Automation in Nuclear Cardiology: Time for Flurpiridaz to Join the Club

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Positron emission tomography (PET) is currently the most accurate modality for myocardial perfusion assessment in patients with known or suspected coronary artery disease (CAD).¹ Notwithstanding its robust diagnostic and prognostic performance as an imaging technology, utilization of PET for myocardial perfusion imaging (MPI) remains low, with widespread adoption likely hampered by many factors, including limited access to PET radiotracers. Most PET radioisotopes have a short half-life, and therefore cannot be obtained from regional radio-pharmacies. Additionally, most laboratories performing PET MPI do not have access to an on-site cyclotron, which makes utilization of ¹³N-ammonia or ¹⁵O-water (both cyclotron-produced PET tracers) for perfusion assessment logistically challenging.² Lastly, whereas relying on ⁸²Rb generator may improve tracer availability, the cost of the generator remains prohibitive for many low-volume laboratories.³ Therefore, there currently exists a need for newer PET radiotracers with superior kinetic properties (half-life, first-pass extraction rate, positron range, etc.) that will not only improve tracer availability, but also avoid the

pitfalls of current tracers and allow performance of PET MPI in conjunction with exercise.

Flurpiridaz, an ¹⁸F-labeled PET radioisotope, has several favorable tracer characteristics that was introduced with the potential to fill the gaps with current tracers.⁴ Due to its high affinity to mitochondrial complex-1, Flurpiridaz has a high first-pass extraction rate, and therefore may be suited for more accurate quantification of myocardial blood flow.⁵ Furthermore, with a half-life of 110 minutes, Flurpiridaz can be made available in unit doses from regional sources, increasing tracer availability and, more importantly, allowing performance of PET MPI with exercise stress. Early studies have demonstrated the safety and tolerability of Flurpiridaz in addition to superior image quality and diagnostic performance in comparison to Tc-99m single photon emission computed tomography (SPECT) MPI.^{6,7} More recently, Flurpiridaz PET was found to have superior image quality, lower radiation exposure and improved detection of severe coronary stenoses compared with Tc-99m SPECT, especially in women, obese patients and those undergoing pharmacologic stress.⁸

So, is the best we can hope for with a novel agent and ‘ideal tracer characteristics’ to outperform Tc-99m in identifying patients with obstructive epicardial coronary disease? Is it possible to further augment the diagnostic yield of PET MPI studies performed with Flurpiridaz? The study by Packard and colleagues in this issue of the *Journal* examines the value of adding automated perfusion quantitation to PET MPI scans performed with Flurpiridaz in patients with suspected CAD.⁹ Exploiting the strengths of machine learning and automated quantitation in analyzing the wealth of data

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available in an imaging study is a promising concept. This has been examined with radionuclide perfusion studies, and also with other imaging modalities, with the aim of improving diagnostic and prognostic yield of studies.^{10–14} The authors in the current study tested the diagnostic accuracy of an automated system for quantification of perfusion defects against core laboratory interpretation by three expert readers with invasive coronary angiography as the reference standard, using data from recent phase-III Flurpiridaz clinical trial.⁸ First, they obtained the normal radiotracer quant in each coronary territory and the global left ventricular myocardium from 40 patients with no CAD. Then, they obtained the lower limits of normal quant distributions and the standard deviation that fits the best diagnostic accuracy using receiver operating characteristic (ROC) curves to detect $\geq 50\%$ and $\geq 70\%$ coronary artery stenosis from 45 patients with exercise stress test and 45 patients with pharmacological stress test. The diagnostic accuracy of the automated system then was examined in 548 patients. The diagnostic accuracy for $\geq 50\%$ and $\geq 70\%$ coronary artery stenosis of both the visual and automated read was similar, around 70–73%, for the entire cohort and pharmacological stress test. The diagnostic accuracy was lower, 65–68%, for exercise stress test for both visual and automated reads. There were no significant differences between both methods in the individual coronary artery except for $\geq 50\%$ the left coronary artery stenosis where the sensitivity has improved 39% to 64% by automation, however, the specificity significantly decreased from 88% to 69%. The interobserver agreement was better with automated methods in both normal and abnormal system.

Although the method employed by the authors is not entirely novel, it has few merits. They standardized the normal limits and what is considered as abnormal in both exercise and pharmacological stress test. In addition, they validated their results in a different population. They have also tested the system in a wide range of patients including normal subjects and patients with single, two and three-vessel disease who were prospectively randomly selected for phase-III clinical trial of Flurpiridaz from multiple centers. However, it is understood the analysis for the current study was retrospective. They have also extensively studied the interobserver agreement in both methods. It also adds to the growing body of literature supporting the future use of the automated analysis of relative perfusion in nuclear myocardial perfusion imaging.^{15–18} These studies help to standardize the assessment of severity and extent of ischemia by quantification. This provides uniform measure of ischemia to follow patients on medical therapy and consider further treatment options. The conclusions of the study have to be interpreted in the

context of the study limitations which were addressed by the authors.

Although we concur with the authors optimistic conclusion about the use of automated quantification of ischemia, we should be vigilant for the phantom of the opera. Despite the promising advantages of Flurpiridaz, the diagnostic characteristics are a little disappointing. The sensitivity and specificity for the global myocardial ischemia and individual coronary artery territory ischemia are much lower than other PET tracers. Whether this is an inherent limitation of the Flurpiridaz or related to the recruitment of lower risk patients in phase-III trials is not clear. The diagnostic accuracy of Flurpiridaz was based on assessment of relative perfusion imaging. Hence, the diagnostic performance may improve if other MPI variables such as myocardial blood flow, coronary flow reserve, ejection fraction reserve and transient ischemic dilation are taken into account. Furthermore, the diagnostic accuracy was evaluated against invasive coronary angiography and not invasive functional testing such as invasive fractional flow reserve. Another interesting finding is the low diagnostic accuracy in the left circumflex territory and whether this would be a limitation in the routine use of Flurpiridaz in routine clinical practice. We must wait for more studies and experience of the real-world practice to answer many of these questions.

Although it is still in its infancy, automated assessment of ischemia has many promising clinical and research applications. It provides a standard assessment of ischemia that can be measured objectively through accurate and reproducible quantification. The diagnostic accuracy of Flurpiridaz is still to be discovered and like Nikola Tesla once said, “*Let the future tell the truth, and evaluate each one according to his work and accomplishments*”.

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