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【 EDITORIAL 】

Spasm Provocation Test Using Acetylcholine in Patients with Bronchial Asthma: An Important Step Forward

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Key words: vasospastic angina, coronary spastic angina, coronary artery spasm, spasm provocation test, acetylcholine, bronchial asthma

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It is well-known that coronary spastic angina, also known as vasospastic angina (VSA), is characterized by transient vasoconstriction of epicardial coronary arteries, leading to myocardial ischemia (1-3). Coronary artery spasm causes rest angina, exertional angina, acute myocardial infarction, sudden cardiac death, and heart failure (3-5). The mechanisms of coronary artery spasm are multi-factorial and include an abnormal autonomic nervous system response, endothelial dysfunction in the coronary artery or systemic peripheral vasculature, vascular smooth muscle cell hyperresponsiveness, magnesium deficiency, genetics, and a certain anatomy of the coronary arteries (3, 6-8). Recently, inflammation has been identified as an important risk factor for coronary artery spasm (9).

Bronchial asthma (BA) is a common disease that is usually associated with airway hyperresponsiveness and inflammation (10). Owing to their common risk factors, many reports have investigated the relationship between VSA and BA (11-14). Hung et al. (11) showed that BA is associated with the development of VSA using Taiwan's National Health Insurance Research Database. Furthermore, they showed that a history of steroid therapy is related to the development of VSA. Hung's study (11) adopted a cross-sectional design, so the relationship between steroid therapy and the development of VSA may have been inconclusive due to the cause or result of development of VSA.

Other case reports have described patients with BA with medically refractory VSA that was controlled with steroid therapy (12-14). Therefore, because BA may be a risk factor for VSA, and because refractory VSA is observed in patients with BA, cardiologists should clarify the presence of VSA in patients with BA using the spasm provocation test (SPT). However, there is an unsolved problem regarding the SPT in such patients. Namely, acetylcholine (ACh), which has been frequently adopted as the provocative drug in the SPT and is the only insurance-reimbursed drug used in the SPT in Japan, is contraindicated in BA patients because of ACh-induced bronchial constriction.

A recent paper by Sueda (15) concerning their retrospective study focused on the safety of the SPT using ACh (off-label use) and some specific findings of the SPT in patients with VSA and BA. In Sueda's study (15), among 495 patients with rest angina, 13 had BA. Complications of the SPT in such patients were reported. There was no significant increase in severe complications with the SPT using ACh in patients with BA compared with patients without BA. Sueda recruited patients with BA according to the following inclusion criteria: presence of well-controlled BA treated with several medications and absence of recent attacks (within three months) of BA. In general, ACh is indeed contraindicated in patients with BA. However, in the SPT, ACh can be diluted in two stages and infused slowly at intervals (3), and the total doses of ACh adopted in the SPT are generally not high. In Sueda's study (15), the median total dose of ACh was about 300 μg. Thus, these conditions, which have not been shown to increase complications in the SPT, may be useful for cardiologists. As shown above, in the clinical setting, we have encountered patients with established BA who are also suspected of having VSA. In these patients, the use of ACh may be able to be avoided, with ergonovine maleate (EM), which is not an insurance-reimbursed drug for the SPT and is adopted for off-label use (14), used instead.

BA is frequently observed in adult women (16). It has been shown that ACh in the SPT provokes coronary artery spasm to a greater degree than EM, especially in women (17). Therefore, considering the condition of the patient, the status of BA control, and the merits and limitations of ACh provocation, for cardiologists, the use of ACh in the SPT may be acceptable, although only for off-label use. Informed consent from patients and ethics committee approval

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at each institution should be obtained. As highlighted in the limitations section (15), the results were obtained from a single center, and the number of patients with BA was small; thus, a multicenter prospective study or multicenter registry for such patients is needed to confirm the safety of ACh in the SPT in patients with BA and to encourage a review of ACh usage guidelines.

In Sueda's paper (15), in patients with BA undergoing the SPT, an increased prevalence of spasm in the left anterior descending coronary artery and multi-vessel spasm was observed. This may indicate a greater degree of coronary spasm in patients with VSA and BA than those without BA. It has been shown that BA is associated with vascular dysfunction, including endothelial and vascular smooth muscle cell dysfunction (18, 19). Prognostic factors have been reported, including variant angina or focal spasm in patients with VSA (20, 21), and the coexistence of BA and VSA may be another prognostic factor for cardiovascular events or medically refractory angina in VSA. To clarify these issues, a multicenter registry or multicenter prospective study is necessary.

In a clinical setting, VSA and BA coexist, and cardiologists need to clarify the presence of VSA using the SPT in patients with BA. However, ACh, which is the only insurance-reimbursed drug available for the SPT, is contraindicated in such patients. Sueda's findings (15) have important clinical implications for cardiologists. I believe that this paper introduces an important step forward that will transform the present situation.

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