Global Biventricular Dysfunction in Patients With Asymptomatic Coronary Artery Disease May Be Caused by Myocarditis

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Background—The causal role of asymptomatic critical coronary artery obstruction in patients presenting with severe global biventricular dysfunction but no evidence of myocardial infarction is uncertain.

Methods and Results—Among 291 patients aged >40 years undergoing a noninvasive (2-dimensional echocardiography) and invasive (catheterization, coronary angiography, and biventricular endomyocardial biopsy, 6 to 8 samples/patient) cardiac study because of progressive heart failure (New York Heart Association functional class III or IV) with global biventricular dysfunction and no history of myocardial ischemic events, 7 patients (2.4%; 7 men; mean age, 49±6.9 years) had severe coronary artery disease (3 vessels in 4 patients; 2 vessels in 1 patient, proximal occlusion of left anterior descending coronary artery in 2 patients). Left ventricular end-diastolic diameter and ejection fraction by 2-dimensional echocardiography were 73±10.5 mm and 23±6.5%, respectively, and right ventricular end-diastolic diameter and ejection fraction were 39±7 mm and 29±7.2%, respectively. Biopsy specimens showed extensive lymphocytic infiltrates with focal myocytolysis meeting the Dallas criteria for myocarditis in all patients (in 5 patients with and 2 patients without fibrosis). Cardiac autoantibodies were detected with indirect immunofluorescence in the serum of 2 patients with active myocarditis. The 2 patients with active inflammation received prednisone (1 mg · kg⁻¹ · d⁻¹ for 4 weeks followed by 0.33 mg · kg⁻¹ · d⁻¹ for 5 months) and azathioprine (2 mg · kg⁻¹ · d⁻¹ for 5 months) in addition to conventional drug therapy for heart failure. At 8-month overall follow-up, cardiac volume and function improved considerably in immunosuppressed patients but remained unchanged in conventionally treated patients, of whom 1 died.

Conclusions—Global biventricular dysfunction in patients with severe asymptomatic coronary artery disease and no evidence of previous myocardial infarction may be caused by myocarditis. Histologic findings may influence the treatment. (Circulation. 1999;99:1295-1299.)

Key Words: myocarditis ■ coronary disease ■ heart failure

Dilated cardiomyopathy may be a common end-stage manifestation of chronic ischemic heart disease in the absence of a history of angina as a result of silent myocardial infarction or of myocardial hibernation.¹

In such patients, postmortem studies document regional or interstitial replacement fibrosis, or both, at the site of infarction and hypertrophy of residual myocytes.² ³

We report on a group of patients with angiographic documented severe coronary artery disease, without evidence of previous myocardial infarction, who presented with progressive heart failure and biventricular dysfunction, in whom diffuse biventricular lymphocytic infiltrates meeting the Dallas criteria for myocarditis was demonstrated by multiple biventricular biopsies.

Methods
Among 291 patients aged >40 years (162 men and 129 women; mean age, 51±6 years) referred to our institution between January 1, 1992, and November 30, 1997, because of progressive heart failure (New York Heart Association [NYHA] functional class III or IV) of recent onset (<6 months) and no history of myocardial ischemic events, 7 patients (2.4%) were found to unexpectedly have severe coronary artery disease at coronary angiography.

Characteristics of Patient Population
All 7 patients (7 men; mean age, 49±6.9 years) were hospitalized due to dyspnea on minimal effort (NYHA class III) in 5 patients and for dyspnea at rest (NYHA class IV) in 2 of recent onset (≤6 months).

No patient had a history of a flulike syndrome, but 6 had risk factors for coronary artery disease: hypertension in patients 1 and 2; hypercholesterolemia in patients 1, 2, 4, 5, and 6; hypertriglyceridermia in patients 4, 5, and 6; smoking in patients 1, 2, 3, and 4; and family history for ischemic heart disease in patients 2 and 3.

Physical examination revealed tachycardia with gallop rhythm in all patients and systolic murmur graded up to 3/6 at the apex in 5. Basal rales were present in 5 patients. Ankle edema with an enlarged and tender liver was present in 5 patients. Chest radiograph showed an enlargement of the cardiac silhouette with pulmonary congestion.

Received August 20, 1998; revision received November 20, 1998; accepted November 23, 1998.

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Circulation is available at http://www.circulationaha.org
and upper lung blood diversion in all patients. All patients underwent routine laboratory tests and serologic tests for cardiotropic viruses (echovirus, coxsackievirus B, cytomegalovirus, adenovirus, influenza virus, and parainfluenza virus) and for *Chlamydia pneumoniae*.

Patient sera were also tested for cardiac autoantibodies through the use of standard indirect immunofluorescence on 4-μm-thick unfixed fresh-frozen cryostat sections of blood group 0 human atrium obtained at the time of cardiac surgery from a patient with atrial septal defect. These sections were incubated with 1:5 to 1:40 dilution of patient sera and, after standard washing, were incubated with anti-human IgG antiserum, conjugated with FITC (Kallestad), and examined for immunofluorescence. Two sera were used as standard positive (antibody titer 1:40) and negative controls and were titrated in every assay; the intensity of immunofluorescence of the positive standard at 1:40 dilution was used as the threshold for positivity.

Cardiac studies included both noninvasive (resting ECG, Holter monitoring, 2-dimensional echocardiography with Doppler analysis, dobutamine stress echocardiography) and invasive (cardiac catheterization, coronary angiography, biventricular angiography, endomyocardial biopsy) examinations.

Dobutamine stress echocardiography was performed on all patients to investigate the presence of myocardial ischemia or hibernating myocardium. Dobutamine infusion was started at 2.5 μg·kg⁻¹·min⁻¹ and increased every 3 minutes to 5, 7.5, 10, 20, 30, and 40 μg·kg⁻¹·min⁻¹. Heart rate, blood pressure, and 12-lead ECG were recorded at rest and during each stage of test.

Endomyocardial biopsies were performed in the septoapical region of both ventricles, which was approached with a 7F (501-613A Cordis) long sheath and identified on a radiographic view using flashing of contrast medium. Three or 4 right ventricular (RV) and 3 or 4 left ventricular (LV) samples were drawn and processed for histology. Tissue specimens were fixed in 10% buffered formalin; 5-μm-thick sections were cut and stained with hematoxylin and eosin, Miller’s elastic van Gieson, and Masson’s trichrome.

**Results**

All values are expressed as mean±SD.

The 12-lead ECG was normal in 3 patients, showed a left bundle-branch block in 2 (1 and 5), and showed abnormal Q waves in the inferior and anteroseptal leads in the remaining 2 patients (patients 4 and 3, respectively). All patients were in sinus rhythm.

Holter monitoring failed to show transient ST-T segment ischemic changes or sustained ventricular arrhythmias, but frequent ventricular ectopic beats with some couples and triplets were present in all patients, and nonsustained ventricular tachycardia was present in patients 1 and 2.

Coronary angiography showed significant coronary artery stenoses (>70% lumen diameter stenosis of ≥1 major epicardial artery) in all patients. Four patients (1, 2, 4, and 6) had 3-vessel coronary artery disease, 5 had 2-vessel disease, and patients 3 (Figure 1, right) and 7 had an isolated proximal occlusion of the left anterior descending coronary artery (LAD). In particular, patient 1 had 95% stenosis of the LAD between the first septal and second diagonal branches, 90% stenosis of the proximal left circumflex artery, and a proximal occlusion of the right coronary artery; patient 2 had 75% stenosis of the LAD between the first septal and second diagonal branches, 80% stenosis of the left circumflex artery after the second obtuse marginal branch, a proximal occlusion of the second marginal branch, and an occlusion of the right coronary artery after the acute marginal artery; patient 4 had 95% stenosis of the first diagonal artery, 99% stenosis of the first obtuse marginal artery, and an occlusion of the right coronary artery after the acute marginal artery; patient 6 had 90% stenosis of the LAD between the first diagonal artery and the first septal branch, 95% stenosis of the left circumflex artery after the first obtuse marginal artery, and 99% stenosis of the posterior descending branch of the right coronary artery; and patient 5 had an occlusion of the LAD between the first diagonal branch and the first septal branch, 75% stenosis of the first diagonal artery, and a proximal occlusion of the right coronary artery. Collateral vessels were not visible in any of the cases. Biplane ventriculography failed to show segmental regional LV wall motion abnormalities and demonstrated global biventricular dilatation in all cases. LV and RV filling pressures and pulmonary artery pressures were elevated (Table).

In all cases, 2-dimensional echocardiography showed a severe global LV dysfunction (LV ejection fraction, 23±6.5%) without segmental wall motion or valvular abnormalities. LV wall thickness was mildly increased in patient 2 (LV posterior wall and interventricular septum, 1.2 mm) and was normal in the others. The LV and RV were dilated (LV end-diastolic diameter, 73±10.5 mm; RV end-diastolic diameter, 39±7; RV ejection fraction, 29±7.2%).

Dobutamine stress echocardiography caused an increase in contractility in the anteroinferior and lateral region at a low dose in patient 3 with isolated proximal LAD occlusion but no signs of ischemia or angina at a high dose. In the other 6 patients, low-dose dobutamine caused a slight, global improvement in the wall motion but no worsening of segmental contractile function or angina at a high dose.

**Histology**

Diffuse inflammatory lymphomononuclear infiltrates associated with focal necrosis of adjacent myocytes were observed in all patients who met the Dallas criteria for myocarditis. In patients 3 and 4, the inflammatory changes were not associated with fibrosis (active myocarditis) (Figure 2, top). Five patients also had interstitial and focal replacement fibrosis. Focal cell necrosis was always associated with inflammatory cells adherent to the sarcolemma of myocardiocytes, which...
maintained their nuclear integrity (Figure 2, top). There were no signs of ischemic damage.

Serology
Serologic tests for the cardiotropic viruses and for C pneumoniae were negative in all patients. Viral particles were not sought. The sera of patients 3 and 4 were weakly positive for cardiac autoantibodies with diffuse cytoplasmic immunofluorescence staining of myocytes at titers ranging from 1:5 to 1:10.

Treatment and Follow-Up
All patients were on full therapy with ACE inhibitors, diuretics, and digitalis for $3$ months. Patient 3, in whom a remarkable improvement of contractility was induced by dobutamine infusion underwent PTCA of the occluded LAD before immunosuppressive therapy. The procedures was successful without residual stenosis and with TIMI 3 flow but were not followed by detectable improvement in biventricular volume and contractility at 2-dimensional echocardiography performed 2 months later. Revascularization procedures were not considered in the other 6 patients because of the severity of global cardiac dysfunction, the absence of improvement after dobutamine infusion, and the presence of the documented myocarditis. Patients 3 and 5, who had evidence of active myocarditis, also received prednisone ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for 4 weeks followed by $0.33 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for 5 months) and azathioprine ($2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for 5 months). The patients were followed clinically, and ECG, chest radiography, and 2-dimensional echocardiography were performed at 4-week intervals. In the 2 patients who received immunosuppressive therapy, repeated cardiac catheterization, angiography, and biopsy at 1-, 3-, and 5-month follow-ups showed considerable improvement in RV and LV function (Figures 1, left, and 3, respectively) and decrease in LV and RV volumes with reduction in pulmonary and ventricular end-diastolic pressures (Table). Cardiac index increased by 1.31 (patient 3) and 0.86 (patient 4) $\text{L} \cdot \text{m}^{-1} \cdot \text{min}^{-1}$. Control biopsies showed the disappearance of myocyte necrosis and reduction of the inflammatory infiltrates (Figure 2, bottom), which became localized in the interstitium remote from the myocardiocyte membrane.

Coronary findings remained unchanged. The other 5 patients, who were receiving conventional anti–cardiac failure treatment, failed to improve, and 1 of them died.

Discussion
Dilated cardiomyopathy is the common clinical stage of posts ischemic, inflammatory, degenerative, and infiltrative...
myocardial diseases. Postischemic dilated cardiomyopathy secondary to occlusive coronary artery disease can be caused by necrosis resulting in multiple small or discrete large areas of scar or by hibernation. In both situations, biopsy and postmortem studies show replacement fibrosis and myocyte hypertrophy without inflammatory infiltrates. Our study demonstrates, for the first time, that progressive global biventricular dysfunction in patients with severe coronary artery disease and no evidence of previous myocardial infarction may be caused by myocarditis. This conclusion is typically illustrated by patient 3, who showed a large reduction in LV and RV volumes with marked improvement in RV and LV ventricular functions. We cannot rule out a coincidental spontaneous resolution of the myocardial inflammatory process, but in both patients, the progressive downward trend was not improved by the administration of full treatment with digitalis, diuretics, and ACE inhibitors and by successful angioplasty (patient 3).

Therefore, in patients with asymptomatic, severe coronary artery disease, the presence of global LV and RV dilatation and dysfunction may not necessarily be related to ischemia and necrosis because preserved LV function was reported even in the presence of left main coronary artery occlusion. In such patients, a myocarditic process should be suspected, and if the diagnosis is proved through endomyocardial biopsy, it may influence treatment and prognosis.

**Acknowledgment**

The financial support of Fondazione Internazionale di Ricerca per il Cuore onlus is gratefully acknowledged.

**References**


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Circulation. 1999;99:1295-1299
doi: 10.1161/01.CIR.99.10.1295
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
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