Cerivastatin, a Hydroxymethylglutaryl Coenzyme A Reductase Inhibitor, Improves Endothelial Function in Elderly Diabetic Patients Within 3 Days

To the Editor:

In the July 24, 2001, issue of Circulation, Tsunekawa et al\(^1\) found that 3 days of statin therapy resulted in significant improvement of endothelial function, independent of lipid-lowering, in a study population of elderly patients with diabetes mellitus. The study provides new insight into statins' direct effect on endothelial function over such a short period of time. However, we have some questions concerning flow-mediated dilatation (%FMD) and nitroglycerin-induced dilatation (%NTG).

Noninvasive techniques for examining endothelium-dependent and endothelium-independent vasodilatation using sonography have been widely applied in human studies since their first publication.\(^2\) Endothelium-dependent dilatation, which is measured as %FMD, is thought to be caused by smooth muscle relaxation secondary to nitric oxide production and/or release from endothelial cells. Nitroglycerin administration is thought to provide nitric oxide exogenously. It is not known whether the amount of nitric oxide provided by sublingual administration of nitroglycerin is greater than that provided by flow stimuli. However, endothelium-independent vasodilatation caused by nitroglycerin is usually greater than %FMD.

Using this method, we have been examining human subjects. The total number of %FMD examinations exceeded 800 subjects, 520 of whom agreed to undergo measurement of %NTG together with %FMD. The coefficient of variation for measurements of %FMD was 5.84±0.25% and for %NTG was 3.97±0.24%, as we reported previously.\(^3\) The coefficient of variation for reproducibility of this ultrasound determination of %FMD was 9.77±0.82% and that of NTG was 7.24±0.49%. Because detection of subtle changes is critical to this method, reproducibility should be determined.

The mean %FMD/%NTG was 0.39, and its standard deviation was 0.26. Only 5 subjects (less than 1%) showed %FMD/%NTG greater than 1. These 5 subjects were patients with atherosclerotic disease who required routine nitroglycerin administration. %NTG tends to decrease according to age, which was discussed in the paper. However, it is difficult to believe that %FMD exceeded %NTG, which was observed after 3 days and after 3 months of statin therapy. We question the mechanism underlying this phenomenon.

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Response

We are grateful to Drs Hashimoto and Akita for their interest in our article.\(^1\) Their criticism concerns the mechanism that determines the level of endothelium-dependent flow-mediated dilatation (%FMD) to be greater than endothelium-independent dilatation induced by nitroglycerin (%NTG), which was observed after statin therapy. They questioned the adequacy of the results of our study based on their examination of %FMD and %NTG in 520 subjects, which showed a mean %FMD/%NTG of 0.39 that rarely exceeded 1.

First, we would like to assert the irrelevancy of comparing %FMD and %NTG using this method, because the conditions of the 2 measurements are completely different (reactive hyperemia and nitroglycerin sublingual perfusion). Moreover, both values were determined by only 1 condition (5 minutes prevention of blood flow and 300 μg nitroglycerin infusion). If one hopes to compare the components of endothelium-dependent smooth muscle cell relaxation with that of endothelium-independent relaxation, the same mode of drug administration or stimulus to induce vascular response should be applied. Further, one should compare the dose-response curve in at least 2 dose administrations. For example, it may be useful to get the results with regard to cumulative concentrations of acetylcholine and nitroglycerin infused in the brachial artery.\(^2\) Another factor to be considered is that %FMD has 2 components of NO release: shear stress-induced basal NO release and the flow stimuli-induced stimulated NO release after cuff release.\(^3\) Therefore, both NO release stimulated by an agonist such as acetylcholine and basal NO release should be measured by infusion of a NO synthase inhibitor such as N\(^6\)-monomethyl-L-arginine acetate or measurement of plasma NO\(_2^-\)/NO\(_3^-\) or cGMP, both of which were applied in our study.\(^1,4\) One should also be aware of patient’s profile, because %NTG could be reduced in elderly diabetic subjects. As was reported previously, both endothelium-dependent and endothelium-independent relaxations can be impaired in diabetic patients,\(^2\) and the impairment of endothelium-independent relaxation was greater than that of endothelium-dependent relaxation according to some reports. In our previous study using a rat model, diabetes and aging synergistically impaired endothelium-independent relaxation. The possible effect of aging in drug absorption by sublingual perfusion should be considered.

In conclusion, although a noninvasive technique using sonography is convenient and insightful, we are aware of the limitation of this methodology for interpreting the results. Inasmuch as our objective was to examine drug effect by comparing the results at different time-points, we must comment that the question raised is neither essential nor relevant because of the reasons described above.

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1. Tsunekawa T, Hayashi T, Kano H, et al. Cerivastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor; improves endothelial function...


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