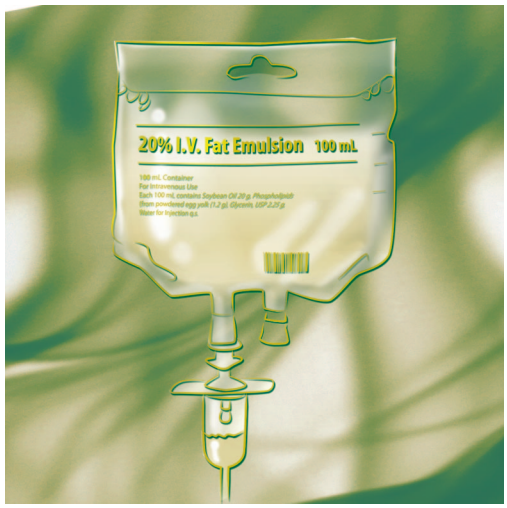
# From Local to Global

## *Lipid Emulsion (Intralipid) Makes a Move*

IN clinical practice, lipid emulsion is used commonly as a component of parenteral nutrition. Lipid emulsion also is used as therapy for severe cardiotoxicity secondary to accidental overdose of local anesthetics, an effect that has been confirmed in animals[1–3] and humans.[4,5] Because patients with local anesthetic-induced cardiac arrest are considered to be less responsive for standard resuscitation methods, this finding is striking, and currently infusion of lipid emulsion is considered the primary treatment for local anesthetic toxicity. In this issue of ANESTHESIOLOGY, Rahman *et al.*[6] report a new and potentially clinically relevant benefit of lipid emulsion therapy.




***"If similar protective effects are demonstrated in patients, lipid emulsion may play a novel and important role as a therapeutic intervention for patients with ischemic heart disease."***

Classic preconditioning[7] produces in the heart a state profoundly protected from ischemia–reperfusion injury; however, the prerequisite for knowing when the ischemic injury will occur has limited the clinical translation and relevance of preconditioning. Recently, a potentially more clinically relevant form of cardiac protection, termed postconditioning, has been described.[8] Postconditioning involves the application of protective interventions (*e.g.*, brief ischemia–reperfusion, volatile anesthetics, opioids, and other classic cardioprotective agents) after ischemia but before reperfusion.

Rahman *et al.* extend the list of postconditioning agents to include Intralipid (Sigma, St. Louis, MO). They show that lipid emulsion infusion just before reperfusion (*i.e.*, postconditioning) protects from myocardial ischemia–reperfusion injury.[9] Subsequent mechanistic studies define a role for glycogen synthase kinase-3$\beta$ and the mitochondrial permeability transition pore (mPTP) in this response. Mitochondria, a source of cellular adenosine triphosphate, are increasingly implicated in cell survival and death signaling in the heart. In particular, the mPTP has been suggested as the final effector in cardiac myocyte protection.[10] The mPTP opening in response to stress leads to an increase in mitochondrial membrane permeability to small molecules, resulting in cellular apoptosis and necrosis. Thus, regulating the mPTP opening has been considered to be a promising target for cardiac protection, and others have suggested the involvement of mPTP in postconditioning.[11,12]

Postconditioning is mediated *via* a complex molecular signaling cascade involving the reperfusion injury salvage kinase and the survivor activating factor enhancement pathways.[13] Rahman *et al.* implicate common survival pathways, such as PI3K-Akt and ERK, in lipid emulsion-induced protection. In addition, they link these upstream survival kinases to downstream regulation of glycogen synthase kinase-3$\beta$. Recent work has shown that increased phosphorylation of glycogen synthase kinase-3$\beta$ reduces the affinity of the adenine nucleotide translocase for cyclophilin D, suggesting that assembly of the complex is targeted by protective signals to limit mPTP opening.[14] Thus, there appears to be a direct link between survival kinase regulation and mPTP end effector function.

These intriguing findings by Rahman *et al.* leave us with some important questions to be addressed in future investigation. First, how does lipid emulsion activate survival kinases—*via* a direct effect or secondary to receptor stimulation? General protective interventions appear to signal through G-protein–coupled receptor pathways,[15] including preconditioning and postconditioning *via* opioids, volatile anesthetics, and other cardioprotective agents. It would be important to determine whether lipid emulsion is sensitive to

*Illustration: J. P. Rathmell/A. Johnson.*

Accepted for publication April 13, 2011. Supported by National Institutes of Health grants HL091071 (to Dr. Patel), GM085179 (to HHP-Co-I), and HL081400 (to Dr. Roth) from the United States Public Health Service, Bethesda, Maryland, and a Veterans Affairs Merit Grant from Biomedical Laboratory Research & Development Service (to Dr. Roth) from the Department of Veterans Affairs, Washington, D.C.

 Anesthesiology 2011; 115:226–8

◆ This Editorial View accompanies the following article: Rahman S, Li J, Bopassa JC, Umar S, Iorga A, Partownavid P, Eghbali M: Phosphorylation of GSK-3$\beta$ mediates Intralipid-induced cardioprotection against ischemia–reperfusion injury. ANESTHESIOLOGY 2011; 115:242–53.

G-protein–coupled receptor inhibition. Second, does intralipid modulate membrane lipid composition to modulate cardiac protection? Signaling components involved in cardioprotection are localized in membrane microdomains (*i.e.*, lipid rafts and caveolae) that are enriched in cholesterol and sphingolipids.[16,17] A recent publication suggests there may be some link between lipid emulsion and caveolin[18]; however, a direct effect of lipid emulsion on caveolins was not tested in this study. Other studies show that perturbing caveolae can alter survival kinase signaling critical to protection from cardiac and neuronal ischemia–reperfusion injury.[19–24] It would be interesting to know whether Intralipid, being a lipid emulsion, affects membrane microdomains such as lipid rafts and caveolae to produce protection. Third, does the protective effect of lipid emulsion identified in this study play some role in the effects of propofol (where 10% lipid emulsion is the vehicle) that have been noted in ischemia–reperfusion injury? The potential protective effects of propofol are controversial,[25,26] and the lipid emulsion effects need to be considered separately from the potential direct effects of propofol. Studies using fospropofol (a water-soluble formulation of a phosphate ester prodrug of propofol) may be useful in resolving this issue.

In summary, the current study by Rahman *et al.* focuses on a potentially important role for lipid emulsion in cardiac protection. Additional studies are needed to focus on mechanisms and potential clinical trials in humans. If similar protective effects are demonstrated in patients, lipid emulsion may play a novel and important role as a therapeutic intervention for patients with ischemic heart disease.

**Yoshitaka Kawaraguchi, M.D.,* David M. Roth, Ph.D., M.D.,† Hemal H. Patel, Ph.D.†** * Department of Anesthesiology, University of California, San Diego, La Jolla, California. † Department of Anesthesiology, University of California, San Diego, and Veterans Affairs San Diego Healthcare System, San Diego, California. hepatel@ucsd.edu

## References

1. Weinberg G, Ripper R, Feinstein DL, Hoffman W: Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med 2003; 28:198–202
2. Weinberg GL, Ripper R, Murphy P, Edelman LB, Hoffman W, Strichartz G, Feinstein DL: Lipid infusion accelerates removal of bupivacaine and recovery from bupivacaine toxicity in the isolated rat heart. Reg Anesth Pain Med 2006; 31:296–303
3. Chen Y, Xia Y, Liu L, Shi T, Shi K, Wang Q, Chen L, Papadimos TJ, Xu X: Lipid emulsion reverses bupivacaine-induced asystole in isolated rat hearts: Concentration-response and time-response relationships. Anesthesiology 2010; 113:1320–5
4. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB: Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology 2006; 105:217–8
5. Litz RJ, Popp M, Stehr SN, Koch T: Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia 2006; 61: 800–1
6. Rahman S, Li J, Bopassa JC, Umar S, Iorga A, Partownavid P, Eghbali M: Phosphorylation of GSK-3$\beta$ mediates intralipid-induced cardioprotection against ischemia–reperfusion injury. Anesthesiology 2011; 115:242–53
7. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation 1986; 74:1124–36
8. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J: Inhibition of myocardial injury by ischemic postconditioning during reperfusion: Comparison with ischemic preconditioning. Am J Physiol Heart Circ Physiol 2003; 285:H579–88
9. Lumini-Oliveira J, Magalhães J, Pereira CV, Moreira AC, Oliveira PJ, Ascensão A: Endurance training reverts heart mitochondrial dysfunction, permeability transition and apoptotic signaling in long-term severe hyperglycemia. Mitochondrion 2011; 11:54–63
10. Javadov S, Karmazyn M: Mitochondrial permeability transition pore opening as an endpoint to initiate cell death and as a putative target for cardioprotection. Cell Physiol Biochem 2007; 20:1–22
11. Argaud L, Gateau-Roesch O, Raisky O, Loufouat J, Robert D, Ovize M: Postconditioning inhibits mitochondrial permeability transition. Circulation 2005; 111:194–7
12. Krolikowski JG, Bienengraeber M, Weihrauch D, Warltier DC, Kersten JR, Pagel PS: Inhibition of mitochondrial permeability transition enhances isoflurane-induced cardioprotection during early reperfusion: The role of mitochondrial KATP channels. Anesth Analg 2005; 101:1590–6
13. Hausenloy DJ, Lecour S, Yellon DM: Reperfusion injury salvage kinase and survivor activating factor enhancement prosurvival signaling pathways in ischemic postconditioning: Two sides of the same coin. Antioxid Redox Signal 2011; 14:893–907
14. Nishihara M, Miura T, Miki T, Tanno M, Yano T, Naitoh K, Ohori K, Hotta H, Terashima Y, Shimamoto K: Modulation of the mitochondrial permeability transition pore complex in GSK-3beta-mediated myocardial protection. J Mol Cell Cardiol 2007; 43:564–70
15. Schultz JE, Hsu AK, Barbieri JT, Li PL, Gross GJ: Pertussis toxin abolishes the cardioprotective effect of ischemic preconditioning in intact rat heart. Am J Physiol 1998; 275: H495–500
16. Patel HH, Murray F, Insel PA: Caveolae as organizers of pharmacologically relevant signal transduction molecules. Annu Rev Pharmacol Toxicol 2008; 48:359–91
17. Roth DM, Patel HH: Role of caveolae in cardiac protection. Pediatr Cardiol 2011; 32:329–33
18. Ok SH, Sohn JT, Baik JS, Kim JG, Park SS, Sung HJ, Shin MK, Kwon YH, Park CS, Shin IW, Lee HK, Chung YK: Lipid emulsion reverses Levobupivacaine-induced responses in isolated rat aortic vessels. Anesthesiology 2011; 114:293–301
19. Head BP, Patel HH, Tsutsumi YM, Hu Y, Mejia T, Mora RC, Insel PA, Roth DM, Drummond JC, Patel PM: Caveolin-1 expression is essential for *N*-methyl-D-aspartate receptor-mediated Src and extracellular signal-regulated kinase 1/2 activation and protection of primary neurons from ischemic cell death. FASEB J 2008; 22:828–40
20. Head BP, Peart JN, Panneerselvam M, Yokoyama T, Pearn ML, Niesman IR, Bonds JA, Schilling JM, Miyanohara A, Headrick J, Ali SS, Roth DM, Patel PM, Patel HH: Loss of caveolin-1 accelerates neurodegeneration and aging. PLoS One 2010; 5:e15697
21. Horikawa YT, Patel HH, Tsutsumi YM, Jennings MM, Kidd MW, Hagiwara Y, Ishikawa Y, Insel PA, Roth DM: Caveolin-3 expression and caveolae are required for isoflurane-induced cardiac protection from hypoxia and ischemia/reperfusion injury. J Mol Cell Cardiol 2008; 44:123–30
22. Patel HH, Tsutsumi YM, Head BP, Niesman IR, Jennings M, Horikawa Y, Huang D, Moreno AL, Patel PM, Insel PA, Roth DM: Mechanisms of cardiac protection from ischemia/reperfusion injury: A role for caveolae and caveolin-1. FASEB J 2007; 21:1565–74

23. Tsutsumi YM, Horikawa YT, Jennings MM, Kidd MW, Niesman IR, Yokoyama U, Head BP, Hagiwara Y, Ishikawa Y, Miyanohara A, Patel PM, Insel PA, Patel HH, Roth DM: Cardiac-specific overexpression of caveolin-3 induces endogenous cardiac protection by mimicking ischemic preconditioning. Circulation 2008; 118:1979–88

24. Tsutsumi YM, Kawaraguchi Y, Horikawa YT, Niesman IR, Kidd MW, Chin-Lee B, Head BP, Patel PM, Roth DM, Patel HH: Role of caveolin-3 and glucose transporter-4 in isoflurane-induced delayed cardiac protection. ANESTHESIOLOGY 2010; 112:1136–45

25. De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, Nelis A, Van Reeth V, ten Broecke PW, De Blier IG, Stockman BA, Rodrigus IE: Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. ANESTHESIOLOGY 2004; 101:299–310

26. Huang Z, Zhong X, Irwin MG, Ji S, Wong GT, Liu Y, Xia ZY, Finegan BA, Xia Z: Synergy of isoflurane preconditioning and propofol postconditioning reduces myocardial reperfusion injury in patients. Clin Sci 2011; 121:57–69

## ANESTHESIOLOGY REFLECTIONS

# Siker's Mapleson-modified Boyle Apparatus for Halothane

After designing his namesake mirror laryngoscope, E. S. "Rick" Siker, M.D. (b. 1926), studied in Wales from 1955–1956 with Professor W. W. Mushin. Before departing Cardiff for Pittsburgh in October of 1956, Dr. Siker (*left*) "was presented with a Boyle's anesthetic machine with a trichloroethylene vaporizer calibrated by Bill Mapleson to deliver precise concentrations of halothane." Using that apparatus (*right*), Dr. Siker conducted America's second large-scale clinical trial of halothane for general anesthesia. The 1973 American Society of Anesthesiologists (ASA) president and the recipient of ASA's 1983 Distinguished Service Award, Dr. Siker has also served as the Anesthesia Patient Safety Foundation's first executive director. He generously donated this historic Boyle Apparatus to the Wood Library-Museum of Anesthesiology. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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