Sleep Apnea and the Cerebrovascular Disease Correlation

Written by Brian Hoyle

Antonio Culebras, MD, SUNY Upstate Medical University, Syracuse, New York, USA, provided on overview of obstructive sleep apnea (OSA) as a risk factor for cerebrovascular disease and stroke [Culebras A, editor. *Sleep, Stroke and Cardiovascular Disease.* Cambridge University Press, 2013].

Sleep apnea may contribute to cerebrovascular disease in a variety of ways (Table 1).

Table 1. Sleep Apnea-Related Contributors to Cerebrovascular Disease

- Increased sympathetic drive/tone at apnea conclusion
- Transient surges in blood pressure
- Hypertension
- Cardiac arrhythmias
- Patent foramen ovale
- Hemodynamic changes
- Failed autoregulation of cerebral hemodynamics
- Intermittent hypoxia
- Systemic inflammation
- Endothelial dysfunction
- Hypercapnia
- Hypercoagulability

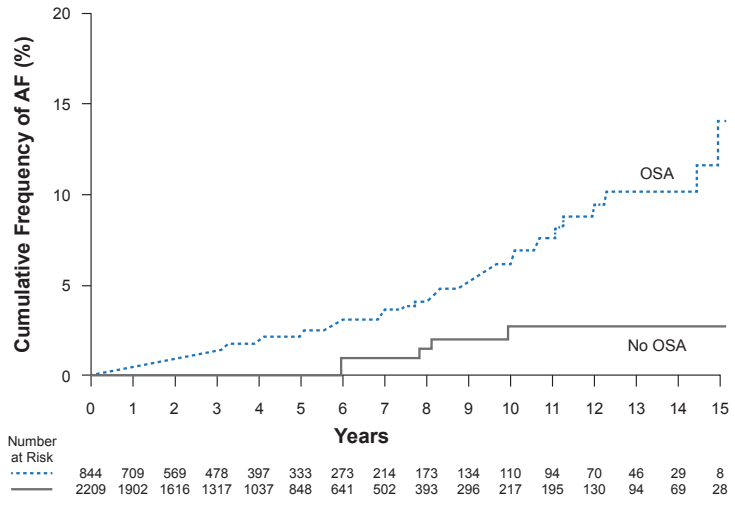
SLEEP APNEA-RELATED HYPERTENSION

The regularity of arousals from apnea influences hypertension [Jamasebi R et al. *Sleep* 2008]. The Sleep Heart Health Study reported a progressive increase in adjusted odds of hypertension with ≥15 episodes of apnea per hour [Nieto FJ et al. *JAMA* 2000].

CARDIAC ARRHYTHMIA

Many atrial fibrillation (AF) episodes (40%) occur during the typical sleep period (midnight to 8:00 AM) and AF risk increases nearly 3-fold with sleep apnea-mediated decreases in blood oxygen. Sleep apnea is significantly more prevalent (p=0.0004) in patients with AF (49%) than in patients with other cardiovascular diseases who are at high-risk for AF (32%) [Gami AS et al. *Circulation* 2004], and significantly more frequent in those with AF compared with age-matched healthy individuals (81.6% vs 60%; p=0.03) [Braga B et al. *Sleep Med* 2009]. OSA is a univariate predictor of AF (Figure 1) [Gami AS et al. *J Am Coll Cardiol* 2007].

Figure 1. Cumulative Frequency of AF for Subjects With and Without Obstructive Sleep Apnea



OSA=obstructive sleep apnea.

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PATENT FORAMEN OVALE

Patent foramen ovale has been significantly associated (p<0.05) with sleep apnea in 27% of subjects compared with 15% of subjects with a normal heart [Beelke M et al. *Sleep Med* 2003]. The presence of right-to-left shunt in 72% of 100 consecutive patients with OSA [Guchlerner M et al. *J Clin Sleep Med* 2012] is evidence of an association of patent foramen ovale with sleep apnea. In a study of 335 patients, OSA lasting ≥20 seconds was associated with wake-up strokes and transient ischemic attack in patients with right-to-left shunt (27/69) compared with patients with apnea alone (70/266; OR, 1.91; 95% CI, 1.08 to 3.38; p=0.03) [Ciccone A et al. *Thorax* 2013].

The data to date supports the suggestion that OSA significantly increases the risk of stroke or death from any cause, independent of other risk factors including hypertension [Yaggi HK et al. *N Engl J Med* 2005]. Additionally, apnea has been linked to cognitive impairment [Yaffe K et al. *JAMA* 2011; Román GC et al. *Lancet Neurol* 2002].

Therapeutic use of continuous positive airway pressure has been explored in OSA. Encouraging findings include lowered cardiovascular risk [Kohler M et al. *Eur Respir J* 2008], decreased blood pressure [Jaimchariyatam N et al. *Sleep Med* 2010; Martínez-García MA et al. *Eur Respir J* 2007], and potential value in reducing mortality [Martínez-García MA et al. A*m J Respir Crit Care Med* 2009].

Improved Outcomes in ICH Achieved With Investigational Minimally Invasive Surgery

Written by **Mary Mosley**

Intracranial hemorrhage (ICH) remains the only untreatable form of stroke. An ICH volume >20 to 30 mL predicts poor outcomes [Broderick JP et al. *Stroke* 1993]. In clinical trials, no benefit has been found with open surgery compared with medical therapy in reducing ICH volume in patients with stable supratentorial large hematomas. The invasiveness and risk of open surgery, particularly for deeper ICHs, and the impact on quality of life are concerns.

Minimally invasive surgical (MIS) approaches (endoscopic, thrombolytic), but not open surgery, were shown to have some benefit in ICH [Prasad K et al. *Cochrane Database Syst Rev* 2008]. The MISTIE technique is the farthest along of the MIS approaches under investigation, said Issam Awad, MD, University of Chicago, Chicago, Illinois, USA.

The feasibility of this technique was shown by a 70% reduction in ICH volume after 4 days of treatment in the Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation trial [MISTIE; NCT00224770]. This Phase 2 trial of patients with >20 cc supratentorial ICH without underlying structural vascular abnormalities compared best medical care with the MISTIE intervention including direct delivery of recombinant tissue plasminogen activator (rt-PA) at progressively larger doses at 8-hour intervals. Imaging-guided catheter placement within the center of the clot is followed by clot aspiration using a rigid cannula.

An association between ideal catheter placement and outcomes was found in the MISTIE trial, and allows for achieving generalizable results said Dr. Awad. The ideal "hot dog in the bun" placement along the axis and within the center of the clot was associated with less residual hematoma than the "eccentric catheter" placement.

At 180 days, achieving an ICH volume <20 mL was associated with good outcomes, while the poor outcomes were associated with poor catheter placement.

The MISTIE procedure did not increase mortality or vegetative survival at 180 days, and a smaller proportion of these patients were in long-term care facilities. For the good outcomes strata of the prespecified mRS score, there was an absolute 11% improvement. These benefits were further improved at 360 days. The hospital length of stay was dramatically shorter with MISTIE, resulting in a 35% reduction in total costs. Subgroup analyses showed the MISTIE intervention was effective for deep and lobar sites and across the Glasgow Coma Scale. Also, MISTIE was equally as effective whether patients were treated within the first 36 hours or the second 36 hours, showing the rush to surgery is not as important as stabilizing the hematoma, said Dr. Awad.

The mechanism of the benefit seen in MISTIE appears to be reduction of clot burden, perhaps saving tissue at risk, and preventing secondary injury from occurring over subsequent days, he stated. Despite the benefits seen in MISTIE, two unanswered questions are whether MIS spares tissue and the amount of clot removal that is sufficient. These may be answered in the Phase 3 Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III trial [MISTIE III; NCT01827046], which enrolled its first of 500 patients in December 2013 and has a similar study protocol.

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