REPLY

We appreciate the comments made by Drs. Lin and Wright. The essence of their letter seems to be that clarification of the mechanism whereby sulfonylurea drug use confers increased risk could prove helpful in determining our best course of patient care. We agree completely, but unfortunately available data are not yet sufficient.

A sensible, although unproven, mechanistic explanation for increased mortality during profound ischemia blames sulfonylurea interference with K_\text{ATP} channel function. This action, as demonstrated in many studies (1), impairs endogenous cardioprotective mechanisms and may enhance arrhythmogenesis. In our study (2), the cause of in-hospital mortality for sulfonylurea-treated patients was chiefly cardiogenic shock plus a few arrhythmic deaths. We sought a relation between sulfonylurea use and malignant arrhythmias, but none was found, suggesting that any such effect must be small relative to interference with other endogenous cardioprotective mechanisms. As noted in our report, however, mechanisms other than interference with K_\text{ATP} channel function could explain increased risk of death with sulfonylurea drug use.

Late all-cause and cardiac mortality rates were described in our report, and, as expected, these patients died chiefly of cardiovascular causes. Obviously, only hospital survivors were eligible for continued monitoring, but it does not follow, as suggested by Drs. Lin and Wright, that an early increased mortality risk would necessarily translate into lower late risk for these patients. Indeed, if the postulate regarding this class of drugs is correct, the survivors continuing on sulfonylurea drugs may have been at continued increased risk. However, it was not known how many survivors continued taking sulfonylurea drugs after hospital discharge.

As Drs. Lin and Wright point out, our report is consistent with a large body of indirect clinical evidence implicating sulfonylurea drugs with increased risk. Alternative hypoglycemic drugs are available, but existing data are not yet sufficient to make a blanket recommendation to switch patients from sulfonylurea drugs. Newer agents, such as the insulin-sensitizing thiazolidinediones (e.g., troglitazone) and the biguanide compounds (e.g., metformin), do not appear to have the deleterious cardiac properties of the sulfonylurea drugs, but may cause other troubles: troglitazone may cause significant hepatotoxicity and is not recommended as first-line therapy (3), and metformin may cause lethal lactic acidosis, especially in patients with renal insufficiency who are exposed to radiologic contrast agents (4). Furthermore, many patients will require combined drug therapy for optimal diabetic control (5).

More research is needed before a policy statement in this matter can be justified. In this regard, corroboration of our findings from larger data sets, data generated by several ongoing studies that tabulate diabetic drug therapies and especially prospective studies such as the planned Bypass Angioplasty Revascularization Investigation (BARI II) trial, will be of great importance.

We would be happy to support the work of Drs. Lin and Wright by providing information on our patients that might be of use in their meta-analysis.

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Risk of Sulfonylurea Drugs Is Underappreciated

Garratt et al. (1) are to be congratulated on their excellent retrospective study, which suggests that sulfonylurea hypoglycemic drugs increase early mortality after direct angioplasty for acute myocardial infarction. The data suggest that the increased mortality associated with the sulfonylurea drugs is due to pump dysfunction with cardiogenic shock. Unfortunately, the report does not include a breakdown of the causes of in-hospital or late mortality. One might predict that because early mortality was higher in the sulfonylurea group, and these were presumably the higher risk patients, late mortality would be less in this group. This predicted decreased risk would be cancelled if the increased risk associated with the sulfonylurea drugs continues, as is likely to be the case. Other information that is missing from this study is when the patients who died took their last dose of sulfonylurea and what sulfonylurea drug they were taking. The most likely mechanism of toxicity of the sulfonylureas drugs—abolishing ischemic preconditioning through inhibition of the K_\text{ATP} channel—would require the presence of a substantive amount of the drug at the time of the myocardial infarction owing to recent intake or a long half-life of the drug in the body.

This study provides further evidence that patients are dying unnecessarily from use of a sulfonylurea drug. It supports the findings of the randomized, controlled trials, such as the University Group Diabetes Program (UGDP) Study (2,3) and the recently published United Kingdom Prospective Diabetes Study (UKPDS) Study (4,5). The UGDP study demonstrated increased cardiovascular mortality in tolbutamide-treated patients as compared with those who received placebo. The UKPDS trial showed a similar reduction of blood glucose with sulfonylurea drugs and metformin as compared with diet, but there was no reduction in cardiovascular events with sulfonylurea drugs (4) and a highly statistically significant reduction in cardiovascular events with metformin (5).

Therefore, there is substantial reason for exercising caution with the prescription of sulfonylurea drugs to diabetic patients. We have done a meta-analysis of studies of diabetic patients who had a myocardial infarction and found that the chances of dying are increased if the patient is taking a sulfonylurea drug versus following a diet alone (unpublished data). If Garratt et al. (1) could separate the group 2 patients into those treated with diet alone, insulin or other hypoglycemic drugs, we could add their results to our meta-analysis. These data, along with the other information mentioned earlier, could be published in response to this letter.
In the meantime, it is essential that doctors become more aware of the risks of the sulfonylurea hypoglycemic drugs and use them cautiously, when all other therapeutic options have been exhausted.

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Describing Patients With Discordant Ventriclearterial Connections

I congratulate Blume et al. (1) on the excellence of their analysis of patients undergoing the arterial switch operation. I am surprised, however, when they state that the larger part of their patient group had “d-transposition,” without providing further definition of this contentious term. Does this mean, for example, that they excluded all those patients with complete transposition in which the aorta was to the left, such as those with mirror-imaged atrial arrangement (transposition [I,L,L])? And did they include those patients with a congenitally corrected transposition in which the aorta was to the right-sided aortas, such as those with the transposition [I,D,D]? The group from Boston should now describe the anatomy of their patients with the same accuracy of analysis which they apply to their results.

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REFERENCE


REPLY

We thank Dr. Anderson for his comments. We agree with him that the importance of anatomic accuracy cannot be overemphasized. We did not exclude, on the basis of the spatial relation of the aortic valve relative to the pulmonary valve, any patient from the analysis. In fact, the interrelations between the semilunar valves were specified in the Results section of our report. Furthermore, we specified that only one patient had transposition of the great arteries with visceralaostral situs inversus (segmental anatomy [L,I,L]), and that patient was included in the analysis. We also specified that patients with physiologically corrected transposition of the great arteries [S,L,L] were excluded.

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Coronary Endothelial Dysfunction After Kawasaki Disease

Although the question addressed in the article by Yamakawa et al. (1) is interesting, there are several issues to be discussed with respect to the methods and interpretation of the results.

Study protocol. The dose–response curve of normal coronary arteries to acetylcholine (ACh) in their study is inconsistent with previously established pharmacologic properties of coronary arteries, on the basis of in vivo and ex vivo data in humans (including children) and animals (2,3). Although ACh, in fact, dilated normal epicardial coronary arteries only at high estimated concentrations (3.0 to 6.0 μmol/liter, estimated final blood concentrations) in their study, it has been established that ACh does so in a dose-dependent manner at 0.01 to 1.0 μmol/liter, at which level the contribution of nitric oxide to ACh-induced response has been demonstrated (2,3). This difference might be due to the short infusion time of ACh (30 s) in their study, as compared with 2 to 3 min in other studies. What could be the mechanism of the ACh-induced vasodilation at 3.0 to 6.0 μmol/liter, but not at 1.0 μmol/liter? In addition, the dose of ACh could be individualized when it is administered into either right or left coronary arteries in children of different ages. Because Yamakawa et al. (1) showed ACh-elicited paradoxic vasoconstriction at 10.0 μmol/liter, the relatively narrow range of effective ACh concentrations, as compared with those in previous reports, might in fact have produced highly variable responses to ACh.

Analysis of coronary angiogram. Although Yamakawa et al. concluded that normal coronary arteries but not regressed aneurysm exhibit a normal ACh response in patients with Kawasaki disease (KD), the angiograms could be investigated more cautiously. They showed in Figure 3 that normal coronary arteries after KD (left main coronary artery and distal portion of the left circumflex artery [LCx]) dilated in response to ACh, whereas the regressed aneurysm (proximal portion of the left anterior descending coronary artery [LAD]) constricted. Readers might observe, however, that other segments (proximal portion of the LCx and...