Absolute Quantification of Myocardial Perfusion
A Method Proves Its Mettle

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Coronary artery disease (CAD) remains the main cause of death in the western world, despite the considerable improvements in its diagnosis and therapy in the past few decades. Today, CAD is widely understood to constitute an advanced stage of atherosclerosis, that is to say, an inflammatory pathology involving both coronary and extracoronary arteries. The diagnosis of CAD is frequently based on morphological observations obtained through invasive coronary angiography (ICA), whereby the presence of at least 1 coronary artery stenosis of at least 50% and a history of myocardial infarction are considered to be diagnostic. It is increasingly appreciated that perfusion imaging brings additional prognostic value compared with morphological imaging alone. In particular, perfusion defects can occur at any stage of atherosclerotic disease, from the earliest signs of endothelial dysfunction to the debut of nonobstructive plaques in coronary arteries, and in cases of intermediate or high-grade coronary artery stenoses. In those patients with myocardial perfusion abnormalities, individual risk for coronary events increases with the size of perfusion defects, irrespective of the nature of underlying structural or functional changes causing these perfusion defects. Thus, myocardial perfusion abnormalities can be understood as the functional consequence of a broad range of present atherosclerotic vessel alterations, bearing considerable significance for the diagnostic and prognostic work-up of CAD.

In daily clinical routine, diagnostic myocardial perfusion is most frequently estimated by single-photon emission CT (SPECT) using $^{99m}$Tc-labeled radiopharmaceuticals, whereby the tracer uptake in the left ventricular myocardium is analyzed semiquantitatively. Compared with SPECT, PET presents advantages with respect to spatial and temporal resolution, leading to higher sensitivity for the detection of perfusion defects. Furthermore, PET perfusion tracers, such as $^{13}$N-ammonia or $^{15}$O-water, have a higher extraction from the blood pool and enable the absolute quantification of myocardial blood flow (MBF) based on methods developed for studies of cerebral perfusion. With the growing availability of cyclotrons at clinical imaging centers, the former impediments to the widespread use of short-lived PET radioisotopes such as $^{13}$N-ammonia and $^{15}$O-water are becoming less of an issue. Moreover, the recent introduction of PET/CT hybrid scanners provides improved allocation of perfusion defects and has instigated the reintroduction of long-known agents, such as the generator product $^{82}$Rb, as well as the implementation of newly developed $^{18}$F-fluorine-labeled PET perfusion tracers.

Of all the SPECT/PET myocardial perfusion tracers, of which at least a dozen have been described to date, $^{15}$O-water is considered the gold standard for noninvasive quantitative measurements of MBF because water is freely diffusible and has no metabolic interactions in tissue. In addition, $^{15}$O-water PET can be used in conjunction with CT using PET/CT hybrid scanners, enabling the allocation of perfusion abnormalities to vessel structures, which brings a considerable improvement in diagnostic accuracy. Thus, $^{15}$O-water bears the greatest potential for detecting perfusion abnormalities, potentially enabling the detection and classification of early CAD stages. However, it has remained uncertain whether the technical difficulties presented by quantitative $^{15}$O-water studies are justified by the diagnostic benefits.

In this issue of Circulation: Cardiovascular Imaging, Kajander et al14 present a prospective study of 107 consecutive patients with chest discomfort who were referred for perfusion imaging for exclusion of present CAD. The authors compared the sensitivities of the absolute quantification of myocardial perfusion measurements with $^{15}$O-water and the conventional visual assessment relative to reference areas with intact perfusion. As expected, absolute quantification proved to be advantageous, particularly in patients with multivessel disease. Most importantly, patients with diffusely reduced MBF despite the absence of significant stenoses were easily identified through absolute quantification. Despite these advantages, few groups are currently applying $^{15}$O-water for myocardial perfusion imaging. Nonetheless, the basic results reported by the Kajander group should be interesting to all clinicians performing PET perfusion imaging, given the important conclusions that can be drawn from the study.

First and foremost, the new study demonstrates that absolute MBF quantification of the entire myocardium is feasible; high diagnostic accuracy is obtained with hybrid PET/CT, whereby MBF abnormalities are easily allocated to their respective coronary vessel or even lesion. This finding highlights the methodological development of the past 30 years such that the absolute quantification of myocardial perfusion with $^{15}$O-water is no longer hampered by issues.
arising from the extensive blood pool of the tracer.\(^\text{15}\) Indeed, the Kajander group\(^\text{16}\) has previously introduced a software package that enables quantitative analysis of \(^{15}\)O-water PET studies with excellent reproducibility. This innovation is appreciated by clinical departments with access to \(^{15}\)O-water, which must be generated by an onsite cyclotron because of the brief physical half-life of the radionuclide (2 minutes). The brief half-life presents a distinct advantage for rest and stress imaging in that serial scans can be performed only minutes apart, albeit with the disadvantage that more physiologically relevant ergometric stress cannot be applied in this setting.

Another notable aspect of the new study is that it represents an invaluable advance through its combined use of ICA and fractional flow reserve (FFR) as an invasive reference standard for the detection of hemodynamically relevant coronary artery stenoses. This is particularly important because stenoses with lumen narrowing ranging all the way from 30% to 70% were measured with FFR. Numerous previous studies demonstrate the usefulness of FFR for identification of hemodynamically relevant stenoses and the superiority of this approach compared with ICA alone with respect to individual risk stratification and therapy guidance.\(^\text{17}\) Particularly in patients with multivessel disease, the invasive FFR approach brings theoretical and practical advantages compared with SPECT because the hemodynamic relevance of a particular lesion is measured directly within the lumen of the diseased coronary vessel.\(^\text{18}\) However, the present study notes potential limitations of the invasive reference standard. In particular, ICA/FFR in clinical practice gives accurate measurements only in proximal parts of the major coronary arteries, and arteries with high-grade stenoses are rarely accessible to the pressure wire. Thus, stenoses as high as 70% to 80% lumen narrowing frequently are rated as hemodynamically relevant in the absence of FFR measurements. However, such stenoses often are precisely those likely to be fed through collaterals or to be present in association with myocardial scars and hibernating myocardium. Consequently, false-negative SPECT/PET results may be obtained if such stenoses are not in fact hemodynamically relevant or if the perfusion defect is rated as a myocardial scar in the absence of formal demonstration of relevant stress-induced ischemia. For reasons noted here, stenoses \(>70\%\) but without FFR measurements were rated as hemodynamically relevant in the present study, which might account for the 2 false-negative results of the absolute quantification method.

Another limitation arising from the Kajander et al ICA/FFR approach was that cases of missing FFR values where stenosis exceeded 50% were also rated as positive, which might have led to false-negative PET results if these particular lesions were indeed not hemodynamically relevant. Furthermore, there were 6 false-positive findings observed for the absolute quantification method of which 5 patients had diffusely reduced flow. However, quantitative \(^{15}\)O-water PET, in contrast to ICA/FFR, not only measures the hemodynamic relevance of vessels with 30% to 70% stenoses, but also (as noted) reflects the sum of all hemodynamically relevant stages of present atherosclerosis, including endothelial dysfunction or instances of calcified but nonobstructive plaque tissue. Consequently, present perfusion abnormalities in PET need not necessarily reflect false-positive results.

A third and final notable aspect of the new study is that the incidences of false-negative (10 patients) and false-positive (18 patients) cases were markedly increased when analyzing only relative myocardial uptake. In this context, it is important to consider the standard procedure guidelines for myocardial perfusion imaging, wherein ECG-gated acquisition poststress and postrest is preferred.\(^\text{19}\) This additional dimension would have revealed cases of balanced ischemia through detection of significantly decreased left ventricular global or regional function between the 2 acquisition conditions, which would in turn have decreased the false-negative rate of the relative uptake analysis.\(^\text{20}\) In addition, the high false-positive rate also may be a reflection of the very sensitive relative perfusion analysis approach, of which some details are lacking in the present report.

In summary, the new study by Kajander et al\(^\text{14}\) shows that \(^{15}\)O-water PET/CT with absolute flow quantification is superior to conventional visual assessment relative to reference areas with intact perfusion. As adequate gated acquisitions cannot be performed with this technique, absolute quantification routinely should be applied whenever possible. Because of the high sensitivity of \(^{15}\)O-water PET/CT, the hemodynamic significance of atherosclerotic burden in the coronary arteries can be estimated, irrespective of the particular CAD stage. Further studies extending this report might reveal the usefulness of this approach not only for excluding the presence of hemodynamically relevant epicardial vessel stenoses, but also for demonstrating the prognostic value of present MBF abnormalities in individual patients.

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**Disclosures**

None.

**References**


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