Climbing the delirium mountain: is alpine anaesthesia the perioperative cause?

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Delirium is an often unrecognized but common event after surgery and is associated with poor cognitive outcomes, prolonged hospitalization, and increased mortality.1–3 The absence of therapies for postoperative delirium is probably related to our incomplete understanding of the underlying pathophysiology. At present, delirium appears as an unassailable perioperative mountain, one that we will never conquer. Some perioperative risk factors for postoperative delirium have been identified, including benzodiazepine exposure,4 anaesthetic depth,5 blood loss,6 and anaemia.7 The role of intraoperative haemodynamics remains obscure; hypotension has been considered important for the development of delirium, but studies have produced discordant results.7,9,10 In this issue of the BJA, Hirsch and colleagues11 attempt to delineate the role of intraoperative hypotension and blood pressure variability (‘alpine anaesthesia’) in the pathogenesis of postoperative delirium. Using multivariate analysis, these authors show that intraoperative blood pressure variability is an important risk factor for postoperative delirium, leading to the question: would reducing ‘alpine anaesthesia’ make the delirium mountain easier to conquer?

Hirsch and colleagues15 conducted a prospective cohort study of 594 subjects undergoing non-cardiac surgery with perioperative cognitive and delirium assessments. Haemodynamic data were largely abstracted after surgery from a paper record (in 91%). Despite several sensitivity analyses, relative and absolute intraoperative hypotension were not associated with delirium. This lack of effect may relate to statistical power, because a larger recent study in 33 330 non-cardiac surgical patients identified a mean arterial pressure of <55 mm Hg to be associated with increased risk of perioperative acute kidney injury, myocardial injury, or both.11,12 Hirsch and colleagues15 did demonstrate that intraoperative blood pressure fluctuations were associated with postoperative delirium after adjusting for confounders, suggesting that repeated blood pressure fluctuations, rather than mean blood pressure values, predispose to delirium. Blood pressure variability has been shown to be harmful in the perioperative period; increased mortality after cardiac surgery has been associated with increased duration and amplitude of change in perioperative systolic blood pressure.13 Another recent study published in the BJA demonstrated that mean arterial pressure during cardiopulmonary bypass above the upper limit of cerebral autoregulation is associated with delirium,14 implying that hyperperfusion provokes subsequent delirium. These findings will need further confirmation but may indicate the need for cerebral autoregulation assessments in vulnerable individuals. Understandably, the study by Hirsch and colleagues11 did not include measurements of cerebral autoregulation; however, they did observe higher intraoperative systolic blood pressure values in patients with subsequent delirium. While Hirsch and colleagues11 provided novel evidence that repeated fluctuation in blood pressure is an important risk factor for postoperative delirium, these associations do not imply causality. It is unclear whether blood pressure variability is a marker or a mediator of perioperative complications, because dysfunctional autoregulation and vascular disease, which predispose to blood pressure variability, predispose to end-organ disease in a wide range of clinical settings. Whether blood pressure variability reflects a chronic predisposition to delirium or is an acute precipitant that causes delirium is unclear.

Cerebral autoregulation alters vascular resistance to maintain constant cerebral blood flow despite changing perfusion pressure.15 This neuroprotective phenomenon prevents decreased cerebral blood flow during periods of hypotension and cerebral oedema during periods of increased cerebral blood flow, such as hypoxia16 or acidaemia.17 Recent studies using near-infrared spectroscopy demonstrated that a wide range of mean arterial pressure permits adequate cerebral oxygenation, but inter-individual variability is high.18 The autoregulatory range is decreased and blood flow more pressure dependent in patients with vascular disease. Patients with vascular risk factors are
at increased risk of postoperative delirium, hence deficient preoperative cerebral autoregulation may predispose to postoperative delirium. Blood pressure fluctuations may be important because of the dynamic nature and the regional and temporal heterogeneity of cerebral autoregulation; the contrasts in hypoperfusion and hyperperfusion may be critical. Several questions remain unanswered. What is the relative importance of cerebral over- or underperfusion and the consequences leading to postoperative delirium? Does ischaemia drive acute changes in key neurotransmitters, such as acetylcholine or other neurotransmitters, in the perioperative period? Future studies investigating these aetiological factors and brain regions affected during blood pressure fluctuations may provide critical insight into the pathogenesis of postoperative delirium.

It is also prudent to consider the null hypothesis; intraoperative blood pressure variability does not causally drive postoperative delirium, but rather is a sign of predisposition toward postoperative delirium. Hirsch and colleagues aptly point out that the associations of intraoperative blood pressure variability and postoperative delirium could be confounded by the type of surgery or anaesthetic care. However, it is equally plausible that differences in patients, such as those with pre-existent vascular or autonomic disease, predispose to both haemodynamic instability and postoperative delirium. The authors attempt to control these confounders, but given the limited sample size and observational nature of the research, residual bias may still be present.

In the community, blood pressure variability affects a range of outcomes, including cognition. Visit-to-visit blood pressure variability is associated with cognitive outcomes such as dementia, stroke, and mild cognitive decline. Blood pressure variability also predicts insult, because it was found to predict cognitive recovery after lacunar stroke. The variability might arise from autonomic dysfunction, small vessel atherosclerotic disease, or brain ischaemia, among other causes, with contributions from perioperative pharmacology. β-Blockers with low cardioselectivity are poor at preventing systolic blood pressure variations and may contribute to adverse perioperative neurological outcomes. Regardless, the relationship between blood pressure variability and cognitive outcomes is striking. Future studies must address the relationship between preoperative visit-to-visit blood pressure variability and intraoperative blood pressure variability. It is plausible that these observations will be linked. Randomized controlled trials of intraoperative blood pressure control with simultaneous cerebral autoregulatory measurement may be required to establish a causal relationship between haemodynamic variability and postoperative delirium. Given the findings by Hirsch and colleagues, we predict that intraoperative and visit-to-visit blood pressure variability may well be correlated; any relationship with postoperative delirium will need to be addressed through additional cohort studies.

Assuming that the hypothesis posed by Hirsch and colleagues is correct, are there current interventions to reduce blood pressure variability and improve neurological outcomes after surgery? Calcium channel blockers reduce visit-to-visit blood pressure variability in the community and in cardiac surgery. When compared with atenolol (which exerts less effect on blood pressure variability), amlopidine treatment decreases the incidence of stroke; but limited data support perioperative calcium channel blocker use. Further studies of perioperative β-blocker and calcium channel antagonist therapy and haemodynamic variability are required. Other approaches to blunt variability, such as clonidine or remifentanil, may also be tested. However, if intraoperative blood pressure fluctuations merely reflect the combination of preoperative haemodynamic variability and associated end-organ damage, we can expect limited benefit.

Overall, the findings by Hirsch and colleagues have unveiled another risk factor for postoperative delirium, namely intraoperative blood pressure variability. However, it is unclear whether there is a causal association between ‘alpine anaesthesia’ and cognitive outcomes. Moreover, we do not yet understand the relationship between preoperative visit-to-visit blood pressure variability and intraoperative blood pressure variability. Intervventional trials targeting a reduction in intraoperative blood pressure variability within autoregulatory thresholds may provide insight into the mechanisms of postoperative delirium. Despite the need for greater evidence, attempts to avoid ‘alpine anaesthesia’ and hypotension remain logical and indicated. Whether interventions to control haemodynamic changes will lead to improved perioperative outcomes needs further research.

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The elusive promise of perioperative hyperoxia

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Arguably, no sphere of contemporary anaesthesia outcomes research has generated more controversy than the question of whether perioperative administration of supplemental oxygen can reduce surgical site infection (SSI). The public health importance of addressing the issue is clear; epidemiological surveys from both England1 and the USA2 show that SSI increases length of stay by ~10 days in colorectal surgery and is associated with substantial excess mortality and cost of care.3 The first randomized controlled trial, published by Greif and colleagues4 in the New England Journal of Medicine in 2000, presented the exciting possibility that a simple perioperative intervention under the control of anaesthetists—delivering 80% oxygen during surgery and for 2 h afterwards—could reduce the incidence of SSI by as much as half. But subsequent attempts to replicate the benefit, including three high-profile randomized controlled trials published in JAMA,5–7 have yielded markedly inconsistent results. Indeed, even meta-analyses of the pooled data are unable to achieve consensus8–12 and have elicited controversy. Studies of other surgeries, including Caesarean section,11,12 have been mostly negative, while secondary analyses have reported