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Hyperdynamic Myocardial Response to Beta-Adrenergic Stimulation in Patients With Chest Pain and Normal Coronary Arteries

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OBJECTIVES The goal of this study was to test the hypothesis that an abnormal response to beta-adrenergic stimulation may play a role in the pathophysiology of chest pain in patients with normal coronary arteries.

BACKGROUND The mechanism of angina-like (AL) chest pain in patients with angiographically normal coronary arteries remains controversial.

METHODS Fifty-eight patients with AL pain and a normal coronary angiogram underwent dobutamine echocardiography (DE) to evaluate regional wall motion and intraventricular flow velocities (IFV). Control patients consisted of 22 matched patients free of angina and coronary artery disease. Abnormal IFV were defined as dagger-shaped Doppler spectrum ≥3 m/s.

RESULTS Dobutamine-induced regional wall motion abnormalities did not develop in any of the patients. An IFV ≥ 3 m/s was found in 28 patients (48%) with AL pain but in only 4 (18%) control patients ($p < 0.05$). In the subgroup of patients with AL pain and IFV ≥3 m/s, plasma renin concentration (PRC) was higher as compared with those with IFV <3 m/s (18 ± 17 pg/ml vs. 9 ± 6 pg/ml, $p < 0.05$). There were no differences in plasma ADR, NADR, or angiotensin-converting enzyme levels. Fourteen patients with angina and IFV ≥3 underwent control DE and blood sampling after 6 weeks treatment with 10 mg of bisoprolol. In these patients, a decrease in IFV (from 3.4 ± 0.35 m/s to 2.46 ± 0.64 m/s, $p < 0.001$) and a decrease in angina score (from 5.4 ± 1.5 to 0.6 ± 1.4, $p < 0.001$) were observed at follow-up.

CONCLUSIONS The present data suggest that an exaggerated myocardial response to beta-adrenergic stimulation plays a role in the mechanisms of chest pain in some patients with normal coronary arteries. (J Am Coll Cardiol 2005;46:1270–5) © 2005 by the American College of Cardiology Foundation

About 10% to 20% of patients with angina-like (AL) chest discomfort undergoing cardiac catheterization present with normal coronary angiograms (1,2). Despite a good prognosis, the persistent AL pain adversely affects their quality of life and increases their health care expenses (2,3), and their clinical management remains difficult. The AL pain syndrome likely represents a heterogeneous entity that depends on a variety of coexisting pathophysiologic mechanisms. A minority of patients meet the criteria of syndrome X with AL pain, normal coronary arteries, and documented signs of myocardial ischemia at exercise electrocardiogram (4), nuclear imaging (5,6), or magnetic resonance imaging (7). The symptoms of these patients were ascribed to microvascular dysfunction (8–10). In many of them, an endothelial dysfunction was found (11) with decreased nitric oxide production and/or increased endothelin-1 release (12–14), further supporting an ischemic origin of the complaints. However, several investigators failed to document myocardial ischemia and reported preserved myocardial blood flow and function in these patients despite stress-induced chest pain (15,16). Accordingly, the pain was attributed to an abnormal pain perception (17–19) and enhanced activity of the sympathetic system (20). Ischemic origin of chest pain has been further challenged by the presence of preserved metabolism (21), hyperdynamic contractility at rest (15,22), or induction of an LV outflow tract obstruction during dobutamine infusion (23), suggesting hyperresponsiveness to beta-adrenergic stimulation as an underlying pathophysiologic mechanism. Therefore, in our study, we tested the hypothesis that a hyperdynamic response to beta-adrenergic stimulation contributes to the occurrence of AL pain in patients with normal coronary arteries.

METHODS

Patients. We studied 58 consecutive patients with AL chest pain and normal coronary arteries. All patients presented with chest pain on effort of characteristic nature, location, irradiation, and associated symptoms prompting referral for cardiac catheterization. Patients with left ventricular (LV) hypertrophy (echocardiographic wall thickness

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Abbreviations and Acronyms

ADR = adrenaline
AL = angina-like
DE = dobutamine echocardiography
IFV = intraventricular flow velocities
LV = left ventricle/ventricular
NADR = noradrenaline
PRC = plasma renin concentration

>11 mm), valvular heart diseases, or cardiomyopathy were excluded from the study. All patients successively underwent clinical evaluation of angina score, coronary angiography, dobutamine echocardiography (DE), and biochemical analysis. Twenty-two patients free of any cardiac symptoms served as control patients. Written informed consent was obtained in all patients in accordance with institutional guidelines. In addition, patients who were given bisoprolol gave their oral informed consent.

Angina score. Patients subjectively scored their chest discomfort on a scale from 1 (minimal angina) to 10 (most severe angina).

Coronary angiography. Two experienced angiographers interpreted the coronary angiograms. Patients were excluded when a coronary stenosis of more than 30% (as assessed by quantitative coronary angiography) was present in any epicardial segment. In six patients, luminal irregularities (<30% diameter stenosis) were visible on the angiogram. Pressure-derived fractional flow reserve was larger than 0.90 in all of them.

Dobutamine echocardiography (DE). Long-acting nitrates and calcium-channel blockers were discontinued at least 36 h before the DE. The beta-blockers were discontinued at least 8 days before DE. The latter was performed with a commercially available system (Acuson Sequoia C256, Mountain View, California) in all patients within 72 h after coronary angiography as described elsewhere (24). Dobutamine was infused intravenously at incremental dosages of 10, 20, 30, and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min. Parasternal long- and short-axis and apical four- and two-chamber echocardiographic images were recorded at rest and at each stage of the test. The LV regional wall motion, LV end-diastolic diameter, LV end-systolic diameter, fractional shortening, systolic wall thickening of interventricular septum, and of posterior wall, contractility index (the ratio of systolic blood pressure to LV end-systolic volume), as well as intraventricular flow velocities (IFV) using high-pulse repetition frequency Doppler in the LV outflow tract and at the midventricular level, were recorded at rest, during incremental dosages of dobutamine, and during recovery. A hyperdynamic response was defined as the occurrence of abnormal IFV characterized by a dagger-shaped Doppler spectrum ≥3 m/s (Fig. 1).

Biochemical analysis. Plasma renin concentration (PRC), plasma noradrenaline (NADR) and adrenaline (ADR), as well as angiotensin-converting enzyme activity were determined using commercially available assays. The PRC was assessed as a marker of systemic enhancement of beta-adrenergic stimulation. It was determined by solid-phase two-site radioimmunometric assay (sampling at rest, in a supine position). The NADR and ADR were determined using high-pressure liquid chromatography. The angiotensin-converting enzyme activity was measured by a colorimetric assay.

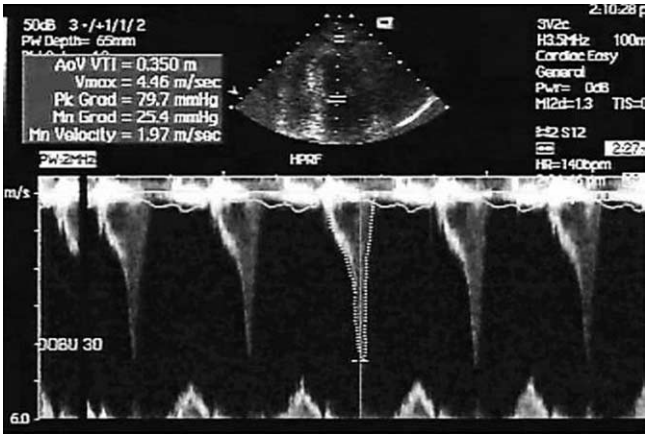

Figure 1. Example of a high-pulsed repetition Doppler flow velocity recording in the left ventricular outflow tract. Abnormal intraventricular flow velocities were defined as a dagger-shaped Doppler spectrum ≥3 m/s.

Follow-up. Fourteen patients with AL pain and in whom an IFV ≥3 m/s developed were treated with bisoprolol 10 mg for 6 weeks. At the end of this period, the patients underwent a control clinical evaluation with DE and blood sampling.

Statistical analysis. All data are presented as mean ± standard deviation for continuous data and as a ratio for categorical data. Gaussian distributions of data were tested using the Kolmogorov-Smirnov test. An unpaired *t* test or nonparametric Mann-Whitney *U* test was used to compare the results of the patients with and without abnormal flow velocity and to compare the results of the patients and the control patients. A paired *t* test or the nonparametric Wilcoxon matched pairs signed rank sum test was used to compare the results of the patients before and after treatment with bisoprolol. The Fisher exact test was used to compare categorical data. A multivariate logistic regression analysis was used to study multiple risk factors and the risk of abnormal flow velocities. For all analysis, a p value of >0.05 was considered nonsignificant. All statistical analyses were performed with the SPSS/PC 11.5 software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics. There were no significant differences in demographics and in risk factors for coronary artery disease (familial history, hyperlipidemia, diabetes, and smoking habits) between patients and control patients except for hypertension (43% in patients vs. 14% in control patients, p = 0.03). Baseline echocardiographic and Dopp-