3 days of storage, indicating increased haemolysis,\(^3\) and infusion of 40-day packed erythrocytes was recently suggested to lead to increased NO production from endothelial NOS, as a compensatory mechanism for reduced NO bioavailability caused by plasma oxyhaemoglobin scavenging of NO.\(^1\) However, although leucoreduced units of packed red blood cells contain fewer than \(5 \times 10^{-6}\) white blood cells, it should be noted that neutrophils, which undergo spontaneous cell death, constitutively express large amounts of arginase\(^4\) and even small contamination of packed red cell bags by neutrophils might, therefore, produce significant levels of arginase activity, apart from that derived from the red cells themselves. Recently, we found raised levels of free arginase in blood stored for long periods, which could corroborate these arguments and have implications for patients in whom immunosuppression is a major challenge.\(^5\)

Thus, we suggest that increased haemolysis might be an important aspect in blood transfusion, leading to elevated levels of arginase and NOS, and, thereby, to \(L\)-arginine depletion that could eventually affect immune function and cancer progression.

**Declaration of interest**

None declared.

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**Reply from the author**

Editor—I have to thank Palomero-Rodríguez and colleagues for their important contribution to this topic as raised in our review.\(^1\) Certainly, \(L\)-arginine and arginase I and II are important modulators of the immune response after blood transfusion. No less important is the evidence provided by several investigators suggesting that a deficiency of \(L\)-arginine also occurs as part of the stress response to surgery and this deficiency has been implicated as one of the mechanisms behind the known shift from a Th1 to a Th2 response after surgery.\(^2\)

This phenomenon may even have been worsened by the transfusion of mainly ‘old’ blood which would further deplete levels of \(L\)-arginine. Perhaps, a more relevant question to answer in the clinical setting is whether the administration of \(L\)-arginine in the context of perioperative immune-nutrition could ameliorate immunosuppression and perhaps improve long-term oncological outcomes in patients in whom blood transfusion cannot be avoided and undergo major surgery.\(^3\)

**Declaration of interest**

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**Factors for perioperative delirium**

Editor—I read with interest the paper by Radtke and colleagues,\(^1\) addressing the important issue of anaesthetic depth and its relationship with postoperative delirium. Any measure which may ameliorate delirium warrants attention, given the personal cost to the patient and patient’s family along with the financial strain that postoperative delirium carries with it for the healthcare system.

I do, however, kindly request clarification regarding two methodological issues with the paper that may affect interpretation of the results presented: (i) benzodiazepine administration and (ii) intraoperative hypotension.

First, perioperative benzodiazepine use is associated with emergence delirium based on earlier work by Radtke and colleagues; in a prospective observational study examining over 1800 patients, those receiving a benzodiazepine as premedication were 2.39 times (95% confidence interval 1.01–5.62) more likely to experience emergence delirium than patients who were not administered a benzodiazepine.\(^2\) According to the methods used in the current study, ‘in case a sedative premedication is needed midazolam is prescribed in a dosage of 0.1 mg per kg’.\(^3\) Given their conclusion that ‘intraoperative neuromonitoring is associated with a lower incidence of delirium’, and in an effort to contextualize their findings with the
methodology described, it would be helpful to have answers to the following questions: (i) How many patients (according to treatment group) received midazolam? (ii) What doses (range and mean) were administered to those patients receiving midazolam?

Secondly, an increasing body of literature highlights an association between intraoperative hypotension and several undesirable perioperative outcomes, including neurological sequelae, such as delirium. With this in mind, would the authors be able to comment on the: (i) definitions of intraoperative hypotension used; (ii) incidence of intraoperative hypotension between treatment groups; and (iii) clinical management of intraoperative hypotension used?

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None declared.

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Perioperative non-invasive estimation of left ventricular elastance (Ees) is no longer a challenge; it is a reality

Editor—We read with great interest the recent article ‘Minimally invasive intraoperative estimation of left-ventricular end-systolic elastance with phenylephrine as loading intervention’ by Boly and colleagues published in BJA. We appreciate the message that the anaesthetist should not rely only on an arterial pressure and heart rate when managing haemodynamic instability, but needs to think in terms of myocardial performance. However, in our opinion, the study raises several concerns.

We are unsure why an interventional or invasive procedure such as administering phenylephrine or clamping the inferior vena cava (IVC) is necessary in high-risk patients since several techniques are available to determine Ees noninvasively. We have, in the past, measured Ees by changing the loading conditions pharmacologically, but have moved to a completely non-invasive method. Moreover, measuring Ees alone, although important, does not provide the full potential of such pathophysiological approach. In fact, measuring Ees in combination with arterial elastance (Ea) offers the opportunity to calculate ventriculo-arterial (VA) coupling, which is a measure of cardiovascular energetic efficiency.

In our experience, these measurements have changed our practice of administering drugs active on the heart and vessels both in the intensive care unit and theatre, introducing a more physiological way of targeting the haemodynamic derangements. We agree with Dr Boly and colleagues that going back to pathophysiology helps to better understand haemodynamics in altered cardiovascular states.

Therefore, as non-invasive single-beat measurement of Ees, Ea, and VA coupling is already feasible and safe in the critically ill setting, we advocate that further efforts should concentrate on implementing ways to continuously and non-invasively determine these entities in a real-time fashion.

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