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Original article

Clinical impact of coronary artery spasm in patients with no significant coronary stenosis in acute coronary syndromes

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ABSTRACT

Background and objective: To clarify the clinical features of coronary artery spasm (CAS) with no significant coronary stenosis in patients with suspected acute coronary syndrome (ACS) in real practice.
Methods: This is a retrospective observational study of patients with suspected ACS ($n=645$) based on symptoms, electrocardiographic changes, and/or positive cardiac biomarkers and vasospastic angina (VSA, $n=90$). ACS patients were divided into two groups: (1) organic ACS ($n=515$), culprit lesion ≥75% coronary stenosis with/without thrombosis; (2) spastic ACS ($n=70$), coronary stenosis <75%, either with positive acetylcholine (ACh) test ($n=51$) or without ACh test but verified spontaneous spasm ($n=19$). The study compared clinical characteristics among organic ACS, spastic ACS, and VSA.
Results: One hundred and thirty suspected ACS patients had a coronary organic stenosis <75% (130/645, 20%). Seventy of those patients (70/130, 54%) were confirmed to have CAS, and these accounted for 11% of all ACS patients (70/645). The rate of cigarette smoking was highest in the spastic ACS. No spastic ACS patients died during their hospital stay or after discharge, whereas acute myocardial infarction occurred in 19%, aborted sudden cardiac death in 6%, multivessel spasm was provoked in 78%, and diffuse spasm was more frequently provoked than in the VSA group (82% vs. 62%).
Conclusions: CAS is not a rare cause of ACS. Although the prognosis of spastic ACS is good, there are occasional critical cases. An initial differential diagnosis including an ACh test is thus important to decide the treatment strategy of ACS.

Introduction

The most common cause of acute coronary syndrome (ACS) is thrombotic occlusion triggered by a ruptured vulnerable plaque in patients with coronary atherosclerosis [1,2]. On the other hand, coronary artery spasm (CAS) is recognized as another important mechanism involved in the pathogenesis of ACS since more than 30 years ago [3–5]. Spasm provocation test using acetylcholine (ACh) or ergonovine has been established as the standard method to verify CAS [6,7]. Several studies attempted to clarify the prevalence and clinical characteristics of CAS in various disease conditions, such as overall coronary artery diseases [8], variant angina [9], or vasospastic angina (VSA) [10], acute myocardial infarction (AMI) or recent MI [11,12], ACS [13,14], and acute or chronic chest pain syndrome [15,16]. CAS is not uncommon and plays an important role in these disease conditions [17,18]. Racial differences in the prevalence of CAS have also been reported, showing that Japanese patients are prone to be hyperresponsive to ACh after AMI in comparison to Caucasian patients [12,19]. Patients with positive CAS after AMI have a poorer prognosis than those with negative CAS [20]. Cigarette smoking is the most common predisposing risk factor for the prevalence and poor prognosis of variant angina/VSA [21,22].

Although the clinical importance of CAS in coronary artery disease is recognized, various issues are still unclear: (1) the prevalence of CAS in ACS at the first appearance in a hospital; (2) impact of coronary risk factors, especially cigarette smoking, on spasm-induced ACS in comparison to VSA; (3) differences in coronary responsiveness to ACh between spasm-induced ACS and VSA. An observational study focusing on the clinical features of CAS with no significant coronary stenosis in patients with suspected ACS was conducted to clarify these issues.

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Methods

Patient population

This is a retrospective observational study in patients who underwent selective coronary angiography (CAG) because of suspected ACS or diagnosis of VSA from March 2006 to July 2010, extracted from the institutional data base based on the following clinical findings:

Patients with suspected ACS

The latest guidelines of American College of Cardiology/American Heart Association [23] were used to select patients that presented with acute ischemic symptoms lasting ≥30 min and ischemic electrocardiogram (ECG) changes, and/or positive cardiac biomarkers (troponin-T and/or creatine kinase-MB). Ischemic ECG changes were defined as transient ST-segment elevation or depression, and newly appeared negative U waves. Sixty-five of 730 patients did not undergo CAG because of conditions unsuitable for cardiac catheterization, such as extremely high-age, marked renal dysfunction, and poor general conditions. Twenty of the remaining 665 patients who underwent selective CAG within 3 days after admission (average 1.2 days) were excluded due to prior coronary artery bypass grafting (CABG). Finally a total of 645 patients were included for further analysis. Quantitative CAG was assessed by visual estimation.

Patients with culprit lesion ≥75% coronary stenosis and/or accompanied with thrombotic obstruction were defined as the coronary stenosis-based group (organic ACS, $n = 515$). These patients thereafter underwent primary/elective percutaneous coronary intervention, CABG, or conservative medical therapy.

The patients with coronary organic stenosis <75% ($n = 130$) were classified into 4 subgroups: (1) positive ACh test; coronary organic stenosis <75% with positive ACh test ($n = 51$); (2) coronary organic stenosis <75% without ACh test but verified spontaneous spasm (spontaneous and transient ST elevation on ECG that was quickly relieved by one tablet of sublingual nitroglycerin, or spontaneous spasm was verified on control CAG, $n = 19$); (3) negative ACh test ($n = 18$); and (4) no ACh test due to the decision of attending physicians ($n = 42$). Both (1) and (2) were defined as the spasm positive group (spastic ACS, $n = 70$).

Fig. 1 shows the disposition flowchart of suspected ACS patients.

Patients with suspected VSA

Patients that presented with repeated ischemic symptoms mainly at rest, especially between night and early morning over the previous year ($n = 90$). Symptoms had been relieved within 5–10 min or quickly by one tablet of sublingual nitroglycerin. An exercise stress test by ECG was either positive or negative, and 83 of 90 patients showed negative responses.

Spasm provocation test

A spasm provocation test using ACh was performed when selective CAG revealed a coronary stenosis <75% and CAS was suspected as a cause of symptoms, with the support of temporary right ventricular pacing under vasodilator-free conditions according to the guidelines indicated by the Japanese Circulation Society [7]. Continuous infusion of isosorbide dinitrate, nitroglycerin, or nicorandil was discontinued 3 h before cardiac catheterization in ACS patients whose symptoms and ECG changes had been relieved by 1–2 tablets of nitroglycerin on admission. Coronary vasodilating agents, such as calcium-channel blockers, isosorbide dinitrate, and nicorandil, were discontinued 48 h before cardiac catheterization in patients with suspected VSA. ACh was selectively injected in incremental doses of 50 and 100 μg into the left coronary artery (LCA) first,

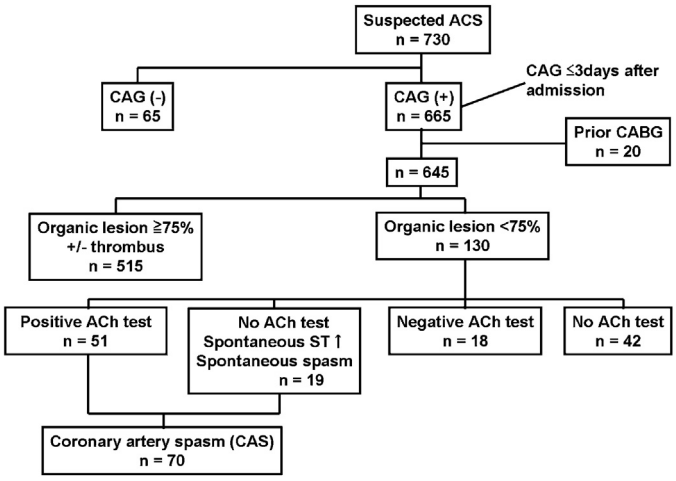

Fig. 1. Disposition flowchart of suspected ACS patients. The following two groups were analyzed in the present study. (1) Organic ACS ($n = 515$): culprit coronary stenosis ≥75% and/or thrombotic obstruction; (2) spastic ACS ($n = 70$): coronary stenosis <75% with positive ACh test ($n = 51$), and organic coronary stenosis <75% without ACh test but spontaneous and transient ST elevation on ECG, or spontaneous spasm on control CAG was documented ($n = 19$). ACS, acute coronary syndrome; ACh, acetylcholine; ECG, electrocardiogram; CAG, coronary angiography; CABG, coronary artery bypass graft.

and then 25 and 50 μg into the right coronary artery (RCA) within 15 s. Documentation of ECG, symptoms, and CAG was performed 60 s after the administration of ACh. Intracoronary administration of 1–2 mg isosorbide dinitrate was given when a severe spasm was provoked in the LCA and it was not relieved within 5 min associated with prolonged chest pain and ischemic ECG changes, and thus no ACh was injected into the RCA. Patients with microvessel spasm were excluded from the present study.

A positive ACh test was defined as: transient total or sub-total occlusion (≥90% stenosis in comparison to the maximal diameter after the intracoronary administration of 1–2 mg isosorbide dinitrate) accompanied by ischemic symptoms and ECG changes. Patients that showed a spontaneous attack with transient ST elevation on ECG that was quickly relieved by sublingual nitroglycerin, or control CAG revealed spontaneous luminal reduction ≥90% accompanied by ischemic symptoms and ECG changes were also diagnosed as CAS without an ACh test. Focal spasm was defined as total occlusion without distal filling or focal subocclusion involving <70% of the segment (vessel from a side branch to the next branch) length with normal or near-normal distal caliber, and segmental spasm was defined as subtotal occlusion involving ≥70% of the segment length as defined previously by Pristipino et al. [12]. Diffuse spasm was defined as subtotal occlusion involving ≥2 consecutive segments. Representative angiograms are shown in Fig. 2. Multivessel spasm was defined as spasm occurring simultaneously in ≥2 vessels of the RCA, left anterior descending (LAD), and left circumflex (LCX) arteries at each ACh dose as defined previously (that is, a combination of RCA and LAD, RCA and LCX, or LAD and LCX) [10,12].

Blood tests were performed on admission under casual conditions and/or after admission serially by necessity. Dyslipidemia was defined as low-density lipoprotein (LDL) cholesterol levels ≥140 mg/dL, high-density lipoprotein (HDL) cholesterol levels <40 mg/dL, and triglycerides levels ≥150 mg/dL.

Written informed consent for cardiac catheterization and data utilization was obtained from each patient, and this study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by this institution's human research committee.