EDITORIAL

Altered Resting Cerebral Blood Flow in Obstructive Sleep Apnea: A Helpful Change or Not?

Commentary on Baril et al. Regional cerebral blood flow during wakeful rest in older subjects with mild to severe obstructive sleep apnea. SLEEP 2015;38:1439–1449.

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Obstructive Sleep Apnea (OSA) is accompanied by disruption in cerebral blood flow (CBF), as shown by Baril et al.[1] in this issue of *SLEEP*. Their findings of hypoperfusion across various brain regions in older OSA patients relative to healthy controls add to prior studies showing resting CBF alterations in middle-aged OSA populations.[2–6] Baril et al.[1] also demonstrate correlations between increased CBF and measures of sleep disruption and obesity, suggesting a more complex relationship than simply OSA leading to hypoperfusion. In fact, as they point out, there are many possible interpretations of these findings including links with neural function (cognitive deficits), impaired systemic or cerebral vascular regulation, altered cellular function, and degenerative processes.

One question is whether the resting CBF differences with respect to healthy people are pathological or reflective of normal cerebral autoregulation in the presence of abnormal physiology associated with OSA. Two other studies[5,6] show recovery of resting CBF to normal levels after treatment with continuous positive airway pressure (CPAP), suggesting the hypoperfusion seen in untreated patients is not due to permanent damage to cerebral vessels. Other, modifiable factors must therefore be contributing to the CBF levels in OSA.

Global cerebral blood flow regulation is dominated by pressure and chemical drives, with the autonomic nervous system also playing a role through the extensive sympathetic enervation of the cerebral vasculature.[7] OSA patients show high sympathetic tone,[8] which may extend to the cerebral sympathetic nerves creating a vasoconstrictive (and likely blood-flow reducing) effect.[9,10] (See Windlewski and Frydrychowqski 2013 for a review.[11]) Reduced metabolic demand, which has been observed in OSA,[12] is another factor that could lead to reduced CBF.[13] On the other hand, OSA patients typically show higher than normal levels of blood carbon dioxide ($PaCO_2$), which has a strong vasodilatory effect, and hence should lead to a higher cerebral blood volume.[14] In theory, both increased cerebral blood volume and reduced CBF could be present, which may be the case in OSA. Cerebral autoregulation also responds to blood pressure changes, but under normal circumstances CBF is relatively stable across varying pressures.[15,16] Under experimental levels of hypercapnia, there does emerge a linear relationship between blood pressure and CBF,[15,16] but given the higher blood pressure and $PaCO_2$ typical of OSA, this relationship would be expected to lead to an increase in CBF in the sleep condition, which is contrary to the findings of Baril et al.[1] High blood pressure in the clinical context of hypertension is associated with lower CBF;[17] but, any link between hypertension and low CBF may not be directly related to blood pressure per se, since CPAP resolves blood flow[5,6] with only small reductions in resting pressure.[18,19] In summary, the characteristics of OSA that are consistent with observed reduced resting CBF are high sympathetic tone and reduced cerebral metabolic activity, with those factors dominating over elevated $PaCO_2$. The influence of blood pressure is unclear.

A region-specific influence on CBF is neural activity, which may underlie the regional symptom-related correlations in CBF observed by Baril.[1] Regional CBF is closely linked to local changes in neuron activity, a phenomenon underlying functional magnetic resonance imaging.[20,21] The regions showing hyperperfusion[1] correlated with higher levels of sleep disturbances and BMI are in or adjacent to the limbic system, including the amygdala, hippocampal areas, insula, and basal ganglia. Assuming these CBF correlations are related to neural activity, the findings could represent either compensatory overactivation (working harder to maintain the same behavior[22]) or symptom-specific elevated activity, such as modulation of increased psychological or physiological stress present in OSA.[23,24] In contrast, the regions showing reduced CBF with increasing sleep disturbance and sleepiness were exclusively in outer cortical regions. Sleep deprivation is linked with CBF reductions in temporal areas[25] similar to those showing sleepiness-related declines in the older OSA patients,[1] suggesting these patients had a pattern of brain activity consistent with state of sleepiness. Thus the OSA brain, at least in older adults, may have normally-functioning resting CBF regulation with respect to neural activity.

Independent of neural activation, hypoperfusion could lead to some brain regions not receiving adequate blood supply, placing them at risk of injury. However, the regions affected by low resting CBF are in many cases distinct from areas of previously-shown structural alterations in OSA,[26–31] so hypoperfusion in the resting state is not likely to be a sole cause of brain injury. Global hypoperfusion is associated with stroke and neurological disorders,[32,33] but the existing findings do not demonstrate overall CBF reductions. A greater concern is acute hypoperfusion during challenges that require an autoregulatory response; OSA is associated with impaired cerebral vascular reactivity during blood pressure changes, which

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presumably would lead to reduced perfusion in the seconds following such changes.[34] How resting CBF affects CBF reactivity is unclear.[35,36]

Sex-specific patterns should be expected in the patterns of CBF alterations in OSA, given large differences in CBF between males and females in healthy populations,[37,38] clinical conditions,[17] and dynamic responses to autonomic challenges in the sleep condition.[39] Baril et al. studied a sample with 15 females,[1] but genders were not compared in the analyses. Even if only descriptive statistics were used, such separation would be of value in future studies.

In summary, the findings of altered resting CBF in OSA raise questions about the origins and possible consequences of the cerebral vascular changes. The evidence to date leaves open the question of whether resting hypoperfusion is a pathophysiological phenomenon, as opposed to a normal cerebrovascular response to altered physiology and brain function. Investigations that identify how resting CBF can be manipulated, and identification of sex differences in alterations, would advance our understanding of the nature and clinical relevance of OSA-related variations in cerebral blood flow.

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