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Association of coronary microvascular dysfunction with restenosis of left anterior descending coronary artery disease treated by percutaneous intervention

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ABSTRACT

Background: Several patients with successful percutaneous coronary interventions (PCIs) show evidence of coronary microvascular dysfunction (CMVD), which can be responsible for persistent positivity of electrocardiographic exercise stress test (EST). In this study, we assessed whether post-PCI CMVD may predict clinical outcome in patients undergoing successful elective PCI of an isolated stenosis of the left anterior descending (LAD) coronary artery.

Methods: We studied 29 patients (age 64 ± 6, 23 M) with stable coronary artery disease and isolated stenosis (>75%) of the LAD coronary artery who underwent successful PCI with stent implantation. Coronary blood flow (CBF) velocity response to adenosine and to cold-pressor test (CPT) was assessed in the LAD coronary artery by transthoracic Doppler echocardiography 24 h and 3 months after PCI. The primary end-point was a combination of death, admission for acute coronary syndromes (ACS) or target vessel revascularization (TVR).

Results: No death or ACS occurred during 36 months of follow-up, but TVR was performed in 5 patients (17.2%). CBF response to CPT at 3 months after PCI was 1.31 ± 0.2 vs. 1.71 ± 0.4 in patients with or without TVR, respectively ($p = 0.03$), whereas CBF response to adenosine at 3 months in these two groups was 1.70 ± 0.3 vs. 2.05 ± 0.4 ($p = 0.059$).

Conclusions: Our data suggest that, in patients with successful PCI of LAD coronary artery stenosis, lower CBF response to the endothelium-dependent vasodilator stimulus CPT is associated with long-term recurrence of restenosis.

1. Introduction

Exercise stress test (EST) plays a pivotal role in the diagnostic and prognostic assessment of patients with suspected or confirmed coronary artery disease (CAD) [1]. However, EST performed after a percutaneous coronary intervention (PCI) has been found of limited utility in identifying patients with coronary restenosis. In particular, previous studies showed that, after PCI, EST-induced ST-segment depression at the electrocardiogram (ECG) can often persist, despite complete revascularization, in a proportion ranging from 13% to 64% [2–5].

Mechanisms responsible for persisting ST-segment depression during EST in this setting include vasoconstriction at the level of, or distally to, the treated lesion and coronary microvascular dysfunction (CMVD) [6,7] and impaired microvascular dilation in chronically adapted post-stenotic vessels. CMVD has been documented in several patients after PCI, and it may correlate with exercise stress test results and persist for several months after the procedure [8–12]. However, no previous study assessed whether CMVD may predict clinical outcome in these patients.

2. Methods

2.1. Study population

The present article reports long-term follow-up of patients included in our original study in which we assessed the relation between EST results and coronary microvascular function in patients undergoing successful PCI. Accordingly, the methods are described in detail in our previous report [12]. Patients gave their written informed consent to participate in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Briefly, consecutive patients who underwent an elective PCI at our hospital between June 2009 and January 2011 were included in this

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study if they fulfilled the following criteria: 1) stable coronary artery disease; 2) positive pre-PCI EST (see below); 3) single-vessel disease of the left anterior descending (LAD) coronary artery (stenosis >75%) at angiography; 4) no stenosis >30% in any other coronary artery; 5) successful PCI (residual stenosis <20% and Thrombolysis In Myocardial Infarction blood flow grade = 3); and 6) no early PCI-related complications.

Exclusion criteria included previous coronary interventions, acute coronary syndromes, inflammatory or malignant disease, asthma and ECG abnormality that could interfere with ST-segment analysis.

Patients underwent symptom/sign-limited EST and assessment of coronary microvascular function 24 h after PCI and at 3 and 6 months after PCI. For the prognostic purposes of this study, only data obtained 24 h and 3 months after PCI were considered.

2.2. Exercise stress test

ESTs were performed in the morning, in a fasting state, according to a standard Bruce protocol. Leads II, V2 and V5 were monitored continuously; a 12-lead ECG was printed and blood pressure was measured at the end of each stage, when clinically indicated, and at 1-min intervals in the recovery phase. End-points for stopping the test included: 1) physical exhaustion; 2) progressive angina (Borg scale >6); 3) relevant clinical events (e.g., dyspnea, hypotension, arrhythmias); and 4) ST-segment depression ≥0.4 mV.

EST was considered positive for myocardial ischemia when a horizontal or downsloping ST-segment depression ≥0.1 mV at 0.08 s from the J-point was induced in any lead but aVR. For statistical purposes and analyses, in patients with negative EST, time, heart rate and blood pressure at 0.1 mV ST-segment depression and at angina were considered those recorded at peak exercise.

2.3. Coronary microvascular function

Coronary microvascular dilator function was assessed by measuring the changes in coronary blood flow (CBF) velocity in response to adenosine and to cold-pressor test (CPT) in the LAD coronary artery by transthoracic Doppler echocardiography (TTDE), using an Acuson Sequoia C512 ultrasound system (Siemens S.p.A., Milano, Italy) [12]. The tests were performed by the same expert echocardiographer.

The patient was positioned in the left lateral decubitus in a quiet, temperature-controlled room (22 °C). The mid-distal part of the LAD coronary artery was imaged in a parasternal view using a 7 MHz transducer, and CBF was visualized using color-Doppler flow mapping guidance, with a velocity range of 12 to 16 cm/s. CBF velocity was measured by pulsed-wave Doppler echocardiography, using a 2.0 mm sample volume placed on the color signal in the LAD artery, with the incident angle kept as small as possible (below 40°). Diastolic CBF velocity measurements were performed offline by contouring the spectral Doppler signals, using the integrated software package of the ultrasound system.

After obtaining a basal recording, an intravenous infusion of adenosine (140 μg/kg/min) was given for 90 s under ECG and blood pressure monitoring and CBF velocity was measured at peak infusion.

After 15 min from adenosine administration, CPT was performed, with the patient putting his/her left hand into ice water for 120 s. CBF velocity was measured immediately before and at the end of the test.

For each measurement, the 3 highest Doppler CBF velocity values were averaged. Coronary microvascular dilator function in response to adenosine and to CPT was measured as the ratio of diastolic CBF velocity at peak of each test to the respective basal CBF velocity values.

Coronary flow reserve assessed by TTDE was previously found to significantly correlate with other, more accurate, methods, including intracoronary Doppler recording, positron emission tomography, contrast echocardiography and cardiac magnetic resonance [13].

2.4. Follow-up

Clinical follow-up was performed by telephone calls and, in case of events, clinical records were checked. The primary end-point consisted of a combination of death, hospital admission for acute coronary syndrome (ACS) or target vessel revascularization (TVR) for LAD restenosis.

2.5. Statistical analyses

Between-group comparisons of continuous variables were done by unpaired t-test, whereas categorical variables were compared by Fisher exact test. Data are reported as mean ± standard deviation or proportions, unless differently indicated. A p value <0.05 was considered as statistically significant. Data were analyzed by SPSS 21.0 statistical software (SPSS Italia, Inc., Florence, Italy).

3. Results

Twenty-nine patients were included in the study, the main clinical and angiographic findings of whom have previously been reported [12]. Mean age of patients was 63.5 ± 6 years, and 23 (79.3%) were males. Overall, 35 stenoses were treated, as 6 patients (21%) showed 2 flow-limiting stenoses in the LAD coronary artery. A proximal LAD stenosis was present in 14 patients (40%); stenosis severity was 87 ± 10%. All patients received drug-eluting stents (DESs), but one patient received a single bare metal stent (BMS). PCI was effective in all patients and no peri-procedural complications were observed.

3.1. Clinical outcome

All patients were followed-up at 36 months after PCI. No patient died or had acute coronary syndromes or stroke. Overall, 8 patients were readmitted to undergo at least one new coronary angiography because of recurrence of chest pain and/or results of non-invasive tests that suggested CAD recurrence. Restenosis was documented in 5 patients (17.2%) who underwent TVR.

Clinical and angiographic data of patients with TVR and those without TVR are summarized in Table 1, while Table 2 shows the EST results in the two groups. As shown, only a familial history of CAD showed a borderline statistical association with TVR (p = 0.054). Results of EST

Table 1
Main clinical and laboratory data of patients with positive or negative EST 24-h after a percutaneous coronary intervention.

	TVR (n = 5)	No TVR (n = 24)	p
Age (yrs)	63.4 ± 4	63.6 ± 6	0.95
Sex (M)	3 (60%)	20 (83%)	0.27
CV risk factors			
Family history of CAD	4 (80%)	7 (29%)	0.054
Hypertension	4 (80%)	19 (79%)	1.00
Smoking	3 (60%)	18 (75%)	0.60
Hypercolesterolemia	5 (100%)	20 (83%)	1.00
Diabetes mellitus	3 (60%)	10 (42%)	0.63
Angiographic data			
Mean LAD stenosis (%)	87 ± 6.7	88 ± 10.5	0.90
Number of stent	1.4 ± 0.6	1.3 ± 0.4	0.51
Length of lesion (mm)	18 ± 7.5	20.7 ± 10.6	0.59
LAD diameter (mm)	3.4 ± 0.7	3.1 ± 0.4	0.25
Drug therapy			
Beta-blockers	4 (80%)	18 (75%)	1.00
Calcium-antagonists	2 (40%)	2 (8%)	0.13
ACE-inhibitors/ARBs	2 (40%)	11 (46%)	1.00
Statins	5 (100%)	17 (71%)	0.30
Diuretics	1 (20%)	5 (21%)	1.00

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; CAD = coronary artery disease; CV = cardiovascular; EST = exercise stress test; HR = heart rate; LAD = left anterior descending coronary artery; LV = left ventricular; PCI = percutaneous coronary intervention.