

## Editorial



# Can C-11 Acetate PET Be a Feasible Option for Assessing Non-Culprit Lesion in STEMI Patients?

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► See the article “Evaluation of Non-infarct-Related Arteries Using C-11 Acetate PET in STEMI With Multivessel Disease” in volume 30 on page 169.

**Received:** Mar 20, 2022  
**Revised:** Apr 23, 2022  
**Accepted:** Apr 26, 2022  
**Published online:** May 16, 2022

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### Conflict of Interest

The author has no financial conflicts of interest.

Primary percutaneous coronary intervention (PCI) improves prognosis in patients with acute ST-elevation myocardial infarction (STEMI),<sup>1)</sup> yet 40–50% of them have a multivessel disease, which is associated with poor prognosis.<sup>2)3)</sup> Although a management strategy for non-culprit lesions has not been established, clinical practice guidelines advocate for complete revascularization of non-culprit lesion.<sup>4-8)</sup> Moreover, PCI of non-culprit lesions is prognostically important for patients with STEMI, and the identification of ischemia and timing of PCI is still controversial.<sup>1)</sup>

Many randomized controlled trials with various criteria have been conducted to optimize non-culprit lesion management post-STEMI. The Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) and CvLPRIT (Complete versus Lesion-only Primary PCI) studies defined recanalization criteria as stenosis  $\geq 50\%$ ,<sup>4)5)</sup> but in the Danish Study of Optimal Acute Treatment of Patients With STEMI: Primary PCI in Multivessel Disease (DANAMI-3-PRIMULTI) and COMPARE-ACUTE studies, reperfusion was performed only for lesions with an fractional flow reserve (FFR)  $\leq 0.80$ .<sup>6)7)</sup> In Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE), the reperfusion procedure was adopted if the stenosis was  $> 70\%$  or if the stenosis was  $> 50\%$  and the FFR was  $\leq 0.8$ .<sup>8)</sup>

In the present study, Cho et al.<sup>9)</sup> prospectively investigated the feasibility of C-11 acetate positron emission tomography (PET) for evaluating the functional significance of non-culprit lesions in patients with STEMI. A total of 31 patients with STEMI and multivessel disease underwent C-11 acetate PET after complete revascularization of the culprit artery. The authors compared PET parameters with stenotic diameter and FFR results. C-11 acetate PET provides quantitative information about myocardial blood flow (MBF) and oxidative metabolism, which are decreased by ischemia.<sup>10)</sup> PET parameters included rest- and hyperemic (adenosine stress) MBF and oxidative metabolism, myocardial flow reserve (hyperemic MBF/rest MBF), and relative flow reserve (RFR), which is a concept similar to FFR implemented in PET and defined as the ratio of the hyperemic MBF of a specific coronary area to the highest segmental MBF in the total left ventricle. FFR was performed only on 25 non-culprit lesions that showed intermediate stenosis (50–70%) on angiography.

Cho et al.<sup>9)</sup> dichotomized the arteries based on the following 3 criteria and compared them:

- 1) Infarction artery (n = 31) vs. non-culprit artery (n = 62)
- 2) Non-culprit artery with  $\geq 50\%$  stenosis (n = 42) vs. non-culprit artery without  $\geq 50\%$  stenosis (n = 20)
- 3) Non-culprit artery with significant stenosis (n = 18) vs. non-culprit artery without significant stenosis (n = 44); significant stenosis was defined as either stenosis  $\geq 70\%$  or FFR  $\leq 0.80$ .

As expected, hyperemic MBF and oxidative metabolism, myocardial flow reserve, and RFR were more reduced in the infarction artery, non-culprit artery with stenosis  $\geq 50\%$ , and non-culprit artery with significant stenosis than in the control group. The mean values differed significantly between the groups created based on the three criteria. However, the values considerably overlapped, limiting the ability to distinguish each group with a specific threshold. Furthermore, RFR correlated with the stenosis diameter of non-culprit lesions ( $r = -0.429$ ,  $p = 0.001$ ), and an RFR threshold  $> 0.81$  could be used to exclude the presence of significant stenosis in the non-culprit artery. However, despite the RFR being  $\leq 0.81$ , the predicted value of significant stenosis was less than 50%. Therefore, according to the study, C-11 acetate PET could be used as an alternative modality in patients at high risk of undergoing angiography, but it could not predict significant stenosis compared with angiography with FFR despite additional PET acquisition.

FFR-guided PCI is the gold standard for the prognostic management of intermediate lesions in stable angina; however, it is not used to evaluate non-culprit lesions in STEMI scenarios. FFR has an important limitation due to the assumption of a normal microvascular structure.<sup>7)</sup> A previous PET study with O-15 water reported microvascular dysfunction due to transient vasomotor dysfunction in both culprit and non-culprit territories following acute STEMI.<sup>11)</sup> Impaired microcirculation may also be related to diffuse atherosclerosis, circulating catecholamines, cardioprotection, or neural sympathetic activity.<sup>12)13)</sup> Microvascular dysfunction increases the unreliability of FFR measurements and suggests the potential of quantitative techniques that consider microcirculation. Myocardial perfusion PET is expected to better reflect myocardial ischemia than angiography or FFR. Unfortunately, reclassification of lesion significance by C-11 acetate PET was not discussed in the article, and the implications of the discordance between C-11 acetate and FFR post-STEMI remains unknown.

Additionally, technical errors may arise in this regard. Although C-11 acetate can analyze MBF, it is not the optimal radiotracer for evaluating MBF and is not the best choice when flow-related parameters are key factors in evaluating non-culprit lesions.<sup>14)</sup> N-13 ammonia PET and/or Rb-82 PET have been approved for clinical use in many countries (including Korea), and Cho et al.'s study<sup>9)</sup> may have demonstrated better diagnostic performance if other radiotracers were used. The main role of C-11 acetate PET is to measure oxidative metabolism. The change in oxidative metabolism is an adaptive response to insufficient oxygen supply; thus, it could be preserved even in areas with reduced MBF. Information about oxidative metabolism from C-11 acetate PET is useful for selecting viable myocardium, which is expected to restore function via reperfusion,<sup>15)</sup> and is therefore less sensitive than MBF in diagnosing ischemia. The results of this study are in line with this hypothesis.

Furthermore, the diagnostic agreement between the two tests near their diagnostic cutoff point could be less effective in the selection of patients with moderate disease, irrespective of the higher accuracy of tests in mild and severe disease. This was demonstrated in a comparison of computed tomography (CT)-derived FFR and invasive FFR.<sup>16)</sup> The prevalence

of the disease and its distribution could bias a test's diagnostic accuracy. Owing to the biological variability in patients with STEMI and narrow range of moderate disease severity, the agreement between C-11 acetate and FFR may have shown insignificant results in the current study.

To the best of my knowledge, the study by Cho et al. is the first to predict significant stenosis in non-culprit lesion post-STEMI using C-11 acetate PET. However, the efficacy of C-11 acetate PET in selecting significant stenosis of non-culprit lesions in acute STEMI could not be sufficiently proved because of the small sample size and flaws in analysis. This study suggests that the physiological status of multivessel STEMI can be evaluated using PET with perfusion quantification, which may help to assess microvascular dysfunction and diffuse atherosclerosis before further invasive evaluation. Therefore, the ideal assessment for non-culprit stenosis should be performed considering an integrated ischemic myocardial burden, rather than only single coronary artery stenosis. However, a multicenter trial randomizing patients with STEMI and multivessel disease to either a perfusion imaging-guided strategy or an invasive physiology-guided strategy is required to confirm these findings.

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