Editorial Commentary

Let us pay more attention to performing coronary function assessment for multivessels!

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Angina with nonobstructive coronary artery disease (ANOCA) is common in clinical practice and has gained increasing attention. Several expert documents and revised guidelines for the diagnosis and treatment of ANOCA have been published in recent years (1-3). The causes of ANOCA have been classified according to the location of the abnormal findings in the epicardial coronary arteries (conduit level) and coronary arterioles (resistance vessel level). Epicardial coronary artery abnormalities include vasospastic angina (VSA), wherein the epicardial coronary arteries transiently constrict, resulting in myocardial ischemia. At the microvascular level of the coronary arteries, abnormalities are classified into microvascular spasms (MVS) and coronary microvascular dysfunction (CMD). MVS is presumed to be the functional vasoconstriction of the coronary arterioles; however, some cardiologists remain skeptical about the relevance and existence of MVS because it is mainly diagnosed on the basis of subjective criteria. CMD is a dilatory dysfunction caused by organic abnormalities of coronary arterioles. VSA and MVS are mainly diagnosed by the spasm provocation test (SPT) with acetylcholine (ACh). Although some cardiac imaging options, such as myocardial perfusion with 13N-ammonia positron emission tomography or stress myocardial perfusion magnetic resonance imaging, have been used to assess CMD (2), CMD is standardly diagnosed through the coronary microvascular function test (CMFT) using a pressure wire with a thermistor or Doppler sensor. Other supplementary methods of diagnosing VSA and MVS include measuring the difference in lactate values between the aorta and coronary sinus (4). However, the procedure is quite complicated and has not been routinely performed. The utility of rechallenge testing after nitroglycerin administration was reported because VSA masked MVS (5); however, this is also not a common practice. Currently, SPT and CMFT are the most important tests to evaluate coronary artery functional dysfunction. Recent reports indicate that when both SPT and CMFT are performed in patients with suspected vasomotor disorder, adding wire-based physiology measurements during spasm testing can help improve and standardize spasm diagnoses (6).

The importance of diagnosing and treating ANOCA is based on the following observations: first, the prospective coronary microvascular angina (CorMicA) trial (7) revealed that despite the lack of difference in major cardiovascular adverse events, medical therapy after clarifying the endotypes of coronary vasomotor dysfunction following SPT and CMFT can significantly improve subjective symptoms. Thereafter, the importance of the endotype of coronary vasomotor dysfunction became widely known, which contributed to advances in its diagnosis and treatment. Recently, another prospective study revealed that

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patients who underwent cardiac computed tomography for screening exhibited no difference in the results of invasive coronary functional tests in terms of improvement of angina symptoms compared with patients treated without such tests (without informing them of the results). Moreover, patient satisfaction was only better in those who underwent invasive coronary function test (8). Given that several guidelines and expert consensus documents (1-3) have standardized the treatment of coronary vasomotor dysfunction based on the results of the CorMicA trial (7), cardiologists are now familiar with the diagnosis and treatment of coronary vasomotor dysfunctions, such as VSA and CMD. This study also reported the low frequency of VSA (8) compared with the VSA rates in the clinical setting. These speculations may account for the differences in the results between the CorMicA trial (7) and the recent study by Sidik *et al.* (8). Thus, the results of the study by Sidik *et al.* (8) did not appear to reduce the importance of performing coronary function tests such as SPT and CMFT. Second, VSA, MVS, and CMD can overlap (2). Suda *et al.* investigated the prognosis of VSA and CMD and their co-occurrence in patients with ANOCA and reported a worse prognosis in those with both VSA and CMD (9). The results of this study indicate the importance of not only diagnosing VSA by SPT but also evaluating for CMD even after confirming VSA. Finally, the pharmacologic treatment of each ANOCA endotype must be addressed. After diagnosing VSA, the first-line treatment is calcium channel blocker therapy; however, beta-blockers are a taboo in VSA (10). Beta-blockers are often the first-line treatment in CMD (1). The greatest advantage of this coronary function test is that if the patient is found to have CMD rather than VSA, beta-blockers can be introduced with confidence.

In terms of the present status of the coronary function assessment for multivessels, some researchers recommend performing the coronary function test only in the left anterior descending coronary artery (LAD) (3), whereas others proposed performing it in the left and right coronary arteries (LCA and RCA, respectively) (11). The recently issued guidelines by the Japanese Circulation Society states that because multivessel coronary spasm attacks are often severe and one of the prognostic factors in VSA, accurate diagnosis of multivessel spasm is important (2); however, the level of recommendation of coronary function assessment for multivessels has not been mentioned.

Recently, Rehan *et al.* reported a clear increase in the diagnostic rates of VSA and CMD when performing multivessel coronary function tests (12). In their study on 80 patients with ANOCA, performing CMFT increased the diagnostic rates of VSA from 47.5% to 60.0%, of CMD from 37.5% to 62.5%, and of coronary vasomotor dysfunction from 68.8% to 86.3%. Moreover, single- and multiple-vessel coronary function tests revealed different diagnoses in 27 patients. Specifically, 15 patients had chest pain of noncardiac origin diagnosed with some types of coronary vasomotor dysfunction, 7 had VSA alone, and 5 had CMD alone, all of who were diagnosed with both VSA and CMD. Thus, treatment was highly likely changed in these cases. Finally, although coronary spasms were more common in LAD, they could also occur alone in 20.8% of patients with RCAs, and the frequency of CMD in the three coronary arteries were comparable, resulting in the increased diagnostic rates of multivessel coronary spasms and multivessel CMD. Herein, we will discuss multivessel coronary spasms and multivessel CMD, as reported by Rehan *et al.* (12).

Multivessel coronary spasms have been identified as one of the prognostic factors for VSA (13,14) in addition to the absence of calcium channel blockers, presence of significant coronary artery disease, ST-segment elevation on electrocardiogram or variant angina, history of out-of-hospital cardiac arrest, smoking, chest pain at rest, beta-blocker therapy, focal coronary spasms, and presence of coronary spasms in the LAD (14-18). In studies reporting multivessel coronary spasms as a prognostic factor of VSA (13,14), Takagi *et al.* retrospectively examined and scored the predictive value of VSA in a multicenter registry (14). They reported the significance of diagnosing multivessel coronary spasms (2 points) as a prognostic risk factor, including history of out-of-hospital cardiac arrest (4 points), smoking (2 points), chest pain at rest (2 points), significant stenotic lesions (2 points), ST-segment elevation (1 point), and beta-blocker therapy (1 point) (14). Previously, we also reported our institutional data on the frequency of multivessel coronary spasms in VSA, with prognosis not different from that of single-vessel spasms, because more coronary dilators were used in multivessel coronary spasms (19). Thus, multivessel spasms have resulted in the intensification of drug therapy, which is a crucial factor that influences treatment. In addition, we have shown that a two-vessel spasm can be determined by spasms found in the LAD and left circumflex coronary artery (LCX) in SPT performed only in the LCA; however, LAD and RCA patterns were more common than LAD and LCX patterns in a two-vessel coronary spasm (20). These findings suggest the significance of performing SPT in the LCA and RCA to

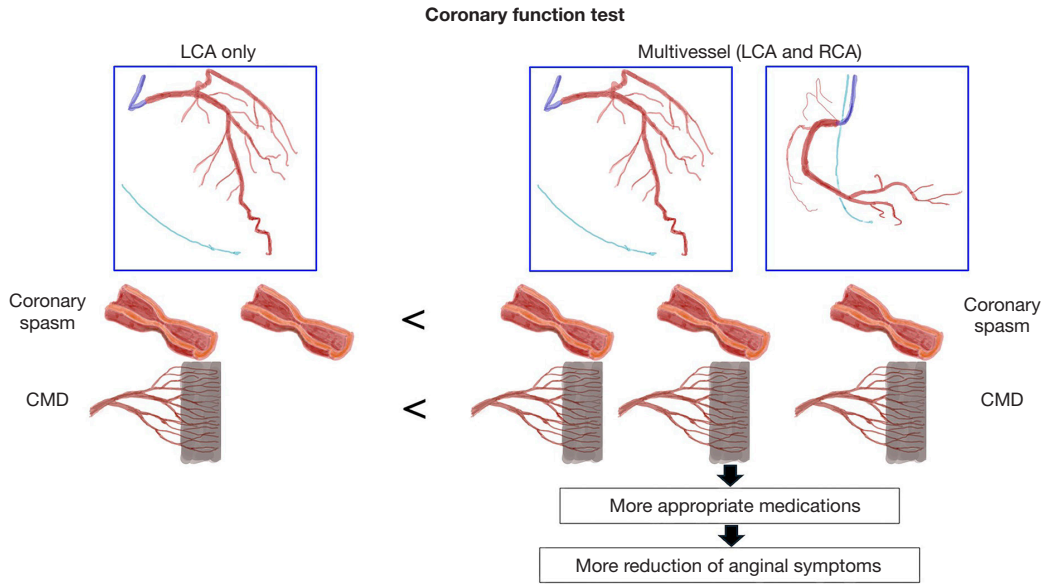

Figure 1 Possible merits of the multivessel coronary function test. Multivessel coronary function tests can increase the diagnostic rate of coronary spasms and coronary microvascular dysfunction, leading to the prescription of more appropriate medications and increased reduction in anginal symptoms. LCA, left coronary artery; RCA, right coronary artery; CMD, coronary microvascular dysfunction.

diagnose multivessel coronary spasms.

Although the prognostic and therapeutic importance of multivessel CMD has not yet been confirmed, CMFT may increase the diagnostic rate, as reported by Rehan *et al.* (12). Many cardiologists may be interested in this, and given the increasing importance of CMFT, clarifying the prognosis of multivessel CMD is desirable. Rehan *et al.* reported a similar frequency of CMD by coronary artery vessel (12), which we mention because it appears inconsistent with previous reports (21,22), showing a higher CMD prevalence in the RCA. Previously, we reported that coronary flow reserve was not different between LADs and RCAs; however, the index of microcirculatory resistance was clearly higher in the RCA, indicating that CMD was more common in this artery (22). We hope that more cardiologists will be interested in performing CMFT in the future after reading the article by Rehan *et al.* (12) and that they will be able to clarify which coronary vessels are more frequently affected by CMD.

In general, performing SPT on the RCA may require temporary pacing (23), and complications of paroxysmal atrial fibrillation due to ACh provocation may increase (24,25). Caution may need to be exercised in CMD assessment because of the complications of atrial fibrillation. Moreover, assessing the presence of CMD in the three coronary arteries will undoubtedly increase the time required for the procedure. Nonetheless, optimal medical therapy should be implemented based on the definite diagnosis of VSA, CMD, or their combination after the coronary function test. The multivessel coronary function test could directly improve not only chest symptoms but also long-term prognosis in patients with ANOCA (*Figure 1*). We sincerely hope that more cardiologists will become interested in multivessel coronary function tests after reading the article by Rehan *et al.* (12) and that the characteristics and prognosis of patients with multivessel CMD will gain clarity in the future.

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