

# Sleep-disordered Breathing and Stroke: A Common yet Ignored Association

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## ABSTRACT

One of the major causes of long-term disability is stroke. It is widely accepted that the morbidity and mortality caused by stroke can be reduced by aggressively treating the risk factors. One of the modifiable and independent risk factors for stroke is Sleep-disordered breathing (SDB). Untreated SDB may be responsible for an increased risk of stroke and death. Severity of SDB could be used to predict the functional dependence of the patient and poor outcome in stroke patients. Treating SDB with positive airway pressure (PAP) therapy in stroke patients may have impact on functional and neurological outcome. This review discusses the common co-occurrence of the stroke and SDB, its pathogenesis, the effects of SDB on stroke morbidity and mortality, impact of stroke on the sleep architecture, and the possibility of improvement with CPAP therapy.

**Keywords:** Positive airway pressure, Sleep-disordered breathing, Stroke.

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## INTRODUCTION

Stroke is loss of brain function(s) that develop rapidly and is due to disturbance in the blood supply to the brain. It is the third common cause of death worldwide after coronary heart disease (CHD) and cancers of various types. It is one of the major causes of long-term disability and affects the patient, both emotionally and socioeconomically. The survivors of ischemic strokes have an increased risk of suffering another vascular event, particularly another stroke, and this is a major cause of increased morbidity and mortality.<sup>1,2</sup>

The primary prevention of stroke must be emphasized through determination of risk factors for cardiovascular diseases. The past few years have witnessed that efforts have been made to determine hitherto preventable and treatable stroke risk factors. Aggressive treatment of these risk factors in such patients is widely accepted as a means of reducing morbidity. It is in this context that Sleep-disordered breathing (SDB) has also been suggested as a modifiable and independent risk factor for stroke. Some studies have demonstrated that patients with stroke and SDB have an increased risk of death or new vascular events.<sup>3,4</sup> SDB is a modifiable risk factor as the diagnosis, and the treatment is straightforward. It for these reasons that SDB is an ideal target for interventions aimed at reducing the cerebrovascular disease burden.

## STROKE AND SLEEP-DISORDERED BREATHING

In recent years, SDB and its impact on the quality of life and the course of cardiovascular disease have caught the attention of many specialists, mainly pulmonologists, cardiologists, and neurologists. There are studies reporting more cases of stroke and SDB occurring together. Partinen and Palomaki published a short note in the *Lancet* reporting up to 40 times higher risk for stroke among snoring inhabitants of the country of Iceland relative to non-snoring Icelanders.<sup>5</sup> Subsequently, Palomaki et al. demonstrated that snoring is an independent risk factor for stroke.<sup>6</sup>

### Sleep-disordered Breathing in Stroke Patients

An early meta-analysis of 29 studies by Johnson et al. reported that SDB was subsequently identified in 72%, 63%, and 38% of

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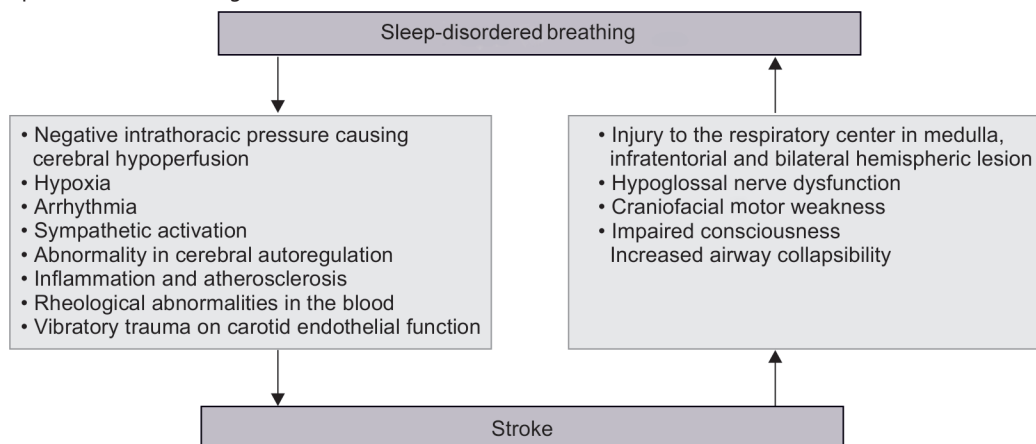
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patients of stroke and transient ischemic attack (TIA) when defined as an apnea-hypopnea index (AHI) of >5, >10, and >20/hour respectively.<sup>7</sup> A recent meta-analysis of 89 studies observed that prevalence of SDB with AHI >5/hour and AHI > 30/hour was found in 71% and 30% of patients, respectively.<sup>8</sup> SDB was diagnosed much more frequently in patients of stroke when compared to the control group of patients who did not have a history of stroke. In fact, the reported frequency likely underestimates the actual prevalence of SDB in stroke patients. Most of the studies excluded patients if they had severe medical conditions, died prior to sleep study, or were unable to consent. Hence, in all probability, the actual prevalence of SDB in stroke patients may be even higher than estimated.

The pathogenesis (Flowchart 1) is believed to be a direct consequence of central nervous system injury; an injury to the respiratory center in the medulla,<sup>9</sup> infratentorial lesions,<sup>10</sup> and bilateral hemispheric lesions can cause SDB. It is also possible that the preexisting SDB may be exacerbated after stroke. This may occur due to the impaired consciousness or the hypoglossal nerve dysfunction and craniofacial motor weakness, leading to increased airway collapsibility.

### Stroke in Sleep-disordered Breathing Patients

There is increasing evidence in the published literature concerning the effect of SDB on the development, occurrence, and course of

**Flowchart 1:** Sleep-disordered breathing and stroke—a bidirectional association

stroke. Marin et al. followed up more than a 1,000 male SDB patients for a mean follow-up of 10.1 years and observed that subjects who had untreated severe SDB presented with a higher incidence of cardiovascular events than those who had mild to moderate OSA.<sup>11</sup> The Wisconsin sleep cohort followed up 1,522 persons over 18 years and reported that long-term cardiovascular morbidity and mortality significantly increased with SDB severity compared to those without SDB.<sup>12</sup> Yaggi et al. stratified 1,022 patients admitted to a sleep laboratory into groups with and without SDB who were followed up over 6 years; they observed the association of increased risk for stroke, TIA, and death with SDB, particularly in patients with severe SDB.<sup>13</sup> A prospective cohort study by Redline et al. followed 5,422 individuals of SDB who did not have a history of stroke for a median of 8.7 years.<sup>14</sup> It was observed that 193 ischemic strokes were observed, especially in the SDB patients with high AHI even after adjustment for potential confounders. In a similar prospective cohort study of 975 women with possible SDB who did not have history of stroke or coronary heart disease at baseline were followed for a median of 6.8 years; it was seen that those with untreated OSA had a markedly increased risk of incident stroke when compared to those without OSA.<sup>15</sup> Chang et al. studied the universal insurance claims database in Taiwan and estimated that the SDB cohort exhibited a 19% higher risk of stroke compared to the control cohort even after controlling for sex and comorbidities.<sup>16</sup>

The pathogenesis (Flowchart 1) of stroke in SDB is quite complex. One suggested mechanism is that there is resultant cerebral hypoxia due decreased cerebral blood flow velocity caused by the negative intrathoracic pressure that is typically generated during an obstructive apnea. Alternatively, in patients with OSA abnormalities of the cerebral blood flow autoregulation, mechanisms may develop due to intermittent hypoxia, oxidant-mediated endothelial dysfunction, increased sympathetic activity, and impaired cerebral vasomotor response to carbon dioxide.<sup>17</sup> The recurrent blood flow abnormalities in the central nervous system (CNS) then precipitate ischemic changes in those patients who have poor hemodynamic reserve (e.g., arterial stenosis), particularly in border-zone areas and terminal artery territories.<sup>18</sup> These episodes of reduced CNS perfusion may also be associated with steep fall in blood pressure, which may lead to abnormalities of CNS circulation particularly in patients with clinically significant occlusion of the carotid or vertebral arteries.<sup>19,20</sup>

Cerebrovascular abnormalities or other risk factors for stroke may be exacerbated by OSA. Patients with OSA have an increased prevalence of systemic hypertension, heart disease, rheological

abnormalities in the blood (increased platelet aggregation and increased blood coagulability), proinflammatory states, impaired vascular endothelial function, accelerated atherogenesis, diabetes, and coexistent or apnea-related cardiac arrhythmias.<sup>21</sup>

Retrospective studies have found that patients with OSA are about twice as likely as controls to have evidence of a patent foramen ovale (PFO) by transcranial Doppler with agitated saline;<sup>22,23</sup> this has been suggested as an additional mechanism for stroke in patients with OSA. It has been thought that in patients with a PFO, nocturnal apneas and pulmonary hypertension associated with OSA could have higher risk of paradoxical embolism and stroke probably due to the right to left shunting. The potential role of vibratory trauma on carotid endothelial function due to snoring has also been suggested.<sup>24</sup>

## CAUSE AND EFFECT?

The finding of increased frequency of SDB in stroke patients raises the question of whether SDB precedes stroke, being a risk factor for it or whether it arises as a consequence of stroke (Flowchart 1). This seemingly simple question has defied a simple answer. Both these disorders share many common risk factors, including increasing age, obesity, and alcohol abuse. If the driving force behind the association between stroke and SDB were that stroke caused the SDB, then the prevalence of SDB would have been equally high in the control group. This hints that SDB may be an outcome of stroke. If this is true, then we also expect the stroke topography to have an impact on SDB. However, most studies<sup>25–27</sup> have failed to determine the link between SDB and the type of stroke or stroke topography. Also, if the hypothesis was correct, then the incidence of SDB would have been higher amongst stroke than in TIA (as the central cause for OSA would have spontaneously recovered). However, the frequency of SDB was similar in patients with stroke and TIA,<sup>25,26,28–30</sup> it has been suggested that SDB maybe consequence of brain injury as well as a preexisting condition.

It is still an open question whether SDB is a cause or a consequence of stroke. The resolution of this enigma would require further studies to disentangle the various factors associated with the disease and to ultimately define the true relationship between SDB and stroke.

## STROKE SEVERITY WITH SLEEP-DISORDERED BREATHING

Various studies have indicated that SDB is known to have an impact on the natural history and outcome of the stroke patients, although

this is not always statistically significant. Iranzo et al. had reported that while a raised AHI was associated with early neurological deterioration, this did not correlate with disability assessed 6 months after the stroke.<sup>31</sup> Similarly, Yan-Fang et al. had observed that the severity of SDB appears to be directly related to a worse functional outcome during the early recovery period.<sup>32</sup> Kumar et al. had observed that the severity of SDB could predict the functional dependence of the patient and poor outcome.<sup>33</sup>

The suggested mechanism by which the SDB affects the functional outcome of stroke is that the recurrent hypoxemia associated with frequent apneas may have a critical effect on the “ischemic penumbra” surrounding the infarcted brain and might result in extension of the neurological damage. Another mechanism is the reverse Robin Hood Syndrome (RRHS); that is, the vasodilatation caused by apnea induced hypercapnea increases the blood flow velocity in unaffected vessels creating an intracranial steal phenomenon, which decreases the blood flow in vessels supplying the ischemic area of the brain.<sup>34</sup> Another possible reason for a poor functional outcome is the increased release of superoxides from neutrophils due to the alternating hypoxemia and reoxygenation accompanying OSA.<sup>35</sup> The large fluctuations of blood pressure and its consequent effects on cerebral blood flow<sup>36</sup> have been associated with an adverse outcome in stroke populations. Also, baroreceptor dysfunction<sup>37</sup> and impaired cardiac baroreceptor sensitivity observed in OSA have been associated with higher mortality after stroke.<sup>38</sup> These mechanisms also support the role of CPAP treatment as means of improving the functional outcome of stroke.

## EFFECT OF TREATING SLEEP-DISORDERED BREATHING IN STROKE PATIENTS

The increased prevalence of SDB in stroke patients prompted researchers to assess the possible benefit of continuous positive airway pressure (CPAP) treatment in these patients to reduce depressive symptoms, improve the subjective well-being, and lower the incidence of new vascular events and mortality. In a group of 41 patients with both stroke and SDB, who were treated over ten days with CPAP, Wessendorf et al. reported an improvement in nighttime blood pressure values and subjective well-being.<sup>39</sup> Sandberg et al. randomized SDB patients who were admitted to a stroke rehabilitation center 2–4 weeks after a stroke to either treatment group (CPAP treatment) or a control group; they observed that the treatment group showed an improvement in depressive symptoms over 28 days although the effect with regard to delirium or functional outcome was not significant.<sup>40</sup> Martínez-García et al. who studied 51 patients with SDB and stroke observed that compared to noncompliant subjects, the 15 CPAP-compliant patients had a lower incidence of new vascular events (7% vs 36%) over a follow-up observation period of 18 months.<sup>41</sup> Martínez-García et al. found that 68 stroke patients with an AHI  $\geq 20$ /hour who did not tolerate CPAP had a higher 5-year mortality than 28 patients who tolerated CPAP.<sup>42</sup> Ryan et al. had performed a randomized, open-label, parallel group trial in a stroke rehabilitation unit with blind assessment of outcomes performed in stroke patients with OSA; patients were assigned to either standard rehabilitation alone or to CPAP.<sup>43</sup> It was observed that although the treatment of OSA by CPAP in stroke patients undergoing rehabilitation improved the functional and motor outcomes, the neurocognitive outcomes were not improved.<sup>43</sup>

There is limited evidence that treatment of sleep-related breathing disorders improves stroke-specific outcomes like stroke severity, functional status, and recurrent vascular events, as the results are conflicting and mixed. Bravata et al. randomized 55 patients with acute stroke to auto-CPAP or standard care; patients assigned to auto-CPAP had greater improvement in stroke severity scores at 1 month compared to those who received usual care.<sup>44</sup> Parra et al. randomly assigned 140 SDB patients with stroke to either auto CPAP or no CPAP and found that the early use of CPAP appears to accelerate neurological recovery and delays the appearance of cardiovascular events, although cardiovascular event-free survival after 2 years was similar in both the groups.<sup>45</sup> In the longer 5-year follow-up, the authors reported that patients in the CPAP group had significantly higher cardiovascular survival than the control group.<sup>46</sup>

However, another large study that assessed the role of CPAP in over 200 SDB patients with coronary or cerebrovascular disease observed that CPAP did not prevent cardiovascular events when results are compared to controls.<sup>47</sup> Hsu et al. randomized patients of SDB and stroke, 15 patients each to treatment with CPAP, and to conventional treatment. The result of this trial showed no benefit from CPAP treatment.<sup>48</sup>

A noteworthy point is that the best outcome results have been often reported in patients with excellent CPAP compliance, and studies without significant improvement have often attributed this to poor CPAP compliance.<sup>49</sup> Poor adherence with CPAP therapy has been attributed to difficulty in tolerating the PAP, poor motivation, cognitive deficits, age, and neglect.<sup>48–50</sup>

In addition to CPAP, behavior modification is advised for all patients who have SDB. This includes encouragement to lose weight, an appropriate sleep position (if positional OSA is detected), and avoidance of alcohol and certain medications, such as benzodiazepines. The other alternative therapies available for the treatment of SDB include oral appliances<sup>51</sup> and upper airway surgeries.<sup>52</sup> However, the efficacy of such therapies in patients who have SDB following a stroke has not been extensively investigated.

## STROKE AND SLEEP ARCHITECTURE

The effect of stroke on sleep architecture has been analyzed in a number of studies. There have been contradictory reports regarding the alterations in the sleep architecture. Most studies, comparing stroke patients to controls, report a poor sleep quality<sup>53</sup> with a reduction in sleep efficiency<sup>54</sup> and increased wakefulness after sleep onset,<sup>55–57</sup> with<sup>56</sup> or without<sup>58</sup> a reduction in total sleep time. A reduction<sup>56</sup> or even an increase<sup>58,59</sup> in stage II sleep has been reported. Similar results are reported for slow-wave sleep (SWS).<sup>56,57,59,60</sup> Also, rapid eye movement (REM) sleep reduction is reported in some studies<sup>58</sup> although not confirmed by others.<sup>56</sup>

Several characteristics of the sleep architectures have been correlated with a poor prognosis in stroke patients. These include reduced sleep efficiency, reduced total sleep time (TST), reduced stage II and REM, increased SWS, and reduced sleep spindles and K complexes.<sup>55,56,58</sup> A relative reduction in REM sleep latency in stroke patients with worse functional outcome was noted in the studies by Bassetti et al.,<sup>55,56</sup> however, the difference did not reach statistical significance.

Terzoudi et al. had demonstrated that stroke patients (without SDB) have reductions in total sleep time and sleep efficiency, reduced stage II and slow-wave sleep, increased wakefulness during sleep, and increased sleep latency.<sup>61</sup> In the presence of SDB, rapid eye movement (REM) sleep is also reduced.

## CONCLUSION AND CLINICAL SIGNIFICANCE

In conclusion, in view of the high frequency of SDB in stroke patients, the effects of SDB on stroke morbidity and mortality, and the possibility of improvement with CPAP therapy, may warrant screening for OSA in all patients of stroke and TIA. However, in the daily clinical practice, physicians pay much less attention to SDB when compared to other associated diseases like hypertension and diabetes. This is presumably because SDB is still not considered a serious disorder and is depreciated as a benign loud snoring. Such a disregard for SDB is rather shocking in view of the common occurrence of SDB in stroke patients which is almost as frequent as generalized atherosclerosis and arterial hypertension and is commoner than diabetes, cardiac arrhythmias, and coagulation disturbances. Hence, it is essential that neurologists and physicians realize the importance of SDB in stroke patients and are trained in its identification.

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