Nitric Oxide in Vascular Endothelial Growth Factor Synthesis and Signaling

To the Editor:

Recently, Matsunaga et al.1 discussed the role of nitric oxide (NO) and vascular endothelial growth factor (VEGF) in coronary collateral growth. They have convincingly demonstrated that multiple occlusion of the left anterior descending coronary artery induced collateralization and was accompanied by VEGF protein production. In control dogs, VEGF peaked at day 3 of the repetitive occlusions but waned thereafter (Matsunaga et al, Figure 3).1 In contrast, in animals treated with N\textsuperscript{-}nitro-L-arginine-methyl ester (L-NAME), the VEGF expression was elevated throughout the entire 21-day experiment. The authors concluded that inhibition of NO synthase (NOS) prevents collateral growth but augments expression of VEGF. In our opinion, however, the results concerning the regulation of VEGF by NO can be interpreted in a different way.

Apparently, the sensitivity of detection of blotted proteins differed in the 2 experiments described by Matsunaga et al. The authors made a densitometric analysis of the expression of endogenous VEGF in comparison with the external standard, and they concluded that VEGF protein was elevated throughout the whole experiment in L-NAME–treated animals but not in controls. We suggest, however, that the external standard is not reliable for validation of the level of expression. The better option would be to use an internal protein standard. Matsunaga et al2 used the same amount of total protein for analysis (400 μg), which might be observed in Figure 4 of Matsunaga et al,1 in which the VEGF signal seems to be significantly lower in L-NAME–treated animals than in controls. To accurately estimate the concentration of VEGF in interstitial fluid, we normalized to a different effect on VEGF synthesis than does short-term treatment with L-NAME.

Our recent data2,3 and studies by Kimura et al4 and Frank et al5 indicate that NO induces VEGF synthesis in vascular smooth muscle cells, tumor cells, and keratinocytes, respectively. Thus, NO is not only a downstream mediator of VEGF signaling in endothelial cells but also can operate in an upstream direction, inducing VEGF synthesis.

We showed that in nonischemic conditions, L-NAME2,3 as well as asymmetric dimethylarginine,2 an endogenous inhibitor of NOS activity, decreased VEGF synthesis. Such an effect can be also observed in Figure 4 of Matsunaga et al,1 in which the expression of VEGF mRNA in nonischemic myocardium seems to be significantly lower in L-NAME–treated animals than in controls. In contrast, L-NAME strongly enhanced VEGF expression in ischemia. Thus, the effect of NO on VEGF synthesis might be different in normoxic and in hypoxic conditions.

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