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Editorial

Recommendation for establishment of guidelines for Prinzmetal's variant angina and vasospastic angina in the USA and Europe

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Guideline

Prinzmetal's variant angina was reported more than half century ago in the USA [1]. Variant angina is characterized by a transient coronary luminal reduction accompanied with reversible ST elevation on electrocardiogram (ECG) with and without organic stenosis. Until Yasue and Okumura et al. reported the usefulness of selective acetylcholine testing in diagnosing patients with coronary artery spasm, the majority of cardiologists in Japan performed acetylcholine test due to selective method and short half-life of acetylcholine [2,3]. However, fewer and fewer cardiologists performed spasm provocation tests in the cardiac catheterization laboratory in accordance with the more widespread use of coronary intervention therapy. At least in North America, Prinzmetal's variant angina has become less frequent for reasons that are unclear, perhaps because of the more widespread use of calcium antagonists. We also reported a decrease in variant angina in Japan due to the widespread use of calcium channel blockers in 2003 [4]. Racial differences concerning coronary artery spasm have been reported [5,6], and coronary artery spasm in Japanese is three times higher than in Caucasians. However, spasm provocation test is not broadly applied on clinical grounds in the USA and Europe, as in Japan. Coronary artery spasm may be involved in the genesis of various cardiac disorders, such as unstable angina, sudden cardiac death, syncope, transient heart failure, serious fatal arrhythmia, and atypical chest symptoms [7–9]. Coronary artery spasm also causes acute coronary syndrome (ACS). In one study, the majority of patients with ACS had culprit lesions and were selected for primary coronary intervention (PCI) or coronary artery bypass graft (CABG). Up to 70% of patients with ACS with typical ECG changes and/or elevation of cardiac markers had culprit lesions, whereas the remaining 30% of ACS patients had no obstructive coronary artery lesions. Cardiologists in the USA do not perform spasm provocation tests routinely in patients with non-obstructive coronary artery disease with chest pain/discomfort in the cardiac catheterization laboratory. However, in Europe, Da Costa et al. reported that 16% of French patients with myocardial infarction and normal coronary arteries had ergonovine-induced coronary spasm [10]. Ong et al. also reported that almost half of German patients with ACS and without culprit lesions who underwent the acetylcholine test had proof of coronary artery spasm. Even in Caucasian patients in Europe with ACS and without culprit lesions, coronary artery spasm may be present in 16–49% [11]. Investigation of spasm on clinical grounds should also be examined in these patients with ACS and without culprit lesions in the USA.

We found a positive relationship between the spasm provocation test numbers and spasm positive numbers in a Japanese questionnaire study of coronary artery spasm [12]. At least in Japan, if spasm provocation tests were not performed, cardiologists did not find vasospastic angina any more. There were few patients with vasospastic angina in hospitals where cardiologists were busy performing PCI and had less time to spare performing spasm provocation tests. Until now, coronary artery spasm might be missed due to fewer procedures of spasm provocation tests in the USA. If spasm provocation tests were performed routinely in the USA and Europe on clinical grounds to clarify the mechanism of ischemic findings in patients with non-obstructive coronary artery disease, Caucasians may also notice like Japanese that coronary artery spasm is associated with various cardiac disorders. Racial difference concerning coronary artery spasm may be lower than the past reports. Moreover, coronary artery spasm may have no racial difference or no racial border.

In the case reported by Choksy et al., before performing PCI in the right coronary artery, no intracoronary administration of nitroglycerine was performed during the first catheterization [13]. Coronary artery spasm was not considered in the first catheterization, and the patient was discharged on numerous medications not including calcium channel blocker and long-acting nitrate. Beta-blocker might have attenuated his chest pain attacks whereas he complained of having recurrent chest pain mostly in the morning since the time of discharge. He remained symptom-free during the follow-up period after starting on vasodilator therapy with amlodipine and isosorbide mononitrate. Not beta-blocker but calcium channel blocker/long-acting nitrate should have been selected for this patient with ACS. Fortunately, coronary stent was not inserted in this patient in the right coronary artery. Until now, PCI including unnecessary implantation of coronary stents sometimes might be performed in these ACS patients in the USA. It is necessary to administer some amount of nitroglycerine into the responsible vessel in patients with ACS during the emergency

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cardiac catheterization to exclude the presence of coronary artery spasm. In the USA and Europe, beta-blocker is the first-line therapy in patients with ischemic heart disease. In contrast, calcium channel blocker is also often employed in patients with ischemic heart disease in Japan [14]. If there was more widespread of spasm provocation tests in USA and Europe to investigate the ischemic evidence in patients with coronary artery disease, not only beta-blockers but also calcium channel blockers may be necessary for Caucasian patients with ischemic and non-ischemic heart disease.

The Japanese Circulation Society established the guidelines for diagnosis and treatment of patients with vasospastic angina in 2008, thus being the first in the world [15]. Until the guidelines had been established, the definition of positive spasm during spasm provocation test was not the same at each hospital in Japan. Vasospastic angina is diagnosed in Japan using criteria independently adopted by individual institutions. The principal characteristics of this guideline have the diagnostic flow chart of vasospastic angina. It is most important point to diagnose vasospastic angina patients with symptoms and using non-invasive tests rather than without performing invasive spasm provocation test aggressively. In this guideline, reference items based on Yasue's statement are included in the diagnostic criteria established for the grades: "definite", "suspected", or "unlikely". The patient is considered to have "definite" vasospastic angina when ischemic change (ST elevation or ST depression of 0.1 mV or more) is clearly observed on the ECG during attacks or a positive finding of coronary spasm on coronary angiography (>90% stenosis) by drug-induced coronary spasm provocation test or hyperventilation test. We diagnosed "suspected" vasospastic angina when an angina-like attack disappears quickly upon administration of a nitrate, and that meets at least one of the following four items: (1) appears at rest, particularly between night and early morning; (2) marked diurnal variation in exercise tolerance is observed; (3) induced by hyperventilation and (4) attacks are suppressed by calcium channel blockers but not by beta-blockers. Clinically, both definite and suspected vasospastic angina are diagnosed as vasospastic angina. In this guideline, PCI in combination with adequate administration of coronary dilators for vasospastic angina patients with severe organic stenosis is classified as Class IIa. And, PCI for vasospastic angina patients without severe organic stenosis is classified as Class III. PCI procedure in this patient has been demonstrated to be useless and possibly harmful at times, or its harmfulness has been widely agreed upon. In the USA, the recognition of Prinzmetal's variant angina is low even by clinical cardiologists. Thus, we recommend the establishment of a guideline for variant angina and vasospastic angina in USA. Therefore, Caucasians in the USA and Europe will recognize the presence of ST elevation in Prinzmetal's variant angina. Moreover, we hope to establish worldwide unified guidelines for diagnosis and treatment of patients with Prinzmetal's variant angina and vasospastic angina in cooperation with the American Heart Association, American College of Cardiology, European Society of Cardiology, and Japanese Circulation Society.

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