contention. Corbett et al. reported that aminoguanidine and N\(^4\)-monomethyl-l-arginine inhibited interleukin 1\(\beta\)-induced nitrite and cGMP formation from RINm5F cells and reduced blood flow in hyperglycemic and diabetic rats. These findings, however, may be more relevant to inducible than constitutive nitric oxide formation and differ from those reported by Bucala and colleagues, who found that aminoguanidine improved endothelium-dependent relaxation when administered prophylactically to diabetic rats. Graier et al. reported that high concentrations of \(\text{D-glucose (44 mol/L)}\) increased calcium mobilization and cGMP formation in porcine aortic endothelial cells. Yet, in other experimental models of hyperglycemia, high glucose concentrations of \(\text{Na}\(^+\)-K\(^+\)-ATPase activity enhanced activity of protein kinase C, and increased production of vasoconstrictor prostanoids, actions that might impair endothelium-dependent relaxation.

Thus, it is often difficult to extrapolate observations made in vitro to the whole organism, in which a variety of factors may account for nitric oxide synthesis and degradation. The majority of reports, both in vitro and in vivo, cited in our article and in a recent review have found that endothelium-dependent relaxation is impaired in experimental models of diabetes and in patients with diabetes mellitus. Our data demonstrate that endothelium-dependent relaxation is abnormal in a cross section of patients with insulin-dependent diabetes mellitus but do not allow us to determine when this abnormality occurs in relation to the onset of vascular complications. We found no correlation between either the duration of diabetes or control of hyperglycemia and endothelial function. Five of the 15 patients with diabetes mellitus had funduscopy evidence of retinopathy. The highest dose of the endothelium-dependent vasodilator methacholine chloride increased forearm blood flow 9.5 ± 1.5 mL per 100 mL/min in patients with retinopathy and 9.6 ± 1.5 mL per 100 mL/min in the group of patients without retinopathy (\(P = \text{NS}\)). All patients had normal renal function as determined by blood urea nitrogen and serum creatinine concentrations. It is possible that either fluorescein angiography or urinary albumin determination would have enabled us to detect a greater number of patients with evidence of microvascular disease. Our results differ from those of Smits et al., who found neither augmentation nor impairment of endothelium-dependent vasodilation in a smaller study of insulin-dependent diabetics who had no microvascular complications.

The correspondents' implications regarding the Diabetes Control and Complications Trial are somewhat misleading. The primary objective of that study was to assess the effect of glucose control on the development of retinopathy, and the study was not powered to evaluate the effect of intensive treatment on macrovascular complications. Nonetheless, intensive therapy reduced the risk of macrovascular disease by 41%, a value that did not quite achieve statistical significance. Thus, unfortunately, atherosclerosis is a frequently encountered complication of young diabetic patients. It remains to be determined whether reduced activity of endothelium-derived nitric oxide contributes to atherogenesis in these individuals.

Based on our findings and those reported by Calver et al. we conclude that endothelium-dependent vasodilation is abnormal in forearm resistance vessels of most patient with insulin-dependent diabetes mellitus and think it is unlikely that enhanced synthesis of endothelium-derived nitric oxide accounts for preserved or increased blood flow in selected regional circulations. In our article, we suggested a number of mechanisms that may explain abnormal endothelial function in these patients, including reduced synthesis or accelerated inactivation of nitric oxide. We have shown previously that l-arginine improves endothelium-dependent relaxation in forearm resistance vessels of hypercholesterolemic humans and agree that this approach should be explored in patients with diabetes. It is unlikely that vascular smooth muscle reactivity was impaired in our patients because their forearm blood flow responses to nitroprusside, verapamil, and phenylephrine were similar to that observed in normal subjects.
on average 5 days after infarction also successfully attenuated a progressive increase in left ventricular volume. The majority of these patients had postinfarction angina or reversible thallium defects. Further work will be needed to confirm this observation that reperfusion days after infarction attenuates remodeling as well as to more clearly define the mechanism by which opening an infarct-related artery influences infarct healing and reduces progressive ventricular structural change.

The authors also state that previous clinical studies have failed to dissociate the benefit of late reperfusion on ventricular dilation and the potential confounding influence on infarct size. However, analysis of a study by Jeremy and colleagues indicates that the beneficial effect of a patent artery on left ventricular volume is independent of infarct size. In this clinical study, left ventricular dilation was more marked in patients with an occluded vessel than in patients with similar-sized infarcts in whom the artery serving the infarcted zone was angiographically patent.

Therefore, although this study by Hirayama and colleagues confirms the previous work of Jeremy and other investigators, many issues regarding the importance of a patent infarct artery need to be resolved. These include the mechanism of benefit of this approach and the time window of benefit during which ensuring patency is likely to be of importance. Finally, studies are needed to assess whether the potential benefit of a patent artery on ventricular remodeling is as crucial in the setting of standard postinfarct care, which today includes pharmacological agents such as converting enzyme inhibitors, which are known to prevent or attenuate early left ventricular volume changes.

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References

Reply
We thank Dr McDonald for his comments on our recent article.1
First, Dr McDonald suggests that the delayed reperfusion beyond 24 hours might be effective for the prevention of left ventricular remodeling according to data of Nidorf and colleagues.2 The late reperfusion group in their study included 13 patients with postinfarction angina or ischemic myocardium and 3 patients with spontaneous thrombolysis after failed thrombolysis. Thus, the exact time of reperfusion in these 3 patients was not clear. We excluded such patients from our study to clarify the duration from the onset to reperfusion. Patients who submitted to angioplasty of the occluded artery later, who were involved in their study, were also excluded because the reocclusion of the reperfused artery may change the reperfusion time. The clinical course of these patients also may be different from the ordinal one in patients with acute myocardial infarction. Thus, we concluded that the benefits obtained by reperfusion of an infarct artery beyond 24 hours has not yet been clarified.

Second, Dr McDonald suggests that the patency of the infarct-related artery reduced the infarct expansion without the reduction of the infarct size according to the study of Jeremy et al.3 This study was well designed and suggested the importance of the patency of the infarct-related artery. However, the time of reperfusion was undefined in patients with a patent infarct-related artery; this group included the early spontaneous reperfusion as well as late spontaneous reperfusion. Nevertheless, they compared the changes in left ventricular size between patients with a reperfused artery and those with an unreperfused artery using the creatine kinase (CK) level. It is difficult to compare the infarct size by CK level between two groups because CK release was enhanced in the case of reperfusion.4,5 We used two indices for determining the infarct size as noted in our article, that is, defect volume and peak CK activity. The dynamics of CK was influenced by the reperfusion; however, defect volume was less influenced by the reperfusion.6 In addition, peak CK activities of the late-reperfused group were greater than those of the nonreperfused group in our study, whereas the defect volume showed reverse relation. Thus, it is difficult to normalize the infarct size by peak CK level between cases with or without reperfusion. Again, we would like to emphasize the point that we clarified the time from onset to reperfusion in each case, measured the infarct size, and compared left ventricular volumes between the patients with or without reperfusion. The conclusion was consistent with that of Jeremy et al, but the study design was completely different.

Finally, we completely agree with Dr McDonald's suggestion mentioning that we should assess whether a patent artery still has beneficial effect on left ventricular remodeling with the use of the pharmacological intervention such as an angiotensin-converting enzyme inhibitor. We do not have the results yet. Additional prospective, randomized study for the combination of late reperfusion and pharmacological intervention is necessary.

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