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

Juraj Madaric, MD,* Jozef Bartunek, MD, PHD,* Katia Verhamme, MD, PHD,† Martin Penicka, MD,* Eddy Van Schuerbeeck, RN,* Paul Nellens, MD,* Guy R. Heyndrickx, MD, PHD,* William Wijns, MD, PHD,* Marc Vanderheyden, MD,* Bernard De Bruyne, MD, PHD*

*Aalst, Belgium*

**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

From the *Cardiovascular Centre Aalst and the †Department of Epidemiology, OLV Clinic, Aalst, Belgium.

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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.

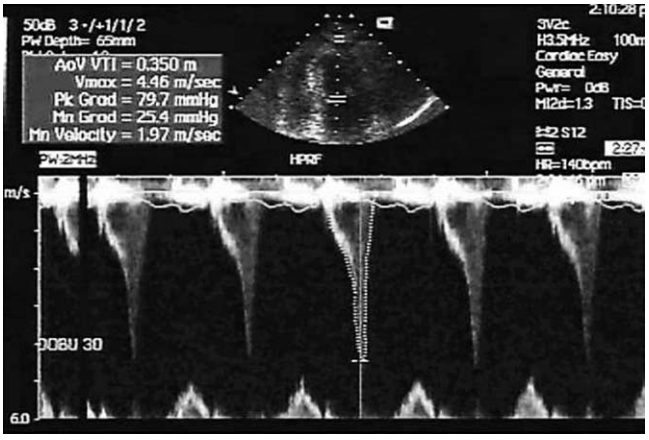


**Figure 1.** Example of a high-pulsed repetition Doppler flow velocity recording in the left ventricular outflow tract. Abnormal intraventricular flow velocities were defined as a dagger-shaped Doppler spectrum ≥3 m/s.

**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-

**Table 1.** Baseline Characteristics of Patients With AL Chest Pain and of Normal Control Patients

| | AL Group (n = 58) | Control Patients (n = 22) | p Value |
|---|---|---|---|
| Age (y) | 61 ± 10 | 56 ± 14 | 0.10 |
| Male (%) | 48.7 | 57.1 | 0.79 |
| HR* (beats/min) | 69 ± 12 | 70 ± 14 | 0.91 |
| SBP* (mm Hg) | 127 ± 17 | 128 ± 17 | 0.52 |
| DBP* (mm Hg) | 73 ± 9 | 75 ± 9 | 0.23 |
| LVEDD (mm) | 51 ± 5 | 51 ± 6 | 0.92 |
| LVESD (mm) | 31 ± 5 | 32 ± 6 | 0.60 |
| IVS* (mm) | 7.5 ± 1.4 | 8.3 ± 1.6 | 0.08 |
| PW* (mm) | 7.2 ± 1.4 | 7.7 ± 1.6 | 0.14 |
| SWT IVS* (%) | 67 ± 34 | 48 ± 37 | 0.05 |
| SWT PW (%) | 99 ± 41 | 80 ± 37 | 0.15 |
| EF* (%) | 67 ± 9 | 67 ± 9 | 0.84 |
| FS (%) | 38 ± 7 | 37 ± 7 | 0.27 |
| IFV* (m/s) | 1.18 ± 0.22 | 0.96 ± 0.30 | 0.03 |

*Tested using the Mann-Whitney *U* test.
AL = angina-like; DBP = diastolic blood pressure; EF = ejection fraction; FS = fractional shortening; HR = heart rate; IFV = intraventricular flow velocities; IVS = end-diastolic septal wall thickness; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; PW = end diastolic posterior wall thickness; SWT IVS = systolic wall thickening of interventricular septum; SWT PW = systolic wall thickening of posterior wall; SBP = systolic blood pressure.

ler indices were similar in both groups except for the baseline IFV (1.18 ± 0.22 in patients vs. 0.96 ± 0.30 in controls, $p < 0.05$, Table 1).

**Dobutamine-induced abnormal flow velocities.** Table 2 shows the echocardiographic and Doppler indices during the peak dose of dobutamine in patients and control patients. None of them developed dobutamine-induced wall motion abnormalities nor a systolic anterior motion of the mitral valve. As compared with the baseline values, heart rate, systolic blood pressure, ejection fraction, fractional shortening, and peak IFV increased significantly and to the same extent during the maximal dosage of dobutamine in both patients and control patients. However, the occurrence of IFV ≥3 m/s was almost three times as frequent in patients with AL pain than in control patients (28 of 58 vs. 4 of 22, respectively, $p = 0.028$) (Fig. 2). These abnormal flow velocities were located at the midventricular level in all patients.

**Table 2.** Echo Doppler Indices in Patients With AL Pain and in Normal Control Patients During the Maximal Dosage of Dobutamine

| | AL Group (n = 58) | Control Patients (n = 22) | p Value |
|---|---|---|---|
| HR* (beats/min) | 129 ± 17 | 131 ± 13 | 0.97 |
| SBP* (mm Hg) | 138 ± 27 | 147 ± 16 | 0.16 |
| DBP* (mm Hg) | 75 ± 12 | 77 ± 6 | 0.51 |
| LVEDD (mm) | 46.9 ± 6.4 | 46.4 ± 5.4 | 0.80 |
| LVESD (mm) | 25.3 ± 4.8 | 25.9 ± 4.8 | 0.65 |
| EF* (%) | 76 ± 8 | 77 ± 6 | 0.78 |
| FS (%) | 45 ± 7 | 44 ± 8 | 0.99 |
| IFV (m/s) | 2.84 ± 1.07 | 2.49 ± 1.09 | 0.19 |
| IFV ≥3 m/s (patients) | 28 (48%) | 4 (18%) | 0.021 |

*Tested using the Mann-Whitney *U* test.
Abbreviations as in Table 1.

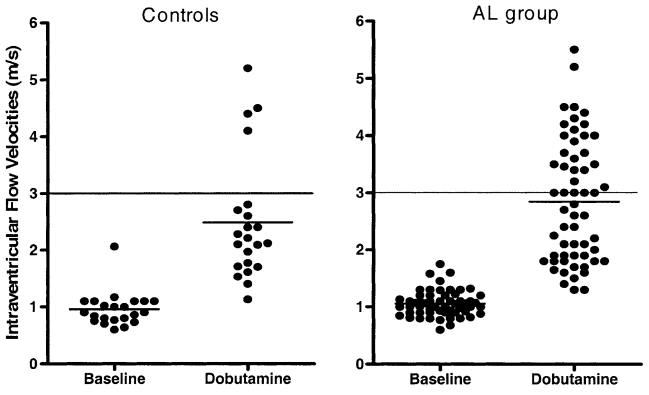


**Figure 2.** Baseline and dobutamine-induced intraventricular flow velocities in control patients and in patients with chest pain. AL = angina-like.

**Patients with normal versus abnormal flow velocities.** Clinical characteristics and echocardiographic and Doppler indices of the patients with AL pain are given in Table 3 according to the presence or absence of IFV ≥3 m/s. The angina score as well as the echo-Doppler parameters at rest were similar in both groups. Nevertheless, patients with IFV ≥3 m/s experienced more frequently chest pain during DE than patients with normal dynamics. In addition, induction of IFV ≥3 m/s was associated with a larger decrease in LV end-systolic dimension and a larger increase in contractility index during DE. There were no differences in systemic

**Table 3.** Clinical Characteristics and Echocardiographic Indices of Patients With AL Chest Pain According to the Presence or Absence of Abnormal IFV

| | IFV <3 m/s (1.95 ± 0.40 m/s, n = 30) | IFV ≥3 m/s (3.80 ± 0.66 m/s, n = 28) | p Value |
|---|---|---|---|
| Angina score* | 4.57 ± 2.01 | 5.25 ± 1.43 | 0.26 |
| Dobutamine-induced AL pain | 3/30 (10%) | 9/28 (32%) | 0.05 |
| Arterial hypertension | 3/30 (10%) | 6/28 (21%) | 0.30 |
| HR (beats/min) | | | |
| Rest | 69 ± 12 | 69 ± 12 | 0.78 |
| Dob | 127 ± 17 | 131 ± 17 | 0.47 |
| SBP (mm Hg) | | | |
| Rest* | 128 ± 19 | 126 ± 15 | 0.92 |
| Dob* | 139 ± 27 | 138 ± 27 | 0.70 |
| DBP (mm Hg) | | | |
| Rest* | 74 ± 10 | 73 ± 8 | 0.82 |
| Dob* | 74 ± 12 | 75 ± 11 | 0.42 |
| LVEDD (mm) | | | |
| Rest* | 51.3 ± 3.6 | 49.9 ± 5.5 | 0.35 |
| Dob | 48.1 ± 6.6 | 45.4 ± 6.0 | 0.17 |
| LVESD (mm) | | | |
| Rest | 31.4 ± 4.6 | 30.8 ± 6.04 | 0.66 |
| Dob | 27.1 ± 3.8 | 22.9 ± 4.9 | 0.001 |
| CI (mm Hg/ml) | | | |
| Rest* | 3.61 ± 2.06 | 4.10 ± 2.17 | 0.22 |
| Dob | 4.76 ± 1.58 | 7.38 ± 3.77 | 0.02 |
| FS (%) | | | |
| Rest | 39 ± 7 | 38 ± 6 | 0.75 |
| Dob | 44 ± 5 | 47 ± 9 | 0.20 |

*Tested using the Mann-Whitney *U* test.
CI = contractility index; Dob = at dobutamine infusion; other abbreviations as in Table 1.

**Table 4.** Biochemical Analysis in Patients With AL Pain With and Without Abnormal IFV

| | IFV <3 m/s (n = 30) | IFV ≥3 m/s (n = 28) | p Value |
|---|---|---|---|
| ADR* (μg/l) | 0.11 ± 0.22 | 0.22 ± 0.28 | 0.14 |
| NADR* (μg/l) | 0.60 ± 0.54 | 0.51 ± 0.42 | 0.55 |
| ACE (U/l) | 31 ± 12 | 37 ± 11 | 0.15 |
| PRC* (pg/ml) | 9 ± 6 | 18 ± 17 | 0.025 |

*Tested using the Mann-Whitney *U* test.
ADR = adrenalin; ACE = angiotensin-converting enzyme; IFV = intraventricular flow velocities; NADR = noradrenalin; PRC = plasma renin concentration.

hemodynamics at rest as well as during dobutamine therapy between both groups.

**Biochemical analysis.** Biochemical parameters of patients with and without abnormal flow velocities are shown in Table 4. There were no differences in plasma NADR or ADR levels, nor in plasma angiotensin-converting enzyme activity in both groups. In contrast, patients with IFV ≥3 m/s showed significantly higher PRC than patients with normal flow dynamics.

When adjusting for age and gender, the risk of abnormal IFV was five-fold higher in patients with a PRC of more than 14 pg/ml compared with patients with a PRC of 14 pg/ml or lower (adjusted odds ratio, 4.7; 95% confidence interval, 1.2 to 18.2). In addition, the risk of abnormal IFV, when adjusting for age and gender, was nine-fold higher in patients with a LV end-systolic diameter during dobutamine of ≤23 mm compared with patients with a LV end-systolic diameter during dobutamine of more than 23 mm (adjusted odds ratio, 9.05; 95% confidence interval, 2.08 to 39.43).

**Clinical follow-up after beta-blocker treatment.** Fourteen patients with AL chest pain and IFV ≥3 m/s received bisoprolol 10 mg daily for 6 weeks. As shown in Figure 3, the angina score was lower in all but one patient (from 5.4 ± 1.5 to 0.6 ± 1.4, p < 0.001). This symptomatic improvement was paralleled by a marked decrease in the extent of IFV (from 3.4 ± 0.35 m/s to 2.46 ± 0.64 m/s, p < 0.001).

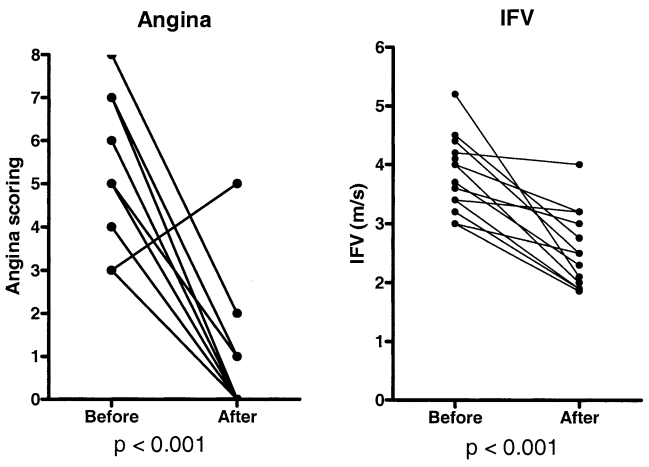


**Figure 3.** Abnormal intraventricular flow velocities and angina score in 14 patients with angina-like chest pain before and after a treatment with 10 mg bisoprolol. IFV = intraventricular flow velocities.

## DISCUSSION

The present study tested the hypothesis that a hyperdynamic response to beta-adrenergic stimulation might contribute to the occurrence of AL pain in patients with normal coronary arteries. The results of the present study can be summarized as follows: 1) The incidence of a hyperdynamic response characterized by dobutamine-induced abnormal IFV was higher in patients with AL chest pain and normal coronary arteries as compared with control patients. 2) Among the group of patients with AL pain, dobutamine-induced IFV of ≥3 m/s were associated with a larger increase in contractility index, a larger decrease in LV end-systolic dimension, and a higher PRC. 3) The treatment with beta-blockers induced a parallel decrease in angina score and in the hypercontractile response of the LV.

**Mechanisms of AL pain in patients with normal coronary arteries.** Patients with AL pain and normal coronary arteries represent a heterogeneous clinical entity. Several pathophysiologic mechanisms might explain the occurrence of chest pain in these patients. These mechanisms are not mutually exclusive, they are interacting, and it is likely that they often co-exist in the same patients. Previous studies observed exercise-induced ST-segment changes, reduced coronary flow reserve, or myocardial perfusion defects in many of these patients (5–10). Because the epicardial arteries were normal, these signs of myocardial ischemia were attributed to microvascular dysfunction. These patients were also shown to have an impaired endothelium-dependent and endothelium-independent coronary vasodilation during various vasoactive stimuli (5), which might contribute to myocardial ischemia. Nevertheless, the sole ischemic hypothesis has been challenged by the observation of a normal LV contractile response and the absence of regional wall motion abnormalities during stress testing (15,22,23).

Second, several studies suggested that an abnormal visceral pain perception might play a role in the pathophysiology of the complaints of these patients. (17,20). However, it remains speculative whether the pain perception is caused by increased local cardiac sensitivity or if it is related to a more complex interaction between abnormal processing of nociceptive stimuli from the periphery to the central nervous system and inappropriate feedback to heart or neighboring organs (17). The current study cannot elucidate the exact origin of the pain.

Third, some data suggest an increased sympathetic activity in patients with AL pain and normal coronary arteries. A large proportion of these patients (75%) seems to have an altered sympathovagal balance with regional abnormalities in $^{123}$I-metaiodobenzylguanidine (norepinephrine analog) uptake and enhanced adrenergic drive (19). Other studies reported increased LV contractility and exaggerated hemo-

dynamic response to exercise and increased baseline LV contractility (22,23). Tousoulis et al. (22) observed resting LV hypercontractility in approximately one-third of patients with chest pain, normal coronary angiograms, and a positive exercise test result. Similarly, Christiaens et al. (23) observed that a dynamic LV obstruction is common during DE in patients with AL pain without epicardial coronary artery disease. These observations raised the hypothesis that an adrenergic hyperdynamic response might contribute to the occurrence of AL chest pain in these patients. In our study, a higher PRC was found in patients with LV hypercontractility, whereas the levels of ADR and NADR did not differ. This finding does not unequivocally confirm enhanced beta-adrenergic myocardial responsiveness, but rather may relate to a systemic phenomenon.

**Hyperdynamic contractile response and abnormal flow velocities in AL pain.** Consistent with earlier observations (25–27), we observed dobutamine-induced abnormal flow velocities in 18% of normal individuals. In contrast, in patients with AL pain and normal coronary arteries, abnormal IFV during a dobutamine stress test were observed in approximately 50% of patients. These proportions obviously depend on the cut-off value used. There is no consensus about the exact limit above which the velocities in the LV outflow tract should be considered abnormal. The dagger-shaped (late-peaking) aspect of the flow velocity pattern seems more important than the actual value of the peak velocity. The present study suggests that abnormal flow velocities and underlying cavity squeezing are not related to different baseline hemodynamics or to particular morphologic factors but rather to a hyperdynamic response to beta-adrenergic stimulation. Indeed, LV dimensions and morphology were similar in patients and in normal individuals. In addition, patients with abnormal flow velocities were characterized by the presence of higher baseline PRC. The beta-adrenergic signaling pathway closely controls patient renin release, and its higher plasma levels for similar levels of ADR and NADR are likely to reflect a higher systemic adrenergic sensitivity in patients with dobutamine-induced abnormal flow velocities. Finally, treatment with beta-adrenergic blockers induced a marked parallel decrease in dobutamine-induced abnormal flow velocities and AL chest pain. These observations are consistent with myocardial hypersensitivity to beta-adrenergic stimulation.

Our data do not allow us to address the molecular basis of the myocardial hypersensitivity. Myocardial effects of dobutamine are primarily mediated by the beta-1 adrenergic receptor, and several genetic variations in the receptor function may underlie the observed hemodynamic response. Of note, arginine switch at codon 389 was recently described to induce hyperreactivity of the receptor to various inotropic stimuli (28). Our data also do not exclude the formal possibility that a parasympathetic rather than a sympathetic dysfunction could be the cause of the autonomic imbalance. Gulli et al. (29) observed reduced parasympathetic tone in two thirds of the patients with AL pain and normal coronary arteries, suggesting also an abnormal adrenergic balance. Taken together, these findings further corroborate the hypothesis that abnormal adrenergic function and response to beta-adrenergic stimulation contribute to AL pain in patients with normal coronary arteries.

**Study limitations.** In the present study, a hypercontractile response was elicited by infusion of dobutamine. Although a dobutamine stress test is an accepted alternative to exercise, it does not entirely simulate hemodynamic conditions during exercise. This may cloud the incidence of abnormal flow velocities during exercise. Second, the absence of dobutamine-induced wall motion abnormalities does not exclude the formal possibility of perfusion abnormalities. It is conceivable that echocardiography may not detect small localized areas of regional ischemia (30). Several investigators raised the hypothesis that myocardial ischemia in patients with normal coronary arteries may be caused by constriction of small vessels characterized by a patchy distribution. Such patchy distribution may be masked by the tethering effect of neighboring hyperdynamic segments, and may be insufficient to cause impairment of a contractile function detectable by echocardiography. In this regard, Lanza et al. (19) showed that abnormal cardiac adrenergic activity, as detected by $^{123}$metaiodobenzylguanidine myocardial scintigraphy scan, is often associated with the presence of perfusion defects. This suggests the possibility that higher cardiac adrenergic activity may partially contribute to microvascular vasoconstriction detected by perfusion scintigraphy.

## CONCLUSIONS

An exaggerated myocardial response to beta-adrenergic stimulation with LV cavity squeezing might play a role in the pathophysiology of chest pain in patients with normal coronary arteries. Further studies are required to decipher the molecular basis of this adrenergic hyperresponsiveness as well as to determine the role of beta-blockers in the treatment of these patients.

**Reprint requests and correspondence:** Dr. Bernard De Bruyne, Cardiovascular Centre Aalst, Moorselbaan 164, 9300 Aalst, Belgium. E-mail: bernard.de.bruyne@olvz-aalst.be or Dr. Jozef Bartunek, jozef.bartunek@olvz-aalst.be.

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