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 phosophatidylinositol-3-kinase inhibitor warrmannin demonstrated the effect to a similar extent.1 As Drenger et al. have mentioned in the Discussion section, this phenomenon is difficult to explain1 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.1,2 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 adenosaline trisphosphate sensitive K+ channels anymore because it is a substrate for the enzyme acyl-CoA synthetase in the electron transport chain of mitochondria,4 and it is capable of playing a role as an inhibitor of sarcolemmal adenosaline trisphosphate 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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References

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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 trials 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 patients3 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...
concentrations in the diabetic insulin-treated rats receiving postconditioning (mean 126 ± 10 mg/dl and 131 ± 9 mg/dl, respectively, in the ischemic and sevoflurane postconditioning groups) were at most marginally controlled. Given the big SDs and small sample size in these groups (n = 6 per group), the glucose concentration in a considerable number of rats in these groups could have been hyperglycemic rather than normoglycemic (defined by the authors as lower than 135 mg/dl). Therefore, it seems reasonable for us to postulate that it was the insufficient acute insulin therapy but not the administration of insulin before ischemia that resulted in the exacerbation of postischemic infarct size seen in the study of Drenger et al. The exact mechanism for this phenomenon is unclear. One possible explanation, in addition to those postulated by the authors, could be that insufficient acute insulin therapy may have abrogated chronic hyperglycemia-induced compensatory increases of myocardial endogenous antioxidant enzymes such as superoxide dismutase enzyme production and activity and rendered the diabetic hearts more vulnerable to oxidative damage after ischemia–reperfusion.

We want to congratulate the authors for their in-depth mechanistic explorations, which showed that phosphorylation of the signal transducer and activator of transcription 3 (STAT3), a key mediator in postconditioning-mediated cardioprotection, was reduced in various parts of the diabetic myocardium (which may contribute to the diabetes-related loss of ischemic and sevoflurane postconditioning). This is an important finding that suggests that enhancing myocardial p-STAT3 may restore postconditioning cardioprotection in diabetes. Indeed, in a similar model of streptozotocin-induced diabetic rats, we found that myocardial p-STAT3 was significantly reduced in rats 4–5 weeks after streptozotocin injection and that treatment with the antioxidant N-acetylcysteine enhanced myocardial p-STAT3 and attenuated postischemic myocardial infarction. Furthermore, we showed in the same model of diabetic rats that N-acetylcysteine treatment restored the responsiveness of diabetic hearts to anesthetic preconditioning with remifentanil. The findings by Drenger et al. and us together with the findings of Kehl et al., who showed that N-acetylcysteine can restore sevoflurane-induced preconditioning against myocardial infarction during hyperglycemia, lead us to postulate that N-acetylcysteine may restore sevoflurane postconditioning in diabetes, possibly by enhancing myocardial p-STAT3. Given that short duration of N-acetylcysteine treatment did not reduce plasma glucose concentration in diabetic rats, we further postulate that N-acetylcysteine and insulin may potentially confer synergy in restoring sevoflurane postconditioning cardioprotection in diabetes.

In summary, we agree with the authors that a longer period of insulin therapy might have a different effect on restoring postconditioning in diabetes. However, we propose that prompt insulin administration, in particular sufficient insulin therapy when added before the planned ischemic period, should also confer beneficial effects, especially when it is used in conjunction with other therapy such as antioxidants, although this hypothesis need to be further tested.

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References

In Reply:
I have read with great interest the comments of Drs. Liu and Xia. Their study on a similar model of streptozotocin-induced diabetic rats confirmed my findings that myocardial signal transducer and activator of transcription 3 (STAT3) concentrations are significantly decreased in the diabetic heart, whereas normal STAT3 concentrations are essential for initiation of the protective process of sevoflurane postconditioning (postC) in diabetes. They also described their findings that STAT3 concentrations might recover in diabetic hearts in...