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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REFERENCES


Describing Patients With Discordant Ventriculoarterial 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 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 viscerotrautal situs inversus (segmental anatomy [I,L,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...
distal portion of the LAD) in normal coronary arteries on the same angiogram, in fact, seem to constrict without aneurysm, suggesting that normal coronary arteries after KD also exhibit impaired ACh-induced vasodilation in their protocol. In other words, even the proximal portion of the LAD could constrict due to only the history of KD, without the effect of aneurysm. The cause of segmentally heterogeneous ACh responses is immediately unknown. To demonstrate the association between aneurysm or history of KD and ACh responses, specific diameter-matched and corresponding segments should be compared among risk factor–matched groups (2–5). Although Yamakawa et al. tried to compare each segment between study groups, they only referred to the “trend” of the difference, not the statistical difference in each segment between study groups. In addition, comparable ACh-induced vascular responses among different types of lesions, as evaluated in multiple segments of patients in their report, would not preclude the possibility that some susceptible segments without aneurysms in KD groups exhibit abnormal ACh responses, as shown in our report (3).

**Interpretation of the results.** Although Yamakawa et al. showed impaired ACh-induced vasodilation in regressed aneurysm, it might not be concluded that “endothelial function” is impaired in these lesions, unless normal responses to an endothelium-independent vasodilator are shown (2,3). In addition, the high concentration of ACh, as used in their protocol, could elicit a stronger “direct” vasoconstrictor response in the disease state, which could have been misinterpreted as representing impaired endothelial function (2). Accordingly, a more accurate conclusion would be that “ACh-induced vasodilation” is impaired late after KD.

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**REFERENCES**


**REPLY**

We appreciate the kind comments of Dr. Mitani regarding our report and for sharing their experiences with us. We agree with him that the adequate dosage of acetylcholine (ACh) required to assess vascular function is uncertain for children. Thus, we preliminarily studied the effects of different doses (5, 15, 30 and 50 μg) in a normal coronary artery and in regressed coronary aneurysms after Kawasaki disease (KD) in four children. If we used 50 μg of ACh, the normal coronary artery became constricted, and if 5 μg was used, the normal coronary artery did not dilate. When we used 15 μg and 30 μg of ACh, significant dilation was observed in the normal coronary arteries, and vasoconstriction appeared in the regressed aneurysms. Thus, we chose a lower dose of 15 μg of ACh in this study. Thus, 15 μg of ACh chloride was diluted in 5 ml of warm 0.9% saline solution (to produce a coronary blood concentration of ~3.0 × 10⁻⁶ mol/liter) and was infused into the left or right coronary artery (LCA or RCA) over 30 s. In addition, in the other study in question, a similar dose of ACh was used to assess endothelium-dependent vasomotor function (2).

In our study, we measured normal sites where coronary aneurysms had not developed to the acute stage and also demonstrated normal findings at follow-up coronary angiography. We chose these sites to include coronary segments located at least 10 mm from the site of previous aneurysms to eliminate the effects of vasoconstriction or vasodilation of other sites, as shown in Figure 3 in our article. The distal portion of the left anterior descending coronary artery (LAD) seems to constrict from reducing the proximal coronary flow caused by vasoconstriction of the distal portion of this artery (Fig. 3). In addition, there was no significant difference in the ACh responses between the LCA (11.2 ± 6.3%) and RCA (13.1 ± 8%) (p = NS) in our control subjects.

Mitani et al. (3) have reported that constriction of a normal region of the coronary artery after KD was constricted with ACh infusion. However, several differences existed between our study and their study. The interval between KD onset and the time of their investigation was shorter than that in our study (3). Pathologic studies have demonstrated that infiltration by inflammatory cells can occur in the coronary artery, even within six months after the acute phase of KD (4,5). We studied only patients with KD with an interval >10 years after the onset of KD to eliminate any direct effects of acute KD vasculitis. In addition, their patients did not have a complete normal coronary artery at the acute stage; instead, they had only a normal LAD. In contrast, in our new study, we investigated the vascular function of the coronary artery using an intracoronary infusion of ACh chloride and isosorbide dinitrate (ISDN) in five patients with KD who had a completely normal first coronary angiogram (6). The patients with a normal coronary artery after KD were not significantly different, in their response to either ACh or ISDN infusion, from the control subjects. These findings suggest that such coronary arteries had normal function of the endothelium and smooth muscle even over the long term. On the basis of our studies (1,6,7), we conclude that patients with long-term persistent coronary aneurysms and regressed coronary aneurysms after KD have vascular dysfunction. These patients should be counseled to avoid potential risk factors for atherosclerosis and that long-term follow-up is needed into adulthood.

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