Assessment of myocardial viability using a [^{15}O]-water perfusion PET: Towards a one-stop shop?

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Since the first surgical aortocoronary revascularization has been successfully performed in the 1960s, many clinical studies have demonstrated an improvement of the myocardial contractile function in patients with coronary artery disease.¹ This led to the introduction of the concept of hibernating myocardium,² describing a state of persistently altered left ventricular function resulting from the reduced coronary blood supply at rest, with improving potential after restoration of the coronary blood supply. To date, many lines of evidence from clinical studies have clearly demonstrated a significant improvement after revascularization of those patients with reduced left ventricular function and dysfunctional, but viable myocardium.³ Therefore, it is of great clinical importance to accurately discriminate those patients who will most likely benefit from coronary revascularization.

In the clinical setting, different techniques have been proposed to detect the reversibly altered myocardium, including the dobutamine stress echocardiography, magnetic resonance imaging, and nuclear imaging, with different diagnostic accuracy.⁴ From the nuclear imaging perspectives, position emission tomography/computed tomography (PET/CT) with fluorine 18-fluorodeoxyglucose (^{18}F -FDG), in

combination with a myocardial perfusion tracer is considered to be the best approach to assess the myocardial viability.⁵ Here, myocardial segments with altered contractile function showing increased ^{18}F -FDG uptake and significant reduction of the perfusion tracer uptake are identified as viable. However, ^{18}F -FDG, as marker of glucose uptake, can be altered by different metabolic conditions.⁶ Furthermore, the assessment of the perfusion-metabolism mismatch requires the performance of two different PET/CT with prolonged examination time and increased irradiation of the patients.

Thereby, alternatives methods have been explored using PET/CT for the simultaneous assessment of perfusion and metabolism. In this perspective, [^{15}O]-water, a diffusible and chemically inert radiotracer for PET/CT,⁷ has progressively emerged as an attractive option. Early evidences on the use of [^{15}O]-water PET/CT for the assessment of myocardial perfusion come from the 1980s, as Bergmann et al⁸ showed in an animal model a good correlation between regional distribution of [^{15}O]-water and labeled microsphere. This technique has been further improved by Iida et al⁹ with the development of the concept of perfusion tissue fraction (PTF) and perfusion tissue index (PTI) using a single-compartment model. PTF represents the fraction of [^{15}O]-water-perfusible tissue capable of rapidly exchanging water within a given region-of-interest (ROI).⁹ Anatomical tissue fraction (ATF) is defined as the mass of extravascular tissue within a given ROI, and can be obtained from a transmission scan.⁹ PTI is either calculated from the ratio of PTF and ATF or can be generated from a single [^{15}O]-water PET/CT.^{9,10} It represents the proportion of [^{15}O]-water-perfusible tissue within the total anatomical myocardial tissue. Therefore, as all extravascular tissues in a normal myocardium should be able to exchange water rapidly, PTI should therefore equal unity. In contrary, PTF is

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reduced in scarred myocardium due to its inability to exchange water rapidly. However, ATF is preserved, as it represents extravascular tissue, independent of its nature. Due to this disparity, PTI is expected to be reduced in scarred myocardium. More investigations have further improved this concept, demonstrating that PTI is also a marker of the heterogeneity of tissue flow in the injured myocardium.¹¹ All these principles enable PTF and PTI derived from [^{15}O]-water PET/CT to be considered for the assessment of the myocardial viability. PTF and PTI have been successfully tested in histopathological studies for the differentiation of myocardial infarction.¹² They have also been shown to accurately predict the recovery of myocardial contractile function after revascularization in patients with acute and chronic ischemic heart disease, with a cut-off of PTI value of less than 0.7 to define non-viable myocardium.^{13,14}

Nowadays, [^{15}O]-water PET/CT is considered to be the gold standard for the absolute quantification of the myocardial perfusion. But unlike PTF and PTI, the ability of resting MBF to assess myocardial viability is not well established. This highlights the importance of the article of Grönman et al,¹⁵ who investigate the value of resting relative MBF (rrMBF), PTF, and PTI to detect myocardial viability, using a pig model of myocardial infarct in the left anterior descending artery territory ($n = 20$). The authors assess the performance of these parameters to detect infarction and viability, compared to histopathological confirmation using triphenyltetrazolium (TTC) staining as a gold standard. The authors establish cut-off values for rrMBF, PTF, and PTI to detect myocardial viability with good accuracy, allowing them to conclude that rrMBF, PTF, and PTI based on [^{15}O]-water PET are useful for assessing myocardial viability. This is a very well-conducted study with rigorous and strong methodology, for which the authors should be congratulated for.

With these results, the authors have confirmed the utility of PTF and PTI to assess myocardial viability, as previously proposed.⁹ More interestingly, rrMBF have similar sensitivities, specificities, and diagnostics accuracy compared to PTF and PTI, however with a slightly better performance of PTI. Moreover, the diagnostic performance of rrMBF appears higher or similar to other diagnostic modalities.⁴ Compared to PTF, rrMBF is more accurate in the detection of discrete and moderate infarction. Interestingly, the authors showed that rrMBF, in contrary to PTF, is not affected by partial volume effect and the size of the ROI, as this is one of the major limitations of PTF in the assessment of myocardial viability, as further demonstrated in this study. Therefore, we appreciate the comparison made between

rrMBF and PTI, as the latter is also not affected by the partial volume effect and the size of the ROI.⁹ These observations strongly suggest that [^{15}O]-water PET study could be sufficient in the evaluation of myocardial viability, solely based on the evaluation of rrMBF.

Of note, the proposed cut-off values for PTI in this study is higher than those generally proposed in literature.¹⁴ Gerber et al¹⁶ also showed higher cut-off values for PTI closed to those seen in this study. A possible explanation could be seen in the method to assess ATF, leading to lower values.¹⁴ Nevertheless, optimal cut-off values in human clinical studies are needed to test this concept. For this purpose, it would be of added value to integrate ^{18}F -FDG PET/CT as the reference for assessing the myocardial viability in the study design. The myocardial recovery after revascularization should also be evaluated, as this represents the most frequently used clinical end-point in studies assessing myocardial viability.

Some other concerns should be taken into consideration before the clinical implementation of this concept. Using rrMBF requires a reference myocardial territorial free from alteration of myocardial function, which could be highly problematic in patients with multi-vessels disease. Moreover, the authors were not able to evaluate the utility of quantitative myocardial perfusion in the assessment of myocardial viability due to concern regarding the use of propofol. Indeed, propofol induces alterations of the cardiovascular hemodynamic leading to systemic vasodilation, and thus higher rest MBF than expected and consequently lower capacity flow reserve (CFR).¹⁷ Thus, a quantitative assessment of the myocardial perfusion was a limitation of this study. This would have improved the assessment of the myocardial perfusion without the restriction of the determination of a reference myocardial territory, as discussed above. Due to the short half-time of [^{15}O]-water, a dedicated onsite cyclotron is required. This issue limits the availability of this radiotracer in nuclear centers, when compared to ^{18}F -FDG with longer half-time and the possibility to deliver it in neighbor centers after production. Nevertheless, this short half-time of [^{15}O]-water also has some practical advantages compared with ^{18}F -FDG. Indeed, the radiation dose can be significantly reduced (by 3.5-7.0 mSv for 185-370 MBq of ^{18}F -FDG¹⁸ down to 0.8 mSv for a single injection of 700 MBq of [^{15}O]-water). Moreover, it could also lead to increased patient throughput. But above all, the perspective of assessing myocardial perfusion and viability in a one-stop shop is very attractive. And this could be possible with the input of further investigations to establish this method as one of the valuable alternatives to ^{18}F -FDG PET/CT for assessing myocardial viability.

Disclosure

C.H. Kamani and J.O. Prior have no conflict of interest to disclose.

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