Editorial

Obstructive sleep apnea and stroke: hand in hand?

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Obstructive sleep apnea (OSA) is a sleep breathing disorder that is increasingly recognized in the general population in developed countries, with current prevalence estimates of 9% to 38%, depending on the diagnostic criteria used (1). While the increase in prevalence rates over the last 30 years has been explained, in part, by increased physician awareness and more readily available diagnostic testing for OSA , there has also been an increase in "real' prevalence, in parallel with the obesity epidemic and longevity (2,3). However, even with this greater awareness of OSA, the vast majority of patients with the disease remain undiagnosed. In contrast to the rising prevalence of OSA, the incidence of stroke in developed countries is on the wane (4). Despite this, stroke is the second leading cause of death worldwide and its societal burden remains considerable, in part, due to the high prevalence of stroke attributable to enhanced survival post-stroke. As such, the primary and secondary prevention of stroke continues to be of major importance, with emphasis on treatment of modifiable risk factors such as hypertension and atrial fibrillation. More recently, OSA has emerged as another potential modifiable risk factor in this regard.

A relationship between the presence of OSA and stroke has been consistently demonstrated in observational studies over the last decade. While this may be explained in part by shared, overlapping risk factors that predispose to both OSA and stroke (e.g., male sex, older age), there is biological plausibility to support a causal relationship; the intermittent upper airway narrowing and collapse that characterises OSA causes intermittent hypoxia, hypercapnia, and the generation of large intrathoracic pressure swings, with subsequent negative impact on sympathovagal balance, hemodynamics and cardiac wall stresses (5). These aforementioned pathophysiological effects may be responsible for both the heightened and differing temporality of cardiovascular and cerebrovascular morbidity and mortality of OSA (6,7). The initial description of a possible relationship between OSA and stroke comes from a case report as recently as 1985 which describes a 34-year-old male with severe OSA and hypertension who developed a stroke with right hemiplegia (8). This was followed by several small retrospective and cohort studies. More robust evidence of the relationship between OSA and stroke came from both the Sleep Heart Health and Wisconsin epidemiological studies. The 2001 Sleep Heart Health study reported an association between OSA and prevalent stroke [OR =4.31, adjusted for hypertension and body mass index (BMI) for an apnea-hypopnea index (AHI) ≥11 events per hour]. Evidence of a causal relationship was later shown in the Wisconsin cohort study, with a 3-fold increased risk of incident stroke in subjects with an AHI ≥20 events per hour, following adjustment for age, BMI and sex. This causal relationship was reaffirmed when data from clinic populations showed a significant association between OSA and incident stroke (9,10).

In the post-stroke population, studies have consistently shown a high prevalence of OSA. These studies have been performed in the acute, subacute and chronic post-

stroke periods (11). The current study under discussion by Huhtakangas *et al.*, published in *Sleep Medicine* (12), aimed to evaluate the prevalence, severity and nature of SA in consecutive adult patients with ischemic stroke within 48 hours of admission to a single-centre stroke unit in Finland over a 21-month time period. Subjects were subsequently stratified into those who received thrombolysis or not. While this is not the first study to evaluate SA prevalence in a post-stroke cohort, it is the first study to stratify the groups into those who did or did not receive thrombolysis (tPA) for treatment of acute stroke. There are also a number of methodological issues and strengths by which this study differs from others in the literature. Concomitant pulmonary disease, heart failure or severe functional impairments were not exclusion criteria as was the case in most (13,14) but not all previous studies (15). Therefore, this study provides a representation of OSA prevalence in unselected hospital-admitted ischemic stroke patients. Secondly, rates of refusal to participate, attrition and invalid recordings were relatively low (20%) compared to rates of 36% and 50% respectively in other studies in this population (13,14).

In this current study, as in other post-stroke studies (16), home sleep apnea test (HSAT) was used to determine the presence of sleep apnea. The device used has been validated for the diagnosis of OSA (17) but not central sleep apnea (CSA). Furthermore, current recommendations from the American Association of Sleep Medicine do not support the use of testing with HSAT due to the absence of validation studies on most of the portable sleep apnea devices (18). One validation study has demonstrated excellent sensitivity and specificity for a portable device (AHI >10 events per hour) in a stroke cohort and therefore, while the concerns regarding HSAT are valid they may be overstated (19).

The prevalence of OSA is very high within the Huhtakangas cohort (91.2%), compared to other similar studies (60–70%). These differences may be due to the lower AHI cut-off (≥5 *vs.* >10 /hour) and the exclusion of those who received thrombolysis from other similar studies (20). This study confirms previous study findings of a very high level of undiagnosed sleep apnea (4.4% prior diagnosis of OSA) within the community (21). While the onset of OSA may be *de novo* post stroke most of the evidence suggests that it usually is a pre-existing condition (5).

Finally, a novel finding in this paper is the higher prevalence of OSA (96.4% *vs.* 85.1%) in those who received thrombolysis compared to those who did not, respectively, despite subjects being of younger age. By design the thrombolysis group had greater severity stroke, but neither they nor other studies were able to demonstrate stroke severity as a predictor of stroke. The authors propose the development of systemic inflammatory response syndrome, cerebral oedema and intracerebral haematoma as potential factors contributing to increased OSA prevalence. The occurrence of *de novo* OSA requires damage to specific brain regions, however, the observational design of the study does not allow for any firm conclusions in this regard. We would propose the possibility that the time spent in a supine sleep position could be a potential reason for this higher prevalence as supine sleep is very common in those with stroke, and even more so in those with severe stroke and significant physical limitations (22). Unfortunately, sleep position data are not available in this study.

In summary, this study confirms the high prevalence of OSA in the post-stroke population. The finding of a greater prevalence of OSA in the thrombolysis group, while interesting, requires further study to investigate the temporal nature of OSA, the role of sleep position, and the effect on medium to long-term outcomes. Some might suggest that if the majority of patients with stroke (91.4%) have OSA, should we not consider its presence as part of the normal aging process which may provide ischemic preconditioning and prevention of greater stroke severity? Observational evidence for early mortality in post-stroke patients with untreated OSA (23) and evidence from randomized control trials of the positive impact of OSA treatment in the post-stroke population on early neurological recovery (24), motor improvements (25), and reduction in recurrent strokes and increased survival (26) suggests otherwise.

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Footnote

Conflicts of Interest: Dr. Lyons previously served on the Research Advisory Board for Breso-Tec. Dr. Ryan has no conflicts of interest to declare.

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