Breathe, Breathe in the Air
The Ins and Outs of Hypoxia Take Their Toll
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In this issue of Hypertension, Capone et al9 examined the hypothesis that intermittent hypoxia impairs the control of brain perfusion and that NADPH oxidase and endothelin 1 (ET-1) play key roles in producing such changes. Their approach included the study of young male mice made hypoxic intermittently by changing the inspired Po2 from ~147 to 70 mm Hg every 90 seconds during their normal sleep time. In addition to quantification of changes in local cerebral blood flow, complementary methodology included measurements of superoxide levels, components of the endothelin system, and arterial blood pressure. Using this model, 14 days of intermittent hypoxia impaired cerebrovascular responses to endothelium-dependent agonists (both NO-dependent and NO-independent) and whisker stimulation. The latter involves activation of the somatosensory cortex and is a common model to examine neurovascular coupling (or functional hyperemia) in this region of the brain. These changes occurred in the absence of a significant increase in arterial pressure (in awake or anesthetized mice). A longer exposure to intermittent hypoxia (35 days) produced mild hypertension and tended to further reduce endothelium-dependent vasodilation and neurovascular coupling. Because impairment of regulation of cerebral blood flow was seen before increases in arterial pressure, the data suggest that intermittent hypoxia produces cerebrovascular changes independent of hypertension.

Focusing on the longer duration of intermittent hypoxia, the authors next addressed potential mechanisms involved. Oxidative stress contributes to vascular abnormalities in many disease models, including models of hypertension and intermittent hypoxia.3,6,10 After intermittent hypoxia, superoxide levels were increased and vasodilator responses to acetylcholine and whisker stimulation were restored to normal by a scavenger of superoxide, an inhibitor of NADPH oxidase, or genetic deficiency in Nox2. Nox2 is the enzymatic component of 1 isofrom of NADPH oxidase, a key source of reactive oxygen species in the vasculature.10

The endothelin system, particularly ET-1, has been implicated previously in vascular disease and hypertension, as well as cardiovascular changes during intermittent hypoxia.3,11,12 Primarily via activation of the endothelin A receptor, ET-1 is a powerful vasoconstrictor but also has proinflammatory and pro-oxidant effects in vascular cells,11 all features seen with intermittent hypoxia.3,6 In the current experiments, intermittent hypoxia increased local expression of endothelin-converting enzyme and endothelin A receptors and produced remarkable increases in the levels of perivascular ET-1 (Figure). These changes were functionally important because an inhibitor of endothelin A receptors reduced superoxide and...
Restored vascular responses (vasodilation to acetylcholine and whisker stimulation) to normal.

Combined with previous reports, the present work suggests that intermittent hypoxia produces endothelial dysfunction in both large and small blood vessels in the brain (Figure). Although many studies have examined effects of obstructive sleep apnea or intermittent hypoxia on endothelial function in vessels outside the brain previously, the current work appears to be the first demonstration that neurovascular coupling is also affected by intermittent hypoxia. Capone et al also provide the first insight into mechanisms by which intermittent hypoxia impairs vasodilator mechanisms in brain, implicating key roles for ET-1, NADPH oxidase, and reactive oxygen species (Figure).

Although the present study provides significant insight into mechanisms, unanswered questions remain and new questions emerge. Beyond ET-1, Nox2, and reactive oxygen species, what cell types and specific molecular targets are involved in mediating these effects? Some may be more obvious. For example, microvascular responses to acetylcholine in the brain are mediated by NO produced by endothelial cells. Thus, Nox2-derived superoxide may affect these responses by reducing NO-mediated signaling initiated by endothelial cells. Decreases in cerebral blood flow during neurovascular coupling are more complex and likely have NO-dependent and NO-independent components. In addition to neurons, functional hyperemia may also involve astrocytes and/or pericytes in the somatosensory cortex. Beyond endothelium, are all of these cells and their relevant cell-specific signaling mechanisms affected by intermittent hypoxia? Vascular structure can be affected by hypoxia, reactive oxygen species, and loss of NO bioavailability, as well as ET-1, NO (or impairment of other endothelium-dependent mechanisms). Obstructive sleep apnea is a risk factor for cognitive impairment and stroke. A major unanswered question is whether the vascular changes described in the current studies are sufficient to affect cellular (neuronal and glial) function. Do the changes in this model predispose to more severe ischemia, greater impairment of collateral-dependent blood flow, or impair recovery from stroke or other forms or brain injury? Although the presence of vascular dysfunction in cerebral blood vessels is analogous to that described before for the periphery, the implications can be much greater in the brain.

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Disclosures
None.

References


