

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.

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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

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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 myocytes⁶ 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

anesthesia-induced hypothermia (Patwardhan *et al.*, unpublished data). As is the case with any drug development, potential adverse effects on organ function can be monitored during clinical testing. Initial studies would be done in patients who are otherwise relatively young and healthy; later studies would be done in specific “at-risk” populations with careful monitoring.

Finally, preclinical literature has suggested a role for transient receptor potential vanilloid 1 in numerous, diverse biologic processes such as immune modulation, renal injury, anxiety, dementia, cognitive function, pancreatic function, airway reactivity, pulmonary hypertension, and gastrointestinal transit, to name a few. Anticipation of all possible side effects of transient receptor potential vanilloid 1 antagonism is not possible. Like all pharmacologic therapies, risks will have to be weighed against benefits in specific patient populations and with use in specific circumstances. Importantly, however, multiple transient receptor potential vanilloid 1 antagonists have been advanced past phase I safety studies and evaluated further in clinical settings where the only reported outcomes were analgesia, decreased thermal sensation that is not a problem in the intraoperative setting, and hyperthermia. We look forward to clinical evaluation of transient receptor potential vanilloid 1 antagonists for perioperative use.

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Competing Interests

Drs. Patwardhan and Porreca declare a financial interest in Catalina Pharmaceuticals Inc. (Tucson, Arizona), which licenses the intellectual property involved in this research. This interest has been properly disclosed to the University of Arizona Institutional Review Committee, Tucson, Arizona, and is managed in accordance with its conflict of interest policies. Drs. Patwardhan, Porreca, and Romanovsky are founders of Catalina Pharmaceuticals Inc. and hold a provisional patent for the use of transient receptor potential vanilloid 1 antagonists in prevention of anesthesia-induced hypothermia. Dr. Romanovsky has consulted for Abbott Laboratories (Chicago, Illinois), AbbVie (Chicago, Illinois), Amgen Inc. (Thousand Oaks, California), Japan Tobacco Inc. (Tokyo, Japan), Teva Pharmaceutical Industries Ltd. (Petah Tikva, Israel), and other pharmaceutical companies, and his research has been supported by Abbott Laboratories, AbbVie, and Amgen Inc. The other authors declare no competing interests.

Andras Garami, M.D., Ph.D., Mohab Ibrahim, M.D., Ph.D., Kerry Gilbraith, B.S., Rajesh Khanna, Ph.D., Eszter Pakai, M.S., Alexandra Miko, M.D., Erika Pinter, M.D., Ph.D., D.Sc., Andrej A. Romanovsky, M.D., Ph.D., Frank Porreca, Ph.D., Amol M. Patwardhan, M.D., Ph.D. University of Arizona, Tucson, Arizona (A.M.P.). apatwardhan@anesth.arizona.edu

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Postoperative Analgesia after Shoulder Surgery

To the Editor:

Dr. Hussain *et al.* have recently published a review and meta-analysis on suprascapular and interscalene nerve blocks for shoulder surgery.¹ The primary objective of the study was to compare postoperative analgesic efficacy between the interscalene nerve block and the suprascapular nerve block. We would like to comment on this very interesting research question.

It is well accepted that the shoulder joint is mainly innervated by the suprascapular and the axillary nerve, but receives contributions from the subscapular and the lateral pectoral nerves.^{2–4} Two nerves provide the cutaneous innervation of