

## ASNC/JSNC JOINT SYMPOSIUM—REVIEW ARTICLE

# Clinical Applications of Coronary Flow Reserve in Patients with Coronary Artery Disease: ASNC/JSNC Joint Session in June 2017

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**Abstract**

Coronary artery disease (CAD) is one of the major causes of death in Japan. Fractional flow reserve with angiography is a well validated method for identifying significant focal stenosis, but is not applied for the estimation of hyperemic vasodilatory capacity in the myocardium. Coronary flow reserve (CFR) estimated from sequential myocardial perfusion images obtained by blood flow tracers and positron emission tomography (PET) is a quantitative value. CFR is regulated not only by focal stenoses but also by diffuse atherosclerosis and coronary microvascular dysfunction (CMD) in patients with CAD. Accordingly, low CFR is shown to be a strong predictor of cardiac death in combination with anatomical disease burden. Optimal medical therapies such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, statins, and medications for diabetes could increase CFR by improving CMD at the early stage of CAD. It is also important to clarify the effects of coronary revascularization for focal stenoses on CFR. This paper focuses on the application of CFR estimated by cardiac PET to the evaluation of per-patient atherosclerotic burden and microvascular dysfunction.

**Keywords:** Coronary flow reserve, Coronary microvascular dysfunction, PET

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Coronary flow reserve (CFR) is a significant biomarker for coronary microvascular dysfunction (CMD) in diabetic patients (1). The CFR is a physiological index integrating coronary atherosclerotic burden and CMD, as shown by our previous studies (2). Despite recent improvements in medical treatment, coronary artery disease (CAD) is still a major cause of cardiac death. Medical treatments are typically based on the coronary atherosclerotic burden such as coronary stenosis and plaque morphology on angiography or ischemic burden on single photon emission computed tomography (SPECT), positron emission tomography (PET), or fractional flow reserve (FFR) (3). However, recent studies by ourselves and others demonstrate that coronary microvasculature with diameter of less than 100 micrometer is impaired in patients with a broad spectrum of CAD and is a significant predictor of cardiac events (4). Accordingly, goals for the evaluation of coronary circulation are to assess CMD in addition to coronary

atherosclerotic and ischemic burden (Fig. 1). A study to evaluate the effects of optimal medical therapy (OMT) on CFR is currently underway at Hokkaido University.

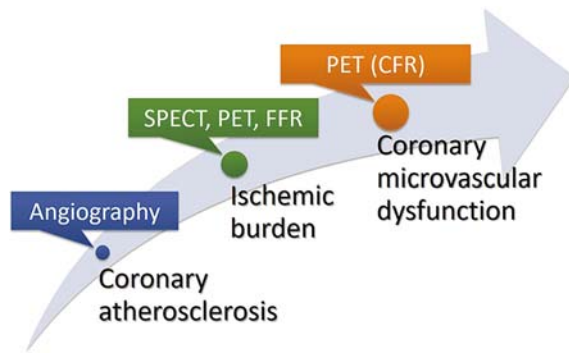
**CMD in diabetes**

Perfusion defects on stress myocardial perfusion imaging (MPI), reflecting the ischemic burden, are significantly associated with cardiac mortality. Importantly, for any degree of myocardial ischemia, patients with diabetes are at considerably higher risk of cardiac mortality than those without diabetes mellitus. A recent study demonstrated that CMD in patients with diabetes mellitus is significantly associated with poor outcomes (1). The coronary microvasculature consists of small arteries, precapillaries, capillaries and venules. The microvasculature cannot be visualized by angiography in humans, but its function can be assessed by CFR (5). Several factors such as mechanical forces, coronary

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**Fig. 1** Goals for the evaluation of coronary circulation.

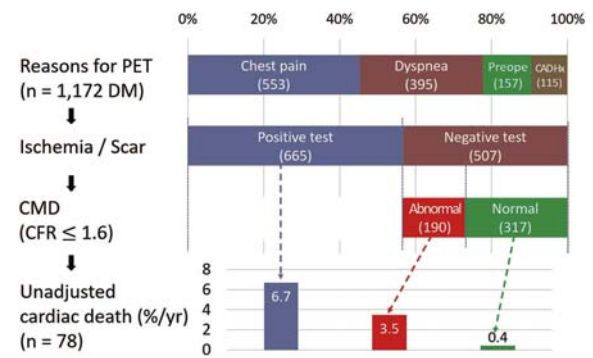
Coronary angiography is a visually interpreted test performed to recognize morphological stenosis of the coronary artery lumen. SPECT, PET and FFR are functional tools to detect stress-induced ischemia. CFR derived from PET can assess coronary microvascular dysfunction.

CFR: coronary flow reserve, FFR: fractional flow reserve, PET: positron emission tomography, SPECT: single photon emission tomography

vasomotor tone, neural factors, and metabolic factors affect autoregulation of the coronary microvasculature according to the oxygen demand in the myocardium. The microvascular function is impaired by microvascular remodeling such as capillary rarefaction, fibrosis, and hypertrophy, and also by disorders of autoregulation caused by inflammation and oxidative stress. In patients without obstructive CAD, but with coronary risk factors such as smoking, diabetes, and hypertension, CFR is reduced due to microvascular dysfunction at the manifestation of early atherosclerosis (6). Diabetes mellitus in particular induces capillary rarefaction. Capillary density assessed by platelet endothelial cell adhesion molecule (PECAM)-1 is reduced in tissue samples of patients with diabetes mellitus undergoing heart transplantation compared to those without (7). The fig. 2 indicates how the CMD measured with CFR influences the prognosis of diabetes patients. The bar graph on the top shows the reasons for PET examinations in patients with diabetes (Fig. 2) (1). Fifty-seven percent of the patients had positive findings on myocardial perfusion imaging. The unadjusted annualized cardiac death of these patients was high (6.7%). Among patients with negative tests on perfusion imaging, significant CMD, defined as a CFR less than 1.6, was observed in 37% of negative MPIs. The annualized cardiac death in patients with CMD was significantly higher than in those without. These data demonstrate that the presence of CMD is a significant predictor of cardiac death in patients with diabetes mellitus.

#### Relationship between per-patient atherosclerotic burden and CFR

There are several scoring systems to evaluate the per-patient atherosclerotic burden, while functional perfusion is estimated by CFR (8-10). It might well be asked how these



**Fig. 2** Coronary microvascular dysfunction in diabetic patients

Diabetic patients with impaired CFR even without CAD have high cardiac event rates, whereas those with preserved CFR have low event rates.

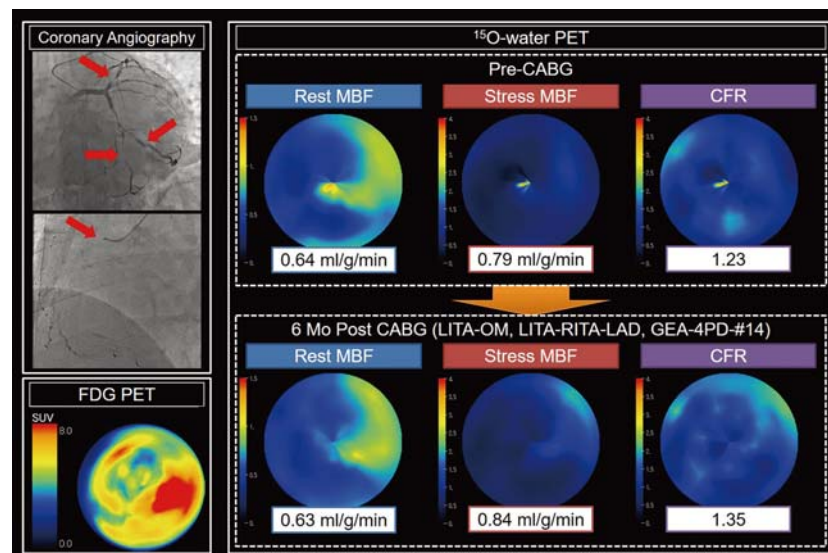
CAD Hx: coronary artery disease history, CFR: coronary flow reserve, CMD: coronary microvascular disease, DM: diabetes mellitus, PET: positron emission tomography

scorings for atherosclerotic burden are associated with CFR in patients with CAD. The purpose of our recent study was to investigate the relevance of the scores indicating anatomic burden, such as the Leaman, Duke, and SYNTAX scores, to functional CFR. These scores are hierarchical indices that assign overall prognostic weights to increasing percent stenoses in 1-, 2-, or 3-vessel classifications, with higher weights for proximal left anterior descending (LAD) or left main artery involvement. The Leaman and SYNTAX scores take into account distal and branched diseases while the Duke score does not. Diffuse atherosclerotic disease is weighted only in the SYNTAX score. Accordingly, diffuse atherosclerosis assessed by the SYNTAX score might contribute to physiological function assessed by CFR.

The CFR is an index integrating both microvascular function and atherosclerotic burden. How do we categorize these two measures? Coronary physiology can be categorized into 4 types: above and below an FFR of 0.8 and above and below a CFR of 2.0. Presumably, low FFR/low CFR is most prevalent in patients with obstructive CAD and coronary risk factors and is associated with poor outcomes. There appears to be widespread physiological variability in CFR in vessels with the absence and presence of ischemia by perfusion imaging. This result suggests that abnormal vascular reactivity can be present in the microvasculature regardless of the absence or presence of ischemia.

#### Effects of optimal medical therapy on CFR in patients with obstructive CAD

We will soon introduce a study to evaluate the effects of OMT on CFR, which is in progress at Hokkaido University. Because CMD cannot be revascularized, optimal medical therapy should be performed for treatment. There are several



**Fig. 3** Representative case.

A case is a patient with three vessel diseases (red arrows). FDG PET shows the decrease of uptake in anterior and inferior walls. Only a modest increase of CFR was observed after CABG (1.23 to 1.35).

CABG: coronary artery bypass grafting, CFR: coronary flow reserve, FDG PET:  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography, FFR: fractional flow reserve, LAD: left anterior descending artery, GEA: gastroepiploic artery, LITA: left internal thoracic artery, OM: obtuse marginal, OMT: optimal medical therapy, PCI: percutaneous coronary intervention, PD: posterior descending, RITA: right internal thoracic artery

studies that demonstrate the effects on CFR of medical treatments such as exercise, smoking cessation, statins, and beta blockers (11-14). These medical interventions can significantly improve CFR. Next, we are also curious about the effects on the CFR of revascularization in patients with obstructive CAD. The aim of this study was to compare the effects of OMT, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) on the CFR. A case in fig. 3 shows the effect of CABG on CFR in a patient who had three-vessel disease. FDG PET shows the decrease of uptake in anterior and inferior walls, indicating poor viability. Six months after CABG, the increase in CFR was only modest. This result suggests that CMD was not ameliorated even after successful revascularization in a patient with ischemic cardiomyopathy and left ventricle (LV) remodeling. A study is currently in the planning stages at Hokkaido University and 3 affiliate hospitals to clarify the effects of medical treatment, PCI and CABG, selected at the cardiologist's discretion according to specific guidelines on CFR.

#### Future directions and alternatives

We hope that CFR becomes a more commonly used tool for the management of CAD. CFR is now available non-invasively on multimodalities such as dynamic CT or MRI perfusion scan (15, 16), SPECT (17), and flow velocity on MRI (18). The cold pressor test (CPT) is another method for stress testing in addition to adenosine stress. MBF during the

CPT reflects endothelial-dependent function. The CPT might be more sensitive than CFR in assessing early coronary atherosclerosis and monitoring function after medical interventions. In hypertensive patients, delta in MBF from rest to CPT was decreased due to the impaired coronary vasodilator response (19). Three months after treatment with angiotensin receptor blockers, delta MBF from rest to CPT was significantly improved, suggesting an improvement in coronary endothelial function.

#### Conclusion

CFR overcomes the limitations of risk stratification by angiographic atherosclerotic burden and by ischemic burden on SPECT, static PET and FFR by combining these two measures and microvascular function into one index in patients with CAD.

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#### Conflicts of interest

None.

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