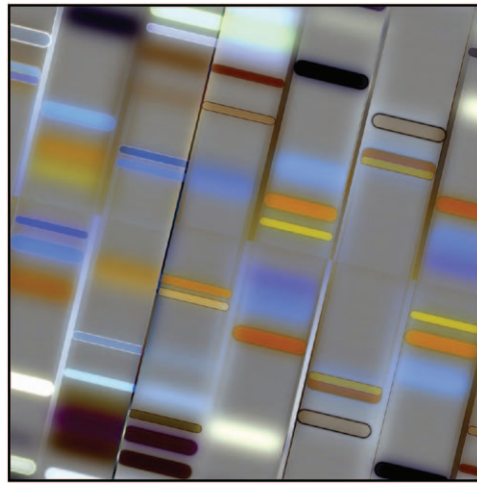


A Slick Way Volatile Anesthetics Reduce Myocardial Injury

Nana-Maria Wagner, M.D., Eric R. Gross, M.D., Ph.D., Hemal H. Patel, Ph.D.

IN 2007, the American College of Cardiology/American Heart Association 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.*⁵ 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. By 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 increased 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, the mitochondrial permeability transitional pore, and other BK channels that are long recognized in mediating volatile anesthetic–induced preconditioning *via* regulation of mitochondrial function.⁶ Although initial reports



“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.”

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 American College of Cardiology/American Heart Association guidelines have been continuously modified to downplay the powerful effects that volatile anesthetics have in reducing myocardial injury in preclinical models. In 2011, the recommendations for patients undergoing coronary artery bypass graft surgery were changed to only recommend the use of volatile anesthetics to facilitate extubation in cardiac patients.¹¹ Further, the 2014 guidelines for patients undergoing noncardiac 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

suggested that a Ca²⁺-activated BK channel (likely Slo1) was responsible for anesthetic preconditioning,^{7–9} the fact that Slo1^{−/−} mice can still be preconditioned by isoflurane,¹⁰ coupled with the results of the study by Wojtovich *et al.*, suggest reevaluation of these early findings.

In their present study, Wojtovich *et al.* 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^{−/−} mice but not in Slo2.2^{−/−} mice subjected to myocardial ischemia–reperfusion injury. By demonstrating Slo2.1-mediated protective effects of volatile anesthetics that are independent of ischemia or pharmacologic 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

Image: ©Thinkstock.

Corresponding article on page 1065.

Accepted for publication November 9, 2015. From the Department of Anesthesiology, Perioperative and Pain Medicine, School of Medicine, Stanford University, Stanford, California (N.-M.W., E.R.G.); VA San Diego Healthcare System, San Diego, California (H.H.P.); and Department of Anesthesiology, University of California, San Diego, La Jolla, California (H.H.P.).

Copyright © 2016, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. *Anesthesiology* 2016; 124:986–8

remained nonevident or controversial in patient populations undergoing noncardiac 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 ATP-sensitive K⁺ 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 that remote ischemic preconditioning 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.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Patel: hepatel@ucsd.edu

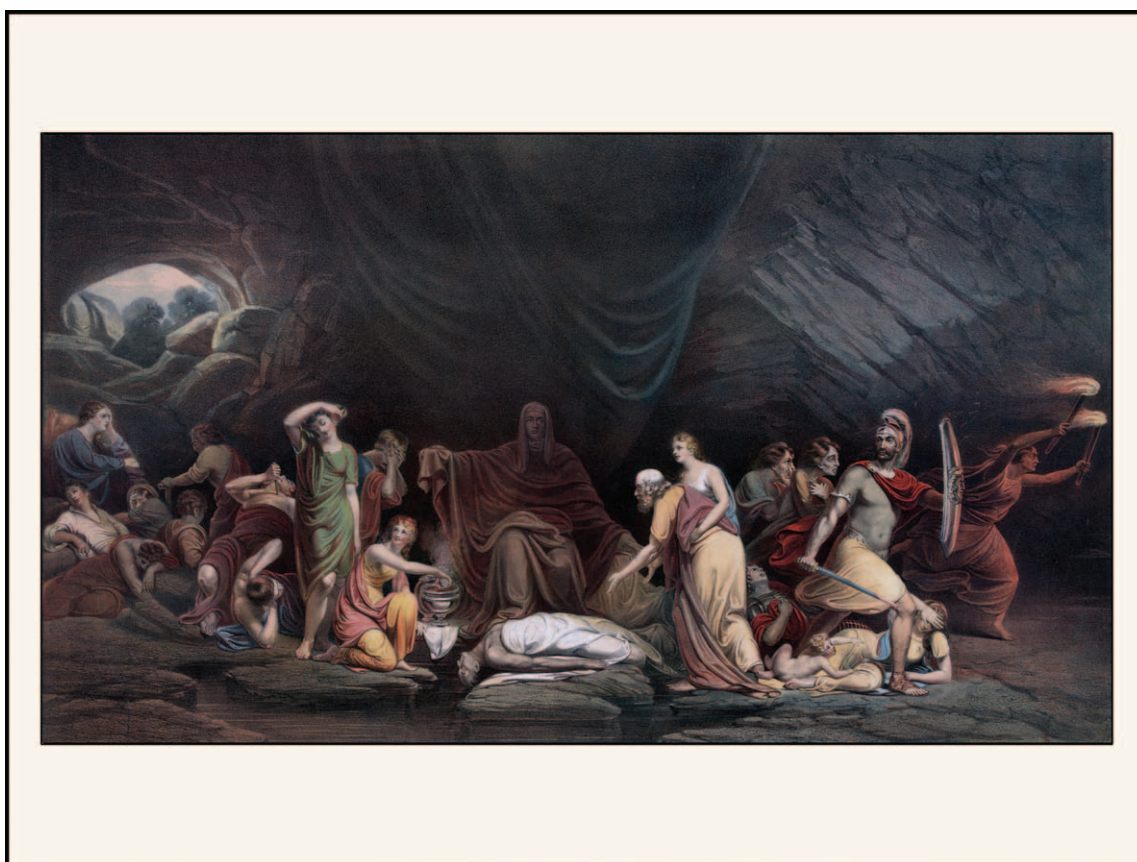
References

1. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Tarkington LG, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery); American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society for Vascular Surgery: 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 (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation* 2007; 116:e418–99
2. Toller WG, Gross ER, Kersten JR, Pagel PS, Gross GJ, Wartler DC: Sarcolemmal and mitochondrial adenosine triphosphate-dependent potassium channels: Mechanism of desflurane-induced cardioprotection. *ANESTHESIOLOGY* 2000; 92:1731–9
3. van Swinderen B, Galifianakis A, Crowder M: Common genetic determinants of halothane and isoflurane potencies in *Caenorhabditis elegans*. *ANESTHESIOLOGY* 1998; 89:1509–17
4. De Hert SG: Cardioprotection in anesthesia. *Minerva Anesthesiol* 2008; 74:259–70
5. Wojtovich AP, Smith CO, Urciuoli WR, Wang YT, Xia X-M, Brookes PS, Nehrke K: Cardiac *Slo2.1* is required for volatile anesthetic stimulation of K⁺ transport and anesthetic preconditioning. *ANESTHESIOLOGY* 2016; 124:1065–76
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
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
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
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
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
11. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, 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
12. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeyesundera DN; American College of Cardiology; American Heart Association: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2014; 64:e77–137
13. Lindholm EE, Aune E, Norén 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
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
15. Ludwig LM, Patel HH, Gross GJ, Kersten JR, Pagel PS, Wartler DC: Morphine enhances pharmacological preconditioning by isoflurane: Role of mitochondrial K(ATP) channels and opioid receptors. *ANESTHESIOLOGY* 2003; 98:705–11

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 Res Cardiol* 2013; 108:381
17. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM; ERICCA Trial Investigators: Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med* 2015; 373:1408–17
18. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaelte G, Böning A, Niemann B, Roesner J, Kletzin F, Strouhal U, Reyher C, Laufenberg-Feldmann R, Ferner M, Brandes IF, Bauer M, Stehr SN, Kortgen A, Wittmann M, Baumgarten G, Meyer-Treschan T, Kienbaum P, Heringlake M, Schön J, Sander M, Treskatsch S, Smul T, Wolwender E, Schilling T, Fuernau G, Hasenclever D, Zacharowski K; RIPHeart Study Collaborators: A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med* 2015; 373:1397–407
19. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guérin 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-Randé JL, Untersee T, Le Breton H, Béard 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

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Colton's Mass Publication of *The Court of Death* by Peale



Years before his successive elections as Anglican Bishop of Chester (1776) and London (1787), Beilby Porteus (1731–1809) garnered Cambridge's Seatonian Prize in 1759 for his poem *Death: A Poetical Essay*. Sixty years later, to survive the Panic of 1819, Rembrandt Peale (1778–1860; artist, Baltimore, Maryland) began painting *The Court of Death*. Peale's gigantic artwork featured 23 life-sized figures inspired by Porteus' prizewinning poem. After exhibiting the painting for decades, Peale sold it in 1858 to showman Gardner Q. Colton (1814–1898), whose nitrous oxide had anesthetized Horace Wells 14 years earlier. After misinvesting the fortune gained from 1849–1850 "Gold Rush" land sales, Colton began supplementing his income from laughing gas demonstrations by offering, at \$1 apiece, 100,000 chromolithographs of Peale's oil painting. Such sales ensured that Colton would survive the harsh antebellum and Civil War circumstances that preceded both his reviving use of nitrous oxide for dental anesthesia and his founding of the "Colton Dental Association" in 1863. (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.