Correspondence

Nitroglycerin and cerebral oxygen saturation

To the Editor:

With respect to the article "Effect of intravenous nitroglycerin on cerebral saturation in high-risk cardiac surgery": the authors should be complimented on conducting a randomized double-blinded study to determine if systemic nitroglycerin administration may improve cerebral oxygenation during cardiopulmonary bypass (CPB).¹ Part of the authors' rationale for utilizing intravenous nitroglycerin was to compensate for potential endothelial dysfunction during CPB by providing an exogenous systemic nitric oxide (NO) donor. Endothelial NO synthase provides an important source on NO within the vasculature which is up-regulated in the brain and kidney during CPB, demonstrating its potential importance in regulating organ blood flow during cardiac surgery.²

In the current study, the authors hypothesized that intravenous nitroglycerin will prevent a decrease in cerebral tissue oxygen tension during CPB. Based on their observeds, they conclude that nitroglycerin infusion maintained cerebral tissue oxygen saturation during CPB, relative to the placebo group. This could be a valuable treatment effect as a recent clinical study has demonstrated improved patient outcome following CPB when brain tissue oxygen saturation is maintained above a target level during CPB.³

As a generalized NO donor, systemic nitroglycerin would be expected to cause indiscriminant systemic vasodilation in all vascular beds resulting in hypotension. This likely occurred as there was a twofold increase in the requirements for noradrenaline (1209 ± 1037 vs 546 ± 563 μ g) and phenylephrine (11303 ± 8910 vs 6330 ± 3931 μ g) in the nitroglycerin group to maintain an adequate mean arterial blood pressure (MAP). The authors comment that this increase was not statistically significant when corrected for CPB time and the relative dose requirement of alpha adrenergic agents during CPB was not provided.

This is an important factor, as systemic administration of alpha adrenergic agonists can increase cerebral blood flow and cerebral tissue oxygen tension in experimental studies.^{4,5} During CPB, phenylephrine administration resulted in preferential cerebral perfu-

sion which occurred at the expense of less vital organs.⁴ Increased cerebral perfusion with alpha adrenergic agonists may occur due to a lower responsiveness of alpha receptors within the cerebral vasculature, relative to systemic vessels. In addition, some cerebral blood vessels dilate in response to alpha adrenergic stimulation. This can occur by alpha adrenergic-mediated release of NO produced by neuronal NO synthase within perivascular nerves in the adventitia of cerebral blood vessels.⁶ The net effect of alpha agonist stimulation is to improve cerebral perfusion.

An alternate interpretation of the data from the current study would be that nitroglycerin caused generalized systemic vasodilation and a reduction in MAP which was effectively treated with double the amount of alpha adrenergic agents. Increased alpha agonist administration resulted in more profound systemic vasoconstriction, relative to cerebral vasoconstriction, leading to maintained, but not increased, cerebral tissue oxygen saturation in the experimental group.

Acknowledging the potential impact of alpha adrenergic agents in this study would assist the readers in determining the potential value of nitroglycerin infusion during CPB. It would also be helpful to know the amount of alpha agonists administered during CPB, as this was the time period during which brain tissue oxygen tension was observed to improve. In addition, the authors do not report how many patients underwent circulatory arrest as outlined in the methods section. This could have a significant impact on cerebral perfusion and outcome. Finally, the potential negative impact of nitroglycerin as an indiscriminant systemic vasodilator requires further discussion, as the nitroglycerin group paradoxically demonstrated evidence of reduced vital organ perfusion with a significant increase in CK-MB and myocardial and renal dysfunction in the two patients who died in the experimental group. The increase in postoperative bleeding in the experimental group may also reflect a negative impact of nitroglycerin therapy.

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Reply:

We thank Dr. Hare for his thoughtful comments regarding our study. His main concern relates to the impact of the higher doses of noradrenaline and phenylephrine administered to patients in the intravenous nitroglycerin group, and a possible confounding influence on the relationship between intravenous nitroglycerin and the cerebral oxygen saturation. Acknowledging the physiological value of his hypothesis, we reanalyzed our data with two separate repeated analyses of covariance models including group, time and vasopressor (one model with noradrenaline and one with phenylephrine). In each model, the interactions between the vasopressor and the two other variables were non-significant. A significant effect was found only for noradrenaline on the right cerebral oxygen saturation, which had no influence over time on cerebral saturations related to intravenous nitroglycerin. The Table shows the P values of the differences in cerebral saturations between groups at different times, with or without noradrenaline. Even in the model including noradrenaline, patients in the intravenous nitroglycerin group better maintained their cerebral saturation over time compared to patients in the placebo group, whose cerebral saturation decreased over time. Therefore, we believe that the use of intravenous nitro-

TABLE Contrast analyses of a repeated analyses of covariance comparing P values with and without the effect of NA

	P-value – pairwise comparisons of times for each groups (adjusted by NA)	P-value – pairwise comparisons of times for each groups (unadjusted)
Placebo: pre nitro vs pre CPB	0.3520	0.4187
Placebo: pre nitro vs post CPB	< 0.0001	0.0004
Placebo: pre CPB vs post CPB	0.0003	0.0068
Nitro: pre nitro vs pre CPB	0.4871	0.1850
Nitro: pre nitro vs post CPB	0.5847	0.4934
Nitro: pre CPB vs post CPB	0.8814	0.7663

CPB = cardiopulmonary bypass, NA = noradrenaline.

glycerin itself was associated with better maintenance of cerebral oxygen saturation under the conditions of our study. Furthermore, only one patient had a circulatory arrest during his surgery, which should not have impacted significantly our results. Finally, we agree that potential negative impact of intravenous nitroglycerin should not be neglected. The higher postoperative CK-MB values and the increase postoperative bleeding observed in the experimental group are concerning. If these effects are shown to be related to the use of nitroglycerin in further studies, the potential benefits for improved brain oxygenation will have to be balanced against the risks of this intervention. This is why we concluded in our article that: “Further studies are warranted to determine if the potentially harmful effects detected in the present study are real and significant.”

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Anesthetic considerations for a steroid-dependent high-risk patient undergoing minimally invasive cardiac surgery

To the Editor:

A minimally invasive cardiac surgery (MICS) approach to mitral valve surgery and atrial septal defect (ASD) repair provides advantages of a smaller incision, less trauma, and more rapid recovery, in addition to a shorter hospital length of stay.¹ The anesthetic requirements for MICS procedures are unique and involve special considerations quite different from