Vasospastic angina can be diagnosed by several established provocation tests, including intracoronary acetylcholine (ACH) injection and the ergonovine loading test, during cardiac catheterization. These methods are also popular for evaluating local "endothelial function" where drug-eluting stents have been implanted. However, we do not fully understand the phenomenon of vasospastic angina because actual vessel behavior at the exact moment of spasm has rarely been visualized.

Here, we report the management of a 72-year-old man with vasospastic angina refractory to maximum-dose pharmacological treatment. The patient also suffered drug-induced eruptions, most likely caused by calcium antagonists. Although coronary intervention for a spastic segment without high-grade luminal stenosis is regarded as harmful (Class III) according to the Japanese Circulation Society Guideline 2008, we concluded that we had no better alternative for this patient than the placement of a bare metal stent at the major spastic segment. It seemed the only way to diminish the spastic attacks as well as reducing the dose or stopping altogether the drugs suspected of causing the side effects. The exact location where the stent should be placed was determined by repeated ACH provocation tests. Written informed consent for these procedures was given by the patient in advance. Detailed...
information and the patient’s clinical course have been published elsewhere.6  

During spasm provocation tests, we used intravascular ultrasound (IVUS) to obtain serial images of endovascular behavior. Specifically, we repeated the provocation test while the IVUS catheter was inserted exactly where focal spasm had been induced by the initial ACH test. Our provocation protocol was as follows: intracoronary ACH injection gradually for approximately 15–20 s and then a saline flush, not exceeding a total injection time of 30 s. Potential risks associated with IVUS catheter placement during provocation testing include prolonged coronary occlusion and enhanced myocardial ischemia. However, because a guidewire was inserted into the artery, any additional catheter-based treatments could be rapidly performed to relieve coronary spasm and to improve myocardial ischemia. In fact, IVUS-guided stent implantation was scheduled just after this observation period. Because this assessment was planned more for research purposes, we explained the procedures in detail and obtained the patient’s permission for the series of observations.

Figure 1 shows the angiographic changes during the repeated provocation tests in the right coronary artery (RCA). Focal vasospasm was induced at the distal RCA segment after coronary injection of 20 μg ACH. Thus, we decided to place the IVUS transducer at this site and obtained serial IVUS images under repeated provocation testing (Figure 2). The baseline IVUS image revealed mild coronary stenosis with moderate accumulation of plaque. In fact, the amount of plaque was greatest at this location compared with the other segments of the RCA. Vasoconstriction had already been initiated in a relatively early phase of ACH injection (15 s). The external elastic membrane (EEM) area gradually decreased in a time-dependent manner, and increased immediately after intracoronary ISDN injection. Low-echoic band boundary of the EEM is most clearly visualized and the most thickened at 60 s. ACH, acetylcholine; ISDN, isosorbide dinitrate; PA, plaque area; s, second.

**Figure 2.** Serial intravascular ultrasound (IVUS) images show the changes of the arterial wall during provocation. Spasm occurred at the portion of the artery with relatively large amounts of accumulated plaque. External elastic membrane area (EEMA) and lumen area (LA) decreased in a time-dependent manner, and increased immediately after intracoronary ISDN injection. Low-echoic band boundary of the EEM is most clearly visualized and the most thickened at 60 s. ACh, acetylcholine; ISDN, isosorbide dinitrate; PA, plaque area; s, second.
lation, less calcification, and negative remodeling. Mildly atherosclerotic segments with these characteristics are well accepted to be frequent sites of vasospasm. In brief, in young healthy subjects, ACH causes vasodilation by releasing nitric oxide from the endothelium. In contrast, in atherosclerotic vessels, endothelial dysfunction may cause an abnormal reaction to ACH (vasoconstriction) and this can be considered the mechanism underlying a positive ACH provocation test, as well as an upstream pathogenetic contributor to the coronary spasm phenomenon.

Lumen narrowing could potentially be primarily caused by constriction of the low-echoic band (ie, layered smooth muscle), due to our finding of the reduced area of the EEM, and the clear thickening of the band. One finding remains difficult to understand, namely the decrescendo of the area of plaque at the spastic segment of the RCA. Proposed mechanisms for this could include (1) mechanical plaque compression between the low-echoic band and IVUS catheter or (2) longitudinal plaque re-distribution during spastic changes. Although volumetric IVUS assessment may have assisted in determining this, unfortunately it could not be carried out because the IVUS catheter was fixed in position and was not withdrawn during the procedure. Considering the thickened low-echoic band, we believe “mechanical plaque compression” may be the primary mechanism. A recent study suggests another potential explanation in terms of the possibility of plaque compression. In atherosclerotic regions of the adult vascular wall, vascular smooth muscle cells with a third phenotype are present, seeming to possess both contractile and proliferative capabilities. This implies that the thickened intimal layer may be able to contract on its own. Thus, potentially, constriction of the intima (plaque) layer could also result in EEM area reduction, passive increase of the thickness of the medial layer by the traction, and a reduction of intima area.

IVUS investigation in this specific case illuminated the possible mechanisms of coronary spastic angina. Further investigations are required to clarify its underlying pathogenesis.

References