17

Novel Insights Into Stenosis on Coronary Angiography–Outline of Functional Assessment of Stable Angina Patients with Angiographic Stenosis

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1. Introduction

Coronary angiography is an invasive technique for imaging the coronary artery lumen and remains one of the most accurate methods for diagnosing coronary artery disease. Furthermore, this invasive technique is the standard method for guiding revascularization procedures such as percutaneous coronary intervention (PCI) and coronary-artery bypass graft (CABG), as well as for guiding stent placement during PCI. However, the degree of coronary stenosis is usually decided by visual estimation of the percentage diameter narrowing using the proximal assumed normal arterial as a reference. There is 20% variation among readings of experienced angiographers, and the same angiographer may even render a different interpretation at a time remote from the first reading. Borderline stenosis, or angiographic narrowing of 40 to 70%, does not always correspond to abnormal physiology and myocardial ischemia (1,2). For such lesions, noninvasive or direct physiological measurements of impaired flow validate the decision to initiate revascularization therapy. Though quantitative coronary angiography can be reproduced for assessment of coronary stenosis, the inability to determine the functional severity of coronary stenosis remains a limitation of coronary angiography.

Intracoronary physiological parameters have been introduced to assess functional coronary lesion severity during cardiac catheterization. Measurement of coronary flow reserve (CFR; coronary flow velocity response to adenosine) and fractional flow reserve (FFRmyo; coronary pressure-derived with adenosine) provide information about functional severity (3). Furthermore, FFRmyo, which is calculated from coronary pressure measurements, is an invasive index used to identify a stenosis responsible for reversible ischemia (4,5,6).

For most patients with stable angina, the goal of treatment is complete, or nearly complete elimination of anginal chest pain and return to normal activities with a functional capacity corresponding to Canadian Cardiovascular Society (CCS) class I angina. This goal should be accomplished with minimal side effects, as well as with a reduced risk of mortality (7). The

topics of this chapter encompass the activities of daily life and functional stenosis in patients with angiographically demonstrated stenosis.

2. Functional severity

For coronary angiographic assessment employing cardiac catheterization, it should be noted that the stenotic lumen is compared to a nearby angiographically normal lumen, which may still show diffuse atherosclerotic disease. Furthermore, lesions containing diffuse, concentric, symmetrical disease, remodeling, or dissection, will be underestimated when disease severity is assessed (Fig.1). CFR and FFRmyo, which provide information about functional severity, can be performed during cardiac catheterization.
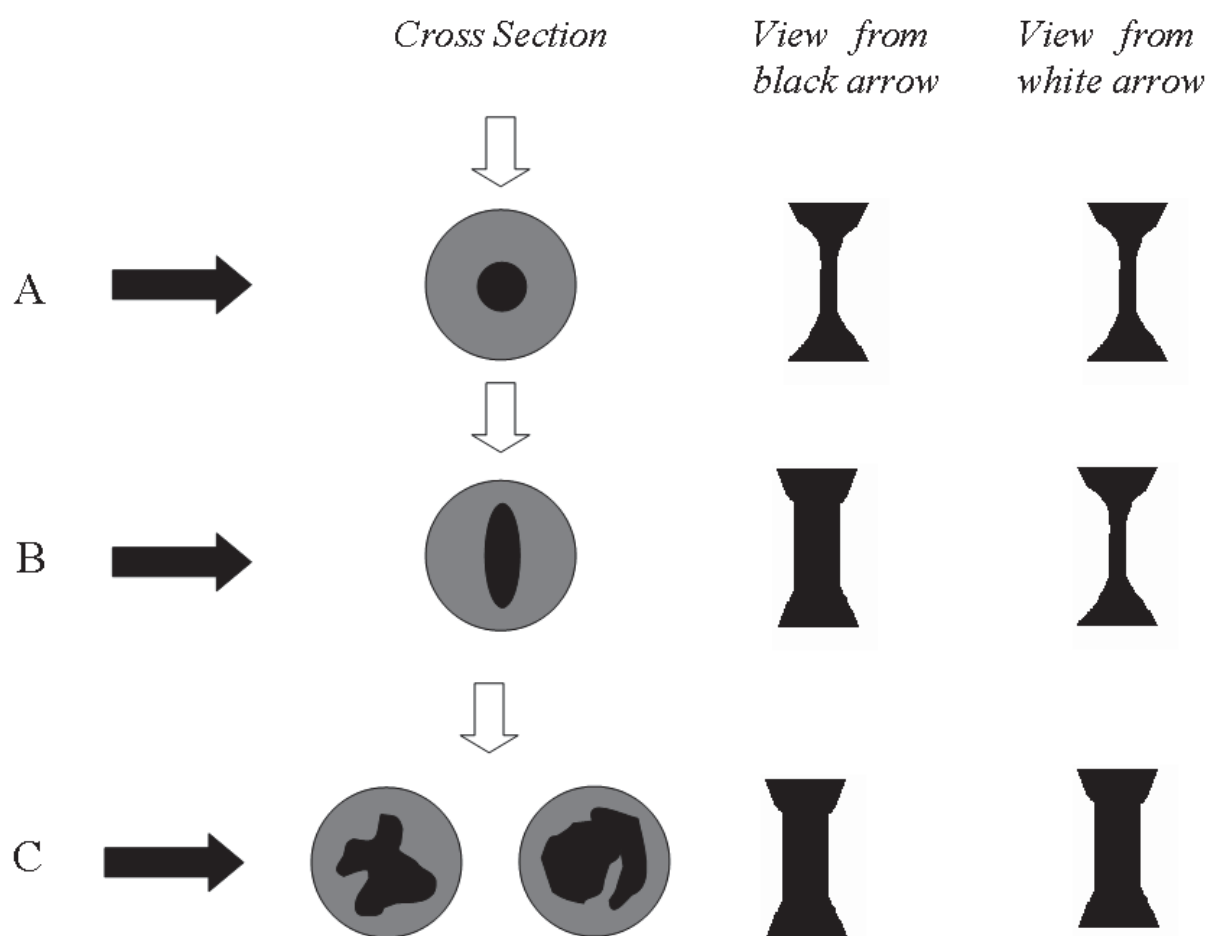

(A) Stenosis can be visualized from multiple angles. (B) Stenosis can be viewed as indicated by the white arrow, but is normally visualized as indicated by the black arrow. Stricture necessitates changing the angle. (C) Vascular conduits appear normal at all angles despite the existence of stenosis.

Fig. 1. Angiographic images and vascular conduits

CFR reflects both epicaudal and microvascular disease but does not identify these entities by itself (8,9). Intra-coronary flow velocity can be measured with a 0.014-inch doppler guide wire during baseline measurements and maximum hyperemia which is induced by administering adenosine. CFR was calculated as the ratio of hyperemic to baseline of the average peak velocity (10,11). CFR can also be measured with a temperature sensor-tipped

guidewire, as the ratio of the inverse mean transit times obtained by thermodilution curves at baseline and during hyperemia (12,13,14). The parameters of CFR show agreement at a cut-off value of 2.0 (11,15).

On the other hand, FFRmyo is an accurate functional index of epicaudal stenosis (4,5). Intra-coronary pressure can be measured with a 0.014-inch pressure-monitoring guidewire, which was first calibrated, then set to be equal with the aortic pressure in the guiding catheter, and finally positioned distal to the coronary lesion. Mean aortic and distal pressures were obtained during baseline measurements, and FFRmyo was calculated as the ratio of the mean distal pressure to the mean aortic pressure during maximum hyperemia (3,4,5).Although a previous report emphasized the importance of combining pressure and flow velocity measurements to evaluate coronary lesion severity and microvascular involvement (11), FFRmyo is a reliable index of the functional severity of coronary stenosis, and an FFRmyo value of 0.75 distinguishes stenoses associated with inducible ischemia from those that are not. Indeed, in patients with stable chest pain, the most important prognostic factor is the occurrence of myocardial ischemia reflected by an FFRmyo of < 0.75 (5,6, Fig.2).
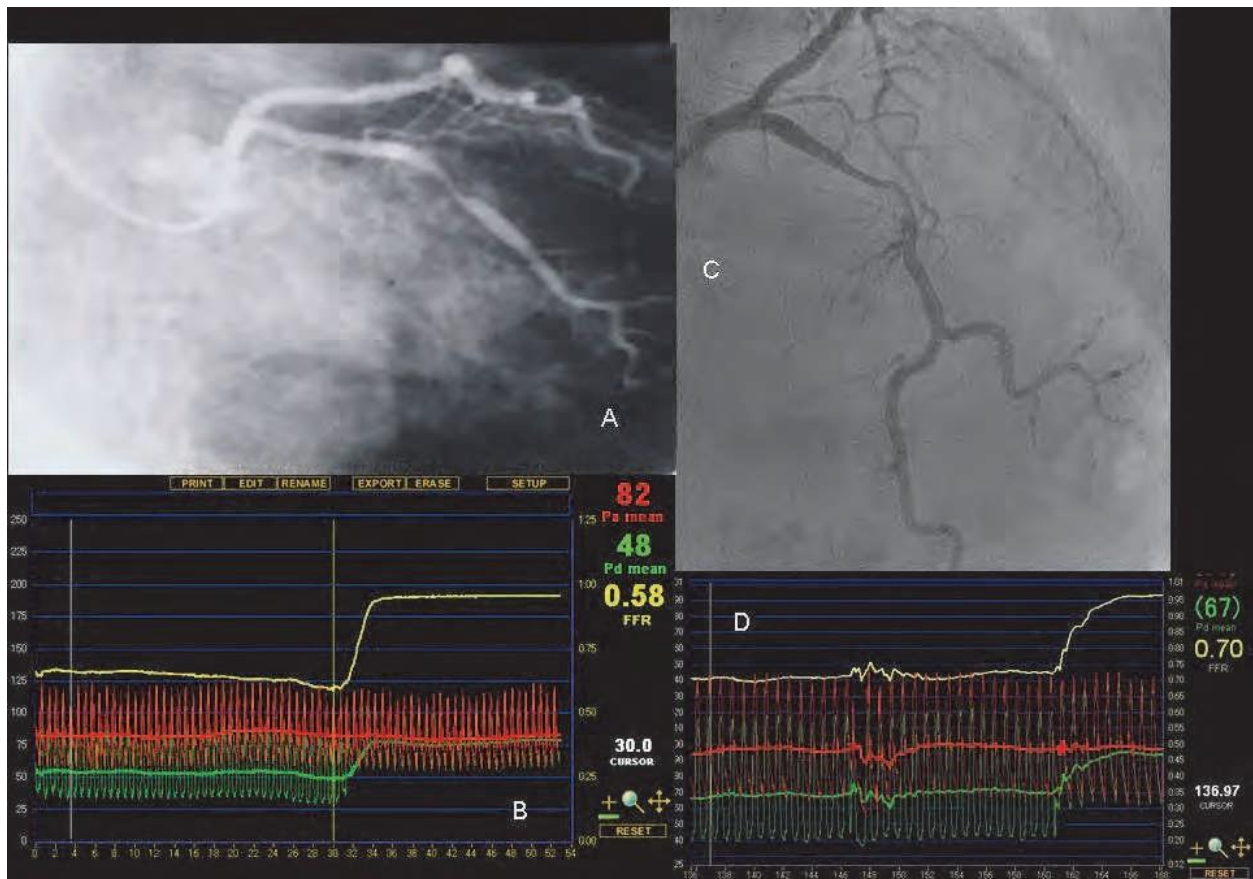

In the case on the left, angiographic stenosis was 56% in the left circumflex branch (LCX) by quantitave coronary angiography (A). During adenosine infusion, the wire was pulled back to track coronary pressure from the far distal LCX to the catheter, and after crossing the lesion produced a change in coronary pressure (FFRmyo = 0.58).

Likewise, in the case shown on the right, angiographic stenosis was 46% in left anterior descending branch (LAD) by quantitative coronary angiography (C), and FFRmyo = 0.70 (D)

Fig. 2. Representative case of FFRmyo

Even when treated with PCI, the clinical outcomes of these patients are significantly worse than those of patients with functionally insignificant stenoses (FFRmyo ≥ 0.75) (16,17). When FFRmyo was used to divide patients into a group in which stenosis was most likely to be physiologically significant (FFRmyo < 0.75) and a group in which it was not, the overlap between the 2 groups in terms of angiographic severity was so large that it suggested angiography (16,17) could not be used to predict the absence or presence of inducible ischemia in individual patients (4,18, Fig.3). In fact, however, in patients with multivessel coronary artery disease undergoing PCI with drug eluting stents, routine measurement of FFR in addition to angiographic guidance, as compared with PCI guided by angiography alone, results in a significant reduction in major adverse events (19).

Source: Circ J 2009;73: 2308–2314   Source: J Cardiol 2010;55,296-302
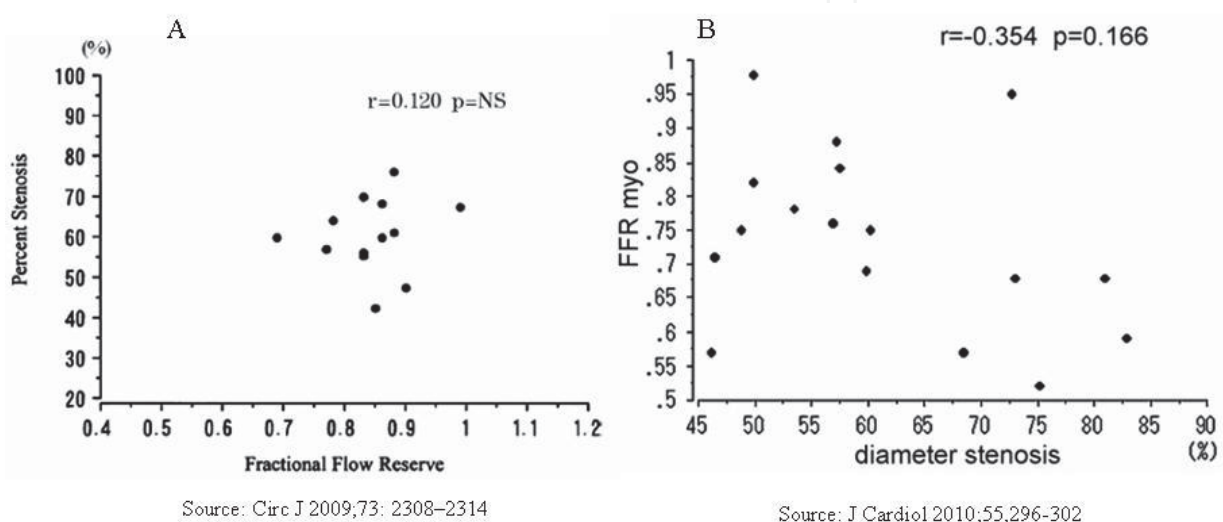
(A) The percent stenosis is likely to be physiological; FFRmyo. (B) The overlap between stenosis and FFRmyo was large.

Fig. 3. Variations in percent stenosis on coronary angiography and FFRmyo

3. Functional capacity

The factors contributing to impaired exercise capacity appear to be multifactorial and include increasing age, sedentary lifestyle, depression, obesity and other comorbidities as well as impaired cardiovascular function. Poor exercise capacity is generally considered to be a predictor of mortality in patients with ischemic heart disease as well as all cause mortality (20,21). Traditional exercise tests such as the treadmill test or walking distance in 6minutes are well-known methods for measurement of exercise capacity.

Additionally, self-assessed questionnaires, such as the Duke Activity Status INDEX (DASI) (22), the Specific Activity Questionnaire (SAQ) (23) and the Veterans Specific Activity Questionnaire (VSAQ) (24), can also measure exercise capacity as a well validated measure of functional capacity that can be expressed as metabolic equivalents (METs) and have been shown to correlate with adverse outcomes. Self-assessed questionnaires can be a simple and easy tool that contributes to the global risk assessment (10).

The cardiopulmonary exercise test (CPX) is useful for measurement of excise capacity employing various parameters at each stage in a series of exercises (Fig.4). A symptom-limited incremental exercise test is usually performed using an upright, electromagnetically braked cycle ergometer or treadmill with measurement of breath-by-breath VO2, carbon dioxide

production (VCO2) and minute ventilation (VE). This evaluates peak VO2, oxygen uptake at the anaerobic threshold (AT) and so on. A 12-lead electrocardiogram (ECG) and heart rate were continuously monitored throughout the test, and cuff blood pressure was measured every minute using an automatic manometer. CPX testing is more useful than self-assessed health status, which is subjective and can vary among patients depending upon symptom complexity and the unique perceptions, expectations and preferences of individuals (7).
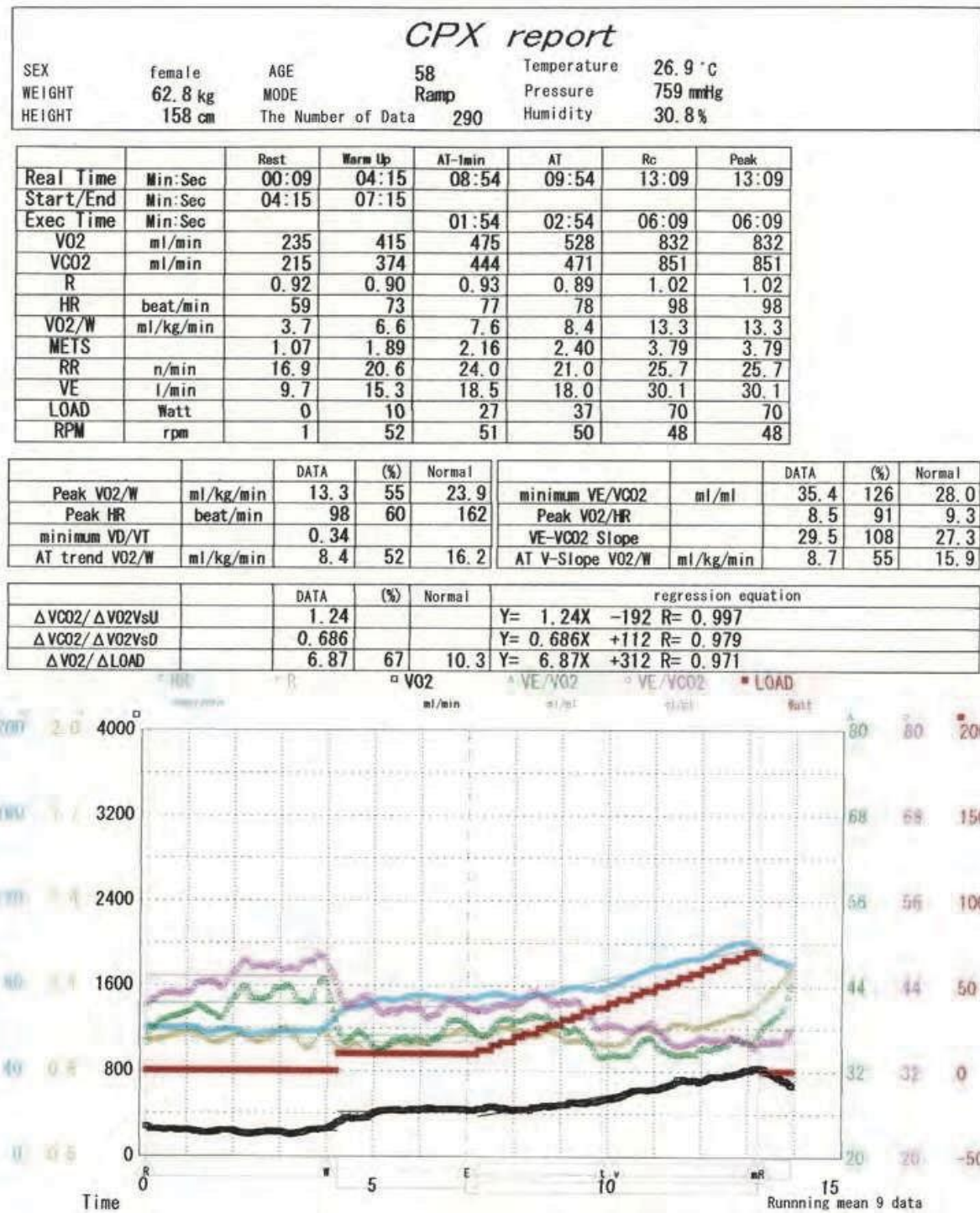

Fig. 4. Representative case of CPX

4. Functional severity and exercise capacity in patients with angiographic stenosis

Coronary angiography employing cardiac catheterization has an important role in revascularization procedures such as PCI, and PCI has become a common initial management strategy for patients with stable angiographic stenosis. However, at present, the initial management strategy of patients with stenosis on coronary angiography should be to reduce not only the risks for major cardiac events but also to eliminate angina and allow a return to normal activities. Previous studies have shown that PCI does not reduce the long-term rates of death, myocardial infarction or other major cardiovascular events with compared to optimal medical therapy alone (25). PCI can provide an incremental benefit in quality of life compared with that provided by optimal medical therapy alone among patients with chronic coronary artery disease for approximately 24 months (26). Another previous study showed that in patients with stable coronary artery disease and an angiographically documented stenosis treatable by PCI, a 12-month exercise-training program resulted in a higher event-free survival rate and higher exercise capacity than standard PCI (27). Additionally, PCI significantly increased exercise capacity values such asAT and peak VO2 in patients with peak VO2 < 15 ml/kg/min, whereas it yielded no significant improvement in those with peak VO2 ≥ 15 ml/kg/min (28). Based on these observations, the existence of stenosis on coronary angiography is an insufficient indication for revascularization. It has been reported that an increase in functional capacity as indicated by self-assessed questionnaire is associated with an increase in CFR, although 86% of subjectsdid not have significant stenosis on coronary angiography (10). Impaired overall functional capacity is independently associated with coronary microvascular dysfunction or endothelial dysfunction, among the most important determinants of myocardial ischemia. On the other hand, routine FFRmyo measurement with angiographic guidance resulted in a significant reduction in major adverse cardiac effects, even when patients underwent PCI with drug-eluting stents (19). Furthermore, FFRmyo is associated with inducible ischemia which other measures are not, thereby providing higher accuracy than for any other invasive or noninvasive test. According to the aforementioned reports, it seemed that the existence of stenosis on coronary angiography is a notwell validated measure of stable angina. FFRmyo and functional capacity should be determined in stable angina patients with angiographic stenosis. Previously, we assessed the relationship between FFRmyo and CPX values (4).

Our study subjects were 15 males (65.8+/-8.9 years old) with stable angina and 75% angiographic stenosis in one coronary artery. Eligible patients had no evidence of acute coronary syndromes, prior myocardial infarction, significant valvular heart disease, diabetes mellitus treated with insulin, smoking; or occupational, orthopedic and other conditions that precluded exercise. Neither did they have left main coronary artery stenosis > 25% or high-grade proximal left anterior descending artery stenosis with significant stenosis (> 75%) of other vessels, nor left ventricular angiography-based detection of abnormal wall motions such as asynergy or diffuse hypokinesis, or reduced left ventricular function (ejection fraction < 55%). The %diameter stenosis (%DS) was determined to be 61.7+/-9.1% based on quantitative coronary angiography. Mean FFRmyo was 0.84+/-0.66, peak VO2 was17.1+/-3.2ml/kg/min and AT was 11.1+/-2.0ml/kg/min. There was no significant correlation between %DS and FFRmyo (r = 0.12, p = ns, Fig.3A), peak VO2 (r = -0.051, p = ns) or AT (r = -0.013, p = ns). By contrast, there was a significant positive correlation (Fig.5) between FFRmyo and peak VO2 (r = 0.534, p < 0.05) and between FFRmyo and AT (r =

Novel Insights Into Stenosis on Coronary Angiography–Outline
of Functional Assessment of Stable Angina Patients with Angiographic Stenosis

337

0.542, p < 0.05). A previous study showed stable angina patients with impaired functional capacity as assessed by a CPX test to likely have reduced FFRmyo. The present study also showed that an FFRmyo value of 0.75 reflects stenoses associated with inducible ischemia and hence appears to correspond to a peak VO2 value of 15.0. A cut-off value of FFRmyo of 0.75 nearly matched the exercise capacity value (peak VO2; 15 ml/kg/min) improvement with PCI. As noted above, exercise capacity in patients with stable angina reflects functional rather than angiographic stenosis. Exercise training can improve myocardial perfusion, as revealed by myocardial scintigraphy, as well as maximal exercise capacity (27). Therefore, that study suggested that it may be possible to improve FFRmyo by increasing exercise capacity through training.
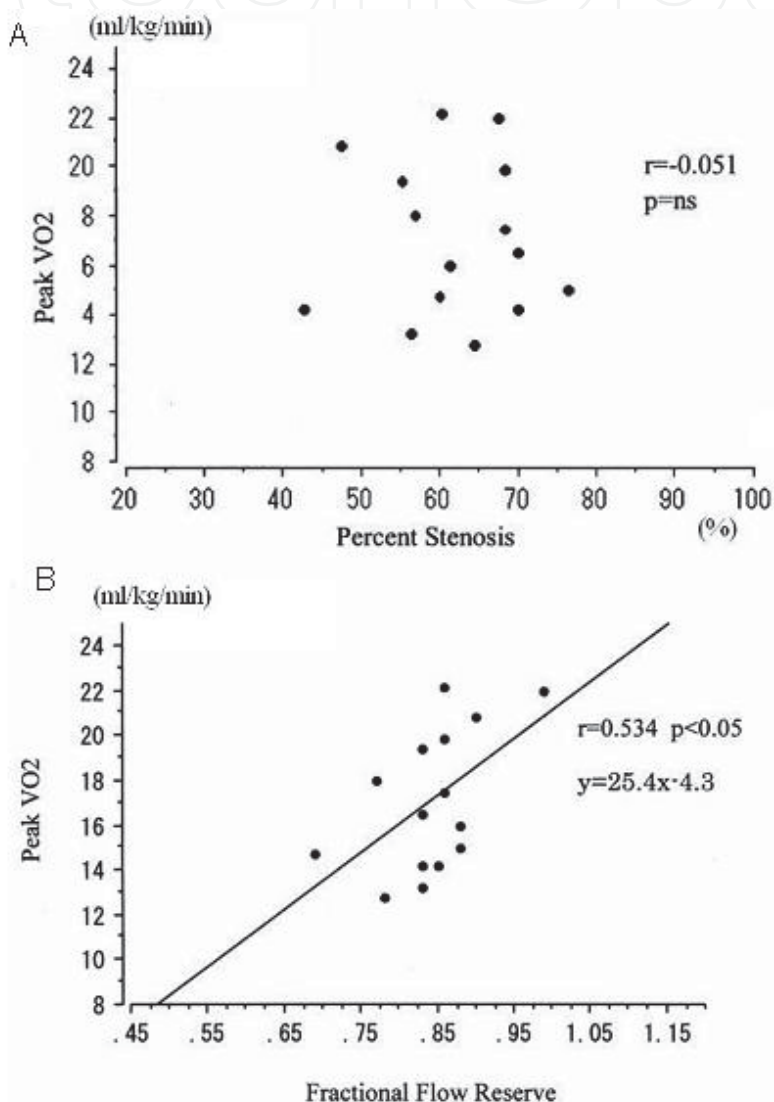
(A) There is no correlation between angiographic stenosis and peak VO2. However, there is a positive correlation between FFRmyo and peak VO2 (B). (Source: Circ J 2009;73: 2308–2314)

Fig. 5. Relationship between exercise capacity and stenosis.

4.1 Case report
This is a representative case showing improvement in functional capacity despite the existence of angiographic stenosis.

A 58-year-old woman presented with unstable angina. Coronary angiography revealed 99% stenosis of the right coronary artery (RCA#3), and 75% stenosis (#11) and 90% stenosis (#12) of the left circumflex branch (LCX). She received stent implantation to #3 in the emergent stage (Fig.6). Thallium-201 scintigraphy with adenosine revealed ischemia in the LCX area (Fig.7A). PCI was recommended, but the patient refused because the condition was asymptomatic in her daily life. This patient did not wish to undergo revascularization of the LCX and continue to receive cardiac rehabilitation (physical training at AT level). Peak VO2 increased from13.3 ml/kg/min (Fig.4) to 16.8 ml/kg/min. Thallium-201 scintigraphy (Fig.7B) with adenosine documented improved myocardial perfusion distal to the LCX. (Ischemia area reduced from 13.7% to 8.75%)

There was (A) 99% stenosis of the right coronary artery (RCA #3) and a (B) stent was implanted. Left coronary angiongraphy revealed 75% stenosis (#11) and 90% stenosis (#12) of the left circumflex branch (LCX).

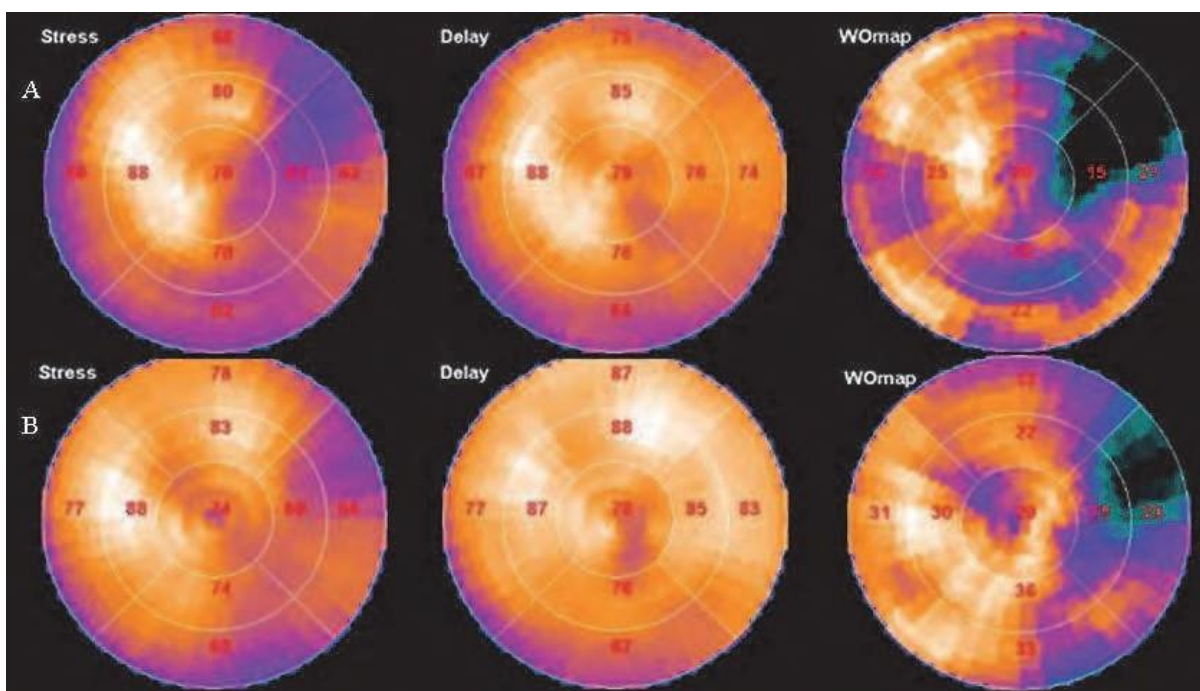Fig. 6. Coronary angiographies of case repor

Fig. 7. Bull's eye image from thallium-201 single-photon emission computed tomography (A) pre-training (ischemic area 13.7%), and (B) post-training (ischemic area 8.75%)

Novel Insights Into Stenosis on Coronary Angiography–Outline
of Functional Assessment of Stable Angina Patients with Angiographic Stenosis

339

5. Functional severity, exercise capacity and tissue characterization

Acute coronary syndrome is triggered by microscopic ulcerations of vulnerable atherosclerotic plaques. The majority of vulnerable plaques appear "angiographically insignificant" before their rupture (less than 75% diameter stenosis). In contrast, most of the "significant" plaques (greater than 75% stenosis) visualized at angiography are at low risk for plaque rupture (29).

Intravascular ultrasound (IVUS) allows cross-sectional imaging of coronary arteries and provides a more comprehensive assessment of the atherosclerotic plaques in vivo (30, Fig 8). Studies using IVUS have indicated that coronary atherosclerosis is underestimated when visually analyzing angiographic results owing to coronary compensatory remodeling and the diffuse nature of coronary atherosclerosis, which frequently makes the reference vessel appear normal angiographically (31).
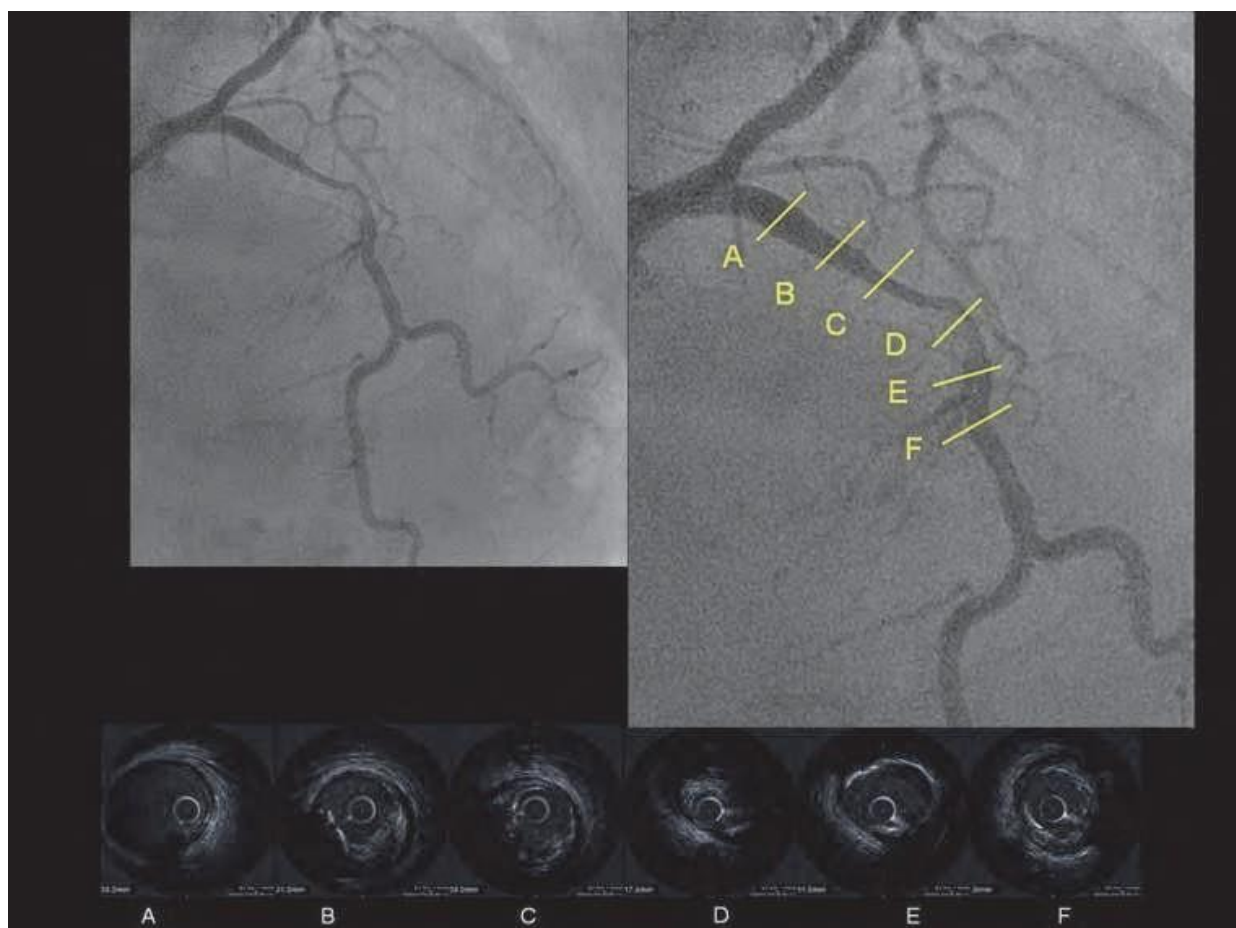

Intravascular ultrasound provides an image of an atheroma in a normal segment (B,E) as well as a stenotic lesion (C,D) on angiography

Fig. 8. Representative angiographic and IVUS images

An integrated backscatter intravascular ultrasound (IB-IVUS) system has been developed in which two-dimensional color-coded maps allowing plaque tissue characterization in coronary arteries can be constructed by computer (32,33). A computer equipped with IB-IVUS software is connected to the IVUS imaging system to obtain radio frequency signal output, signal trigger output, and video image output. IB is calculated as the average power

of the ultrasound backscattered signal from a small volume of tissue using fast Fourier transform measured in decibels (dB) (32). IB-IVUS is a useful method for analyzing coronary plaque tissue (Fig.9), which accurately and quantitatively differentiates among calcification, dense fibrosis, fibrosis and lipid components (33). IB-IVUS results previously suggested that classifying plaques as vulnerable or stable using this technique is an effective means of predicting acute coronary syndrome. When evaluated using IB-IVUS, plaques are deemed vulnerable when the lipid area is > 65% and the fibrotic area is < 25% (30). Thus, functional stenosis and tissue characterization may be linked to clinical outcome. Previously, we assessed the relationship between functional stenosis and the characterization of plaque tissue using FFRmyo and IB-IVUS (18).
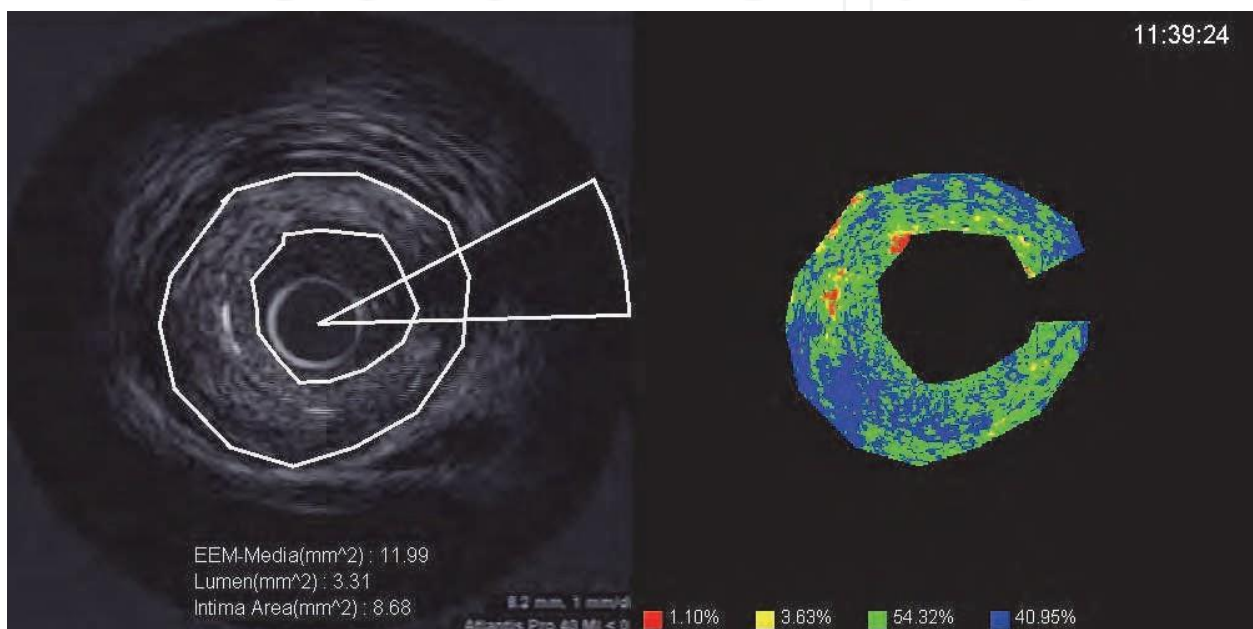

The initial image was constructed by tracing the lumen and the external elastic membrane. In the color-coded map, red is calcification, yellow and green are fibrosis, and blue represents the lipid pool.

Fig. 9. Representative IB-IVUS images

We studied 17 lesions showing 75%-stenosis visually by coronary angiography in 17 stable angina patients (64.2+/-9.1 years old, 11 males). We found no correlation between FFRmyo and %DS (r = -0.354, p = 0.166, Fig.3B). Nor was there a correlation between FFRmyo and plaque burden (r = -0.241, p = 0.359, Fig.1B), or between FFRmyo and minimum lumen cross-sectional area (r = -0.002, p = 0.995). Likewise, neither %DS nor plaque burden correlated with the tissue characterization values (Figs.10A). There was no correlation between FFRmyo and %CA (calcification area) (r = -0.068, p = 0.799). By contrast, weobserved a significant positive correlation between FFRmyo and %F (r = 0.620 p = 0.0067), and a significant negative correlation between FFRmyo and %LP (lipid pool area) (r = -0.524,p = 0.0293) (Fig.10B).

Our previous findings indicate that the tissue characteristics of coronary plaques in intermediate lesions affect functional stenosis. Fibrous tissue and FFRmyo also correlate positively. Lipid pool and FFRmyo correlate negatively. The apparently contradictory results obtained in this study might be explained by the progression of humanatherosclerotic lesions leading to increasing fibrosis and stenosis. Distal pressure, additionally, decreases with the severity of coronary narrowing in the epicardial arteries,

contributing to the progression of atherosclerosis. However, intermediate or moderate lesions remain distinct in terms of functional and angiographic severity. The increase in fibrous tissue is likely an adaptive response to this distal pressure aimed at redistributing and modulating the mechanical stress (34). The increased fibrosis may also be an adaptive response to reduced elasticity of the arterial wall in the area of the lesion. An earlier in vivo study showed that elasticity in the area of stenosis can exacerbate the pressure drop across the lesion, thereby reducing flow (35).
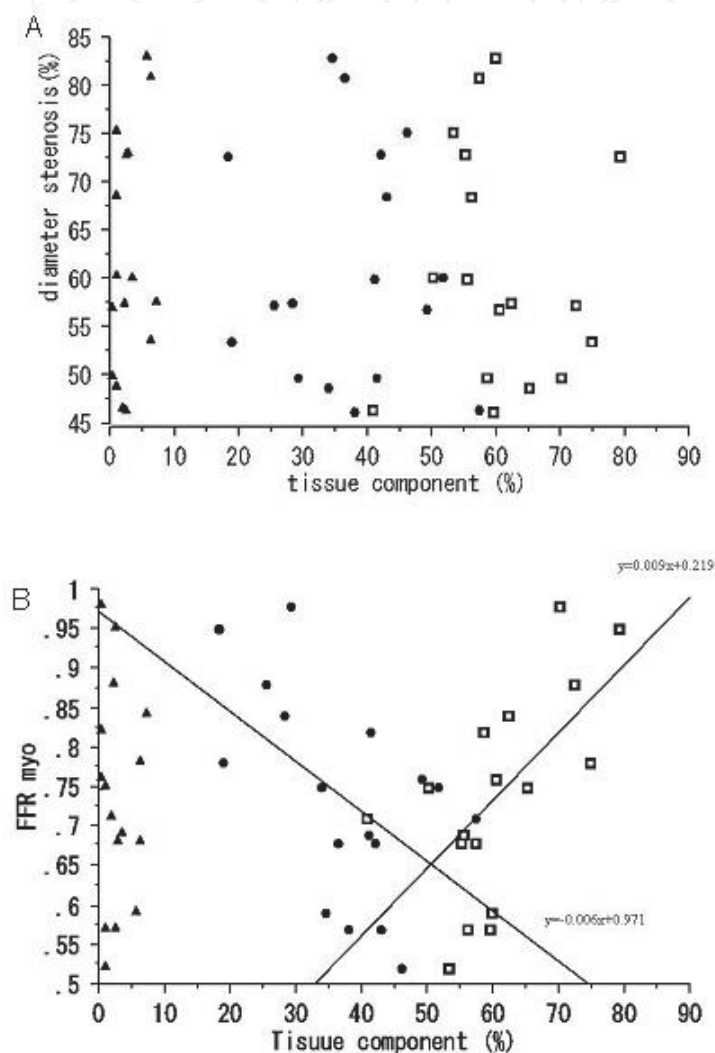
(A) There was no correlation between angiographic stenosis and tissue characterization (B). There was a significant positive correlation between FFRmyo and fibrosis, and a significant negative correlation between FFRmyo and the lipid pool: ▲, %CA = percent calcification area; □, %F = percent fibrotic area; ●, %LP = percent lipid pool area. (Source: J. Cardiol; 2010 ;55,296－302)

Fig. 10. Relationship between stenosis and tissue characterization

Our studies showed that angina patients with reduced FFRmyo are likely to have reduced functional capacity, and that the tissue characteristics of coronary plaques in intermediate lesions affect functional stenosis. According to these studies, high exercise capacity inpatients with stable angiographic stenosis is linked to the stability of coronary plaques. Another report on coronary computed tomographic angiography indicated that coronary

plaque characteristics were identified in patients with progressively reduced exercise times, and that functional ischemia was more severe in those with mixed plaque. (36)

Thus, though coronary angiography is one of the most accurate methods for diagnosing coronary artery disease, comprehensive assessment of health status is necessary for stable angina patients with angiographic stenosis.

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Novel Insights Into Stenosis on Coronary Angiography–Outline
of Functional Assessment of Stable Angina Patients with Angiographic Stenosis

343

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