

One of the most important strengths of our study is that the diagnosis of OSA preceded the acute stroke event. Work from Bassetti et al.<sup>15</sup> showed that OSA severity improves significantly over the 6 mo after a stroke. Similar results are documented from multiple studies that have followed severity of sleep apnea after acute stroke.<sup>15–17,45,46</sup> These data suggest that strokes have a causative role in the development of OSA and in worsening of severity. The causative mechanisms may be through facial or oropharyngeal weakness or potentially through other factors.

In a previous study by Bassetti et al.,<sup>15</sup> large-artery occlusion strokes were found to be more common in patients with OSA. A recent study by Brown et al.<sup>19</sup> found no significant differences in stroke etiology in subjects with and subjects without OSA. However, in each of these studies, evaluation for OSA was made in the poststroke setting; thus, it is unclear whether OSA was present before the stroke or whether it developed as a consequence of the stroke. The mixed stroke etiologies in the OSA group may have stemmed from inclusion of both patients with prestroke OSA (in whom OSA contributed to cerebrovascular risk) and patients in whom OSA developed as a result of the stroke (in whom the stroke was caused by other factors). An important distinguishing factor of our study is that the diagnosis of OSA was made before the stroke event. Our data suggest OSA exerts its influence as a risk factor for stroke by increasing risk of CE.

An additional strength of our study is the systematic evaluation of the cause of infarction in patients with OSA compared

with a well-matched group of controls. Controls were proved to have no significant sleep disordered breathing by polysomnography. We performed analyses to account for the potential influence of other cerebrovascular risk and demonstrated that there continues to remain a significantly increased risk for CE stroke in the OSA group compared with controls.

There were several limitations of our study, including its retrospective nature and limited sample size. The study was performed at a single academic tertiary referral medical facility, which may lead to referral bias. However, most of the subjects were from the regional area and presented to a Mayo Clinic hospital in the acute stroke setting.

Our study concludes that the majority of strokes in patients with OSA are CE in etiology. This may be due to the relationships between OSA and AF; OSA may also induce other cardiovascular changes predisposing to CE. Careful cardiac evaluation is warranted in OSA patients who present with cryptogenic stroke in order to appropriately identify those who would benefit from anticoagulation rather than antiplatelet therapy to reduce recurrent stroke risk.

Large, multicenter, prospective analyses are required to better understand the mechanisms by which OSA contributes to stroke risk and how these change with the treatment of sleep apnea. Studies of the complex cardiovascular physiologic changes in patients with OSA are necessary to determine how OSA contributes to CE strokes. This information will be essential for optimizing clinical management strategies to reduce the risk of recurrent stroke in patients with OSA.

## ABBREVIATIONS

- AF, atrial fibrillation
- CCS, Causative Classification of Stroke
- CE, cardioembolic
- OSA, obstructive sleep apnea
- TOAST, Trial of Org 10172 in Acute Stroke Treatment

## DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Somers has consulted for NeuPro, GlaxoSmithKline, PriceWaterhouseCooper, Sorin, Inc., ResMed, Respicardia, and Ronda Grey. The other authors have indicated no financial conflicts of interest. Portions of this manuscript have been published in abstract form: *Sleep* 2012; 35(Abstract Supplement):A279.

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