Coronary Endothelial Dysfunction in Patients With Hypertrophic Cardiomyopathy

To the Editor:

I read with great interest the letter by Kodama-Takahashi et al.1 I and disagree with their comments on several points, outlined here.

First, temporal occlusion of the left anterior descending (LAD) coronary artery that developed in some patients was induced by acetylcholine infusion at the highest dose.2 This occlusive response was also classified as a marker of coronary endothelium-dependent dysfunction.2 Importantly, at a lower dose, acetylcholine constricted the LAD in these patients.2

Second, in some patients, even a high dose of acetylcholine (100 μg) induced mild vasodilatation (not vasoconstriction) in LAD.3

Last, Maseri et al4 proposed that it would be reasonable to assume that nonocclusive spasm (defined as segmental constriction reducing local diameter by at least 50% in arteries without significant stenosis) represents the obligatory substrate of occlusive spasm in response to a stronger stimulus. In the article by Kodama et al,5 the stronger stimulus seems to be the highest dose of acetylcholine. In some patients with endothelial dysfunction, acetylcholine induced vasoconstriction, reducing the diameter >50%.2,6 To evaluate whether patients in the study by Kodama et al2 have coronary endothelial dysfunction, I postulated that the authors should present precise data. The dose-dependent effect of acetylcholine (according to the method description, acetylcholine was infused to LAD in increasing doses of 20, 50, and 100 μg) on reduction of LAD diameter should be provided. Also data concerning the occurrence of risk factors of endothelial dysfunction (hypertension, hypercholesterolemia, smoking, and/or diabetes mellitus) are needed to explore whether endothelial dysfunction is an intrinsic abnormality in the coronary artery system of patients with hypertrophic cardiomyopathy (HCM).3 On the basis of his previous work,4,5 he has demonstrated that impaired endothelium-dependent vasodilatation of coronary resistance vessels, which is one of the potential mechanisms of myocardial ischemia, is seen in HCM, and that verapamil therapy improves this endothelial dysfunction.

When provocation tests for coronary vasospasm are performed in the catheterization laboratories of our hospitals, an intracoronary bolus injection of acetylcholine of 20 to 100 μg is used because of its effectiveness and safety.5,6 In our two previous studies,1,2 acetylcholine tests were performed in order to evaluate whether vasospasm at the level of epicardial coronary arteries occurred in patients with and without HCM. The purpose of the acetylcholine injections was not to evaluate whether subjects had coronary endothelial dysfunction. In the first study,1 coronary vasospasm was induced in 10 of 36 patients (25%) with HCM. At the dose we used, the specificity of the provocation tests using acetylcholine to detect coronary vasospasm is very high in the Japanese patient population.6 Furthermore, the same dose of acetylcholine does not induce coronary vasospasm in patients without vasospastic angina in Western populations.8 Thus, the transient total or subtotal occlusion of the epicardial coronary artery that is induced by the highest dose of acetylcholine we used is classified as coronary vasospasm, even in HCM patients.

Acetylcholine has two opposing effects: an endothelium-dependent vasodilator effect and a direct vasoconstrictor effect. The net coronary vasoconstritor response, either vasodilatation or vasoconstriction, depends on the balance between these two effects. In normal coronary arteries with a functionally intact endothelium, a low concentration of acetylcholine will induce vasodilatation. However, in diseased coronary arteries with dysfunctional endothelium, acetylcholine is expected to induce vasoconstriction even at the same concentration. Thus, a low concentration of acetylcholine, which corresponds to an estimated blood concentration in the coronary bed of 10^8 to 10^9 mol/L, has been used as a probe for testing endothelial function.9 However, even normal coronary arteries with intact endothelial function can be induced to respond to higher concentrations of acetylcholine by the direct effect of the agent on vascular smooth muscle. The dose of acetylcholine that we used, which corresponds to an estimated blood concentration in the coronary bed of approximately 10^9 mol/L, is so high that the direct vasoconstrictor effect overrides the endothelium-dependent vasodilator effect.9,10 Thus, a relatively high dose of acetylcholine is left ventricular contractile response to stress in the absence of coronary artery disease. Am J Cardiol 1998; 82:710–714

To the Editor:

We wish to thank Dr. Dimitrow for his continued interest in our articles.1–3 In his letter, he disagreed with our comment that from our two studies alone we are unable to conclude that endothelial dysfunction is an intrinsic abnormality in the coronary artery system of patients with hypertrophic cardiomyopathy (HCM).2 On the basis of his previous work,4,5 he has demonstrated that impaired endothelium-dependent vasodilatation of coronary resistance vessels, which is one of the potential mechanisms of myocardial ischemia, is seen in HCM, and that verapamil therapy improves this endothelial dysfunction.

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not suitable for separating the role of endothelial dysfunction from that of smooth-muscle hyperreactivity in epicardial coronary vasoconstriction.

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References


Cryptogenic Hemoptysis and Smoking

To the Editor:

Boulay et al (August 2000) showed that hospitalization for hemoptysis followed a seasonal pattern: the distribution of cumulative monthly hospitalizations for hemoptysis peaked in early spring and was lowest in summer. In their report, hospitalization for cryptogenic hemoptysis did not statistically differ from hospitalization for noncryptogenic hemoptysis in seasonal variation. Therefore, the hypothesis of infection being the most frequent cause of cryptogenic hemoptysis is dismissed.

A total of 42.2% of all hemoptysis cases were classified as cryptogenic in their article, a percentage that is markedly high compared with other previously published articles. CT scanning (often high-resolution CT) together with chest radiography and fiberoptic bronchoscopy has recently been performed to diagnose hemoptysis. Hirshberg et al reported a 93% diagnosis rate for hemoptysis using fiberoptic bronchoscopy together with CT. Even in a previous study, where CT was not used in the analysis, only 3 to 22% of all hemoptysis cases were classified as cryptogenic. Although the study by Boulay et al was multicenter with a large number of patients, their study design was retrospective and diagnostic procedures differed among institutions. Noncryptogenic hemoptysis may have been classified as cryptogenic because cryptogenic hemoptysis is an exclusive diagnosis. Boulay et al did not comment about the amount of expectorated blood for indication of hospitalization, so biases of disease may not have been limited among institutions.

Boulay et al also did not comment about smoking in their article. Adelman et al reported that 71.6% of cryptogenic hemoptysis patients were smokers, although they did not discuss enough about the causal relationship between cryptogenic hemoptysis and smoking. We have observed 51 hospitalized patients with hemoptysis from 1995 through 2000 in Kure Kyosai Hospital (the volume of expectorated blood was 20 to 500 mL/d). Six hemoptysis patients (12%) were considered cryptogenic according to the findings of CT and fiberoptic bronchoscopy. Four patients were men, and two patients were women. Almost all patients were middle-aged men, except for an 83-year-old man. Nineteen of 51 patients were smokers, although they did not discuss enough about the causal relationship between cryptogenic hemoptysis and smoking. Endobronchial appearance was normal except for bleeding. Four patients had bleeding from the upper lobe, and two patients had bleeding from the middle lobe or lingular segment. CT showed only local pulmonary opacity, which was compatible with bleeding. After discharge, four patients ceased smoking and two continued, but none relapsed. We think smoking is one of the causes of cryptogenic hemoptysis. Cryptogenic hemoptysis and smoking have not been adequately studied and further examination is needed.

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