Coronary artery spasm is an important mechanism in ischemic heart disease. Vasospastic angina (VSA) is not uncommon in Far-east Asia, including Japan and Korea, than in Western countries, for genetic as well as environmental reasons. 

However, it has been given little attention by many cardiologists and there are still many controversies about both the methodology of the pharmacological provocation test for coronary spasm and the treatment strategy for VSA.

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Calcium-channel blockers (CCB) are the established standard drug for VSA; however, the duration of treatment is still unclear. A rebound of anginal symptoms may occur when the CCB is discontinued. All generations of CCB have similar efficacy in relieving symptoms, and they also suppress asymptomatic ischemia and would improve patients' prognosis. Indeed, most patients with VSA can be controlled with CCBs with a relatively good quality of life and prognosis. Diltiazem as benzodiazepine, amiodipine and nifedipine as dihydropyridine, and verapamil as phenylalkylamine were indicated for VSA according to the Food and Drug Administration of United States in 2005. Unfortunately there are no data for benidipine because it is not commercially available in the USA so far. And there are no outcome data for VSA so far.

How does the class effect of different CCBs affect the similar outcome of VSA? In this issue of the Journal, Nishigaki et al demonstrate a class difference of CCBs in VSA, and in particular benidipine had a significantly more beneficial prognostic effect than other CCBs (eg, diltiazem, amiodipine, nifedipine) according to this meta-analysis in Japan. This is good information for clinicians selecting the right drug for patients according to evidence-based medicine, even though this meta-analysis data was not obtained from a prospective randomized controlled clinical study.

The exact mechanisms of coronary spasm remain to be elucidated. Endothelial dysfunction, oxidative stress, gene polymorphisms such as eNOS, oxidative stress, chronic low-grade inflammation, hypercontractility of coronary smooth muscle, and magnesium deficiency play critical roles in the pathogenesis of coronary spasm. 

Hypercontraction of coronary smooth muscle triggered by an increase in intracellular Ca²⁺ in the presence of an increased Ca²⁺ sensitivity is an especially important mechanism of developing coronary spasm. It has been shown that the RhoA/ROCK pathway is involved in Ca²⁺ sensitivity and that reduced endothelial NO activity results in increased Ca²⁺ sensitivity through an enhanced RhoA/ROCK pathway.

CCBs act as coronary vasodilators, producing variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. Several criteria have been used to classify CCBs' action on the cardiovascular system. 

The simplest classification is based on their chemical structures and subdivides them into benzodiazepines, dihydropyridines, and phenylalkylamines. Each group has a specific site of action on the r-channel α-1 subunit. Another popular subclassification subdivides the compounds within each structural group into first-, second-, and third-generation compounds.

CCBs widely differ in terms of selectivity within the cardiovascular system. Verapamil and diltiazem have a low vascular-to-cardiac selectivity ratio, and nifedipine and amlo- dipine have intermediate selectivity. Benidipine is a dihydropyridine L-type/T-type CCB possessing a stronger vasodilating effect and a higher vascular selectivity, compared with amloidipine. This higher vasoselectivity and affinity of benidipine for coronary arteries may be involved not only in its preventive effects on coronary spasm, but also in its better prognostic results. The beneficial prognostic effect of benidipine as compared with other CCBs was noted at the 6th year in this meta-analysis, suggesting that the vasoprotective role of benidipine was involved.

According to this meta-analysis data, a prospective randomized controlled clinical study is necessary to elucidate which drug has the more beneficial cardiovascular outcome in VSA. At the 74th Annual Scientific Meeting of the Japanese Circulation Society in Kyoto, March 2010, Shimokawa, Maseri, Beltrame and I had a fireside seminar about VSA and agreed to create a prospective international multicenter registry of VSA with the same pharmacological provocation protocol used for coronary spasm in Japan, Italy, Australia and Korea. It is the first prospective international multicenter registry for VSA as far as I know and will help obtain much more information about VSA in future.

In conclusion, it is a time to rethink the importance VSA in daily clinical practice. The prospective international multicenter registry and a prospective randomized controlled clinical study will be helpful for finding the right answers to the many unsolved questions about VSA in evidence-based medicine.
References


