synthase kinase-3β and ultimately leads to delayed opening of the mitochondrial permeability transition pore (mPTP). In contrast to the mPTP inhibitor cyclosporine-A or other proven postconditioning agents,[6,7] however, intralipid is a mixture of various different compounds: fractionated soybean oil, fractionated egg phospholipids, and glycerol.[8,9] Which of these compounds is ultimately responsible for the cardioprotective effect? Is this truly a receptor-mediated effect, or could it simply be a metabolic switch from glucose to fatty acid metabolism that paradoxically protects the heart as suggested in another of Dr. Eghbali's publications[10] and by us?[11,12] Since intralipid is metabolized *in vivo* and its contents may reach the heart in a very different form[8] than in the isolated heart preparation, both models are difficult to compare directly in this context. Lastly, as much as delayed mPTP opening appears to be a common end-effector in many different animal models of protection against myocardial reperfusion injury,[13] Li *et al.*[2] show once more that inhibition of the mPTP may be necessary but by far not sufficient for cardioprotection: although not formally done in their study, the extent of delayed mPTP opening in control, cyclosporine-A-, and intralipid-treated animals does not correlate with the observed degree of functional and tissue protection in the three groups. Therefore, despite these interesting findings, it may still be a long way to a potential clinical usage of intralipid in preventing myocardial reperfusion injury.

Matthias L. Riess, M.D., Ph.D.,* Mihai V. Podgoreanu, M.D. *Veterans Affairs Medical Center, and Medical College of Wisconsin, Milwaukee, Wisconsin. mriess@mcw.edu

References

1. Rahman S, Li J, Bopassa JC, Umar S, Iorga A, Partownavid P, Eghbali M: Phosphorylation of GSK-3β mediates intralipid-induced cardioprotection against ischemia/reperfusion injury. Anesthesiology 2011; 115:242–53
2. Li J, Iorga A, Sharma S, Youn JY, Partow-Navid R, Umar S, Cai H, Rahman S, Eghbali M: Intralipid, a clinically safe compound, protects the heart against ischemia-reperfusion injury more efficiently than cyclosporine-A. Anesthesiology 2012; 117:836–46
3. Umar S, Nadadur RD, Li J, Maltese F, Partownavid P, van der Laarse A, Eghbali M: Intralipid prevents and rescues fatal pulmonary arterial hypertension and right ventricular failure in rats. Hypertension 2011; 58:512–8
4. 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
5. 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
6. Feng J, Lucchinetti E, Ahuja P, Pasch T, Perriard JC, Zaugg M: Isoflurane postconditioning prevents opening of the mitochondrial permeability transition pore through inhibition of glycogen synthase kinase 3beta. Anesthesiology 2005; 103:987–95
7. Huhn R, Heinen A, Weber NC, Kerindongo RP, Oei GT, Hollmann MW, Schlack W, Preckel B: Helium-induced early preconditioning and postconditioning are abolished in obese Zucker rats *in vivo*. J Pharmacol Exp Ther 2009; 329:600–7
8. Nordenström J, Thörne A: Comparative studies on a new concentrated fat emulsion: Intralipid 30% *vs.* 20%. Clin Nutr 1993; 12:160–7
9. Morris S, Simmer K, Gibson R: Characterization of fatty acid clearance in premature neonates during intralipid infusion. Pediatr Res 1998; 43:245–9
10. Partownavid P, Umar S, Li J, Rahman S, Eghbali M: Fatty-acid oxidation and calcium homeostasis are involved in the rescue of bupivacaine-induced cardiotoxicity by lipid emulsion in rats. Crit Care Med 2012; 40:2431–7
11. Podgoreanu MV, Ma Q, Mackensen GB, Zhang Z, Kohl F, Smith M, Bain J, Newgard C, Drew K, Barnes B: Metabolic correlates of cardioprotection following deep hypothermic circulatory arrest in hibernating arctic ground squirrels. Presented at: Annual Meeting of American Society of Anesthesiologists, Chicago, Illinois: A0008, October 15, 2011
12. Podgoreanu M, Ma Q, Zhang Z, Bain J, Newgard C, Riess M, Barnes B: The cardioprotective phenotype in mammalian hibernators is associated with attenuation of reperfusion-induced nuclear factor-kappa B regulated myocardial inflammation. Circulation 2012; 126: A1952.
13. Hausenloy DJ, Boston-Griffiths EA, Yellon DM: Cyclosporin A and cardioprotection: From investigative tool to therapeutic agent. Br J Pharmacol 2012; 165:1235–45

(Accepted for publication January 29, 2013.)

In Reply:

We thank Drs. Reiss and Podgoreanu for highlighting our recent findings[1–4] on intralipid and raising all these important questions about the mechanisms underlying the cardioprotective action of one of the most promising agents.

In the acute cardioprotective action of intralipid as in ischemia–reperfusion injury[2] and bupivacaine overdose,[3] inhibition of mitochondrial permeability transition pore (mPTP) opening seems to be one of the key mechanisms. We found that inhibition of mPTP by intralipid is due to increased phosphorylation of glycogen synthase kinase 3 beta[1] and/or decreased pH by improving mitochondrial electron transport chain function through fatty acid oxidation pathway.[3] The fact that cyclosporine-A, which inhibits the opening of the mPTP as efficiently as intralipid, is not able to reduce the infarct size and improve the heart function as intralipid,[1] may suggest that inhibition of mPTP opening, although necessary, certainly is not the only mechanism underlying intralipid-induced cardioprotection. However, it is important to note that the effect of cyclosporine-A on the mPTP is not selective, because cyclosporine-A can also inhibit the phosphatase calcineurin activity.[5] This interaction of cyclosporine-A with phosphatase calcineurin is independent of its action on mPTP.[5] However, it is possible that the effect of cyclosporine-A on calcineurin may limit the cyclosporine-A–induced cardioprotection. Therefore, to clarify whether there is a correlation between the degree of functional and tissue protection with inhibition of mPTP opening, intralipid must be compared with a nonimmunosuppressive cyclosporine-A

Support was provided by National Institutes of Health (Bethesda, Maryland) grant HL089876.

analog, which lacks the ability to inhibit calcineurin such as N-methyl-4-isoleucine cyclosporin 811.[6]

We agree with Drs. Riess and Podgoreanu that it is important to identify which component of intralipid is exerting this cardioprotective effect. Despite several attempts from our group, we have not been able to make the individual compounds lipid soluble. We will however proceed to examine the relative contributions of each subcomponent of intralipid on the cardiac functional recovery and infarct size after ischemia in the acute setting and in the chronic setting as in pulmonary hypertension. We believe that elucidating the cardioprotective effects of each of the components of intralipid may also shed light on possible different mechanisms of action *in vivo* versus *ex vivo* because *in vivo* intralipid is metabolized. We recently elucidated the involvement of opioid receptors in mediating the cardioprotective action of intralipid; as in the presence of opioid receptor antagonists, intralipid failed to rescue bupivacaine-induced cardiac arrest.[7] Future studies are needed to identify which component(s) of intralipid is(are) in fact interacting with the opioid receptor and whether this interaction is direct or indirect.

The cardiac ischemia–reperfusion injury coincides with significant metabolic abnormalities. Numerous studies have suggested that high circulating levels of free fatty acid during cardiac ischemia may increase myocardial damage.[8–12] However, other studies have shown that improving the capacity of fatty acid oxidation at reperfusion may improve the cardiac mechanical performance.[13–15] Non-glucose substrates have also been shown to play an important role in maintaining energy expenditure during catecholamine stimulation after myocardial stunning.[16] All these findings suggest that pathophysiologic mechanism of ischemia–reperfusion is at least partially related to deficient turnover of energy substrates, more specifically free fatty acid. It is reasonable therefore to speculate intralipid may shift the metabolism from glucose to fatty acid at reperfusion and consequently lead to more myocardial energy production. In fact, in the context of bupivacaine overdose, the rescue action of intralipid was completely abolished in the presence of an inhibitor of β-oxidation.[3] Facilitating β-oxidation in the postischemic heart through the addition of carnitine has also proven to be beneficial to myocardial recovery.[17,18]

Modulation of membrane lipid composition and formation of caveolae on the sarcolemma could be one of the other possible mechanisms of protection as suggested by Dr. Patel's group.[19] Improving membrane fluidity by intralipid might also contribute to reducing the myocardial injury. Intralipid may help the myocardium after an ischemic episode to better tolerate calcium overload and excessive production of reactive oxygen species in the first few minutes of reperfusion as seen in ischemic postconditioning and in controlled reperfusion as shown in Ovize's laboratory.[20]

The rescue action of intralipid in the chronic setting observed in pulmonary hypertension, on the other hand, could be mediated by its genomic effect through transcription factors leading to stimulation of angiogenesis, suppression of inflammation, fibrosis, and hypertrophy, in both lung and right ventricle.[4]

Our findings, as have been highlighted by Drs. Riess and Podgoreanu, raise the intriguing possibility that intralipid could serve as a promising cardioprotective agent not only for resuscitation of the local anesthetic cardiotoxicity but also for treatment of acute myocardial infarction and pulmonary hypertension. Our exciting work certainly calls for further investigation in unraveling other possible mechanisms involved in both the acute and chronic rescue action of intralipid.

Jingyuan Li, Ph.D., Jean C. Bopassa, Ph.D., Siamak Rahman, M.D., Mansoureh Eghbali, Ph.D.* *David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California. meghbali@ucla.edu

References

1. Li J, Iorga A, Sharma S, Youn JY, Partow-Navid R, Umar S, Cai H, Rahman S, Eghbali M: Intralipid, a clinically safe compound, protects the heart against ischemia-reperfusion injury more efficiently than cyclosporine-A. Anesthesiology 2012; 117: 836–46
2. Rahman S, Li J, Bopassa JC, Umar S, Iorga A, Partownavid P, Eghbali M: Phosphorylation of GSK-3β mediates intralipid-induced cardioprotection against ischemia/reperfusion injury. Anesthesiology 2011; 115: 242–53
3. Partownavid P, Umar S, Li J, Rahman S, Eghbali M. Fatty-acid oxidation and calcium homeostasis are involved in the rescue of bupivacaine-induced cardiotoxicity by lipid emulsion in rats. Crit Care Med 2012;40:2431–7
4. Umar S, Nadadur RD, Li J, Maltese F, Partownavid P, van der LA, Eghbali M: Intralipid prevents and rescues fatal pulmonary arterial hypertension and right ventricular failure in rats. Hypertension 2011; 58: 512–8
5. Javadov S, Karmazyn M, Escobales N. Mitochondrial permeability transition pore opening as a promising therapeutic target in cardiac diseases. J Pharmacol Exp Ther 2009;330:670–8
6. Readnower RD, Pandya JD, McEwen ML, Pauly JR, Springer JE, Sullivan PG. Post-injury administration of the mitochondrial permeability transition pore inhibitor, NIM811, is neuroprotective and improves cognition after traumatic brain injury in rats. J Neurotrauma 2011;28:1845–53
7. Partownavid P, Umar S, Rahman S, Sharma S, Eghbali M. Intralipid fails to rescue bupivacaine-induced cardiotoxicity in the presence of the opioid antagonist naloxone. Circulation 2012; 126:A220
8. Kurien VA, Yates PA, Oliver MF. Free fatty acids, heparin, and arrhythmias during experimental myocardial infarction. Lancet 1969;2:185–7
9. Kurien VA, Yates PA, Oliver MF. The role of free fatty acids in the production of ventricular arrhythmias after acute coronary artery occlusion. Eur J Clin Invest 1971;1:225–41
10. Liedtke AJ, Nellis S, Neely JR. Effects of excess free fatty acids on mechanical and metabolic function in normal and ischemic myocardium in swine. Circ Res 1978;43:652–61
11. Prinzen FW, van der Vusse GJ, Coumans WA, Kruger R, Verlaan CW, Reneman RS. The effect of elevated arterial free fatty acid concentrations on hemodynamics and myocardial metabolism and blood flow during ischemia. Basic Res Cardiol 1981;76:197–210
12. Smiseth OA, Mjøs OD. Haemodynamic and metabolic consequences of elevated plasma free fatty acids during acute

ischaemic left ventricular failure in dogs. Scand J Clin Lab Invest 1985;45:515–20
13. Paulson DJ, Traxler J, Schmidt M, Noonan J, Shug AL. Protection of the ischaemic myocardium by L-propionylcarnitine: Effects on the recovery of cardiac output after ischaemia and reperfusion, carnitine transport, and fatty acid oxidation. Cardiovasc Res 1986;20:536–41
14. Montessuit C, Papageorgiou I, Tardy-Cantalupi I, Rosenblatt-Velin N, Lerch R. Postischemic recovery of heart metabolism and function: Role of mitochondrial fatty acid transfer. J Appl Physiol 2000;89:111–9
15. Lou PH, Zhang L, Lucchinetti E, Heck M, Affolter A, Gandhi M, Kienesberger PC, Hersberger M, Clanachan AS, Zaugg M: Infarct-remodelled hearts with limited oxidative capacity boost fatty acid oxidation after conditioning against ischaemia/reperfusion injury. Cardiovasc Res 2013; 97: 251–61
16. McFalls EO, Ward HB, Fashingbauer P, Palmer B. Effects of dobutamine stimulation on regional myocardial glucose uptake poststunning as measured by positron emission tomography. Cardiovasc Res 1994;28:1030–35
17. Liedtke AJ, Nellis SH. Effects of carnitine in ischemic and fatty acid supplemented swine hearts. J Clin Invest 1979;64: 440–7
18. Folts JD, Shug AL, Koke JR, Bittar N. Protection of the ischemic dog myocardium with carnitine. Am J Cardiol 1978;41:1209–14
19. Kawaraguchi Y, Roth DM, Patel HH. From local to global: Lipid emulsion (intralipid) makes a move. Anesthesiology 2011;115:226–8
20. Bopassa JC, Ferrera R, Gateau-Roesch O, Couture-Lepetit E, Ovize M. PI 3-kinase regulates the mitochondrial transition pore in controlled reperfusion and postconditioning. Cardiovasc Res 2006;69:178–85

(Accepted for publication January 29, 2013.)

Desflurane, Isoflurane, and...Ragweed

To the Editor:

Recent discoveries in the mechanism of action of ragweed sensitivity may have a bearing on the choice of anesthetic agent. We review some pathways that affect bronchial motor tone and how they may influence the choice of anesthetic agent. Bronchial motor tone is regulated by the parasympathetic nervous system, which exerts a contractile action through activation of M_3 receptors, and by the nonadrenergic noncholinergic pathways having both inhibitory and excitatory effects. The bronchial response to stimulation is in part due to C-fibers in the bronchial wall that are responsible for a local axon reflex, with irritant stimulation of nerve endings leading to the release of bronchoconstricting tachykinins such as substance P, neurokinin A, and calcitonin gene-related peptide.[1,2] While sevoflurane does not induce increased airway resistance, desflurane-elicited airway constriction appears to be mediated by the release of these tachykinins.[3]

The transient receptor potential (TRP) family of cation channels is highly expressed by a subset of C-fiber nociceptors, including those in the lung.[4,5] TRPA1 is expressed in sensory neurons, and colocalizes with TRPV1, calcitonin gene-related peptide, substance P, and bradykinin receptors.[6] TRPA1 is activated by the pungent ingredients in mustard and garlic extracts, allyl isothiocyanate [7] and allicin.[8] Sensory neurons from TRPA1-deficient mice show greatly diminished responses to each of these compounds, demonstrating that the TRPA1 channel is the primary molecular site by which they activate the irritant and pain pathway,[9,10] as well as initiate the asthmatic airway inflammation.[11] TRPA1 receptors are activated by desflurane and isoflurane,[3,7,12] similar to the effects of several air pollutants and chemicals that cause airway constriction, such as αβ-unsaturated aldehydes and acrolein that activate the axon reflex release of tachykinins.[8,13]

It has been recently reported that the TRPA1 receptor is also activated by the sesquiterpenoids present in the pollen from common ragweed (*Ambrosia artemisiifolia*), and activation of this receptor may contribute to the various respiratory symptoms caused by inhalation of this pollen.[14] The sensitivity of a patient to ragweed suggests enhanced response of the TRPA1-activated tachykinin pathway. This sensitivity may have implications for anesthetic choice in patients with allergy to ragweed and possibly other pollens. Activation of TRPA1 by desflurane and isoflurane may be more likely in this setting of heightened sensitivity, leading to increased airway resistance and decreased lung compliance[15] as well as causing bronchospasm and cough.[16,17] These effects may in part be counteracted by volatile anesthetics' ability to directly relax airway smooth muscle[18] and by desensitization of the TRPA1 receptor during sustained exposure.[19] Nevertheless, the activation of TRPA1 receptors in the upper airway has been suggested to be in part responsible for the clinical observation of cough and laryngospasm due to desflurane.[3,4,13]

The role of TRPA1 receptor in irritant-induced cough and increased airway resistance and their stimulation by desflurane and isoflurane could account for some of the clinical side effects of these drugs. Clinicians may want to take these findings into consideration when choosing an anesthetic for their patients. The lack of stimulation of TRPA1 receptors by sevoflurane[3,12] may explain its relative lack of irritation[16,17] and make it a less irritating choice in patients who have demonstrated heightened airway sensitivity to ragweed pollen or other chemical irritants.

Mohamed Tiouririne, M.D.,* Carl Lynch III, M.D., Ph.D. *University of Virginia, Charlottesville, Virginia. mt9y@virginia.edu

References

1. Canning BJ: Reflex regulation of airway smooth muscle tone. J Appl Physiol 2006; 101:971–85
2. Lamb JP, Sparrow MP: Three-dimensional mapping of sensory innervation with substance P in porcine bronchial mucosa: Comparison with human airways. Am J Respir Crit Care Med 2002; 166:1269–81
3. Satoh J, Yamakage M: Desflurane induces airway contraction mainly by activating transient receptor potential A1 of sensory C-fibers. J Anesth 2009; 23:620–3