most important protein of the cardiac gap junctions, Cx43, causing cellular uncoupling and arrhythmias. In a model of myocardial infarction by coronary ligation carried out in both wild-type and inducible nitric oxide synthase (iNOS)−/− knockout mice, Jackson et al.2 showed that increased nitric oxide production by iNOS has a role in reducing the myocardial content in phosphorylated Cx43 and the ratio of phosphorylated to total Cx43. The mice with iNOS deletion were, as compared with the wild-type mice, relatively protected against reduced Cx43 expression and the consequent depression in cardiac performance.

Propofol has also been shown to down-regulate iNOS expression in macrophages activated by lipopolysaccharide3 and in a model of testicular ischemia-reperfusion injury in rats.4

Furthermore, propofol, as compared with sevoflurane, provides major protection against ischemia reperfusion injury induced by aortic clamping in a piglet model,5 reducing more the systemic inflammatory response and the expression of nuclear factor-kappa B and iNOS.

It is therefore possible that the stronger depressive effect of propofol on iNOS, as compared with sevoflurane, causes a minor down-regulation of total and phosphorylated Cx43, contributing to the antiarrhythmic effects observed in Hirata et al.’s study.

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In Reply—We are grateful to Dr. Siracusano for the helpful comments regarding our article.1 As Dr. Siracusano suggests, the effects of propofol on inducible nitric oxide synthase (iNOS) might be another factor of preservation of phosphorylated-connexin 43 contributing to the antiarrhythmic effect.

While we have suggested that propofol reduced ischemia-induced arrhythmias through vagal nerve stimulation, the effect of propofol on nitric oxide production or iNOS have not been mentioned in our manuscript.

It has been reported that propofol has a number of nonanesthetic effects. Regarding nitric oxide, not only does propofol inhibit iNOS, but it also stimulates constitutive nitric oxide production as previously shown by Yamamoto et al.2 They showed that propofol caused the enhancement of nitric oxide production in cultured rat ventricular myocytes mediated by muscarinic acetylcholine receptors activation. This cholinergic nitric oxide–cyclic guanine monophosphate signaling pathway might be associated with our suggestion that propofol would stimulate the cardiac vagal nerve system.

Regarding the relation between antiarrhythmic effects via vagal nerve stimulation and nitric oxide production, there have been several studies showing that nitric oxide plays an important role. Black et al.3 demonstrated that nitric oxide mediates the vagal protective effect on ventricular fibrillation, and that those effects were blocked using the NOS inhibitor Nω-nitro-arginine and reversed by replenishing the substrate for nitric oxide production with L-arginine in an isolated rabbit heart. Moreover, Zhang et al.4 showed that a nitric oxide donor, S-nitroso-N-acetyl-L-1-penicillamine, partially inhibits the hypoxia-induced reduction of connexin 43 in H9c2 cells, immortalized ventricular myoblasts from rat embryos. This cholinergic nitric oxide-cGMP signaling pathway could be associated with not iNOS, but neural NOS.5

Based on these results, further investigation of the effects of propofol on nitric oxide production, iNOS, and neural NOS, which is associated with ischemia-induced arrhythmias, is required.

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