

Correspondence

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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 values² 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, milieu 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 neurodegenerative diseases, including Alzheimer's disease,⁴ make them important not to ignore.

Preliminary evidence suggests that anaesthesia-induced neurotoxicity 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.

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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.

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- 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.

- 3 Yalcin S, Aydoğan H, Yuce HH, Kucuk A, Karahan MA, Vural M, et al. Effects of sevoflurane and desflurane on oxidative stress during general anesthesia for elective cesarean section. *Wien Klin Wochenschr* 2013; **125**: 467–73.
- 4 Kalimeris K, Kouni S, Kostopanagiou G, Nomikos T, Fragopoulou E, Kakisis J, et al. Cognitive function and oxidative stress after carotid endarterectomy: comparison of propofol to sevoflurane anesthesia. *J Cardiothorac Vasc Anesth* 2013; **27**: 1246–52.

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Physiotherapists can help implement physical activity programmes in clinical practice

We read with great interest the editorial by McNamee *et al.*¹ The authors made an important call for evidence-based physical activity research and interventions to reduce the physical health disparity seen in people with schizophrenia. Since this an area which is constantly evolving, we wanted to highlight some new evidence that is available that may assist clinicians and researchers to develop evidence-based physical activity interventions.

McNamee *et al.*¹ report some important barriers to physical activity uptake and maintenance. However, our understanding of the barriers to physical activity participation go beyond negative symptoms, side-effects of medication and social isolation.¹ Recent review evidence² incorporating 25 013 people with schizophrenia provides further indications of specific barriers which should be considered in this population. This comprehensive review² suggests that cardiometabolic comorbidity, lack of knowledge on cardiovascular disease risk factors, lower self-efficacy and other unhealthy lifestyle habits, including smoking, must be carefully considered as barriers when developing physical activity interventions for patients with schizophrenia.

We agree with McNamee *et al.*¹ that there is a high need for theoretically based research on the motivational processes linked to the commencement and continuation of physical activity in patients with schizophrenia. Research has recently started to meet this call. New evidence relying on the self-determination theory³ suggests that people with schizophrenia's level of autonomous motivation towards an active lifestyle (which involves the experience of volition and choice), feelings of competence and social relatedness may play an important role in the adoption and maintenance of physical activity.

We also agree with McNamee *et al.*¹ that it is essential that all members of the mental health multidisciplinary team (MDT) should promote and empower people with schizophrenia to engage in physical activity. The International Organization of Physical Therapists in Mental Health (IOPTMH)⁴ recently

emphasised that the mental health MDT's approach to the care of patients with schizophrenia should take this into account, at both policy-making and clinical levels. Without this crucial step the physical health of patients with schizophrenia is unlikely to be improved. The IOPTMH therefore endorses the editorial of McNamee *et al.*¹ that active physical health promotion must be routinely included in the care plans of people with schizophrenia and accepted as the responsibility of all healthcare staff. The IOPTMH is committed to supporting future research in this field and believes that physiotherapists are well placed to lead the translation of physical activity in clinical practice,⁵ which McNamee *et al.*¹ called for. Future research is required and this should, for example, define which strategies mental health physiotherapists should adopt in order to assist persons with schizophrenia in the transition from hospital to community care.^{4,5} Together with McNamee *et al.*¹ we are convinced that this is essential in order to ensure that physical activity is successfully used to significantly improve the physical health and health-related quality of life of people with schizophrenia.

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Corrections

Highlights of this issue. *BJP*, 204, A3: was written by Sukhwinder S. Shergill. The online version has been corrected post-publication, in deviation from print, and in accordance with this correction.

Skype and narcissistic disturbances: a unique opportunity (letter)? *BJP*, 204, 79. In the third paragraph, lines 2 and 6: the surname of the author discussed is Kohut.

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