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Let's Go Down the Correct Path(way)

To the Editor:

"Acquired Liver Injury in the Intensive Care Unit" by Lescot *et al.*¹ is an excellent discussion of the multifaceted causes of liver injury. One correction is in order, however. The review incorrectly states that the international normalized ratio reflects intrinsic pathway activity. It is the activity of the *extrinsic* coagulation pathway, often now referred to as the tissue factor pathway, that is measured by the international normalized ratio and initiates the coagulation cascade.² An understanding of the specific pathway measured by a coagulation test is paramount to the treatment of defects secondary to liver disease. It should also be pointed out that the international normalized ratio, one component of the model for end-stage liver disease scoring used to prioritize liver transplantation waiting lists, can be highly variable depending on the laboratory analyzing the sample.³

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In Reply:

We thank Drs. Johnson and Rice for correcting our inadvertent error from our article¹ and agree with their comments.

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Intralipid: The New Magic Bullet in Cardioprotection?

To the Editor:

In two recent publications in *ANESTHESIOLOGY*, Dr. Eghbali's group reports the attenuation of myocardial reperfusion injury in rodents by intralipid administered on reperfusion.^{1,2} Taken together with another study by the same group in which intralipid prevents and even rescues pulmonary hypertension,³ and the serendipitous landmark discoveries of lipid rescue therapy against bupivacaine-induced cardiotoxicity first in dogs⁴ and then humans,⁵ intralipid appears to have become a new magic bullet for cardioprotection. Nevertheless, many questions remain. Li *et al.*² state that intralipid acts through the phosphorylation of Akt/extracellular signal-regulated kinase-1/glycogen

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synthase kinase- β 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 publications¹⁰ and by us?^{11,12} Since intralipid is metabolized *in vivo* and its contents may reach the heart in a very different form⁸ 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.

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In Reply:

We thank Drs. Riess 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 injury² 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 β 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

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