This issue's letters

- Hypoxia and Alzheimer disease
- Splinting in the intensive care unit

Hypoxia and Alzheimer disease

Christopher Patterson and colleagues reviewed the modifiable risk factors for Alzheimer disease but did not mention that hypoxia may stimulate the development of this illness.[1] Cigarette smoking, severe head injury with loss of consciousness and systolic hypertension in older people are risk factors that may cause hypoxia directly or induce it via neuronal ischemia; the disruption of neurovascular coupling has been implicated in hypertension,[2] ischemic stroke and Alzheimer disease. We are interested in the authors' views on this issue as many patients with Alzheimer disease also have vascular infarctions[3] and these patients deteriorate faster.[4]

Prolonged or chronic hypoxia has been shown to alter the excitability and functional expression of ion channels, which possibly contributes to neurodegeneration. Reduced oxygen levels result in the formation of β-amyloid protein through amyloidogenic processing of amyloid precursor protein, leading to upregulation of native L-type calcium channels and disruption of calcium homeostasis.[5] Cholinergic neurons may be especially vulnerable to β-amyloid protein toxicity.[6] The dysregulated calcium expression following hypoxia in central neurons may contribute to the neurotoxicity of β-amyloid protein and subsequent development of Alzheimer disease.

Patients with chronic obstructive pulmonary disease and obstructive sleep apnea syndrome often complain of memory lapses, which may result from intermittent or chronic hypoxic injury to the forebrain. Sun and colleagues defined the molecular mechanism of hypoxia leading to dementia and showed that hypoxia leads to increased β-secretase activity and production of β-amyloid protein.[7] Until specific therapy becomes available, simple measures to prevent chronic hypoxic injury to the brain may help to prevent Alzheimer disease or may benefit people who already have the condition.

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[One of the authors responds:]

My coauthors and I thank Sujoy Khan and Ioan Davies for their thoughtful response to our article.[1] Before establishing a relationship between hypoxia and subsequent development of Alzheimer disease, one must consider 2 issues. The first is whether the cognitive changes observed during or after hypoxia are due to Alzheimer disease or other cognitive disorders. Recoverable cognitive dysfunction[2] can persist for many months after hospital admissions and may simulate a dementia, although it is probably a type of subsyndromal delirium. The second is whether there are factors other than hypoxia (such as chronic inflammation[3,4]) that may account for cognitive changes. In addition to hypoxemia, tobacco smoking causes prolonged exposure to carbon monoxide, numerous carcinogens and other potential neurotoxins. Head injury not only produces localized hypoxemia but it may also influence the subsequent development of Alzheimer disease through the effects of hemorrhage, contusion and inflammatory responses. Both hypertension and tobacco smoking increase the risk of stroke, and the synergistic effect of Alzheimer disease and cerebrovascular disease is well known.[5] In chronic obstructive lung disease, inflammatory cytokines,[6] recurrent infections and conceivably the effects of anticholinergic medications could all contribute to the observed cognitive changes. Heart failure may also be associated with cognitive deficits, but many factors other than hypoxia, such as activation of neuroendocrine pathways, rheologic changes and consumption of numerous medications with known anticholinergic side effects, offer alternative explanations.[7] Finally, the existence of anatomic changes pathognemonic of Alzheimer disease does not guarantee a phenotype of dementia.[5]

Khan and Davies raise an intriguing hypothesis, but our review cannot answer their question as we were limited by the methodologic constraints of longitudinal cohort studies, none of which consistently measured arterial oxygen tension or transcutaneous oxygen saturation levels. Only prospective studies will be able to answer their question.

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Splinting in the intensive care unit

Heidi Clavet and colleagues recently reported the results of a study in a much-needed area of research that receives little attention.[1,2] Conservative treatment of contractures is time consuming and often results in few gains in cases of significant contracture.[3] The wait time for a procedure to lengthen the Achilles tendon at a Toronto tertiary care centre is about 2 years. As mentioned by Clavet and colleagues, intensive care units do not have enough physiotherapists, occupational therapists and nurses to provide sufficient passive range of motion exercises to prevent the onset of contractures.

The most frequent and functionally limiting contractures I see are ankle plantar flexion contractures (which limit independent transfers and ambulation) and contractures of the intrinsic muscles of the hand (which limit eating, dressing and writing). Given the lack of resources, it may be prudent to consider recommending the use of over-the-counter ankle–foot orthoses to promote ankle dorsiflexion and gloves or splints to stretch the intrinsic hand muscles for all patients admitted to the intensive care unit for longer than 2 weeks. These devices are easily applied and do not interfere with lifesaving devices; however, the patients need to be monitored for skin breakdown. As well, teaching the family to do range of motion exercises for the hands and ankles (which again would not interfere with lifesaving devices) could be beneficial to patients, the health care team and family members, who desperately want to feel they are helping their loved ones.

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Correction

In the full-text version of the Health and Drug Alert "The Evra (ethinyl estradiol/norelgestromin) contraceptive patch: estrogen exposure concerns,"[1] the doses of ethinyl estradiol, norelgestromin and norgestimate were mistakenly listed in milligrams rather than micrograms. This error did not occur in print or in the PDF and has now been corrected on www.cmaj.ca.

REFERENCE

1. Wooltorton E. The Evra (ethinyl estradiol/norelgestromin) contraceptive patch: estrogen exposure concerns. *CMAJ* 2006:174;164-5.

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