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# Correlation between coronary microvascular function and angina status in patients with stable microvascular angina

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**Abstract. – BACKGROUND: Classical anti-ischemic drugs are the first-line form of treatment in patients with microvascular angina (MVA), but they often fail to achieve a satisfactory control of angina symptoms. It is unknown whether there is any relation between improvement of angina status and changes in microvascular function induced by classical anti-ischemic drugs in MVA patients.**

**AIM: To assess whether, in MVA patients, the effects of classical anti-ischemic drugs on symptoms and quality of life (QoL) are related to changes in coronary microvascular function.**

**PATIENTS AND METHODS: We studied 51 patients (59±10 years; 15 men) with MVA. Coronary blood flow (CBF) response to adenosine (ADO) and to cold pressor test (CPT), Seattle Angina Questionnaire (SAQ) and EuroQoL scale were assessed at baseline, in pharmacological washout, and after 12 months under anti-ischemic therapy. Patients were divided into 2 groups: (1) Group 1 included patients with no improvement of QoL (EuroQoL score change < 10 points); (2) Group 2 included patients with QoL improvement (increase in EuroQoL score ≥ 10 points).**

**RESULTS: At baseline, the 2 groups were similar in age, gender, cardiovascular risk factors, CBF response to ADO and to CPT, SAQ and EuroQoL scores. At follow-up the 2 groups differed only for beta blockers use (27% vs. 88% in group 1 and 2, respectively; $p < 0.001$). A significant improvement in SAQ score was observed only in group 2. CBF response to both ADO and CPT showed a similar improvement in the 2 groups. No relation was found between changes in coronary microvascular function and in angina status.**

**CONCLUSIONS: In MVA patients beta-blockers are more effective than other anti-ischemic drugs in improving angina symptoms. The improvement of angina status does not seem to be mediated by changes in coronary microvascular function.**

*Key Words:*
Microvascular angina, Coronary flow reserve, Drug therapy, Follow-up, Quality of life.

## Introduction

Primary stable microvascular angina (MVA) is characterized by the occurrence of typical anginal pain during effort, evidence of myocardial ischemia on non-invasive tests, normal coronary arteries at angiography and absence of any other cardiac disorder[1]. A dysfunction of resistance coronary artery vessels (< 500 μm), not visible at coronary angiography, has been shown to be responsible for stable MVA in most cases[1,2]. The notion that microvascular dysfunction is a major cause of angina in these patients derives, in particular, from studies which assessed coronary blood flow (CBF) response to vasodilator stimuli (e.g. adenosine [ADO], cold pressor test [CPT], dipyridamole, papaverine, acetylcholine)[3-9]. However, the existence of a correlation between symptomatic status, quality of life and changes in microvascular function induced by pharmacological therapy has poorly been investigated.

In this study we examined whether, in patients with stable MVA, the effects of drug therapy on angina status and quality of life (QoL) are related to changes in coronary microvascular function.

## Patients and Methods

### Study Population

We enrolled 51 patients (mean age 59±10.3 years; 15 men) who were diagnosed to have MVA at our Institute according to typical clinical features, including angina episodes exclusively or mainly related to efforts, a positive symptom/sign limited exercise stress test and completely normal epicardial coronary arteries at angiography. Coronary artery spasm was excluded by ergonovine test when clinical history suggested the possibility of vasospastic angina. Ergonovine test was per-



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formed by injecting increasing doses of methylergometrine at 5-minute intervals either intravenously (1, 2 and 3 mcg/kg) or intracoronary (8, 16 and 32 mcg). Other specific cardiac diseases were excluded on the basis of full non-invasive and invasive investigation. Patients with a definite diagnosis of diabetes and those with evidence of left ventricular hypertrophy and/or left ventricular dysfunction at 2D-ecocardiography were excluded from the present study.

Patients were also excluded if they were already taking anti-anginal drugs.

All subjects were informed of the purpose and nature of the study and provided written, informed consent before participation. The study was approved by the Ethical Committee of our Institution.

### Study Protocol

All patients were studied at enrolment and at 12-month follow-up. Data about cardiovascular risk factors, drug therapy and associated clinical conditions were carefully recorded. Anginal status and quality of life were assessed by the Seattle Angina Questionnaire (SAQ) and EuroQoL score, whereas coronary microvascular function was investigated by assessing CBF response to ADO and CPT (see below).

According to inclusion criteria, at baseline patients were studied in the absence of any anti-anginal drug. Treatment of patients was then left at the discretion of their attending/reference cardiologist, and all patients were reassessed under their usual drug therapy after 12 months.

### Anginal Status and Quality of Life

Anginal status was assessed by SAQ. Each SAQ item (physical limitation, angina frequency, angina stability, treatment satisfaction and disease perception) is scored on a 0-100 scale, with higher scores indicating better levels of functional status[10,11].

QoL was assessed by the validated EuroQoL visual analogic scale (VAS), graduated from 0 (worst condition) to 100 (best condition)[12].

### Coronary Microvascular Function

Non invasive assessment of coronary microvascular response to ADO and to CPT, which mainly assess endothelium-independent and endothelium-dependent vascular dilator function, respectively[13], was performed in the early afternoon, in a fasting state, by the same expert echocardiographer, following methods described in detail elsewhere[9,14]. Subjects were positioned in the left lateral decubitus and the left anterior desceding (LAD) coronary artery was imaged by a 7 MHz transducer connected to an Acuson Sequoia C512 ultrasound system (Siemens S.p.A., Milan, Italy). Blood flow in its mid-distal tract of the vessel was interrogated using color and pulsed wave Doppler mapping. After basal Doppler spectral tracing of diastolic coronary blood flow velocity (CBFV) was recorded, an infusion of ADO (140 μg/kg/min) was given for 90 seconds under ECG and blood pressure monitoring and CBFV was recorded at peak infusion.

After 15 minutes from ADO administration and return to basal value of heart rate and blood pressure, a new basal CBFV was obtained. Then, CPT was performed by putting the patient's left hand into ice water for 120 seconds and CBFV was measured at the end of the test.

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

### Statistical Analysis

The distribution of variables was assessed by Kolmogorov-Smirnov test and continuous variables were compared by unpaired *t*-test or Mann Whitney U-test as indicated. Fisher exact test was used to compare categorical variables. Correlation analyses were performed using Pearson or Spearman test, as indicated. The analysis of variance with a repeated measure design was applied to compare the changes of outcome variables during follow-up. Data are reported as mean±standard deviation or proportions. A two-tailed $p$ value $< 0.05$ was considered as statistically significant. Data were analyzed by the SPSS 17.0 statistical software (SPSS Italy, Inc., Florence, Italy).

## Results

Patients were divided into 2 groups, according to changes in QoL at follow-up compared to baseline: (1) Group 1 included patients who did not show significant improvement at follow-up, as indicated by either no changes, an increase < 10 points or a reduction at EuroQoL score, when compared to baseline values; (2) Group 2 included patients who showed significant improvement, as indicated by an increase of EuroQoL score ≥ 10 points, compared to baseline values.

Table I reports the main clinical characteristics of the 2 groups of patients and their treatment at follow-up assessment. There were no differences between the two groups with regard to age, gender and cardiovascular risk factors. The two groups at follow-up differed in β-blockers use (27% vs. 88% in group 1 and 2, respectively; $p < 0.001$), whereas no differences were found for other drugs.

Among patients taking beta-blockers a calcium-antagonist was associated with the β-blocker in 3 out of 7 patients (43%) in group 1 and in 8 out of 22 patients (36%) in group 2 ($p = 0.76$). A nitrate was associated with a beta-blocker in only 4 patients, and a triple anti-ischemic therapy (beta-blockers+calcium-antagonist+nitrate) was taken by 1 out of 7 patients (14%) taking beta-blockers of group 1 and by 3 out of 22 (14%) patients taking beta-blockers of group 2 ($p = 0.97$).

Data about coronary microvascular function are summarized in Table II. There were no significant differences between the 2 groups in CBF response to both ADO and CPT at baseline. Furthermore, coronary microvascular response to both vasodilator stimuli showed a similar improvement in the two groups at follow-up.

Basal SAQ and EuroQoL scores were similar in the 2 groups. At follow-up, together with the EuroQoL score, a significant improvement of SAQ scores was observed in Group 2, but not in Group 1 (Table III).

No significant correlations were found between CBF response to ADO and CPT and all SAQ scores at baseline and at follow-up in both groups (data not shown).

## Discussion

The following main data emerge from our study. First, more than 50% of patients with a new diagnosis of MVA show persistence or worsening of symptoms after 12 months in spite of classical anti-anginal therapy. Second, changes in coronary microvascular function do not seem to significantly affect symptomatic outcome. Finally, the only difference between patients showing vs. those not showing clinical improvement at follow-up was in the large use of β-blockers in the former group, thus suggesting that β-blockers may constitute a more effective form of treatment for MVA patients, compared to the other classes of anti-ischemic drugs.

Treatment of MVA is a frequent challenging matter for the cardiologist. Indeed, 20% to 30% of patients have progressive worsening of symptoms, with a significant deterioration of quality of life[1,15,16]. β-blockers seem a rational first-line approach in most patients because the dominant symptom is effort-related angina. β-blockers

**Table I.** Main clinical characteristics of patients enrolled in the study.

| | Group 1 (n=26) | Group 2 (n=25) | p |
|---|---|---|---|
| Age (years) | 58 ± 8 | 60 ± 11 | 0.45 |
| Gender (M/F) | 10/16 | 5/20 | 0.22 |
| BMI (kg/m$^2$) | 27 ± 4 | 28 ± 5 | 0.44 |
| **Cardiovascular risk factors** | | | |
| Family history of CVD | 16 (61%) | 18 (72%) | 0.55 |
| Hypertension | 17 (65%) | 21 (84%) | 0.19 |
| Hypercholesterolemia | 14 (54%) | 18 (72%) | 0.24 |
| Hypertriglyceridemia | 6 (23%) | 7 (28%) | 0.75 |
| Active smoking | 4 (15%) | 5 (20%) | 0.72 |
| **Drug therapy at follow-up** | | | |
| β-blockers | 7 (27%) | 22 (88%) | < 0.001 |
| Calcium channel blockers | 13 (50%) | 11 (44%) | 0.78 |
| Nitrates | 6 (23%) | 5 (20%) | 1 |
| Antiaggregants | 17 (65%) | 17 (68%) | 1 |
| ACE-inhibitors | 9 (35%) | 9 (36%) | 1 |
| ARBs | 4 (15%) | 8 (32%) | 0.19 |
| Statins | 11 (42%) | 12 (48%) | 0.78 |
| Diuretics | 8 (31%) | 9 (36%) | 0.77 |
| Bamiphylline | 2 (8%) | 2 (8%) | 1 |

ACE = angiotensin-converting enzyme; ARBs = angiotensin-II receptor blockers; BMI = body mass index; CVD = cardiovascular disease.

**Table II.** Coronary flow reserve assessment in the two study groups.

| | Group 1 | | Group 2 | | |
|---|---|---|---|---|---|
| | Baseline | 12 month FU | Baseline | 12 month FU | *p* for change |
| CBFR-ADO | 1.70 ± 0.3 | 2.05 ± 0.2* | 1.72 ± 0.4 | 2.05 ± 0.2* | 0.79 |
| CBFR-CPT | 1.66 ± 0.4 | 1.80 ± 0.4† | 1.56 ± 0.3 | 1.70 ± 0.3* | 0.6 |

CBFR-ADO = coronary blood flow response to adenosine; CBFR-CPT = coronary blood flow response to cold-pressor test. *$p < 0.001$ vs. baseline. †$p = 0.06$ vs. baseline.

were, indeed, found to improve anginal symptoms in several studies, particularly in patients with evidence of increased adrenergic activity (i.e., high heart rate at rest or during low-workload exercise and/or depressed heart rate variability)[17-19].

Calcium antagonists have, instead, shown conflicting results on angina symptoms in previous small trials[17-19], whereas long-acting nitrates were investigated only in a small trial, with poor results[17].

Interestingly, in our study, the use of β-blockers was more frequent in patients of group 2 (i.e., patients with an improvement of clinical conditions) than in those of group 1 (i.e., patients who did not show an improvement, or even showed worsening, of clinical status), thus, further suggesting that β-blockers may be a more effective form of treatment in MVA patients compared to $Ca^{++}$-antagonists or long-acting nitrates, which, instead, did not differ between the 2 groups.

The lack of any significant relation between the effects on coronary microvascular dysfunction and on angina symptoms in our study is also in agreement with the apparent better results observed with β-blockers rather than with vasodilator drugs. While the effects of β-blockers on coronary blood flow and coronary flow reserve are indeed variable and often unfavorable[20-23], their relevant anti-ischemic action is mainly mediated by a reduction of myocardial oxygen consumption through decrease in heart rate, left ventricular contractility and arterial blood pressure.

Of note, it can also be speculated that β-blockers might contrast the heightened painful perception of cardiac stimuli, which can significantly contribute to pain occurrence and severity in MVA patients[24]. By reducing the effort-related myocardial hypercontractility and the parallel increase of myocardial ischemic metabolites, indeed, β-blockers might blunt the easier mechanical and chemical stimulation of pain fibers responsible for the abnormal cardiac nociceptive function of these patients[25].

The apparent failure of vasodilators in MVA can be explained by a combination of limited effects of these drugs on coronary microvascular resistance[26,27], the presence of structural, rather than only functional abnormalities of small coronary artery vessels, the possible negative effects on coronary perfusion pressure (due to hypotension), and reflex adrenergic activation, with increased tachycardia and possible vasoconstriction during physical activity.

**Table III.** Seattle Angina Questionnaire scores in the two study groups.

| | Group 1 | | Group 2 | | |
|---|---|---|---|---|---|
| | Baseline | 12 month FU | Baseline | 12 month FU | *p* for change |
| Physical limitation | 68 ± 19 | 71 ± 19 | 67 ± 12 | 80 ± 11* | 0.005 |
| Angina stability | 46 ± 30 | 48 ± 24 | 42 ± 27 | 74 ± 27* | < 0.001 |
| Angina frequency | 71 ± 18 | 69 ± 17 | 66 ± 14 | 78 ± 18* | 0.001 |
| Treatment satisfaction | 80 ± 12 | 81 ± 12 | 72 ± 19 | 84 ± 15* | 0.03 |
| Disease perception | 59 ± 22 | 58 ± 20 | 54 ± 23 | 68 ± 25* | 0.003 |
| EuroQoL | 57 ± 13 | 56 ± 21 | 57 ± 14 | 73 ± 15* | < 0.001 |

*$p < 0.01$ vs. baseline.

Some criticisms of our study should be acknowledged. This was not a controlled study; therefore, we cannot completely exclude selection biases in the choice of drugs by reference cardiologists. The number of patients is relatively small; however, it should be considered that the kind of patients included is not frequent to find in clinical practice, particularly when selected according to strict inclusion criteria as in our study. Some patients were treated with a combination of anti-ischemic drugs which may have influenced the results. However, only a minority of patients were treated with drug combinations and these did not differ between patients taking beta-blockers in group 1 and 2, thus suggesting that our data regarding individual classes of drugs are sufficiently reliable.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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