Case Report

Successful Treatment of Symptomatic Coronary Endothelial Dysfunction With Enhanced External Counterpulsation

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Enhanced external counterpulsation (EECP) is a valuable therapeutic option for patients with coronary artery disease and refractory angina. Although the exact mechanisms by which this technique exerts favorable effects remain unclear, improvement in endothelial function is considered a potential mechanism contributing to the clinical benefit associated with EECP. We describe a young woman with severely symptomatic coronary endothelial dysfunction in the absence of obstructive coronary artery disease who experienced a dramatic and sustained reduction in symptoms in response to a standard 35-hour course of EECP.

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ACE = angiotensin-converting enzyme; CAD = coronary artery disease; ECG = electrocardiography; EECP = enhanced external counterpulsation; LAD = left anterior descending coronary artery

Enhanced external counterpulsation (EECP) is considered a valuable treatment option for patients with coronary artery disease (CAD) and refractory angina who are not amenable to standard revascularization procedures.[1] Prospective clinical trials and large treatment registries have shown major reductions in anginal symptoms and improvements in objective measures of myocardial ischemia in response to EECP in patients with symptomatic CAD.[2-5] By sequential early diastolic inflation and systolic deflation of 3 pairs of pneumatic cuffs wrapped around the lower extremities, EECP increases diastolic aortic pressure (diastolic augmentation) and reduces systolic pressure (systolic unloading) while enhancing venous return.[1] Although the exact mechanisms by which these hemodynamic effects translate into clinical benefit are unknown, improvement in endothelial function is thought to contribute to the favorable clinical effect of EECP. We describe a young woman with severely symptomatic coronary endothelial dysfunction in the absence of obstructive CAD who had a dramatic and sustained reduction in symptoms after a standard 35-hour course of EECP.

REPORT OF A CASE

A 29-year-old woman with a 2-year history of recurrent exercise-induced chest pain was referred to our institution for evaluation of coronary endothelial function. The patient was otherwise healthy and had no cardiovascular risk factors. Myocardial perfusion imaging with dipyridamole and sestamibi performed 2 years previously had identified anterior ischemia. Coronary angiography was unremarkable except for the occurrence of focal catheter-induced spasm of the proximal portion of the right coronary artery that promptly resolved after administration of nitroglycerin. Subsequently, the patient was treated with calcium antagonists, which led to a slight reduction of symptoms. Nitrates were not tolerated because of headaches. However, 3 months before the current presentation, the patient was hospitalized because of worsening chest pain. At that time, electrocardiography (ECG) showed ST-segment depression in the inferolateral leads without elevation of cardiac enzymes. Repeated coronary angiography revealed smooth coronary arteries and normal left ventricular function. The chest pain subsided after administration of nitroglycerin and nicardipine. However, despite continued therapy with various calcium antagonists (nifedipine, nicardipine, amlodipine, verapamil), a β-blocker (metoprolol), and an antidepressant (imipramine), the patient continued to have daily anginal episodes, with ambulatory ECG tracings suggestive of ischemia associated with these symptoms.

On presentation at our institution, the patient was pain free. Physical examination (including blood pressure) and ECG findings were within normal limits. Results of hematologic, rheumatologic, and endocrine studies were unremarkable. Coronary angiography, including intravascular ultrasonography of the left main coronary artery and left anterior descending coronary artery (LAD), revealed structurally normal vessels. Administration of adenosine into the left coronary system showed an intact endothe-

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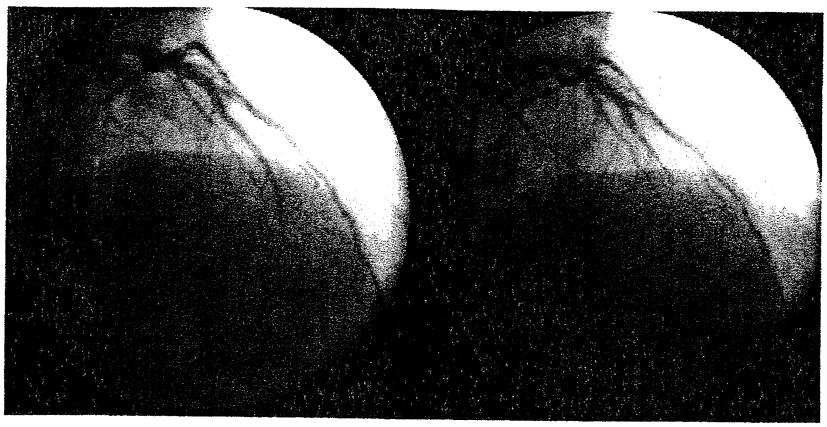

Figure 1. Coronary angiography of the left coronary artery at baseline (left) and during intracoronary infusion of the endothelium-dependent vasodilator acetylcholine (10^{-4} mol/L) (right). A Doppler guidewire within a coronary-infusion catheter is positioned in the left anterior descending coronary artery. Acetylcholine infusion leads to paradoxical vasoconstriction with complete obstruction of the otherwise normal left anterior descending coronary artery.

lium-independent microvasculature response, with a normal coronary flow reserve of 2.5. Coronary endothelial function testing with intracoronary infusion of graded doses of the endothelium-dependent vasodilator acetylcholine (10^{-6} to 10^{-4} mol/L) into the LAD was associated with a progressive decrease in coronary blood flow and paradoxical vasoconstriction of the LAD ultimately resulting in complete LAD occlusion, compatible with the presence of severe endothelial dysfunction of both the coronary microvasculature and the coronary macrovasculature (Figure 1). Importantly, intracoronary administration of increasing doses of acetylcholine was also accompanied by typical chest pain. In consideration of these findings, an angiotensin-converting enzyme (ACE) inhibitor (lisinopril) and L-arginine supplementation were added to the patient's existing treatment regimen.

Despite maximized calcium channel blockade, ACE inhibitor therapy, L-arginine supplementation, and nitrates (as tolerated), the patient's symptoms worsened during the subsequent months and severely impaired her functional capacity (Canadian Cardiovascular Society class IV angina). Because of her severe, medically refractory symptoms, the patient elected to undergo a 35-hour course of EECP. After completion of EECP treatment, the patient was free of angina and was able to perform her daily activities without the dyspnea or fatigability experienced before EECP. At the last follow-up visit 3 months after completion of EECP therapy, the patient was symptom free with a medical regimen of calcium channel blockade, ACE inhibition, and L-arginine supplementation.

DISCUSSION

Endothelial dysfunction is considered a key early event in atherogenesis.[6] Moreover, coronary endothelial dysfunction contributes to the manifestation of stable and unstable coronary syndromes in patients with established CAD.[7] Importantly, coronary endothelial dysfunction may lead to myocardial ischemia even in the absence of extensive obstructive CAD.[8,9]

Although our patient had no traditional cardiovascular risk factors and no manifestations of advanced atherosclerotic disease, severe coronary endothelial dysfunction was present. Importantly, the abnormal ECG tracings recorded during spontaneous symptoms and the fact that intracoronary acetylcholine administration was associated with typical chest pain similar to that experienced during exercise suggest that the patient's symptoms were indeed related to coronary endothelial dysfunction.

Several pharmacological strategies have produced long-term improvement in endothelial function, including ACE inhibitors, statins, and L-arginine.[10] However, clinical response to these interventions may vary depending on patient-related factors, as was true of our patient who remained severely symptomatic despite extensive medical therapy.

Enhanced external counterpulsation is considered a valuable therapeutic alternative for patients with CAD and refractory angina. Up to 80% of patients who undergo EECP therapy have a positive clinical response.[1] However, despite growing evidence for the clinical benefit and safety of EECP, the mechanisms contributing to its beneficial effects remain unclear.[11] Enhanced external counterpulsa-

tion is associated with an immediate increase in blood flow in various vascular beds, including the coronary arteries.[12,13] This increased blood flow may translate into enhanced vascular shear stress, a major stimulus for endothelial production and release of nitric oxide and a key factor in endothelial homeostasis.[14,15] Thus, improvement in endothelial function is considered a potential mechanism involved in the clinical benefit associated with EECP.[11] In support of this hypothesis, EECP treatment was shown to be associated with both an immediate and a midterm increase in plasma levels of nitric oxide in patients with CAD.[16,17] Moreover, we recently showed that EECP exerts both immediate and prolonged favorable effects on peripheral endothelial function in patients with symptomatic CAD.[18] These previous findings provided the basis for the off-label use of EECP in the current patient. The dramatic reduction in symptoms observed in our patient suggests that EECP may exert a favorable effect on coronary endothelial function.

It is well known that the use of medical devices may be associated with an enhanced placebo effect.[19] Thus, it may be argued that the reduction in symptoms experienced by our patient was due to a major placebo effect. Indeed, data from studies in patients with CAD who experienced considerable reductions in angina even in the absence of an optimal hemodynamic effect of EECP indicate that a placebo effect may contribute to the symptomatic benefit of EECP.[20,21] However, the results from the randomized placebo-controlled multicenter study of enhanced external counterpulsation (MUST-EECP) trial, which compared the effect of active EECP vs a sham EECP procedure, suggest that placebo effects have only a minor role as a mechanism responsible for the clinical benefit of EECP.[3] Moreover, although a certain placebo effect may be inherent in EECP, the presence of severe coronary endothelial dysfunction and the clear association between intracoronary acetylcholine infusion and typical symptoms before EECP therapy, as well as the sustained favorable effect of EECP on the patient's symptoms, suggest that improvement in coronary endothelial function is a likely mechanism responsible for the observed benefit in our patient.

In summary, by showing major clinical improvement in response to a standard course of EECP in a patient with isolated and severely symptomatic coronary endothelial dysfunction, our case further supports the concept that enhancement of coronary endothelial function may represent an important mechanism by which EECP exerts clinical benefit.

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