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Vasoconstrictive versus Vasodilatory Effects of Alpha-2 Adrenergic Agonists on the Spinal Microcirculation

To the Editor:—I read with interest the study about the effect of α -2 adrenergic agonists on the spinal pial microcirculation in dogs.¹ Using an *in vivo* technique, the authors observed a significant constriction of both pial arterioles and venules after topical application of clonidine or dexmedetomidine. They suggested that α -2 agonists might be superior to epinephrine or phenylephrine as local anesthetics additives since the latter induced a greater constriction of pial microvessels and therefore may jeopardize spinal blood flow. It has been known that α -2 adrenoceptors are present on both vascular smooth muscles and endothelial cells. The stimulation of α -2 adrenoceptors on vascular smooth muscles is associated with constriction in most vascular beds, whereas activation of endothelial α -2 adrenoceptors relaxes the vascular smooth muscle through a release of endothelium-derived nitric oxide. Distribution of α -2 adrenoceptors may be heterogeneous in various vascular beds. While α -2 adrenergic stimulation induces constriction of canine pial¹ and rat intestinal arterioles,² vasodilation predominates in response to clonidine in the porcine coronary³ and rat coronary⁴ and uterine⁵ microcirculation in which nitric oxide plays an important role in the regulation of regional blood flow. Thus, net effect of vascular α -2 adrenergic stimulation is determined by basal α -2 adrenergic activity in the vascular smooth muscle and endothelium. In addition, alterations in endothelial function and structure may affect endothelium-dependent α -2-adrenoceptor-mediated relaxation because of changes in the signal transduction of α -2 adrenergic pathway and production of nitric oxide. Previous study has shown that endothelial injury increases constriction of coronary arterioles to clonidine in septic rats.⁴ An increase in relaxation response to clonidine is observed in uterine arterioles of pregnant rats,⁵ likely caused by increased release of nitric oxide. However, no prior study has determined the effect of activation of endothelial α -2 adrenoceptors on vascular reactivity of the spinal microcirculation under different physiologic and pathophysiologic states (e.g., pregnancy and arteriosclerosis). It is plausible that changes in the endothelium-dependent α -2 adrenoceptor-mediated relaxation of pial microvessels may alter vaso-

constrictive effect of α -2 agonists and even duration of spinal anesthesia. Therefore, the conclusion about effectiveness of α -2 adrenergic agonists as local anesthetics additives needs to be reached from the experiment in which the contribution of endothelial α -2 adrenoceptors is determined.

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In Reply:—The question raised by Dr. Wang is very important on a scientific basis as well as on a basis of clinical relevancy of our study.¹

It is well known that vasoconstrictors such as epinephrine, phenylephrine, and clonidine prolong the duration of action of various local anesthetics after subarachnoid administration. The mechanism(s) for this prolongation involve both vasoconstriction and antinociception from α -2-stimulation. As Dr. Wang pointed out, vasoconstrictive response to α -2-adrenergic stimulation could be influenced by release of nitric oxide. Coughlan *et al.*² reported in an *in vitro* study that

N^w-nitro-L-arginine methyl ester, an inhibitor of nitric oxide synthase, was associated with exaggerated constrictor response to dexmedetomidine in coronary, but not in cerebral arteries. *In vivo*, McPherson *et al.*³ demonstrated that inhibition of nitric oxide synthase by systemic N^w-nitro-L-arginine methyl ester did not affect dexmedetomidine-induced decreases in cerebral blood flow. In addition, we also found that pretreatment with N^w-nitro-L-arginine methyl ester failed to influence the response of cerebral pial arterioles to 10⁻³M dexmedetomidine in the same experimental design.⁴ Further oppositely, it has been re-

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ported that in isolated rat's cerebral artery, dilation produced by α_2 -agonist was blocked with inhibition of nitric oxide synthase.⁵ Because we did not examine the effect of activation of endothelial α_2 -adrenoceptors on vascular reactivity of the spinal microcirculation *via* production of nitric oxide, we cannot exclude the possibility that the change of endothelial function attributable to different physiologic and pathologic states may alter the vasoconstrictive effect of α_2 -agonists and the effectiveness as local anesthetic additives.

In addition, we previously reported that the pial vascular effects of α_2 -agonists were modulated *via* potassium channel activation using a cranial window preparation. The vasoconstrictive effects of dexmedetomidine and clonidine seem to be mediate *via* activation of α_2 -adrenoceptors, and partly counterbalanced vasodilation *via* activation of adenosine triphosphate sensitive potassium channels.^{4,6} Moreover, we also reported that local anesthetics such as bupivacaine and ropivacaine *per se* affect spinal pial vessels, even to the different direction, affecting the duration during spinal anesthesia.⁷

Therefore, it is possible that not only nitric oxide, but also other possible vasoactive condition including adenosine triphosphate sensitive potassium channels activation and concomitantly used local anesthetics could modulate the vasoconstrictive effects of α_2 -agonists.

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Bias in a Further Model for Predicting PONV May Not Advance Current Knowledge

To the Editor:—Although we were happy to welcome a further addition to the literature on postoperative nausea and vomiting by Sinclair and colleagues, we were amazed by its omissions and a little more by its contents. In April 1998, an editorial posed the question "Can we predict who will vomit after surgery?"¹ and we were therefore surprised that this was not quoted by Sinclair and colleagues in their similarly entitled publication "Can postoperative nausea and vomiting be predicted?", which was submitted about half a year later.² We were even more surprised that the authors stated in the introduction that "the degree to which factors are predictors of PONV remains unknown." This is plainly incorrect since a number of authors have attempted to quantify risk factors for postoperative nausea and vomiting (PONV) using logistic regression models.³⁻⁷ None of these studies

were quoted in the introduction and some were briefly mentioned in the discussion only to be dismissed. The introduction gives the misleading impression that a completely new idea and concept has been developed.²

Palazzo and Evans were the first to use logistic regression analysis to quantify the relative impact of fixed patient factors on the probability of PONV in 1993.³ Their study was criticized for being only applicable to one type of surgery.² However, Dr Sinclair and colleagues failed to mention that this model was tested by Toner *et al.* in patients from a different hospital having a wide spectrum of operations with all sorts of anesthetists and anesthetics to test its robustness as a model.⁸ The study of Koivuranta *et al.*⁶ was criticized for no analysis of anesthesia-related factors. Again, this was misquoted as general and regional