ischemic adaptation in group C versus group N. Unfortunately, the authors have not taken into account that the ECG measures the sum of CR and IP and not IP, as they indicated for the group N (see above). As long as one cannot be certain that the instrument for the measurement of collateral flow is very sensitive, it is conceptually wrong to disregard a contribution of CR to IT in patients with (possibly) poor collateral channels. Considering the quality of their Figure 1, it is questionable whether the accuracy and precision of MCE are sufficient to discern subtle changes in collateral perfusion during subsequent occlusions, a prerequisite to answer the question of this study. Using the alternative conclusion, the interpretation of the data of the study is straightforward:

1. MCE was sharp enough to detect collateral perfusion during the first occlusion in group C.

2. The group with well developed collateral channels did not reveal marked ST segment changes during the first occlusion because the collateral channels were sufficient to (almost) prevent myocardial ischemia. "Sufficient" collateral channels providing a flow ≥30% compared with the antegrade flow through the patent vessel prevent intracoronary ECG signs of ischemia (2,3).

3. Absent ECG signs to start with in group C could not diminish further during subsequent occlusions, even in the presence of IP or prominent CR, or both (i.e., in this situation, the ECG was too blunt to detect IT due to CR or IP). However, it did not detect no IP.

4. Conversely, MCE was too blunt to detect collateral perfusion during the first occlusion in group N.

5. The collateral perfusion present but undetected in group N was insufficient to prevent ECG signs of myocardial ischemia. It cannot be determined whether the reduction of ST segment elevation during subsequent occlusions was caused by CR or IP. Data from our laboratory using intracoronary measurements of collateral flow indicate that CR contributes to diminished ECG signs of ischemia during repeated occlusions also in patients with few collateral channels.

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Reply

In animal experiments, it has been shown (1–3) that ischemic preconditioning (IP) occurs in the absence of collateral recruitment (CR). In a recent issue of the Journal (4), we studied whether IP also occurs in humans. Myocardial contrast echocardiography (MCE) was used to demonstrate that ischemic tolerance is acquired independently of CR in patients during repeated coronary occlusion and hence to conclude that IP and CR may play independent roles in ischemic adaptation in humans as well as in animals.

Seiler assumed the presence of significant collateral circulation, which was too poor to be detectable with MCE, and claimed that collateral flow contributes to IP. His consideration is based on his own data that intracoronary measurements of collateral flow increased during repeated coronary occlusion in patients with few collateral channels (5,6). Although the question he raised is quite interesting and important, it is difficult to admit all of his claims. Epicardial collateral flow may well be different from myocardial perfusion through collateral channels. This difference has been clearly shown even in humans by several groups. In addition, MCE is usually more sensitive than other conventional techniques in detecting myocardial perfusion in humans. Most important, the presence of epicardial collateral flow, which is commonly assessed with coronary angiography and measurements of coronary flow velocity patterns, is not necessarily evidence of myocardial perfusion through collateral channels (7,8). Epicardial collateral steal and changes in the hemodynamic state are included in such features. Of course, there may well be some collateral perfusion even in patients without MCE-determined collateral flow. However, we may state that 1) MCE is the only currently available method for assessing myocardial perfusion through the collateral circulation in the clinical setting; 2) it is remarkable how the two groups of patients can be differentiated with the data of MCE-determined collateral flow; and 3) many experimental investigations have shown evidence of IP independently of CR. Accordingly, we may conclude that IP occurs independently of CR during repeated coronary occlusions in humans, at least in terms of MCE-determined CR.

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Angiographic Findings and Outcome in Diabetic Patients With Myocardial Infarction—the GUSTO-I Experience

In their article on the results of thrombolytic therapy in diabetic patients, Woodfield et al. (1) found a higher mortality rate among

patients with than among those without diabetes. This finding could not be explained by the presence of heart disease itself, even after clinical and angiographic variables were adjusted. Diabetes was thus concluded to be an independent determinant of mortality at 30 days after myocardial infarction. In a previous report (2), the same authors observed that 24% of patients died of strokes, without noting the variable of diabetes. Hemorrhagic strokes are known to be more common in diabetic patients (3), and if we also consider that there were more patients with hypertension in the diabetic group (53 vs. 34, $p < 0.001$), this would explain the higher death rate in that group (4). However, in their latter report, we do not know how many patients died of strokes.

The authors did not find any difference in left ventricular function after myocardial infarction, despite clinical variables that showed a higher rate of heart failure among diabetic than nondiabetic patients. The lack of association seems to be an issue of overmatching (5) rather than of diabetic myocardiopathy, as the authors suggest. Patients with reocclusion treated with either scheduled or emergency angioplasty were not included in the analysis of ventricular function; it seems that only a small number of patients with a patent infarct-related artery (<20% of the whole group) were chosen. In other words, patients selected had undergone successful thrombolysis with normal flow and had no recurrent ischemia or angina pectoris. That said, we would like to know how many of the 455 patients experienced heart failure so to establish whether a difference in left ventricular function truly exists in the diabetic group.

Finally, we would like to point out the possibility of a selection bias in this study. The GUSTO-1 group included only patients who had experienced <6 h of pain, thus making the results valid only for those diabetic patients admitted to coronary care units and not for the greater number of patients first admitted into other hospital wards or who simply remain at home during a silent heart attack. The mortality rate for diabetic patients with an asymptomatic heart attack is considered to be 50%. This rate suggests that patients with a silent heart attack could have a more serious coronary illness or that they may have lacked access to timely care such as that proposed by the GUSTO-1 group (6).

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Reply

Iris and Villasis have suggested that the mortality difference we noted between patients with and without diabetes in the GUSTO-1 angiographic study (1) may be at least in part due to differences in the incidence of stroke between these groups. The stroke rates in patients with and without diabetes were not significantly different: 2.6% (8 of 309) versus 1.5% (32 of 2,113), respectively ($p = 0.17$). Hemorrhagic stroke was a rare event, occurring in 3 patients with and 13 patients without diabetes. There is no information available regarding hemorrhage in the three patients with stroke. Strokes were hemorrhagic in 43% of patients with diabetes and in a similar proportion of those without diabetes ($p = 0.9$). The mortality rate 30 days after myocardial infarction was 50% (4 of 8) in patients with diabetes who had a stroke versus 31% (10 of 32) in those without diabetes ($p = 0.3$). However, the cause of death, was considered to be stroke in only one patient, and this patient did not have diabetes. Contrary to the assertion of Iris and Villasis, the initial GUSTO-1 angiographic trial report (2) did not state that 24% of patients died of stroke. Only the number of strokes and intracranial hemorrhages were reported (2), not mortality as a result of these events. It is clear from the above data that mortality due to stroke did not contribute to the excess mortality noted in patients with diabetes in this trial. We would also like to point out that diabetes was not an independent determinant of hemorrhagic stroke in the 41,021-patient GUSTO-1 trial (3).

Iris and Villasis have suggested that the failure to find a difference in systolic left ventricular function between patients with and without diabetes despite the higher incidence of heart failure in the diabetic patient group may have been the result of the subgroup of patients we chose for ventricular function analysis (i.e., only those with patent infarct-related arteries 90 min and 5 to 7 days after thrombolysis), which contained only a small number who developed heart failure. 1) We would like to point out that as stated in the introduction of the report, the specific purpose of our study was to determine whether diabetes has an effect on the response to ischemic injury and subsequent reperfusion after myocardial infarction—hence the choice of that particular subgroup of patients. However, it is correct that there is no difference in the proportion of patients with and without diabetes who experienced heart failure during the hospital period in this particular subgroup (4% vs. 7.4% respectively, $p = 0.4$). However, analysis, of the entire group of patients who underwent ventriculography within 24 h of entry into the trial, regardless of infarct-related artery patency status (215 with, 1,467 without diabetes) demonstrated no difference in ejection fraction between those with and without diabetes ($58 \pm 0.4\%$ vs. $57 \pm 1.0\%$, respectively, $p = 0.2$) despite a difference in the proportion of those with and without heart failure (18.7% in those with diabetes vs. 12.1% in those without diabetes, $p = 0.007$). Also, similar ejection fractions were noted in this group at 5- to 7-day postinfarction ventriculography in those with and without diabetes (58 ± 0.4 vs. 57 ± 1.3, respectively, $p = 0.4$). These data support our original observation that the difference in heart failure after myocardial infarction in patients with compared with those without diabetes is not explained by differences in systolic left ventricular function. We would also point out that diabetes was not a significant determinant of either regional or global systolic ventricular function 90 min or 5 to 7 days after thrombolytic therapy by multivariable analysis (1).

We would agree with the last point raised by Iris and Villasis that the results of this study may not necessarily apply to all patients with