Ischemia Testing for Stable Coronary Artery Disease

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Testing for myocardial ischemia is the single-most relevant one for diagnosis and appropriate management of coronary artery disease (CAD). The clinical challenge for a physician diagnosing and taking care of the patients is which tests should be necessary for whom. The diagnostic work-up of suspected CAD includes choosing the most appropriate modality for the individual patient to achieve a conclusive and clinical helpful diagnosis and to minimize use of personal and financial resources. In addition, myocardial ischemia testing has to be the most important tool for deciding whether or not to revascularize. Therefore, this review outlines the current clinical work-up including the appropriate selection of ischemia testing in the diagnosis of suspected obstructive CAD, as well as when making a decision of revascularization therapy.

KEY WORDS: coronary artery disease, ischemia, pre-test probability

I. Myocardial ischemia

Coronary artery disease (CAD) is a disorder that causes myocardial ischemia, where the blood flow to the myocardium is inhibited by obstruction and stenosis of the coronary artery, and the balance of supply and demand of oxygen in the myocardium is disturbed. In general, it is used almost synonymous with ischemic heart disease. Based on the condition of ischemia, it is roughly classified into angina, silent myocardial ischemia (SMI), and myocardial infarction.

The development of myocardial ischemia, whether silent or painful, represents the cumulative impact of a sequence of pathophysiologic events over time and this sequence of events can be termed the ischemic cascade (Fig. 1). Specifically, these events include diminished left ventricular compliance, decreased myocardial contractility, increased left ventricular end-diastolic pressure, ST-segment changes and, occasionally, angina pectoris. Cardiac rhythm disturbances and breathlessness as a consequence of ischemic left ventricular dysfunction may also be recognized. There are three types of mechanism causing ischemia in coronary artery ; obstruction of epicardial coronary artery, coronary microvascular dysfunction (MVA: microvascular angina), and coronary spasm (CSA: coronary spastic angina), but the mechanisms are often overlapped.

II. Initial assessment

First of all, medical history of the thoracic symptoms must be taken in detail. Then, risk factors that accelerate the development of CAD and are associated with a worse prognosis need to be assessed. They comprise hypertension, dyslipidemia, diabetes, smoking, obesity, and a positive family history for CAD. After a thorough history taking and physical examination, the following tests should be applied ; biochemical tests, chest x-ray examination, resting 12 lead electrocardiogram (ECG), and resting echocardiography. Biochemical tests are necessary for the evaluation and management purposes of the conventional risk factors. Not to mention lipid profiles, check and follow-up of glucose metabolism abnormalities are indispensable. Chest x-ray examination is useful for differential diagnosis of chest pain and dyspnea. While resting ECG will rarely show acute ischemic changes such as dynamic ST depression or T-wave inversion, left bundle branch block or Q waves may point towards existing CAD, even if the patient is unaware. A resting echocardiography is performed to evaluate the presence of other heart disease and cardiac function. The presence of regional wall motion abnormalities makes the diagnosis of CAD more likely. Patients with a reduced left ventricular ejection fraction (LVEF) of < 50% and typical angina are at high risk for cardiovascular events and invasive coronary angiography (CAG) should be considered without previous testing¹⁾.

III. Pre-test probability (PTP)

Several studies have indicated that large numbers of cardiovascular imaging tests are ordered with no clinically valuable in-

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Fig. 1 Relationship between ischemia cascade and ischemia testing. CAG: coronary angiography, CFR: coronary flow reserve, CMR: cardiac magnetic resonance, CTA: computed tomography angiography, ECG: electrocardiography, FFR: fractional flow reserve, iFR: instantaneous wave-free ratio, SPECT: single photon emission computed tomography.

dications and have shown that inappropriately ordered cardiovascular imaging tests neither improve outcomes nor resulted in therapeutic interventions²). Therefore, the calculation and assessment of ‘pre-test probability’ (PTP) before selecting a specific ischemia testing modality are necessary for (further) work-up of suspected CAD, as outlined by Montalescot et al. in the 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD¹) (Table 1). Patients with stable chest pain can be divided into risk groups by age, gender and character of pain and the PTP dictates the mode of further investigation:

- low risk (< 15% risk): can be managed without further testing
- medium risk (15–85%): could/should have a non-invasive imaging functional test
- high risk (> 85%): need risk stratification only

It is noteworthy that the presence of coronary spasm and/or microvascular disease is not evaluated in this analysis. Hence, the PTP value is important in assessing the clinical likelihood of ‘obstructive’ atherosclerotic CAD as one possible reason for chest pain—but not appropriate regarding the presence of other pathophysiological mechanisms such as coronary spasm or microvascular disease³). Also, PTP generally depends on the patient’s group being diagnosed and is different among patients with different pathological background and prevalence rate of CAD. There are some reports that both U.S. and European measures may markedly overestimate PTP rates⁴). Therefore, this table may not apply to the clinical practice in Japanese subjects as it is, however, the assessment of PTP is crucial for the test selec-

Table 1 Clinical pre-test probabilities (PTP, %) in patients with stable chest pain symptoms

	Typical angina		Atypical angina		Non-anginal pain	
Age	Male	Female	Male	Female	Male	Female
30 – 39	59	28	29	10	18	5
40 – 49	69	37	38	14	28	8
50 – 59	77	47	49	20	34	12
60 – 69	84	58	59	28	44	17
70 – 79	89	68	69	37	54	24
80 <	93	76	78	47	65	32

- a PTP < 15%; can be managed without further testing.
  - a PTP of 15–85%; could/should have a non-invasive imaging functional test.
  - a PTP > 85%; need risk stratification only.
- Adapted from 2013 ESC guidelines¹).

tion, and the accuracy will increase by adding the assessment of risk factors.

IV. Diagnostic tests

The relationship between the diagnostic tests and pathophysiologic aspects during the ischemic cascade is demonstrated in Fig. 1. Perfusion abnormalities occur very early in the course of myocardial ischemia. This may explain why myocardial perfusion is such a sensitive diagnostic test for myocardial ischemia. Next, diastolic function becomes impaired, since relaxation for the heart muscle is an active, energy-consuming process. As ischemia is ongoing, systolic function becomes abnormal – the patient will develop wall motion abnormalities on imaging. Fairly late in the ischemic process, ECG will show ischemic abnormalities. Later still, the patient will develop chest pain⁵).

Accuracy of tests commonly used to diagnose the presence of CAD is shown in Table 2. They have typical sensitivities and specificities of approximately 85% and can be divided into anatomical and functional tests.

1. Exercise ECG

The exercise load includes master, treadmill, ergometer tests, etc. Although it is simple, the sensitivity is low, which is higher when other exercise data such as the blood pressure response and symptoms are considered as well. The diagnostic value of exercise ECG is further limited in the presence of left bundle branch block (LBBB), paced rhythm, LV hypertrophy, Wolff-Parkinson-White (WPW) syndrome, digitalis treatment, and electrolyte disturbances.

2. Stress echocardiography

This is a highly sensitive and specific modality which can detect myocardial wall motion abnormalities caused by ischemia. Two types of stress are performed; exercise and pharmacological. The former is the best stressor, and the latter, dobutamine

Table 2 Characteristics of tests commonly used to diagnose the presence of coronary artery disease

	Diagnosis of CAD	
	Sensitivity (%)	Specificity (%)
Exercise ECG	45 – 50	85 – 90
Exercise stress echocardiography	80 – 85	80 – 88
Exercise stress SPECT	73 – 92	63 – 87
Dobutamine stress echocardiography	79 – 83	82 – 86
Dobutamine stress CMR	79 – 81	81 – 91
Vasodilator stress echocardiography	72 – 79	92 – 95
Vasodilator stress SPECT	90 – 91	75 – 84
Vasodilator stress CMR	67 – 94	61 – 85
Coronary CTA	95 – 99	64 – 83
Vasodilator stress PET	81 – 97	74 – 91

CMR: cardiac magnetic resonance, CTA: computed tomography angiography, ECG: electrocardiogram, MRI: magnetic resonance imaging, PET: positron emission tomography, SPECT: single photon emission computed tomography.

Adapted from 2013 ESC guidelines¹⁾.

stress in most cases, is used in patients with limited exercise tolerance. The diagnostic accuracy of stress echocardiography is remarkable considering the simplicity, wide availability, and low costs of this method. However, limitations of stress echocardiography comprise, in particular, technical challenges such as a poor acoustic window, a difficult assessment of wall motion abnormalities in segments with previous myocardial infarction, and a non-neglectable degree of intra- and inter-observer variability of test results⁶⁾.

3. Cardiovascular magnetic resonance (CMR)

Stress CMR commonly refers to vasodilator stress with adenosine, a potent coronary vasodilator with a very short half-life. Myocardial perfusion is compared during stress and at rest using first-pass perfusion of a gadolinium-based contrast agent. This test is more sensitive, but less specific than stress echocardiography. The lower specificity regarding the detection of CAD is partly explained by the presence of microvascular disease, which may also cause myocardial ischemia in the absence of obstructive CAD⁷⁾. If vasodilator stress CMR is unsuitable, dobutamine stress is a viable alternative, and the sensitivity and specificity of dobutamine stress CMR are similar to those of dobutamine stress echo, with slightly higher sensitivity because of better endocardial definition with CMR. Apart from local expertise in performing CMR studies, correct patient selection is important; patients with dyspnea unable to hold their breath or those with arrhythmia (atrial fibrillation, recurrent extrasystole) are not suitable for a high yield CMR study.

4. Myocardial perfusion scintigraphy (SPECT)

This test uses a radionuclide tracer such as ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin (less commonly ²⁰¹Tl-thallium) to assess myocardial blood flow. Blood flow during stress and at rest are compared, similar to perfusion CMR and with similar sensitivity and specificity, but inferior negative predictive value than CMR. Scans performed at resting conditions allow the assessment of regional myocardial viability, whereas those additionally performed during exercise or adenosine perfusion enable the assessment of both myocardial ischemia and viability. Previous SPECT studies suggested a high sensitivity of 90–91%, but a lower specificity of 75–84%, for detection of obstructive CAD⁸⁾. Although it has an issue of radiation safety, it can be easily, rapidly and successfully performed not only in patients with severe dyspnea, but also in those with arrhythmias, implanted devices, and/or advanced renal disease.

5. Coronary CT angiography (coronary CTA)

It is now one of the indispensable tests in the non-invasive anatomical diagnosis of CAD, especially in the cardiovascular outpatient clinic in Japan. Coronary CTA is used to visualize the coronary lumen and wall in order to assess the presence of lumen narrowings and plaque formation in the vessel wall. Especially the negative predictive value is very high 96–99%, and if it is diagnosed that there is no organic stenosis lesion in coronary CTA, effort angina and acute coronary syndrome may be denied. On the other hand, the positive predictive value is not necessarily high, there is a problem of narrowing evaluation difficulties between moderate and high stenotic lesions, in highly calcified lesions (defined as an Agatston score >400), and in lesions with small stent. It is a test that should be used mainly for cases with a low to intermediate PTP of 1–50% while taking into account the risks of radiation exposure and contrast agent use and the advantages/disadvantages described above¹⁾.

When we choose the ischemia test, we should consider local expertise, cost effectiveness aspects, and subsequent use of hospital resources in addition to selection of suitable patients for the test. Information on diagnostic accuracy is helpful for decisions on the choice of a diagnostic test. However, we should note that referral bias was not considered in most previous reports, and that diagnostic accuracy itself might not translate into patient benefits⁹⁾.

Recently, the importance of improving imaging outcomes evidence for low-/intermediate-risk stable chest pain has been recognized. Several studies have reported coronary CTA to be a useful clinical tool in this regard. Coronary CTA as an initial strategy for evaluating suspected stable CAD may be associated with favorable outcomes^{10, 11)}. Clinicians may need to consider both coronary CTA and functional imaging when evaluating eli-

Table 3 Definitions of risk for various test modalities in patients with confirmed myocardial ischemia

Exercise stress ECG	High risk	CV mortality >3%/ year
	Intermediate risk	CV mortality between 1 and 3%/year
	Low risk	CV mortality <1%/year
Ischemia imaging	High risk	Area of ischemia >10% (>10% for SPECT; limited quantitative data for CMR-probably $\geq 2/16$ segments with new perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments; ≥ 3 segments of LV by stress echo)
	Intermediate risk	Area of ischemia 1–10% or any ischemia less than high risk by CMR or stress echo
	Low risk	No ischemia
Coronary CTA	High risk	Significant lesions of high-risk category (three-vessel disease with proximal stenoses, LM and proximal anterior descending CAD)
	Intermediate risk	Significant lesion(s) in large and proximal coronary artery(ies) but not high-risk category
	Low risk	Normal coronary artery or plaques only

CAD: coronary artery disease, CMR: cardiac magnetic resonance, CTA: computed tomography angiography, CV: cardiovascular, ECG: electrocardiogram, LV: left ventricle, LM: left main, SPECT: single photon emission computed tomography.

Adapted from 2013 ESC guidelines¹⁾.

gible patients¹²⁾. However, the overall effect of non-invasive imaging modalities on downstream testing and clinical outcomes remains unknown and inconsistent¹³⁾. Future adequately powered diagnostic randomized controlled trials are necessary, which will provide the most conclusive evidence regarding patient outcomes, and represent a rigorous approach to diagnostic test evaluation.

V. Risk stratification

As the basis of CAD management, it should be considered that there are two goals of the improvement of symptoms and QOL, and the prevention of cardiac events such as myocardial infarction and sudden death (improvement of prognosis). In order to achieve the latter, it is necessary to assess the risk and respond accordingly. The treatment should be tailored to the patient's event risk. The basic strategy is as follows; Those with low event risk (<1 % mortality per year) should receive optimal medical therapy; patients with an intermediate risk may be tried on medical therapy, while invasive CAG should be considered in patients with relevant comorbidities such as renal disease or diabetes, or if the patient wishes. High-risk patients with an expected mortality of >3 % per year should be offered invasive CAG $\pm$ coronary revascularization $\pm$ optimal medical therapy¹⁾. A lot of risk stratification methods have been reported such as those by clinical evaluation, by stress testing, and by coronary anatomy. For example, Table 3 explains how results of further diagnostic imaging will inform options for treatment.

VI. Revascularization decision

Myocardial perfusion imaging has long been the main arbitra-

tor due to a strong belief that functional testing best provides evidence for ischemia required to guide revascularization. Several studies, but not trials, have suggested that the extent of ischemia in myocardial perfusion imaging is a major determinant of the response to revascularization¹⁴⁾. A large retrospective analysis of more than 10,000 patients referred for myocardial perfusion scintigraphy suggested that the benefits of revascularization were confined to patients with an extent of inducible ischemia of 10% or more of the left ventricular myocardium (Fig. 2a). In contrast, making revascularization decisions based on anatomy is imperfect, especially in intermediate coronary stenosis (30 – 70% lesions). With the improved efficacy of medical treatment, interventional or surgical treatment of coronary artery stenosis is more and more considered not useful in patients without significant myocardial ischemia, even in the presence of significant coronary artery stenosis¹⁵⁾. Recently, the introduction of fractional flow reserve (FFR), a coronary pressure-derived estimate of the impact of the coronary stenosis on coronary flow, has played a pivotal role in decision-making regarding revascularization. Accumulating evidence supports the argue that FFR-guided revascularization is superior to revascularization based on CAG alone^{16, 17)}. Lesions with lower FFR values may receive larger absolute benefits from percutaneous coronary intervention (PCI) (Fig. 2b). In a met-analysis, stress myocardial perfusion imaging with CMR, CT, or positron emission tomography (PET) can accurately rule out hemodynamically significant CAD and can act as a gatekeeper for invasive revascularization and SPECT and stress echocardiography are less suited for this purpose¹⁸⁾. However, it remains a matter of debate whether PCI must be performed in all lesions with FFR <0.8 to avoid the future need to

Fig. 2 Relationship between ischemia testing and treatment strategy.

a: Relationship between extent of ischemia by stress SPECT and cardiac death by pharmacological versus revascularization. Dotted lines indicate 95% CI. Adapted from Pfisterer ME, et al., 2010¹⁴⁾.

b: Conceptual Relationship Between FFR and Outcomes. Adapted from Johnson NP, et al., 2010¹⁷⁾.

FFR: fractional flow reserve, PCI: percutaneous coronary intervention, SDS: summed difference score (a measure of the extent of ischemia), SPECT: single photon emission computed tomography.

urgent revascularization¹⁹⁾. Also, FFR is not the same as the direct measures of coronary flow from which it was derived, and which are the critical determinants of signs and symptoms of myocardial ischemia²⁰⁾. Direct assessment of coronary flow may have the clinical potential to improve risk stratification and decision making in CAD²¹⁾.

VII. Conclusions

In the diagnosis of stable obstructive CAD, taking medical history of chest pain, assessment of risk factors, and appropriate evaluation of PTP are necessary for choosing the non-invasive ischemia tests or coronary CTA. We should consider not only the diagnostic accuracy but also various things such as local expertise and cost effectiveness in addition to patient characteristics. The diagnostic approach for MVA and CSA should be noted. After diagnosis, we need to proceed from prognostic risk assessment to selection of treatment. Decision-making regarding revascularization is frequently performed based on the FFR values, but do not forget that the presence of ischemia is in the basic. It is also necessary to keep in mind that ischemia testing is utilized for the diagnosis and treatment for SMI.

Conflicts of interest

None.

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