Published in final edited form as:

Anesthesiology. 2016 May ; 124(5): 986–988. doi:10.1097/ALN.0000000000001047.

A slick way volatile anesthetics reduce myocardial injury

Nana-Maria Wagner, MD¹, Eric R. Gross, MD, PhD¹, and Hemal H. Patel, PhD^{2,3}

¹Department of Anesthesiology, Perioperative and Pain Medicine, School of Medicine, Stanford University, Stanford, CA 94305

²VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161

³Department of Anesthesiology, University of California, San Diego, La Jolla, CA 92093

Keywords

anesthetic preconditioning; cardioprotection; mitochondria; BK channels; Slo gene; ischemia reperfusion injury

In 2007, the ACC/AHA guidelines first recommended perioperative volatile anesthetic use in patients at risk for myocardial ischemia.¹ Numerous animal studies from canines to nematodes provided evidence for volatile anesthetic protection against myocardial ischemia-reperfusion injury.^{2,3} Several clinical trials conducted in patients undergoing coronary artery bypass grafting suggested the experimental study results translated into clinically relevant cardioprotection.⁴ However, almost a decade later, the primary molecular mechanisms mediating volatile anesthetic-induced cardioprotection still remain to be identified. In this month's issue of *Anesthesiology*, Wojtovich et al. aim to provide novel insight into this limitation by deciphering the identity of a cardiac myocyte mitochondrial potassium channel that mediates volatile anesthetic-induced preconditioning. Using a genetic knock-out approach in mice, the authors identify the *Slo2* gene family encoded potassium channel subtype Slo2.1 in cardiac myocyte mitochondria as a key determinant of volatile anesthetic-induced preconditioning from myocardial ischemia reperfusion injury.⁵

Both Slo2.1 (Kcnt2/'Slick') and Slo2.2 (Kcnt1/'Slack') are potassium channels activated by elevated intracellular sodium levels and belong to the "big" conductance K⁺ channel (BK) family. The newly identified localization of Slick in cardiac myocyte mitochondria may add another piece to the puzzle of mitochondrial ion channels apparently involved in the complex response of cardiomyocytes to ischemia-reperfusion injury, including the mitochondrial ATP-sensitive K⁺ channel (mK_{ATP}), the mitochondrial permeability transitional pore (mPTP), and other BK channels that are long recognized in mediating volatile anesthetic-induced preconditioning via regulation of mitochondrial function.⁶ While initial reports suggested a Ca²⁺ activated BK channel (likely Slo1) was responsible for anesthetic preconditioning,^{7–9} the fact that Slo1^{−/−} mice can still be preconditioned by

Correspondence: Hemal H. Patel, PhD, University of California, San Diego, VA Medical Center, San Diego (125), 3350 La Jolla Village Drive, San Diego, CA 92161-5085, Phone: (858) 552-8585, FAX (858) 534-0104, hepatel@ucsd.edu.

No conflicts of interest.

isoflurane,¹⁰ coupled with the results of Wojtovich et al., suggest re-evaluation of these early findings.

In their present study, Wojtovich report for the first time evidence that volatile anesthetic-induced K⁺ flux is abolished in cardiac myocyte mitochondria isolated from mice lacking Slick (Slo2.1^{-/-}). Subsequently, isoflurane-induced preconditioning effects were absent in Slo2.1^{-/-} but not Slo2.2^{-/-} mice subjected to myocardial ischemia and reperfusion injury. By demonstrating Slo2.1 mediated protective effects of volatile anesthetics that are independent of ischemia or pharmacological K⁺ channel openers, the authors provide specificity for a novel molecular target for volatile anesthetic specific effects.

Thus, in the era of precision medicine, this study may provide us with more extensive knowledge to which patients undergoing cardiac surgery will benefit from receiving volatile anesthetics to reduce ischemia-reperfusion injury. The recommendations of the 2007 ACC/AHA guidelines have been continuously modified to downplay the powerful effects volatile anesthetics have in reducing myocardial injury in pre-clinical models. In 2011, the recommendations for patients undergoing coronary artery bypass graft surgery were changed to only recommend use of volatile anesthetics to facilitate extubation in cardiac patients.¹¹ Further, the 2014 guidelines for patients undergoing non-cardiac surgery recommend similarly the use of either volatile or intravenous agents.¹² Primary endpoints such as a reduction in postoperative troponin levels or improved cardiac function were often met only in elective and highly selective cardiac patient populations⁴ and remained non-evident or controversial in patient populations undergoing non-cardiac surgery.^{13,14} Numerous reasons may explain the clear lack of translation from experimental models to heterogeneous patient populations. Conditions such as diabetes likely attenuate the ability to precondition the myocardium and medications such as K_{ATP} channel inhibitors, used clinically to manage diabetes, may further block the effects of volatile anesthetics.¹⁴ Intravenous agents including opioids may also synergistically act with volatile anesthetics to reduce myocardial injury.¹⁵

Advances in patient care are urgently needed to reduce perioperative myocardial reperfusion injury. Numerous preclinical studies provide a wealth of promising data on how volatile anesthetics or strategies like remote ischemic preconditioning effectively exert myocardial protection. Although the latter involves different mechanisms and requires additional molecular mediators,¹⁶ recently published results from two large studies show remote ischemic conditioning strategies fail in providing benefit to patients.^{17,18} These data add to the litany of agents and interventions proposed to limit reperfusion injury that have failed in the clinic, including even cyclosporine A.¹⁹ The controversial data from clinical trials however must bring us back to better understand underlying molecular and cellular mechanisms in the basic science laboratory. Technology is moving in the direction where one day there may be a “preconditioning gene panel” that is run on every patient preoperatively to customize choice of anesthetic regimen for surgery. Candidate genes specific to volatile anesthetics, as that identified in the current manuscript, move us one step closer to identifying novel mechanisms to address the shortcomings of failed clinical translation.

References

1. Fleisher LA, Beckman JA, Yancy CW. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2007; 116:e418–99. [PubMed: 17901357]
2. Toller WG, Gross ER, Kersten JR, Pagel PS, Gross GJ, Warltier DC. Sarcolemmal and mitochondrial adenosine triphosphate- dependent potassium channels: mechanism of desflurane-induced cardioprotection. *Anesthesiology*. 2000; 92:1731–9. [PubMed: 10839925]
3. van Swinderen B, Galifianakis A, Crowder M. Common genetic determinants of halothane and isoflurane potencies in *Caenorhabditis elegans*. *Anesthesiology*. 1998; 89:1509–17. [PubMed: 9856727]
4. De Hert SG. Cardioprotection in anesthesia. *Minerva Anesthesiol*. 2008; 74:259–70. [PubMed: 18500198]
5. Wojtovich APSC, Urciuoli WR, Xia X-M, Brookes PS, Nehrke K. Cardiac Slo2.1 is required for volatile anesthetic stimulation of K⁺ transport and anesthetic preconditioning. *Anesthesiology*. 2015; XX:XXX–XXX.
6. Agarwal B, Stowe DF, Dash RK, Bosnjak ZJ, Camara AK. Mitochondrial targets for volatile anesthetics against cardiac ischemia-reperfusion injury. *Front Physiol*. 2014; 5:341. [PubMed: 25278902]
7. Bentzen BH, Osadchii O, Jespersen T, Hansen RS, Olesen SP, Grunnet M. Activation of big conductance Ca(2+)-activated K⁺ channels (BK) protects the heart against ischemia-reperfusion injury. *Pflugers Arch*. 2009; 457:979–88. [PubMed: 18762970]
8. Redel A, Lange M, Jazbutyte V, Lotz C, Smul TM, Roewer N, Kehl F. Activation of mitochondrial large-conductance calcium-activated K⁺ channels via protein kinase A mediates desflurane-induced preconditioning. *Anesth Analg*. 2008; 106:384–91. table of contents. [PubMed: 18227289]
9. Xu W, Liu Y, Wang S, McDonald T, Van Eyk JE, Sidor A, O'Rourke B. Cytoprotective role of Ca²⁺-activated K⁺ channels in the cardiac inner mitochondrial membrane. *Science*. 2002; 298:1029–33. [PubMed: 12411707]
10. Wojtovich AP, Sherman TA, Nadtochiy SM, Urciuoli WR, Brookes PS, Nehrke K. SLO-2 is cytoprotective and contributes to mitochondrial potassium transport. *PLoS One*. 2011; 6:e28287. [PubMed: 22145034]
11. Hillis LD, Smith PK, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011; 124:e652–735. [PubMed: 22064599]
12. Fleisher LA, Fleischmann KE, Wijeysundera DN. 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: Executive Summary. *Journal of the American College of Cardiology*. 2014; 64:2373–405.
13. Lindholm EE, Aune E, Noren CB, Seljeflot I, Hayes T, Otterstad JE, Kirkeboen KA. The anesthesia in abdominal aortic surgery (ABSENT) study: a prospective, randomized, controlled trial comparing troponin T release with fentanyl-sevoflurane and propofol-remifentanyl anesthesia in major vascular surgery. *Anesthesiology*. 2013; 119:802–12. [PubMed: 23838709]
14. Zaugg M, Lucchinetti E, Behmanesh S, Clanachan AS. Anesthetic cardioprotection in clinical practice from proof-of-concept to clinical applications. *Curr Pharm Des*. 2014; 20:5706–26. [PubMed: 24502570]
15. Ludwig LM, Patel HH, Gross GJ, Kersten JR, Pagel PS, Warltier DC. Morphine enhances pharmacological preconditioning by isoflurane: role of mitochondrial K(ATP) channels and opioid receptors. *Anesthesiology*. 2003; 98:705–11. [PubMed: 12606915]
16. Gross ER, Hsu AK, Urban TJ, Mochly-Rosen D, Gross GJ. Nociceptive-induced myocardial remote conditioning is mediated by neuronal gamma protein kinase C. *Basic research in cardiology*. 2013; 108:1–11.

17. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. *New England Journal of Medicine*. 2015; 373:1408–17. [PubMed: 26436207]
18. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaelte G, Böning A, Niemann B. A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. *New England Journal of Medicine*. 2015; 373:1397–1407. [PubMed: 26436208]
19. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guerin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit JF, Jouve B, Motreff P, Tron C, Labeque JN, Steg PG, Cottin Y, Range G, Clerc J, Claeys MJ, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, De Poli F, Morice MC, Ider O, Dubois-Rande JL, Untersee T, Le Breton H, Beard T, Blanchard D, Grollier G, Malquarti V, Staat P, Sudre A, Elmer E, Hansson MJ, Bergerot C, Boussaha I, Jossan C, Derumeaux G, Mewton N, Ovize M. Cyclosporine before PCI in Patients with Acute Myocardial Infarction. *N Engl J Med*. 2015; 373:1021–31. [PubMed: 26321103]