activity. In particular, the identification of abrupt slow-wave emergence trajectories in some individuals indicates a higher resistance to brain state changes on emergence, *i.e.,* these individuals have a higher degree of neural inertia. This quite marked interindividual hysteresis is lost unless within-subject analyses are performed as we have done. Furthermore, our categorization of abrupt (rather than graded) emergence trajectories takes into account three factors: the electroencephalographic brain state, behavioral state, and hypnotic drug concentrations. While we acknowledge that the use of population-based propofol effect concentrations is a minor limitation, these abrupt trajectories were also identified in the clinical studies using the more accurate measurement of end-tidal volatile agent concentrations.

We believe our findings provide additional support to Kelz and coworkers' hypothesis that a neural effect contributes to anesthetic hysteresis, further highlighting that this is not purely a pharmacokinetic issue. Based on our findings, we proposed a more general definition of neural inertia as "a tendency of the central nervous system to resist transitions between conscious and unconscious states" in the article's Discussion. This allows for inclusion of different brain state transitions, as inferred by electroencephalographic methods, functional brain imaging, and/or behavior. While Colin *et al.* have tended to focus on pharmacokinetic mechanisms and behavioral read-outs, the shortcomings of which for assessing true neural inertia are elegantly detailed by Proekt and Kelz,[4] we suggest our systems-level approach is more suitable and indicates that both disruption of neuronal function and impairment of neural network dynamics play a key role in neural inertia.

## Competing Interests

Dr. Warnaby and Irene Tracey were listed as inventors on patent applications filed by Oxford University Innovation, the technology transfer company of the University of Oxford (Oxford, United Kingdom; formerly Isis Innovation) on perception loss detection using slow-wave activity saturation. The remaining author declares no competing interests.

**Catherine E. Warnaby, Ph.D., Jamie W. Sleigh, M.D., Irene Tracey, M.A. (Oxon), D.Phil., F.R.C.A., F.Med.Sci.**
University of Oxford, Oxford, United Kingdom (C.E.W.).
katie.warnaby@ndcn.ox.ac.uk

## References

1. Warnaby CE, Sleigh JW, Hight D, Jbabdi S, Tracey I: Investigation of slow-wave activity saturation during surgical anesthesia reveals a signature of neural inertia in humans. Anesthesiology 2017; 127:645–57
2. Ni Mhuircheartaigh R, Warnaby C, Rogers R, Jbabdi S, Tracey I: Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. Sci Transl Med 2013; 5:208ra148
3. Whitham EM, Pope KJ, Fitzgibbon SP, Lewis T, Clark CR, Loveless S, Broberg M, Wallace A, DeLosAngeles D, Lillie P, Hardy A, Fronsko R, Pulbrook A, Willoughby JO: Scalp electrical recording during paralysis: Quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. Clin Neurophysiol 2007; 118:1877–88
4. Proekt A, Kelz M: Schrödinger's cat: Anaesthetised and not! Br J Anaesth 2018; 120:424–8
5. Friedman EB, Sun Y, Moore JT, Hung HT, Meng QC, Perera P, Joiner WJ, Thomas SA, Eckenhoff RG, Sehgal A, Kelz MB: A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: Evidence for neural inertia. PLoS One 2010; 5:e11903
6. Kuizenga MH, Colin PJ, Reyntjens KMEM, Touw DJ, Nalbat H, Knotnerus FH, Vereecke HEM, Struys MMRF: Test of neural inertia in humans during general anaesthesia. Br J Anaesth 2018; 120:525–36

*(Accepted for publication May 7, 2018.)*

# Risks of Impaired Organ Protection with Inhibiting Transient Receptor Potential Vanilloid 1

*To the Editor:*

With great interest we recently read the manuscript by Garami *et al.*,[1] which illustrates how the transient receptor potential vanilloid 1 antagonists, AMG 517 and ABT-102, prevent anesthesia-induced hypothermia and simultaneously decrease opioid requirements for postoperative hyperalgesia in rodents. These preclinical data suggest that transient receptor potential vanilloid 1 antagonists may be useful as opioid-sparing modalities for analgesia intraoperatively and postoperatively while also providing hyperthermia to pharmacologically counteract anesthetic-induced hypothermia. This finding is novel and may lead the way to developing new opioid-sparing drugs to be used perioperatively. However, it would be of benefit if the authors may comment on some of the potential shortcomings we see of using transient receptor potential vanilloid 1 antagonists during surgery and the potential strategies to overcome these barriers we outline below.

For example, intravenous administration of transient receptor potential vanilloid 1 antagonists may also block endogenous mechanisms of organ protection. It is important to recognize that untreated transient receptor potential vanilloid 1 knockout mice or mice treated with a transient receptor potential vanilloid 1 inhibitor subjected to ischemia-reperfusion injury using an isolated heart model produce impaired functional recovery compared to wild-type transient receptor potential vanilloid 1 mice.[2] Further, in a deoxycorticosterone acetate–salt hypertension model, ablation of transient receptor potential vanilloid 1 gene in the C57BL/6 mice exacerbates renal damage compared to deoxycorticosterone acetate–salt-treated wild-type mice, indicating that transient receptor potential vanilloid 1 may constitute a protective mechanism against end-organ damage induced by hypertension.[3] Additionally, transient receptor potential vanilloid 1 channel activation reduces organ

injury for the lung,[4] kidney,[5] and brain.[6] Furthermore, transient receptor potential vanilloid 1 antagonists may interfere with the agents or interventions administered perioperatively that may decrease organ injury, such as a surgical incision or opioids that appear to provide their protective effect by a transient receptor potential vanilloid 1–dependent mechanism.[7] Therefore, using transient receptor potential vanilloid 1 antagonists for surgeries undergoing organ reperfusion injury or in a patient population with cardiovascular disease who are at higher risk of having an intraoperative myocardial infarction may possibly cause an unwanted side effect of exacerbating organ injury during ischemia-reperfusion or block the abilities for agents we commonly administer in the operating room to limit cellular injury.

Hypothermia induced by transient receptor potential vanilloid 1 activation is also considered as a promising intervention for organ protection. Rinvanil, a transient receptor potential vanilloid 1 agonist, induces mild hypothermia (33°C), which is associated with 34% smaller cerebral infarct size volumes in mice subjected to transient middle cerebral artery occlusion *versus* vehicle-treated controls.[5] Thus, drugs specifically inhibiting transient receptor potential vanilloid 1 may interrupt the benefits of hypothermia associated with organ protection.

In conclusion, it is important to consider whether blocking transient receptor potential vanilloid 1 to reduce opioid requirements or raise body temperature may have some unknown risks.

## Research Support

Funded by National Institutes of Health, Bethesda, Maryland, grant Nos. HL109212 and GM119522 (to Dr. Gross), the Priority Department of Second Affiliated Hospital of Anhui Medical University, Hefei, China (to Dr. Wu), and the China Scholarship Council (201608535052; to Dr. Qian).

## Competing Interests

Dr. Gross holds a U.S. patent titled "Peptide Modulators of Specific Calcineurin Protein–Protein Interactions." The other authors declare no competing interests.

**Yu Wu, M.D., Eric R. Gross, M.D., Ph.D., Jinqiao Qian, M.D., Ph.D.** Stanford University, Stanford, California, and the First Affiliated Hospital of Kunming Medical University, Kunming, China (J.Q.). qianjinqiao@126.com

## References

1. Garami A, Ibrahim M, Gilbraith K, Khanna R, Pakai E, Miko A, Pinter E, Romanovsky AA, Porreca F, Patwardhan AM: Transient receptor potential vanilloid 1 antagonists prevent anesthesia-induced hypothermia and decrease postincisional opioid dose requirements in rodents. Anesthesiology 2017; 127:813–23
2. Wang L, Wang DH: TRPV1 gene knockout impairs postischemic recovery in isolated perfused heart in mice. Circulation 2005; 112:3617–23
3. Wang Y, Babánková D, Huang J, Swain GM, Wang DH: Deletion of transient receptor potential vanilloid type 1 receptors exaggerates renal damage in deoxycorticosterone acetate-salt hypertension. Hypertension 2008; 52:264–70
4. Wang M, Ji P, Wang R, Zhao L, Xia Z: TRPV1 agonist capsaicin attenuates lung ischemia-reperfusion injury in rabbits. J Surg Res 2012; 173:153–60
5. Chen L, Markó L, Kaßmann M, Zhu Y, Wu K, Gollasch M: Role of TRPV1 channels in ischemia/reperfusion-induced acute kidney injury. PLoS One 2014; 9:e109842
6. Muzzi M, Felici R, Cavone L, Gerace E, Minassi A, Appendino G, Moroni F, Chiarugi A: Ischemic neuroprotection by TRPV1 receptor-induced hypothermia. J Cereb Blood Flow Metab 2012; 32:978–82
7. Heymann HM, Wu Y, Lu Y, Qvit N, Gross GJ, Gross ER: Transient receptor potential vanilloid 1 inhibitors block laparotomy- and opioid-induced infarct size reduction in rats. Br J Pharmacol 2017; 174:4826–35

*(Accepted for publication May 8, 2018.)*

*In Reply:*

We thank Wu *et al.* for their thoughtful comments on our article, in which we proposed the novel concept of intraoperative use of transient receptor potential vanilloid 1 antagonists as a pharmacologic therapy for anesthesia-induced hypothermia.[1] Wu *et al.* point out that as transient receptor potential vanilloid 1 may play a critical role in ischemia-reperfusion injury, perioperative blockade of transient receptor potential vanilloid 1 might have deleterious consequences. We believe this may not be a significant concern regarding our proposed use of intraoperative transient receptor potential vanilloid 1 antagonists for several reasons.

First, we are proposing the possibility of the use of transient receptor potential vanilloid 1 antagonists to "prevent" anesthesia-induced hypothermia to ensure normothermia, not to cause hyperthermia. Our data in preclinical models support this outcome. We realize that there are specific surgical cases where hypothermia may be beneficial (*e.g.*, cardiac arrest). In these circumstances, transient receptor potential vanilloid 1 antagonists would simply be avoided as maintaining normothermia is not the desired medical outcome.

Second, whether hypothermia is beneficial as a protection strategy for organs such as the brain remains uncertain.[2,3] Current guidelines recommend maintenance of normothermia in most surgical cases given the preponderance of evidence in favor of normothermia.[4,5]

Third, the overall effect of transient receptor potential vanilloid 1 antagonism on various organ systems is likely complex and dependent on the particular preclinical model being studied. For example, while the articles cited by Wu *et al.* demonstrate a protective role of transient receptor potential vanilloid 1 agonism in postischemic recovery, others have shown that transient receptor potential vanilloid 1 antagonism may have protective role in ischemia-reperfusion in cardiac myocytes[6] and in the brain,[7] as well as in models of hemorrhagic shock, cardiac hypertrophy,[8,9] and lung injury.[10] These differences could be secondary to the relative lack of specificity of the antagonist studied (*i.e.*, capsazepine) or unknown compensation in the global knockout phenotype. Notably, in our studies, we observed increased anesthesia-induced hypothermia in transient receptor potential vanilloid 1 knockout mice, and capsazepine had only modest efficacy in preventing