Including myocardial flow reserve by PET in prediction models: Ready to fly?

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Received Mar 10, 2023; accepted Mar 11, 2023
doi:10.1007/s12350-023-03259-7

See related article, pp. 2043–2053

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are the foremost nuclear medicine techniques for evaluation of myocardial perfusion. In 1986, Strauss and Elmaleh[1] discussed what were considered at that time the relative merits and limitations of these two approaches. The conclusion was that both PET and SPECT are very useful and appropriate to study cardiac physiology and pathology and that the future of each technique will be determined by their relative power to provide timely information for clinical decision making. More recently, Di Carli[2] supported and explained the point of view according to which PET imaging is the future of nuclear cardiology in the work-up of cardiovascular disease. This scenario is more likely when one considers the promise of cardiac PET/CT and the evolving of artificial intelligence tools.[3] Indeed, since the seminal study by Zaret et al.[4], the radiopharmaceuticals, hardware, software, and methodology for myocardial perfusion radionuclide imaging have evolved over the years. In 1975, Ter-Pogossian et al.[5] published emission transaxial images obtained sections of organs containing positron-emitting radiopharmaceuticals. However, the beginning of the PET era myocardial perfusion imaging can be traced back to the researches of Lance Gould[6] and of Heinz R. Schelbert.[7] Nowadays, the value of cardiac PET is well appreciated, as indicated by the increase from 2010 to 2019 in the rate of cardiac PET performed by cardiologists both in the office (193%) and hospital outpatient departments (189%) in the Medicare population.[8]

With the limitations of any classification, it is useful to distinguish two main classes of radiotracers: (1) for myocardial perfusion imaging and (2) for myocardial metabolism, viability, and inflammation/infection. The main advantages of PET tracers for the evaluation of myocardial blood flow is the absolute quantification of global and regional myocardial blood flow (MBF) in milliliters per gram per minute and of myocardial flow reserve (MFR).[9] Well-known PET radiotracers for evaluation of MBF are ^{82}Rb, ^{13}N-labeled ammonia ($^{13}NH_3$), and ^{15}O-labeled water (^{15}O-H_2O). The first tracer has a very short-half live, allowing significant reduction of the radiation burden, is metabolically extracted and trapped into cardiomyocytes and is obtained from ^{82}Sr by a generator system, therefore, differently from $^{13}NH_3$ and ^{15}O-H_2O do not require an on-site cyclotrons. Thus, ^{82}Rb PET has become the standard modality for MPI in many centers. As a consequence, in 2011 a strontium shortage affected supply of Rb-82 generators. ^{15}O-H_2O requires an on-site cyclotron and is considered the ideal perfusion tracer because of its physiological properties. However, this radiotracer is free diffusible with low tissue accumulation and challenges with image quality, thus it is primarily used for research. $^{13}NH_3$ enters the

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J Nucl Cardiol 2023;30:2054–7.
1071-3581/$34.00

myocardium either passively as NH_3 or through $Na^+/K^+ - ATPase$ as NH_4^+ and is then trapped intracellularly as ^{13}N-glutamine. However, the very high extraction fraction of about 80% at baseline MBF, decreases nonlinearly with increasing flows. Cardiac $^{13}NH_3$ imaging has a good resolution according to its long half-life ($\sim$ 10 minutes) and the short mean positron range ($\sim$ 1.8 mm in water).[10] However, the positron range of $^{3}NH_3$ is about three times that of ^{18}F-labeled tracers. Among these new potential radiotracers, ^{18}F-Flurpiridaz binds to mitochondrial complex 1, has an excellent spatial resolution, due to the long half-life ($\sim$ 110 minutes), high flow-independent myocardial extraction, and short mean positron range ($\sim$ 0.6 mm in water). This tracer is under evaluation in phase 3 trials.[11]

In this issue of the Journal, Miura et al.[12] investigated the relationships between PET-assessed extent of myocardial ischemia, and MFR, and the impact on predicting the occurrence of future major adverse cardiac events taking in account the effect of early revascularization. The Authors found that impaired MFR was significantly associated with increased risk of events in patients with $\leq$ 10% myocardium ischemia, but not in those with ischemic burden $>$ 10%. Moreover, quantification of MFR provided incremental prognostic information over semiquantitative PET assessments and pretest CAD probability scores.

These results confirm and extend previous observations of the same group[13] and other groups[14–16] and by recent meta-analyses[17,18] supporting the prognostic value of physiology-based variables, such as MFR, for effective risk stratification in patients with suspected or known CAD. Despite all these data, it has been rightly remarked that full integration of MBF and MFR in clinical practice, especially in risk prediction models, has not yet been widely implemented.[19]

Nowadays, clinical prediction models are largely used, comprehensively covering the spectrum of all branches of medicine. In 1979, Diamond and Forrester[20] published what can be considered the first diagnostic algorithm to simply estimate, according to the Bayes theorem, the probability of CAD, considering only age, gender, and type of chest pain. On the other hand, the Framingham risk score may be considered the first population-based prognostic algorithm to predict the risk of subsequent cardiovascular events.[21] The longevity of these algorithm is somewhat surprising, considering the speed by which medical knowledge has evolved in the last 50 years and the parallel technological advances in the field of genetics, omics sciences, molecular biology. Probably, the greatest strength of these algorithms is represented by their accuracy-simplicity trade-off, with optimal comprehensibility by physicians and other caregivers and, perhaps more importantly. The patients itself. Over the years, several clinical prediction models have been published for patients with suspected and known CAD.[22,23] Clinical prediction algorithms can be very useful in reducing medical errors, especially those implicitly related to individual decision making. However, it is always necessary for clinical algorithms to undergo external validation in populations other than those in which the algorithms were developed. Furthermore, if applied incorrectly, they can lead to inaccurate or distorted predictions with negative consequences. For each algorithm it is also advisable to verify over time the need to update the features to be selected and their importance within the model, due to the epidemiological and therapeutic changes of the various diseases. Methodological standards for the development and evaluation of clinical prediction algorithms have been recently.[24]

Since the turn of this century, there have been dramatic changes in the epidemiology of cardiovascular disease, particularly CAD, due to changes in demographics, disease management, and also in the way CAD and related events are counted and valued. Different models may include different biomarkers, genetic, epigenetic, and radiomic features. As an example, a recently published study demonstrated that the use of polygenic risk scores improves significantly risk classification of people at clinically-determined intermediate-risk of atherosclerotic cardiovascular disease.[23]

More recently, artificial intelligence, including machine learning, has established itself as a fundamental tool not only for data analysis, but also (radiomics) for the extraction of features from imaging tests that cannot be recognized by human. Cardiology is one of the fields of medicine with the highest interest in its applications.[25] Thus, complex machine learning approaches are increasingly used to build diagnostic and prognostic decision algorithms. This scenario performs best in the presence of big data, which could be unmanageable with traditional statistical and computational approaches. However, machine learning needs an operative strategy of data-storage and data-analysis economically sustainable and technically feasible in the context of everyday clinical and research practice in medical departments, with limited resources, time, and manpower. For big data sets, the best choice is to analyze data and build the model where the data already resides, avoiding data transmission. Several databases support that, at least partially but they may differ in characteristics. Indeed, in many healthcare facilities, even in the western world, health information technology is only taking its first steps and many institutions still rely on local spreadsheets, which have obvious limitations when trying to handle large amounts of relational data.[26] To store, share, and analyze health information, a professional

electronic system should ensure privacy and security of electronic health records including encrypting electronic information, so that only authorized people can access, and perform real time scripted analysis on subsets of extracted data.

In their study, Miura et al.[12] evaluated MBF and MFR by single-day stress (pharmacological)/rest $^{13}NH_3$ PET with a PET/CT scanner in the 3D list mode. The pharmacological stress scan was performed during adenosine triphosphate (ATP)-induced hyperemia for 5 minutes, at a rate of 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 13NH3 - ammonia dose of 3 $MBq \cdot kg^{-1}$ was injected for 30 seconds, 3 minutes after ATP infusion commencement. The rest scan was performed with 3 $MBq \cdot kg^{-1}$ of $^{13}NH_3$ for 30 seconds, 1 hour after the stress scan. Of note, there is intense research to develop other non-invasive methods for the quantification of MBF and MFR, such as dynamic contrast-enhanced cardiac computed tomography (CT) and Cardiac magnetic resonance imaging CM. However, for this latter the normal reference values may differ according to the magnetic field strength of the scanner, pulse sequence, or different manufacturers and software. The new generation of solid-state CZT-SPECT cameras are taking a leading role in this competition, representing a chief technological progress in this field.[27,28] Recently, D'Antonio et al.[29] summarized the state of the art on MBF and MPR evaluation by dynamic CZT-SPECT, highlighting its lights and shadows and the major issues to solve to optimize this technique. Dynamic CZT-SPECT-based MBF quantization is sure to play an increasingly important role as an alternative to PET, and new data are continually being published confirming this trend. Acampa et al.[30] reported a head to head comparison of stress and rest MBF and MFR measured by ^{82}Rb PET imaging and ^{99}mTc-sestamibi CZT-SPECT in patients with available coronary angiography data. Hyperemic MBF and MFR values obtained by CZT-SPECT were higher than those measured by ^{82}Rb-PET imaging, with a moderate correlation between the two methods. However, CZT-SPECT showed good diagnostic accuracy for the identification of obstructive CAD. Indeed, various studies have demonstrated that the evaluation by CZT-SPECT of MBF and MFR, in addition to providing a good correlation not only with noninvasive but also invasive measures and good diagnostic ability in the presence of significant strictures, it can also be helpful in the identification of microvascular compromise when considered in the clinical context.[29] These findings may encourage the use of this new technique to a better risk stratification and patient management. The wide availability of CZT SPECT will facilitate the clinical use of SPECT MBF quantification, both for diagnostic and prognostic purposes. However, it has been recently suggested that current SPECT-derived estimates of MFR lack precision for relevant categorization of CAD patients and require further optimization for clinical risk stratification, and today PET remains the ''gold standard'' for MBF and MFR estimation, but CZT-SPECT with 99mTc-labeled tracers is still proving its feasibility and reliability in clinical practice, especially for areas where MBF PET quantification is not accessible with PET scans or alternatively PET-CT is preferentially used for cancer management of cancer patients.

The study of Miura et al.[12] has several limitations, such as a single-center observational retrospective design, limited subgroup sample size, and model overfitting models for the numbers of events. The evidence was insufficient for analyzing differential effects of an impaired MFR based on the level of myocardial ischemia as assessed by PET-MPI. Moreover, all myocardial perfusion PET examinations were performed with pharmacological stress testing, and exercise stress testing that can be a more physiological procedure with added prognostic value. Finally, the relative prognostic strength of MFR, perfusion defects, and coronary artery calcium score is of great interest[31] but was not assessed. Despite all these limitations, and others reported by the authors, the study by Miura et al.[12] emphasizes the accuracy and efficacy of $^{13}NH_3$ PET for qualitative and quantitative analysis of myocardial perfusion and support its use to stratify cardiac risk by adding prognostic information over the extent of myocardial ischemia.

Disclosures

Mario Petretta, Mariarosaria Panico, Ciro Gabriele Mainolfi, and Alberto Cuocolo declare that they have no conflict of interest.

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