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Coronary microvascular spasm triggers transient ischemic left ventricular diastolic abnormalities in patients with chest pain and angiographically normal coronary arteries

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ABSTRACT

Aims: Impaired coronary microvascular dilatory function can lead to exercise induced myocardial ischemia and angina pectoris even in patients without significant (>50%) obstructive coronary atherosclerosis (APWOCA). Diffuse distal vessel epicardial spasm and microvascular spasm have been also proposed as a plausible explanation for angina at rest in these patients. However, objective systematic evidence for the latter i.e. echocardiographic wall motion abnormalities during angina, is lacking at present. Coronary epicardial and microvascular spasm can be triggered in susceptible patients by the administration of intracoronary acetylcholine (Ach). We sought to assess whether Ach induced diffuse distal epicardial coronary artery spasm (≥75% diameter reduction) and coronary microvascular spasm can cause transient ischemic left ventricular dysfunction, as assessed by echocardiography.
Methods: 50 patients (19 men aged 60.5 ± 8.9 years) with stable APWOCA were assessed for coronary spasm and myocardial ischemia with intracoronary Ach infusion, 2D transthoracic echocardiography (before and during Ach testing), continuous 12-lead ECG monitoring, and ultrasensitive cardiac troponin (US-cTn) measurement before and within 4 h after Ach testing.
Results: 14 patients (28%) had a "negative" Ach test, 14 (28%) developed coronary microvascular spasm and 17 (34%) had diffuse distal epicardial spasm. In 5 patients (10%) the test was inconclusive. Echocardiographic variables including deceleration time, EF slope and E/A, as well as ultrasensitive-cTn concentrations were abnormal during Ach induced ischemic ECG changes. Conclusions: We have, for the first time, demonstrated that Ach induced coronary microvascular spasm is associated with echocardiographic changes and ultrasensitive-cTn elevations, indicative of myocardial ischemia.

1. Introduction

In recent years it has become apparent that coronary microvascular dysfunction (CMD) plays a pathogenic role in the syndrome characterized by angina pectoris without significant (>50%) obstructive coronary atherosclerosis (APWOCA) and also in certain subgroups of patients with significantly obstructed coronary artery disease (CAD) [1–3]. Functional coronary vasomotor abnormalities such as impaired coronary microvascular dilatation and microvascular coronary artery spasm have been proposed as a plausible explanation for angina in these patients [4,5]. Indeed, both these mechanisms have been shown to occur in cardiac syndrome X (CSX) patients, who characteristically present with exercise-

Abbreviation list: Ach, acetylcholine; APWOCA, angina pectoris without obstructive coronary atherosclerosis; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CSX, cardiac syndrome X; ECG, electrocardiogram; LCA, left coronary artery; RCA, right coronary artery; MVD, microvascular disease; msec, milliseconds; NCV, normal coronary vasoreactivity; LV, left ventricle; PHT, pressure half time; SPECT, single-photon emission computed tomography; US-cTn, ultrasensitive cardiac troponin.

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induced angina, positive exercise stress-test responses and angiographically non-obstructed coronary arteries [1,3,6]. Of importance, CMD has been also documented in patients with chronic stable angina pectoris and those with acute coronary syndromes [5,7]. Identifying patients with CMD is important as this mechanism may provide a rational basis for therapy in at least a proportion of the large number of patients undergoing coronary angiography for suspected CAD and who are found to have non-obstructed coronary arteries (i.e. ≤50% stenosis diameter reduction) [8,9]. Intracoronary Ach causes distal epicardial and microvascular coronary constriction in patients with CSX [10] and focal occlusive spasm in patients with Prinzmetal's variant angina [11]. Interestingly, however, while Ach induced occlusive coronary artery spasm, as seen in patients with Prinzmetal's variant angina [12], has been shown to cause transient ischemic LV dysfunction, an unequivocal relation between Ach induced severe distal epicardial coronary artery vasoconstriction or microvascular coronary artery spasm and ischemic LV dysfunction has not been categorically demonstrated in patients with MVD, except in recently reported anecdotal cases [13].

We therefore sought to assess whether Ach-induced diffuse distal epicardial vasospasm and coronary microvascular spasm can cause transient echocardiographic changes suggestive of myocardial ischemia in patients with chest pain without obstructive CAD.

2. Methods

2.1. Patients

From February to November 2012, 548 patients with chronic stable angina pectoris (typical exertional chest pain present for at least 3 months) suggestive of CAD were investigated with coronary angiography (Fig. 1); 408 had obstructive CAD (stenoses ≥ 50%) and 140 had stenoses <50% diameter reduction (completely normal coronary arteriograms in 75% of patients); the latter were considered for inclusion in the study, of whom 50 were recruited after excluding patients with chronic obstructive pulmonary disease, cardiomyopathy, heart valve disease, pregnant or lactating women, subjects with chronic kidney disease and those with allergic reactions to iodinated contrast media. Demographic and clinical data of the patients included in the Ach study are shown in Table 1. The definition of “current smoker” used in the present study was that of the National Cholesterol Education Program [14] i.e. any cigarette smoking in the past month. Thirty two patients had undergone non-invasive assessment of myocardial ischemia prior to diagnostic coronary arteriography; 19 had a positive (>1 mm ST segment depression) exercise ECG treadmill test, 8 had transient perfusion defects on single-photon emission computed tomography (SPECT) and 5 transient regional wall motion abnormalities on the stress echocardiogram. Eighteen patients underwent diagnostic coronary arteriography without prior assessment of myocardial ischemia, based on their high pre-test probability of CAD. 22 patients had effort angina only, while the other 28 have had occasional episodes of chest pain at rest.

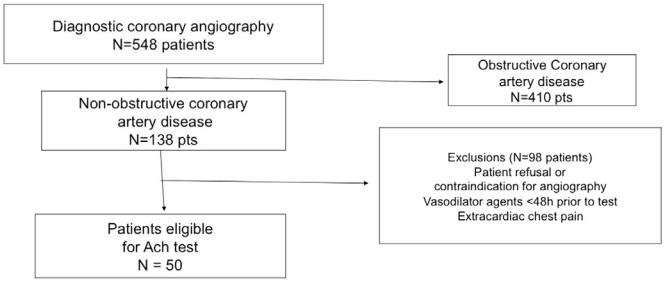

Fig. 1. Flow chart showing patients included en the study. — Ach = Acetylcholine.

Table 1
Demographic characteristics, cardiovascular risk factors, previous medication, baseline ultra-sensitive troponin concentration and baseline echocardiographic parameters in patients with normal responses to acetylcholine administration and those with coronary artery spasm.

	Ach test patients
	N = 50
Age	60.5 ± 8.9
Men	19 (38%)
Hypertension	27 (54%)
Diabetes	13 (26%)
Current smoking	10 (20%)
Hypercholesterolemia	23 (46%)
Family history of CAD	21 (42%)
Previous medication:	
- Sublingual nitroglycerine	12 (24%)
- Non-dihydropyridine CCBs	7 (14%)
- Dihydropyridine CCBs	9 (18%)
- Beta-blockers	26 (52%)
Stenoses <50% on coronary angiography	13 (26%)
Baseline US-cTn (ng/L)	8.6 ± 2.5
Baseline PHT (msec)	71 ± 8.4
Baseline E deceleration time (msec)	241 ± 32
Baseline E wave downslope (msec)	2.83 ± 0.49

CAD = Coronary artery disease.
CCB = Calcium Channel Blocker.
msec = milliseconds.
PHT = Pressure half time.
US-cTn = Ultrasensitive cardiac troponin.

2.2. Study protocol

The study protocol was approved by the institutional Ethics Committee and all patients signed written informed consent prior to study entry.

2.2.1. Ach-test

All 50 patients underwent intracoronary Ach infusion, which was carried out immediately after diagnostic coronary arteriography using a previously validated protocol as reported previously by ourselves and other investigators, [4,5]. None of the patients had received vasodilator therapy in the 48 h preceding the Ach test. Incremental doses of Ach 2, 20, 100, and 200 μg [5,7] were administered over a period of 3 min each into the left coronary artery (LCA) via the angiographic catheter. In the patients who did not develop symptoms or ischemic ECG changes, we subsequently injected Ach into the right coronary artery (RCA) (80 μg over 3 min). After the administration of Ach or when chest pain and/or coronary spasm developed, 0.2 mg glyceryl trinitrate were injected into both the LCA and RCA. Heart rate, blood pressure, and the 12-lead-ECG were continuously monitored throughout the procedure. A quantitative approach to the angiographic evaluation of coronary anatomy was used both at baseline and during Ach testing. All Ach tests were quantitatively analyzed with QCA-CMS 7.0 (Medis-Software, Leiden, the Netherlands).

2.2.2. Definition of myocardial ischemia

For qualitative analysis the presence or absence of myocardial ischemia was established for each of the tests performed (i.e. ECG, echocardiogram, and US-Tn). Regarding ECG changes, ischemia was diagnosed when ST-segment depression or elevation ≥0.1 mV, or typical T-wave inversion developed in at least 2 contiguous leads during Ach testing. Ischemic echocardiographic changes during ACH infusion were systolic wall motion abnormalities, a change >1 standard deviation in deceleration time (50 msec) , E/A [1,7] and/or