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ORIGINAL PAPER

Coronary microvascular dysfunction in patients with acute coronary syndrome and no obstructive coronary artery disease

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Abstract

Background Between 10 and 15% of patients admitted for non-ST-segment elevation acute coronary syndrome (NSTE-ACS) show no obstructive coronary artery disease (NO-CAD) at angiography. Coronary microvascular spasm is a possible mechanism of the syndrome, but there are scarce data about coronary microvascular function in these patients.

Objectives To assess coronary microvascular function in patients with NSTE-ACS and NO-CAD.

Methods We studied 30 patients (67 ± 10 years, 19 female) with NSTE-ACS and NO-CAD. Specific causes of NSTE-ACS presentation (e.g., variant angina, takotsubo disease, tachyarrhythmias, etc.) were excluded. Coronary blood flow (CBF) velocity response to IV ergonovine (6 µg/kg up to a maximal dose of 400 µg) was evaluated before discharge by transthoracic Doppler echocardiography. CBF response to IV adenosine (140 µg/kg/min) and cold pressor test (CPT) was also assessed after 1 month. Ten age- and sex-matched patients with non-cardiac chest pain served as controls. Vasoactive tests were repeated after 12 months in 10 NSTE-ACS patients.

Results The ergonovine/basal CBF velocity ratio was 0.79 ± 0.09 and 0.99 ± 0.01 in patients and controls, respectively ($p < 0.001$). The adenosine/basal CBF velocity ratio was 1.46 ± 0.2 and 3.25 ± 1.2 in patients and controls, respectively ($p < 0.001$), and the CPT/basal CBF velocity ratio was 1.36 ± 0.2 and 2.43 ± 0.3 in the 2 groups, respectively ($p < 0.001$). In 10 patients assessed after 12 months, CBF velocity responses to ergonovine, adenosine, and CPT were found to be unchanged.

Conclusions Patients with NSTE-ACS and NO-CAD exhibit a significant coronary dysfunction, which seems to involve both an increased constrictor reactivity, likely mainly involving coronary microcirculation, and a reduced microvascular dilator function, both persisting at 12-month follow-up.

Keywords Coronary microvascular dysfunction · Acute coronary syndrome with no obstructive coronary artery disease · Microvascular spasm

Introduction

While coronary atherothrombosis is the classical cause of acute coronary syndromes, several studies have shown that approximately 10–30% of patients admitted with a suspect of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) have normal coronary arteries or non-significant coronary artery disease (i.e., no stenosis $\geq 50\%$) at angiography [1–6]. Although the mechanisms responsible for NSTE-ACS presentation in this subset of patients are multiple [1, 7], coronary microvascular spasm has been suggested to be involved in a sizeable number of patients [8, 9].

Yet, only few studies tried to investigate the presence and characteristics of an abnormal coronary microvascular reactivity in these patients [10, 11]. This is, at least in part, justified by the fact that this task can only be adequately achieved by invasive methods [12–15]. Non-invasive methods, indeed, do not allow to distinguish whether an abnormal response to vasoconstrictor stimuli, as indicated, for example, by a significant reduction of coronary blood flow (CBF), occurs in epicardial vessels or in the coronary microcirculation [16–18].

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In this study, we aimed to fully investigate coronary vascular function in patients presenting with NSTE-ACS but showing no obstructive coronary artery disease (NO-CAD) at angiography, by assessing CBF response to both vasoconstrictor and vasodilator stimuli by a non-invasive diagnostic method.

Methods

We enrolled consecutive patients admitted to the Intensive Coronary Care Unit of our University Hospital with a diagnosis of NSTE-ACS, who were found to have NO-CAD (i.e., normal coronary arteries or < 50% coronary stenosis in major epicardial coronary arteries) at angiography and satisfied all the inclusion/exclusion criteria of the study, as delineated below.

All patients had been referred to the Emergency Department of our Hospital because of one or more episodes of chest pain at rest, typical enough to suggest a cardiac ischemic origin, associated with ST-segment and/or T-wave abnormalities on the electrocardiogram (ECG) and/or increased serum troponin T levels, as assessed by a high-sensitivity electro–chemo–immune-luminescence assay (Roche Italia, Monza, Italy) with the 99th URL percentiles of 0.014 ng/mL [19].

Patients were excluded if specific diagnoses for the clinical presentation had been achieved during the in-hospital diagnostic work-up (e.g., variant angina, takotsubo syndrome, coronary embolism, myocarditis, tachyarrhythmias, and pulmonary embolism). Typically, the diagnosis of myocarditis was based on the results of cardiac magnetic resonance imaging, pericarditis on clinical and echocardiographic findings, and that of acute pulmonary embolism on laboratory (blood gas analysis and D-dimer concentrations), echocardiographic findings, and, when required, computed tomography pulmonary angiography. Furthermore, patients were excluded in case of: (1) documentation of transient ST-segment elevation (suggesting epicardial spasm) on the admission ECG and/or during any possible angina attack and (2) induction of epicardial spasm during intracoronary acetylcholine test. Patients were also excluded in case of: (1) a history of previous acute myocardial infarction, coronary revascularization (percutaneous and/or surgical), or other significant heart diseases (cardiomyopathy and valve disease); (2) abnormalities on the ECG that might have influenced the correct assessment of the patients or the results of the study investigation (e.g., atrial fibrillation, pacemaker rhythm, and left bundle branch block); (3) significant comorbidities, such as respiratory failure, renal failure (glomerular filtration rate < 60 mL/min, as calculated by the Cockcroft–Gault method, and/or creatinine levels higher than 1.5 mg/dL), and chronic inflammatory diseases; (4) a bad echocardiographic window and/or difficulties in the interrogation of blood flow in the left anterior descending coronary artery by echocardiography; and (5) contraindications to the administration of the investigational drugs of the study (ergonovine and adenosine).

Detailed clinical data were acquired in all patients, including cardiovascular risk factors. Hypertension was defined as a blood pressure (BP) ≥ 140/90 mmHg or use of anti-hypertensive drugs. Hypercholesterolemia was defined as total cholesterol levels > 220 mg/dL or use of anti-cholesterolemic drugs. Diabetes mellitus was defined as a glycated hemoglobin level > 6% or use of antidiabetic drugs. Active smoking was defined as having smoked any cigarettes in the last 6 months.

A group of consecutive patients admitted to the Emergency Department because of atypical chest pain (i.e., no retrosternal location and/or constrictive pain, possible changes with breathing or postural changes, etc.), in whom a cardiac origin was also excluded because of normal electrocardiogram (ECG) during pain, no changes in high-sensitivity troponin levels, as well as normal echocardiographic examination and maximal exercise stress test, served as controls.

The study was approved by the Ethics Committee of our Institution. Patients were carefully informed of the scope and procedures of the study and gave informed written consent to participate in the study.

Assessment of coronary microvascular constriction

Before discharge patients underwent ergonovine test with assessment of CBF response by transthoracic Doppler echocardiography (TTDE), using an Acuson Sequoia C512 ultrasound system (Siemens S.p.A., Milano, Italy) and methods described in detail elsewhere [20, 21]. All tests were performed after withdrawal of vasoactive medications for at least 48 h.

Briefly, 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 12–16 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. 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 methylergometrine (6 μg/kg up to a maximal total dose of 400 μg) was given in 15 min, under ECG and blood pressure monitoring, and CBF velocity was measured at peak infusion. For each measurement, the three highest Doppler CBF

velocity values were averaged. The response to ergonovine was measured as the ratio of diastolic CBF velocity at peak of drug infusion to the basal CBF velocity value. The tests were performed by the same expert echocardiographer.

Assessment of coronary microvascular dilation

In NSTE-ACS patients, coronary microvascular dilator function was assessed after 1 month from discharge by two kinds of stimuli and the same methods described above for ergonovine test.

Briefly, CBF velocity was measured at baseline and at peak of intravenous administration of adenosine (140 μg/kg/min for 90 s). After 15 min from returning of CBF velocity at baseline, CPT was performed, with the patient putting his/her left hand into ice water for 90 s. CBF velocity was measured immediately before and at the end of the test. For each measurement, the three highest diastolic Doppler CBF velocity values were averaged and the CBF response was assessed as the ratio of CBF velocity at peak of each test and the respective basal value.

Control group

Coronary blood flow velocity responses to ergonovine and both adenosine and CPT were done on two consecutive different days in control patients, following the same methods applied in NSTE-ACS patients.

Follow-up of NSTE-ACS patients

Vasoactive tests were repeated after 12 months in a subgroup of 10 randomly selected patients, following the same methods described above. The tests were performed in the same session; adenosine and CPT were performed first. Then, ergonovine test was performed 15 min after full recovery of basal hemodynamic conditions.

Statistical analysis

Data are reported as means with standard deviations for continuous variables and number and proportions for discrete variables. The comparisons between groups were done by independent *t* test and Fisher exact test, respectively. Within-group comparisons were done by paired *t* test. A generalized linear model analysis was applied to adjust the differences in CBF changes between patients and controls for possible confounding variables, including age, sex, cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, smoking family history of ischemic heart disease, and body mass index), and left ventricle ejection fraction. Correlation analyses were done by Pearson's test. A $p < 0.05$ was always required for statistical significance. Data were analyzed by the SPSS 21.0 statistical software (SPSS Italia, Inc., Florence, Italy).

Results

General results

Overall, 30 patients and 10 controls were enrolled in the study. The main clinical characteristics of the two groups are summarized in Table 1. The two groups did not differ significantly with regard to the main clinical characteristics, laboratory findings, and drug therapy. Left ventricle ejection fraction was normal and largely comparable in the two groups, although it was slightly lower in patients.

In the NSTE-ACS group, 28 patients (93.3%) were found to have increased troponin T serum levels and were, therefore, discharged with a diagnosis of myocardial infarction with NO-CAD [22, 23]. In agreement with troponin data, patients showed higher levels also of creatin kinase-MB, compared to controls (Table 1). Twenty-two patients (73.3%) showed normal coronary arteries, whereas 8 patients (26.7%) showed non-significant stenosis in one or more epicardial vessels at angiography. An intracoronary acetylcholine test (maximal dose 100 μg) had been performed in 6 patients (20%) and none had developed chest pain, ECG changes or significant (≥ 50%) epicardial constriction during the test.

CBF velocity response to ergonovine

Ergonovine test was completed in all patients without any relevant adverse event. An undefined discomfort and nausea were reported by 12 patients (40%); 1 patient had a hypertensive response to ergonovine that was resolved by oral administration of 5 mg of nifedipine. No patient referred chest pain during the test and no ECG changes or left ventricle wall motion abnormalities at the echocardiogram were detected.

CBF velocity response to ergonovine was significantly different between the 2 groups; the peak/basal CBF velocity ratio was indeed 0.79 ± 0.09 vs. 0.99 ± 0.01 ($p < 0.001$), as a result of significant reduction of CBF velocity after ergonovine, compared to baseline ($p < 0.001$), in patients but not in controls (Fig. 1). The difference remained statistically significant after adjustment for all potentially confounding variables ($p < 0.001$). A CBF velocity reduction ≥ 20% in response to ergonovine was found in 18 patients (60%), but in none of control subjects.

The peak/basal CBF velocity ratio was similar in the 6 patients who underwent and the 24 patients who did not undergo acetylcholine testing during coronary angiography 0.76 ± 0.06 vs. 0.79 ± 0.09, respectively; $p = 0.46$).

Table 1 Main clinical characteristics of the two groups

	Patients ($n=30$)	Controls ($n=10$)	p
Age (years)	67.0 ± 10	62.2 ± 3	0.13
Female sex (%)	19 (63.3)	6 (60.0)	0.57
Hypertension (%)	19 (63.3)	5 (50.0)	0.35
Dyslipidemia (%)	16 (53.3)	4 (40.0)	0.36
Diabetes mellitus (%)	4 (13.3)	1 (10.0)	0.63
Smoking (%)	15 (50.0)	2 (20.0)	0.096
Family history (%)	14 (46.7)	2 (20.0)	0.13
BMI (kg/m^2)	26.4 ± 3.2	26.8 ± 5.5	0.75
LVEF (%)	60.1 ± 3.4	62.7 ± 3.3	0.04
ECG changes			
ST-segment depression (%)	9 (30)	–	
T-wave abnormalities (%)	11 (36.7)	–	
Peak hs-TnT (ng/mL)	0.87 ± 1.46	–	
Creatine kinase-MB (ng/mL)	6.93 (2.6–10.6)[a]	–	
C-reactive protein (mg/L)	2.92 (1.6–12.6)[a]	–	
Coronary angiography			
NCA (%)	22 (73.3)	–	
Epicardial stenosis < 50% (%)	8 (26.7)	–	

BMI body mass index, *ECG* electrocardiogram, *LVEF* left ventricle ejection fraction, *NCA* normal coronary arteries, *TnT* troponin T

[a]Median (interquartile interval); normal values for creatine kinase-MB < 4.0 ng/mL and for C-reactive protein < 0.5 mg/L

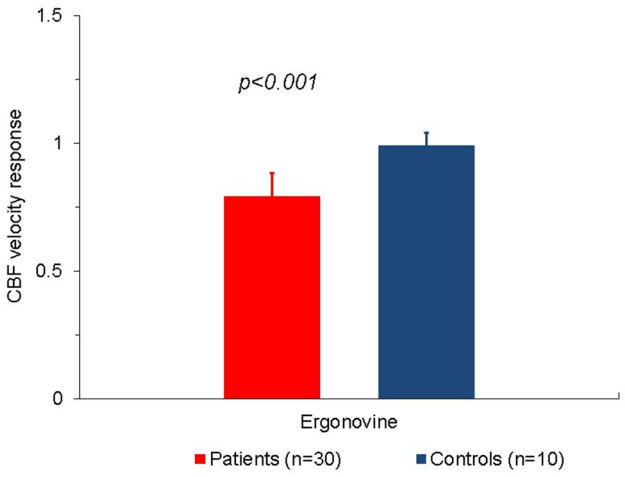

Fig. 1 CBF velocity response to intravenous ergonovine administration in patients and controls

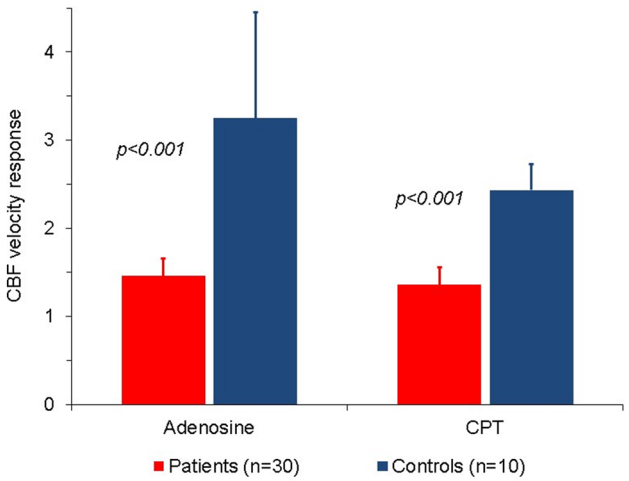

Fig. 2 CBF velocity response to intravenous adenosine administration and cold pressor test (CPT) in patients and controls

Coronary microvascular dilator function

No symptoms, ECG changes, or echocardiographic abnormalities were observed during the adenosine and CPT tests performed after 1 month from the acute phase.

CBF velocity response to adenosine and CPT were significantly lower in patients compared to control subjects (adenosine 1.46 ± 0.2 vs. 3.25 ± 1.2, $p < 0.001$; CPT 1.36 ± 0.2 vs. 2.43 ± 0.3, $p < 0.001$). The differences remained statistically significant after adjustment for all potentially confounding variables ($p < 0.001$ for both).

All patients showed a CBF response to adenosine or CPT < 2.0, which was not observed in any control subject (Fig. 2). A significant correlation was found between CBF velocity response to adenosine and CPT ($r = 0.69$; $p < 0.001$). CBF velocity response to ergonovine, however,

was not correlated to both CBF velocity response to adenosine ($r=-0.16$; $p=0.41$) and to CPT ($r=-0.15$; $p=0.42$).

Follow-up assessment

Adenosine test, CPT, and ergonovine test were repeated at 1-year follow-up in 10 patients (age 70 ± 9 years, 5 female). CBF velocity response to adenosine and CPT remained unchanged at 12 months compared to the 1-month assessment (1.44 ± 0.15 vs. 1.40 ± 0.06, $p=0.39$ and 1.35 ± 0.19 vs. 1.21 ± 0.20, $p=0.08$, respectively). No significant changes were also observed in the CBF velocity response to ergonovine at 12 months compared to the acute phase (0.84 ± 0.09 vs. 0.90 ± 0.06, respectively; $p=0.34$) (Fig. 3).

Discussion

Our data show that patients with NSTE-ACS but NO-CAD, in whom specific causes of chest pain are excluded, have evidence of functional coronary abnormalities in response to both vasoconstrictor and vasodilator stimuli. Importantly, the functional coronary abnormalities in our patients persisted unchanged at 12-month follow-up, thus suggesting that they were not confined to the acute phase, but could represent a pathophysiologic substrate predisposing to acute coronary events.

Of note, while the lower increase of CBF in response to adenosine and CPT observed in our patients demonstrates an impairment of coronary microvascular dilation, it is not possible to attribute with certainty the significant reduction of CBF in response to ergonovine to a constrictive response of epicardial or resistance coronary artery vessels. In the previous studies, indeed, constrictive stimuli were found to induce epicardial spasm in 30–49% of patients with acute coronary syndromes but NO-CAD [11, 24].

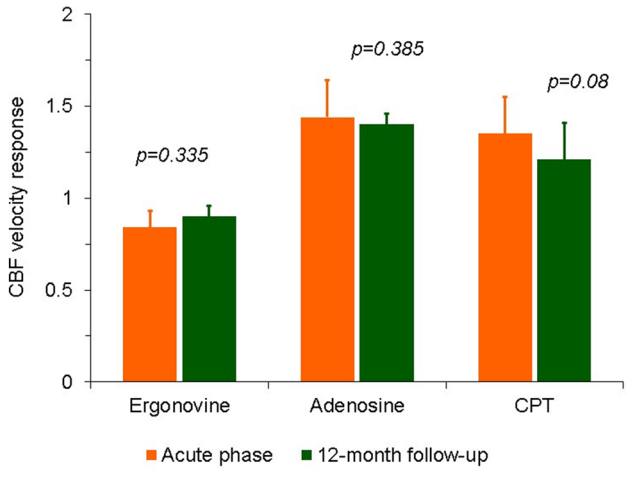

Fig. 3 CBF velocity response to intravenous ergonovine and adenosine administration and to cold pressor test (CPT) in the acute phase and at 12-month follow-up in 10 patients

We suggest, however, that the constrictive response to ergonovine in our patients mainly involved coronary microcirculation. The induction of a flow-limiting epicardial constriction was indeed very unlikely in the six patients who had negative intracoronary acetylcholine testing. At the same time, the fact that the other 24 patients, who did not undergo acetylcholine testing, showed a degree of CBF reduction similar to that of patients with a negative acetylcholine test (24 vs. 21%) suggests a similar coronary microvascular constrictive mechanism.

Data from medical literature tend to support this view, as ergonovine test rarely induced epicardial spasm in patients without a chest pain pattern of variant angina [17, 18] and only sporadically was found to induce epicardial spasm in patients with acute coronary syndromes but NO-CAD [25, 26].

Of note, as we used submaximal doses of ergonovine, we cannot exclude that the administration of higher doses might have triggered epicardial spasm (possibly suggested by chest pain with ST-segment elevation) in our patients [17, 18]. Sun et al. indeed showed that acetylcholine-induced epicardial spasm can be preceded, at lower doses, by microvascular constriction during increasing acetylcholine dose administration [27].

Patients with NSTE-ACS and NO-CAD represent a heterogeneous population of patients, with different mechanisms responsible for the clinical presentation, including clear epicardial spasm, transient thrombosis, coronary embolism, takotsubo disease, myocarditis, and tachyarrhythmias [1–7]. In about 50% of patients, however, no specific pathophysiologic mechanism can be identified [1, 7].

Coronary microvascular spasm has been suggested to be responsible for the NSTE-ACS presentation in a number of these cases [8, 9, 28]. However, only very few studies demonstrated the involvement of coronary microcirculation in this setting. Beltrame et al. first suggested that coronary microvascular spasm could be responsible for unstable angina in NO-CAD patients by showing evidence of coronary slow flow at angiography and an increased constrictor response to CPT and acetylcholine in 12 such patients [10].

In the more recent study by Montone et al. [11] in 80 patients admitted with a diagnosis of acute myocardial infarction with NO-CAD [22, 23], a diagnosis of coronary microvascular spasm was achieved in 16% of patients by invasive provocative tests, but the induction of epicardial spasm in 30% of patients might have precluded the possibility to detect microvascular spasm.

In our study, a significant reduction of CBF (> 20%) in response to submaximal doses of ergonovine, compatible with coronary microvascular constriction, was observed

in 18 out of 30 patients (60%), thus suggesting a possible higher rate of coronary microvascular involvement in these patients.

Importantly, our data show that, in addition to enhanced coronary microvascular constriction, impaired coronary microvascular dilatation was also present in our patients. Indeed, we found a lower increase of CBF in response to both adenosine and CPT compared to controls. These findings are at variance with those by Beltrame et al. who did not find an impairment of CBF increase in response to atrial pacing [10]. The reasons for this difference are not clear, but patients included in the Beltrame et al. study represented a specific subgroup of ACS-NO-CAD patients with coronary slow flow; thus, it is not clear whether their data may apply to the more general population of patients with NSTE-ACS with NO-CAD, as those included in our study.

The simultaneous presence of abnormal coronary microvascular constriction and dilatation in our patients suggests that they may present a generalized coronary microvascular dysfunction and that both the impaired dilatation and the increased reactivity predispose to and favor acute microvascular spasm under specific precipitating conditions.

Limitations of the study

Some limitations of our study should be acknowledged. First, the sample size was rather small; thus, our data need to be confirmed in larger populations of patients.

Second, although, as discussed above, various findings suggest a microvascular origin of the ergonovine-induced CBF reduction in our patients, we should stress again that an epicardial involvement, in particular of distal vessels, cannot be completely excluded; a study that would compare the effects of ergonovine on coronary circulation simultaneously assessed by an invasive and non-invasive method might definitely clarify whether our hypothesis is correct.

Third, due to practical issues, adenosine test and CPT were not assessed in the acute phase, but at 1-month follow-up, however, the results at 12 months were unchanged, suggesting that their assessment in the acute phase was unlikely to have added significant information to our data.

Fourth, control subjects were also admitted for acute chest pain and we cannot completely exclude that some degree of coronary microvascular dysfunction could also be present in at least some of these patients; however, a cardiac origin of chest pain was excluded after careful diagnostic work-up (see "Methods").

Fifth, coronary microvascular function in our study was assessed by TTDE, which may present some limitations in the correctness and reproducibility of CBF measurements; however, TTDE has been previously validated as a sufficiently reliable method [16, 29]; furthermore, in our study, the tests were always performed by the same expert operator and only patients with adequate echocardiographic window and Doppler signal in the left anterior descending artery were included.

Finally, the reasons why the appreciable reduction of CBF did not cause chest pain and ischemic ECG changes remain to be clarified. However, similar findings were reported in some previous invasive studies using different vasoconstrictor agents [13, 30].

Conclusions

Patients with NSTE-ACS and NO-CAD without an apparent cause exhibit a significant coronary dysfunction, which seems to involve both an increased constrictor reactivity, likely mainly involving coronary microcirculation, and a reduced microvascular dilator function, both persisting at 12-month follow-up.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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