BJPsych The British Journal of Psychiatry (2014) 204, 163–164

Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

Contents

Might hyperoxia during surgical anaesthesia contribute to older patients' higher dementia risk?

Chen *et al*[1] present data showing that patients aged 50 and over have an earlier onset and higher hazard ratios for dementia following surgery and anaesthesia than controls, irrespective of the type of anaesthesia used – intravenous or intramuscular, regional or general. This finding begs the question: what common denominators exist among anaesthetics that produce increased dementia risks?

One factor common to all anaesthesia types is supplemental oxygen used to sustain or raise arterial oxygen saturation levels as a 'safety hedge' during respiratory depressant drug use. During anaesthesia, arterial oxygen saturation data from pulse oximeters are proxies for tissue oxygen partial pressure values. Notably, normal ageing produces progressive decreases in oxygen saturation values[2] that do not require treatment, especially under circumstances where oxygen consumption is diminished by both age and anaesthetisation. Rather, when ventilation and tissue perfusion are maintained, mitochondrial oxygen consumption occurs at physiochemical rates determined by local respiratory complex reactions governed by mitochondrial oxygen partial pressure needs and adenosine triphosphate levels that cannot be increased through super-maximal oxygen tissue tensions. In fact, interference with normal cell signalling functions occurs when hyperoxia dominates the internal milieu. Herein resides one of the dangers of oxygen over-supplementation, especially relevant to dementia studies, given that tau hyperphosphorylation can occur in the presence of oxidative stress without anaesthesia.[3]

Anaesthesia is but one clinical circumstance where iatrogenic hyperoxia can 'trip' the pro-oxidant/antioxidant ratio switch at the subcellular and mitochondrial level towards excessive reactive oxygen and nitrogen species formation, but it is an important one. In the USA, in 2010, over 51 million in-patient surgical anaesthetisations occurred. This figure excludes out-patient procedures, so the total surgical anaesthesia hyperoxia exposure rate is even higher. Pro-oxidant conditions stemming from free-radical reactions cascading unchecked until squelched sufficiently by antioxidants are promoted by hyperoxia. In this manner, milieux under oxidative stress experience cell-signalling dysregulation, lipid membrane damage via peroxidation, protein nitrosylation, mitochondrial and nuclear DNA damage, intrinsic and extrinsic pro-apoptotic cascade activation, and increased susceptible cell population death. That such events have implications for neuro-degenerative diseases, including Alzheimer's disease,[4] make them important not to ignore.

Preliminary evidence suggests that anaesthesia-induced neuro-toxicity is mitigated in a limited animal model when the mitochondrial pro-oxidant/antioxidant balance is manipulated.[5] Although this finding may not apply to humans, it suggests that oxidative stress, to which hyperoxia contributes, acts synergistically with neuroexcitatory phenomena caused by *N*-methyl-D-aspartate antagonist and gamma-aminobutyric acid agonist drugs used to produce clinical anxiolysis, sedation and anaesthesia. Another oxidative stress synergism is surgery-induced inflammatory phenomena that augment anaesthetic and hyperoxic neurotoxic cascades. Given that oxidative-stress subcellular damage occurs via mechanisms that parallel radiation-induced damage, it is no surprise that delayed clinical dementia diagnoses occur. This may help explain the earlier onset and higher hazard ratios found in Chen *et al*'s study of older patients having surgical anaesthesia compared with controls. What remains certain is that hyperoxia-induced oxidative stress is preventable. Perhaps limiting supplemental oxygen to minimal amounts required to maintain age-appropriate arterial saturation levels is a protective strategy the ageing brain deserves during surgical anaesthesia.

1 Chen P-L, Yang C-W, Tseng, Y-K, Sun W-Z, Wang J-L, Wang S-J, et al. Risk of dementia after anaesthesia and surgery. *Br J Psychiatry* 2013; Jul 25, doi: 10.1192/bjp.bp.112.119610 (Epub ahead of print).

2 Wahba WM. Influence of aging on lung function: clinical significance of changes from age twenty. *Anesthes Analg* 1983; **62**: 764–76.

3 Melov S, Adlard PA, Morten K, Johnson F, Golden TR, Hinerfeld D, et al. Mitochondrial oxidative stress causes hyperphosphorylation of tau. *PloS One* 2007; **2**: e536.

4 Martin LJ. Mitochondrial and cell death mechanisms in neurodegenerative diseases. *Pharmaceuticals (Basel)* 2010; **3**: 839–915.

5 Boscolo A, Starr JA, Sanchez V, Lunadri N, DiGruccio MR, Ori C, et al. The abolishment of anaesthesia-induced cognitive impairment by timely protection of mitochondria in the developing rat brain: the importance of free oxygen radicals and mitochondrial integrity. *Neurobiol Dis* 2012; **45**: 1031–41.

Vincent J. Kopp, Department of Anesthesiology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, NC 27599-7010, USA. Email: vkopp@aims.unc.edu

doi: 10.1192/bjp.204.2.163

Authors' reply: We agree with Professor Kopp that hyperoxia during surgical anaesthesia might contribute to the higher risk of dementia following anaesthesia and surgery. Growing evidence has demonstrated that oxidative stress may augment the production and aggregation of amyloid-beta and facilitate the phosphorylation of tau. Evidence has suggested that oxidative stress is an important factor contributing to the initiation and progression of Alzheimer's disease.[1] Animal and human studies have also demonstrated increased oxidative stress following anaesthesia and surgery.[2,3] Furthermore, Kalimeris *et al* showed that propofol, which has antioxidant effects, seemed to improve cognitive performance after carotid endarterectomy, compared with sevoflurane.[4] Therefore, oxidative stress after anaesthesia and surgery might contribute to the hazard risk of dementia development. Although the exact mechanism of oxidative stress remains elusive, the perioperative events contributing to oxidative stress include ischaemia-reperfusion damage, surgical trauma,[2] and also iatrogenic hyperoxia during anaesthesia, as Professor Kopp elaborated. However, further studies need to be conducted to demonstrate the exact mechanism of oxidative stress due to anaesthesia and surgery in humans, and to demonstrate the effect of antioxidant agents to prevent the potential detrimental effect on cognitive function following anaesthesia and surgery.

1 Zhao Y, Zhao B. Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxid Med Cell Longev* 2013; **2013**: 316523.

2 Lee JY. Oxidative stress due to anesthesia and surgical trauma and comparison of the effects of propofol and thiopental in dogs. *J Vet Med Sci* 2012; **74**: 663–5.