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Rehabilitation of Cardiovascular Disorders and Sleep Apnea

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**INTRODUCTION**

Obstructive sleep apnea (OSA) syndrome is a disorder affecting 2\% to 4\% of the general population in the United States.\textsuperscript{1–3} It is characterized by recurrent episodes of upper airway collapse during sleep. This condition presents in more than half of patients with acute coronary heart disease who are eligible for enrollment in cardiac rehabilitation programs.\textsuperscript{4} Because of the hemodynamic fluctuations associated with OSA, those patients with concurrent OSA who enter cardiac rehabilitation programs may be placed at greater risk for arrhythmias and exercise-related complications.\textsuperscript{5} This risk can lead to an increase in major adverse cardiac events such as revascularization, heart failure (HF), hospital readmission, functional limitation, and reduced quality of life in cardiac patients.

In contrast, stroke, with an incidence of 2 to 18 per 1000 per year, is the second leading cause of death worldwide and more than 50\% of survivors have mental and physical impairment.\textsuperscript{6,7} Although sleep disordered breathing (SDB) has been recognized in patients with stroke since the early nineteenth century,\textsuperscript{8} over the last 2 decades it has been emerging as an important cardiovascular risk factor.

In the poststroke period, patients with OSA have greater disability and higher mortality than patients without OSA.\textsuperscript{9,10} However, OSA is under-recognized during the poststroke period because of a lack of symptoms or lack of gross obesity, despite evidence that managing this risk factor may benefit those patients.\textsuperscript{11} There is growing evidence that treatment of coexisting OSA with continuous positive airway pressure (CPAP) or mandibular advancement devices can successfully treat OSA, resulting in improved rehabilitation outcomes and improved health-related quality of life.\textsuperscript{12–15}

**KEYWORDS**

- Obstructive sleep apnea
- Sleep disordered breathing
- Cardiac rehabilitation
- Stroke rehabilitation
- Cardiovascular disease
- Stroke

**KEY POINTS**

- Obstructive sleep apnea (OSA) is a common disorder in patients entering cardiac rehabilitation units.
- Sleep disordered breathing is underdiagnosed in the poststroke period.
- Early screening and treatment of OSA are important in the management of the poststroke period or after cardiac events.
- Failure to treat OSA in cardiac patients and patients with stroke can have negative impacts on outcomes during rehabilitation.

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PREVALENCE OF OBSTRUCTIVE SLEEP APNEA IN PATIENTS ENTERING CARDIAC REHABILITATION PROGRAMS

It is well known that patients with different types of cardiovascular diseases have higher prevalence of SDB. Several studies have shown that OSA is an independent risk factor for development of hypertension and has a dose-response relationship between severity of OSA and incidence of hypertension. SDB is also estimated to have a prevalence of 30% to 69% in patients with coronary artery disease (CAD) and 50% to 70% in patients with systolic HF. However, fewer data are available in HF with preserved ejection fraction (EF) than in those with reduced EF. The largest study on this group was done on 244 consecutive patients: 97 patients (39.8%) presented with OSA and 72 patients (29.5%) with central sleep apnea (CSA).

In the postdischarge period after coronary revascularization procedures, 52% to 64% of patients had moderate to severe OSA. A recent study suggested that, overall, 53% of patients entering cardiac rehabilitation programs are at high risk, or are previously diagnosed with OSA. However, the experts believe that the prevalence of OSA is substantially higher and is largely under-recognized in patients entering cardiac rehabilitation programs.

PREVALENCE OF OBSTRUCTIVE SLEEP APNEA IN THE POSTSTROKE PERIOD

In the past decade, longitudinal studies have shown that people with SDB have a greater risk for stroke. The reported prevalence in the literature is very high, ranging from 40% to 90%, likely reflecting different study designs and definitions of SDB. Yaggi and colleagues followed 1022 patients over 6 years and found that OSA is associated with an increased risk for stroke, transient ischemic attack, and death. This finding was true even after adjusting for age, gender, body mass index (BMI), arterial hypertension, diabetes, atrial fibrillation, hyperlipidemia, and smoking habits. Patients with severe SDB had a higher chance of having stroke (hazard ratio [HR], 3.3; confidence interval [CI], 1.7–6.3). These results were confirmed by other investigators as well.

It has been shown that many patients experience a recurrent stroke within 5 years of their first attack, and those with recurrent stroke have a higher chance of having SDB compared with first-time stroke victims. Note that presence of an apnea-hypopnea index (AHI) greater than 10 per hour is an independent risk factor for stroke recurrence.

The prevalence of sleep apnea is highest early following stroke and may decrease during recovery, reflecting a decrease in sleep apnea in most patients, although it can also be caused by a higher mortality in those with more severe form of disease. Although SDB tends to improve spontaneously several weeks after stroke, approximately 50% of patients still have OSA 3 months after the acute event. Szucs and colleagues reported that the frequency and severity of sleep apnea were unchanged 3 months later in most patients with ischemic stroke, whereas it was greatly improved in patients with hemorrhagic stroke. Moreover, hemorrhagic strokes lead more often to central apneas.

Both OSA and, less frequently, CSA have been identified as risk factors for stroke. However, only OSA is recognized as a mortality risk for ischemic stroke. Periodic breathing (PB) may also develop in patients with stroke in the absence of cardiopulmonary disease, disturbed consciousness, or HF. During the acute phase of stroke, obstructive apnea is the most predominant type. Central apneas are associated with altered mental status, brain edema, and ischemia of brainstem and their incidence diminishes during recovery after stroke. Rowat and colleagues investigated the impact of PB in the awake state on mortality in the immediate phase after stroke. They investigated 138 patients with stroke at a median of 4 hours after stroke and found that those with PB were more likely to have severe stroke and more likely to be dead or dependent at 3 months. In contrast, another study showed that CSA was not related to early death among the patients with stroke. Only patients with OSA (AHI >10) had an increased risk of early death.

In a prospective study on 161 patients admitted to a stroke unit, no relationships were found between sleep-related respiratory events and the topographic location of the neurologic lesion or vascular involvement.

WHY OBSTRUCTIVE SLEEP APNEA IS UNDER-RECOGNIZED IN STROKE AND CARDIAC REHABILITATION UNITS

OSA is rarely considered in rehabilitation units despite evidence that managing OSA, when present, may benefit patients with cardiovascular diseases. It has been shown that, despite higher prevalence of SDB among patients with stroke, none of them had been referred for diagnostic studies because SDB had not been suspected clinically because of less sleepiness and lower BMI.
The late diagnosis of sleep apnea can potentially have a negative impact on the outcomes and rehabilitation processes of these patients. Two key clinical symptoms, excessive daytime sleepiness and obesity, do not seem to be prevalent in patients after stroke or HF. Bassetti and colleagues showed that those with ischemic strokes were neither obese nor sleepy despite having severe OSA. They reported that 26 out of 152 patients with stroke had severe OSA with an AHI greater than or equal to 30, but their mean Epworth Sleepiness Scale (ESS) score was 6 and BMI of 27.9 kg/m² indicated that they were not obese and did not have excessive daytime sleepiness.

Similarly, Wessendorf and colleagues showed that, in 105 patients with stroke and moderate to severe OSA (AHI ≥15), the mean ESS score was 7 and mean BMI was 28.7 kg/m². Kaneko and colleagues made similar observations as well (mean ESS score of 5 and BMI of 28.8 kg/m²).

The ESS relies on the self-perception of sleepiness. In patients without stroke and cardiovascular disease, the ESS correlates modestly, but significantly, with the AHI and with objective measures of sleepiness such as the Multiple Sleep Latency Test and the Oxford Sleep Resistance Test. There are several possibilities that might explain the lack of sleepiness in patients with stroke, including cognitive impairment, low physical activity, or drug-related factors. In one study, patients with stroke were only mildly impaired and there was no significant relationship between Mini-Mental State Examination and ESS scores. This finding indicates that cognitive impairment probably is not the reason for the lack of reported daytime sleepiness.

Another proposed potential explanation for the lower ESS scores in patients with stroke is low level of physical activity, so they may be less likely to feel sleepy. The investigators suggest that most of their physical needs are met by hospital personnel, and as a result they are less physically active, which might affect subjective sleepiness. Although it seems a plausible reason, there is no evidence to accept this as the cause of less daytime sleepiness.

Another possible reason is that drugs commonly used in patients with cardiac disease, such as β-receptor blockers, diuretics, statins, thrombocyte aggregation inhibitors, and antiarrhythmics, may cause a reduced perception of daytime sleepiness through a central nervous system–stimulating effect. However, none of them are known to have such effects, and none have been reported to reduce perception of sleepiness. Therefore, it is unlikely that these drugs could explain lower levels of sleepiness in patients with stroke.

These findings in patients with stroke are similar to those previously described in cardiovascular patients, who also had less daytime sleepiness at any given OSA severity. Arzt and colleagues reported that patients with HF with any OSA severity had lower mean ESS (7), indicating less sleepiness despite sleeping less. This finding in patients with HF shows that the absence of subjective sleepiness is not a reliable means of ruling out OSA.

Another finding was the lack of an association between BMI and the severity of OSA in patients with stroke, which contrasts with the well-established relationship between increasing BMI and increasing severity of OSA in patients without stroke.

All of the studies discussed earlier showed that lower ESS scores and BMI in patients with stroke or HF and OSA cannot be explained by differences in the severity of OSA or other confounding factors and that those are not sensitive independent predictors of the presence of OSA.

Therefore, regardless of the underlying mechanisms, lower ESS scores and BMI may make the diagnosis of OSA less likely in the rehabilitation period, and as a result may have a negative impact on clinical course and outcome.

**OBSTRUCTIVE SLEEP APNEA AND REHABILITATION OUTCOME**

Stroke and cardiac rehabilitation programs combine physical rehabilitation with education, self-management, and psychological support. The goal of postacute rehabilitation is to facilitate return home by assisting patients in achieving independence in personal care activities. In addition, it provides an opportunity to identify any comorbidity such as hypertension, and diabetes that may delay recovery. Therefore, early recognition and treatment of OSA during acute rehabilitation should be important parts of recovery. There is growing evidence that failure to treat OSA in cardiac patients can have a negative effect on postoperative recovery and increase mortality and morbidity, reduce quality of life, and lead to worse outcomes during and after the cardiac rehabilitation. Hargenes and colleagues studied patients entering an early outpatient cardiac rehabilitation program and found that cardiac patients with OSA had significantly lower cardiac output, stroke volume, and contractility index. They suggested that the decreased cardiac function in the OSA group, likely because of pressure and volume alteration associated with apneic events, may place these patients at a disadvantage in recovering from their cardiac events, and at increased risk for secondary complications.
In a recent study in which 67 consecutive patients referred for coronary artery bypass grafting (CABG) underwent clinical evaluation and were followed for a mean of 4.5 years after CABG, 56% of patients had moderate-severe OSA. Those with sleep apnea had significantly higher major adverse cardiac or cerebrovascular events (35% vs 16%; P = .02) and new revascularization (19% vs 0%; P = .01). OSA was an independent factor associated with these events in the multivariate analysis.

In a prospective observational study, patients with acute myocardial infarction (MI) and percutaneous coronary intervention underwent cardiovascular magnetic resonance to define salvaged myocardium and infarct size within 3 to 5 days and at 3 months after acute MI. Of the 56 patients included, 29 (52%) had SDB. Patients with SDB had significantly less salvaged myocardium, smaller reduction in infarct size within 3 months after acute MI, a larger final infarct size, and a lower final left ventricular EF. In a multivariate analysis, including established risk factors for large MI, AHI was independently associated with less myocardial salvage and a larger infarct size 3 months after acute MI.

In contrast, the presence of OSA in the setting of stroke is associated with unfavorable clinical course, including early neurologic worsening, delirium, depressed mood, impaired functional capacity and cognition, longer period of hospitalization and rehabilitation, and increased mortality. In addition, severe OSA not only increases the risk of stroke recurrence but also increases the incidence of fatal and nonfatal cardiovascular events as well as sudden death during sleep. The higher blood pressure and its swing during episodes of upper airways obstruction lead to worse outcome following stroke. Sleep apnea probably promotes this functional impairment through intermittent nocturnal hypoxia, reduced cerebral perfusion, and fragmented sleep.

Sleep quality can influence the rehabilitation process. The development of poor sleep with frequent arousals may be particularly important and persist long after stroke symptoms have resolved. In addition, poor sleep quality might have a negative impact on patients' motivation, level of energy, and participation in rehabilitation. Prior study suggests that SDB and poor sleep during rehabilitation were associated with less functional recovery between admission and discharge. This association can persist up to 3 months after admission and persisted when analyses were adjusted for other significant independent predictors of functional recovery, including total hours of therapy received, mental status, acute hospital transfer during the rehabilitation stay, and reason for admission to rehabilitation facility. This finding is particularly important because, although many other predictors of rehabilitation outcomes are difficult or impossible to change, abnormal sleep pattern can be a modifiable predictor of rehabilitation outcomes. Interventions to improve abnormal sleep/wake patterns and early treatment of SDB during rehabilitation may result in better functional recovery among older people. Studies in other institutional settings (eg, nursing homes, acute care hospitals) suggest that sleep problems are associated with social isolation, poor health, and functional impairment in older people. Those with excessive daytime sleepiness required more assistance with self-care activities, engaged in fewer social interactions, and showed worse health-related quality of life. In addition, they had slower recovery of functional abilities and longer stay in rehabilitation units. These outcomes can lead to increased caregiving needs at home, nursing home placement, or death, and may have detrimental effects on rehabilitation and long-term outcome.

Functional independence in personal care activities can be measured using the motor subscale of the Functional Independence Measure (mFIM), which is widely used in rehabilitation settings to assess functional limitations and changes in functional status with rehabilitation therapy. Prior work suggests that a 1-point improvement in mFIM score is associated with 2.2 fewer minutes of help required from another person each day, which translates into 15 minutes of caregiving per week for every 1-point change in mFIM. Every 10% reduction in daytime sleepiness is associated with 1-point additional improvement in mFIM during rehabilitation. This degree of change in daytime sleepiness is achievable by using interventions to improve sleep patterns. It was also associated with increased participation in social and physical activities. This relationship between more daytime sleepiness and less favorable immediate-term and long-term functional recovery suggests that sleep is an important modifiable predictor of rehabilitation outcomes for this vulnerable patient population.

Good and colleagues found that patients with recent stroke and sleep apnea had poorer functional outcomes assessed with the Barthel Activities of Daily Living (ADL) index at discharge from rehabilitation as well as 3 and 12 months after stroke onset. Soon after admission to the stroke rehabilitation unit, these patients are more dependent in their ADLs and have longer latency in
reaction and in response to verbal stimuli, impairing their ability to acquire new skills. In addition, the presence of SDB was associated with a worse Barthel index at 6 months after stroke and predicted a higher mortality during the following 10 years. Note that high mortality was found only in patients with OSA but not CSA.

Other symptoms in patients with stroke and cardiac disorders are impaired memory, lack of ability to concentrate, and tiredness, which are common in patients with OSA. These patients are less adherent to rehabilitation programs because of decreased functional capacity and depression. Poor sleep and fatigue are associated with neuropsychiatric and cognitive disturbances, and result in worse outcomes in rehabilitation and quality of life. Depression occurs in 30% to 60% of patients with stroke and poor sleep strongly correlates with health complaints and depressive symptoms. Previous studies have shown that depression and cognitive impairment commonly occur in patients with sleep apnea but without stroke, and improve after CPAP treatment. This finding indicates that emotional instability in this population might be sleep related and therefore it is reasonable to consider and investigate the SDB, if other symptoms exist.

Poststroke fatigue is an independent predictor of dependency and death. In a cohort study of 8194 patients with stroke, 39% of patients reported fatigue 2 years after their stroke. Patients with fatigue were more likely to be institutionalized and had increased mortality in the subsequent year.

In some studies, delirium was reported in up to half of patients, especially in the first week after ischemic stroke. This delirium can prolong hospital stay and increases risk of dementia and admission to an institution. Well-known risk factors for delirium are hypoxemia and OSA, which can be reversed by CPAP treatment.

These studies show high prevalence of OSA at different time points from stroke onset or cardiac event and OSA exerts a negative effect on the functional recovery of these patients. Therefore, patients with cardiovascular diseases should be screened for OSA early in the course of their disease.

However, the question remains whether early intervention for treatment of OSA shortly after stroke or cardiac event alters the neurologic recovery and/or outcome.

**EARLY TREATMENT OF OBSTRUCTIVE SLEEP APNEA IN STROKE REHABILITATION**

The central nervous system is very sensitive to hypoperfusion in the poststroke period. Therefore, interventions designed to improve poststroke functioning are more effective the earlier they are delivered after symptom onset to reduce mortality and disability. Upper airway obstruction presents a potential therapeutic target to improve outcomes, because control of sleep apnea may prevent hypoxemia, large fluctuations in blood pressure, and cerebral hypoperfusion. To address this, previous studies have examined the potential beneficial effects of OSA treatment on neurologic and cognitive functions of patients during the stable phase of stroke in a rehabilitation setting. Bravata and colleagues randomized 55 patients to an intervention group (stroke standard of care plus auto-CPAP) and control group (only stroke standard of care). Patients with stroke randomized to the intervention group received 2 nights of auto-CPAP, but only those with evidence of OSA received auto-CPAP for the remainder of the 30-day period. Change in stroke severity was assessed by comparing the National Institutes of Health (NIH) Stroke Scale (NIHSS) score at baseline versus at 30 days. Intervention patients had greater improvements in NIHSS score than control patients (−1.0; P = .03). Among patients with OSA, greater improvement was observed with increasing auto-CPAP use.

In another randomized study on 50 patients with stroke, CPAP use within 24 hours of hospitalization resulted in a significant improvement in the NIHSS score. In both trials, greater improvement was noted with increasing CPAP use.

Both sleep apnea and blood pressure variability confer a poor prognosis after stroke and are potentially treatable. Treatment of coexisting OSA decreases both nocturnal and diurnal blood pressure and as a result reduces risk of stroke recurrence, reduces mortality, and improves quality of life. Because SDB improves after the acute phase of stroke, auto-CPAP systems may be preferable.

Among the most prominent potential benefits of CPAP therapy are motor and functional outcomes. However, randomized controlled trials were not strong enough to show this effect. Some studies found that CPAP improved 1 or more neurologic function outcomes, sleepiness, or mood, whereas the others found no benefit of CPAP treatment in these areas. However, the negative studies had small sample sizes and patients had low CPAP compliance, which may have affected the results.

One of the obstacles of OSA treatment in the stroke population has been poor compliance. There are several reasons for poor compliance, including spontaneous improvement of SDB, lack of excessive daytime sleepiness in some patients,
and motor (facial and bulbar palsy) and cognitive (confusional states, dementia, aphasia) deficits. Compliance has been reported to be as low as 25% to 50% in the acute or subacute stroke phase, whereas other groups reported rates as high as 70% in the rehabilitation setting. This finding indicates the importance of CPAP acclimation by skilled respiratory therapists.

In summary, previous research suggests that treatment of OSA with CPAP improves functional recovery during stroke rehabilitation, but that the effect of CPAP treatment on cognitive function in patients with stroke is still unclear.

EARLY TREATMENT OF OBSTRUCTIVE SLEEP APNEA IN CARDIOVASCULAR REHABILITATION

Before the availability of CPAP, the only known definitive therapy for OSA was tracheostomy. One of the earliest studies that showed the impact of treatment of OSA was a retrospective cohort in the 1970s. There were 198 patients followed for 7 years. Seventy-one patients received tracheostomy and 127 received conservative treatment consisting of recommended weight loss. The tracheostomy group (as curative treatment) developed considerably fewer vascular complications. Another observational cohort study examined the impact of CPAP on long-term cardiovascular outcomes in patients with sleep apnea and showed that CPAP therapy reduces fatal and nonfatal cardiovascular events and protected against death from cardiovascular disease.

Short-term randomized trials have been studying systemic blood pressure as the outcome. Although the results have been different with respect to the magnitude of blood pressure reduction, it seems to be a clinically important blood pressure reduction. Those studies showed that patients who had more severe and symptomatic sleep apnea and hypertension experienced more benefit from the longer use of CPAP. Patients less likely to experience benefit were those with asymptomatic mild OSA who had normal blood pressure at baseline. In a double-blind, randomized trial comparing therapeutic airway pressurization with sham CPAP, therapeutic airway pressurization was associated with a reduction of 3 to 7 mm Hg in mean 24-hour systemic arterial blood pressure. In extrapolating from pharmacologic antihypertensive trials, this blood pressure reduction, in itself, is expected to result in a 20% stroke risk reduction.

To date, there are very few data available about the treatment of OSA in the context of cardiac rehabilitation and, overall, the data supporting the treatment of OSA in patients with CAD are less robust than for systemic hypertension.

A case-control study of 192 patients with acute MI (63 patients without OSA, 52 untreated patients with OSA, and 71 patients with OSA treated with CPAP), over a 6-year follow-up, showed that the risk of recurrent MI and revascularization procedures was lower in treated than in untreated OSA and was similar to patients without OSA.

In another study, in 390 patients who had undergone percutaneous coronary intervention, over a median follow-up of 4.8 years, untreated OSA was independently associated with a significant increased risk of repeat revascularization that was reduced by CPAP treatment.

SDB, in both forms of OSA and CSA, is common in patients with HF and has been suggested to increase the morbidity and mortality in these patients.

The mainstay of OSA treatment in HF is CPAP. Small studies showed that CPAP in patients with HF and CSA reduced 30-day hospital readmission and emergency visits. It also improved systolic function, blood pressure, and heart rate. In long-term studies, CPAP decreased mortality and improved hospitalization-free survival in patients with HF and OSA. However, there are no double-blind randomized, controlled trials to evaluate these effects, particularly in the rehabilitation setting.

In contrast, studies in patients with HF and CSA suggested that CPAP also can improve EF but does not show any survival benefit. A recent randomized controlled trial (Adaptive Servo Ventilation in Patients with Heart Failure [SERVE-HF]) examined the effect of adaptive servoventilation in patients with reduced EF and CSA. This trial showed no significant positive effect, but increased both all-cause (HR, 1.28; 95% CI, 1.06–1.55; \( P = .01 \)) and cardiovascular mortality (HR, 1.34; 95% CI, 1.09–1.65; \( P = .006 \)).

Therefore, until the results from further studies are available, optimization of HF management should be the first-line therapy in patients with concurrent CSA. Although the appropriate therapy for CSA in patients with HF remains controversial, CPAP remains widely accepted for OSA in patients with HF.

All of the studies discussed earlier show the beneficial effect of OSA treatment in the context of cardiac rehabilitation, and those patients should be screened early and considered for CPAP treatment until further robust clinical trials have been done.

SUMMARY

Several cohort studies have shown that OSA significantly increases the risk of cardiovascular
disorders independently of potential confounding risk factors. This finding is particularly important given that sleep apnea is a potentially modifiable risk factor. Randomized controlled trials of CPAP in patients with OSA with follow-up of cerebrovascular and cardiovascular outcomes suggest a clinically significant risk reduction associated with the use of CPAP.

In view of potential benefits of noninvasive ventilation on prognosis and functional outcome with improving the quality of life, cognitive function, and acceleration of recovery in the rehabilitation of patients with cardiovascular diseases, clinicians should have a low threshold to evaluate their patients for SDB.

The reasons discussed earlier support the need for cardiac and stroke rehabilitation units to include sleep apnea screening and treatment as an integral component of their care.

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