The Effect of Insulin May Not Be So Simple

To the Editor:

Drenger *et al.* have demonstrated that sevoflurane postconditioning is cancelled in the rat heart with type 1 diabetes mellitus and that this adverse effect by glucose intolerance cannot be restored by the adjustment of blood glucose using insulin.[1] This study appears to have many questions regarding the mechanisms of insulin's action, whereas we would congratulate their impressive results. In the study by Drenger *et al.*, the treatment with insulin significantly increased the infarct size in rats with diabetes mellitus, and a phosphatidylinositol-3-kinase inhibitor wartmannin demonstrated the effect to a similar extent.[1] As Drenger *et al.* have mentioned in the Discussion section, this phenomenon is difficult to explain[1] because insulin is a well-known phosphatidylinositol-3-kinase activator in the cardiac myocytes.[2] As a previous elegant study showed that diabetes abolishes the morphine-induced postconditioning effect in the rat heart, evaluation of the related pathways, including glycogen synthase kinase 3β, janus-activated kinase, signal transducer and activator of transcription 1, phosphatidylinositol-3-kinase/Akt, and extracellular signal-related kinase, in addition to signal transducer and activator of transcription 3, would help in understanding the study by Drenger *et al.*[1,3] Diabetes mellitus may down-regulate a redox sensitive transcription factor, NF-E2-related factor 2 activity *via* extracellular signal-related kinase, resulting in impairment of the sevoflurane postconditioning effect because this pathway has been proved to be induced by the oxidative stress in the diabetic heart.[2] We also have to keep in mind that 5-hydroxydecanonate is not a selective inhibitor of mitochondrial adenosine triphosphate sensitive K^+ channels anymore because it is a substrate for the enzyme acyl-CoA synthethase in the electron transport chain of mitochondria,[4] and it is capable of playing a role as an inhibitor of sarcolemmal adenosine triphosphate sensitive K^+ channels.[5] Therefore, further studies are needed to clarify the mechanistic role of insulin in relation to diabetes mellitus on the sevoflurane postconditioning effect toward the ischemic heart.

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This letter was sent to the author of the above-referenced article, who felt that a reply was necessary only to the letter below by Liu and Xia.—James C. Eisenach, M.D., Editor-in-Chief.

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Potential Synergy of Antioxidant *N*-Acetylcysteine and Insulin in Restoring Sevoflurane Postconditioning Cardioprotection in Diabetes

To the Editor:

We read with great interest the article recently published by Drenger *et al.*[1] The authors demonstrated in their study that in rats with streptozotocin-induced type 1 diabetes, the cardioprotective effects of either ischemic postconditioning or the volatile anesthetic sevoflurane postconditioning were lost and that short duration (48 h) of insulin treatment to "normalize" glucose concentration failed to restore the sensitivity of the hearts from early-stage (4–5 weeks after streptozotocin injection) diabetic rats to postconditioning. Of interest, the author showed that insulin administration before ischemia–reperfusion event in the model of diabetic rats exacerbated postischemic myocardial infarction than without insulin therapy. Accordingly, they suggested that caution should be taken not to add insulin before the planned ischemic period.

However, we cannot completely agree with the authors' suggestion. Hyperglycemia-induced increase in mitochondrial superoxide anion production has been shown to represent a key mechanism of hyperglycemic damage.[2] Results of prospective, randomized clinical trails have shown that aggressive control of blood glucose achieved by intensive insulin therapy (target glucose concentration of 80–110 mg/dl) significantly decreased mortality in critically ill patients[3] whereas poor or marginal intraoperative blood glucose control was associated with a worse hospital outcome after cardiac surgery in diabetic patients.[4] In the study by Drenger *et al.*,[1] the blood glucose