

Hot Topic, Why will PET be the future of nuclear cardiology?

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Radionuclide myocardial perfusion imaging (MPI) has been an indispensable tool in the management of patients with suspected or known coronary artery disease (CAD) for almost half a century. Although radiopharmaceuticals and imaging technology for radionuclide MPI has evolved since its introduction by Zaret and Strauss in 1973,¹ the basic concepts of reversible and fixed perfusion defects as manifestations of ischemia and scar remain to this day key information used for clinical decision making. Semi-quantitative evaluation of regional myocardial perfusion with SPECT imaging has been standard practice in nuclear cardiology for more than three decades. The enduring impact of SPECT MPI in patient management is based on the fact that the test is accurate, highly reproducible, and most importantly, a powerful tool for risk stratification. However, there are powerful signs that the paradigm that served as the clinical rationale for radionuclide MPI for many decades may be insufficient to maintain a clinically relevant role for cardiovascular medicine in the future.

Evolution of diagnostic testing for CAD evaluation

Over the last decade, we have witnessed an evolution in the diagnostic testing options available for patients with suspected CAD. These advances are leading to rapid changes in the way we utilize various testing options along the spectrum of CAD risk.² There is little argument on what to do at the ends of the clinical risk spectrum- no testing necessary for very low risk patients and consideration of coronary angiography for high risk patients.² However, testing options for patients with intermediate risk are changing. Coronary CT angiography with its high sensitivity and negative predictive value to exclude CAD makes it an attractive test for patients with low-intermediate likelihood of obstructive CAD. This choice is now supported by clinical trial evidence and associated with improved outcomes, largely resulting from identification of patients in need of preventive therapies.³ The emergence of coronary CTA is shifting the use of radionuclide MPI towards higher risk patients with a high prevalence of cardiometabolic risk factors.²

Changing epidemiology and presentation of CAD

In addition to the changing landscape of testing options, we are witnessing a dramatic change in the epidemiology of CAD especially with the exponential rise of cardiometabolic diseases. Over the last 20 years, there has been a steady rise in the prevalence of obesity, metabolic syndrome and diabetes, and their associated complications including chronic kidney disease. Current statistics indicate that ~50% of the US population is either overweight or obese and that this number is projected to increase to ~80% in the next decade.⁴ The obesity epidemic has led to a sharp rise in the prevalence of diabetes, which

currently affects 10.5% of the U.S. population and 26.8% of those age 65 and older. Moreover, it is estimated that 1 in 3 individuals age 65 and older have pre-diabetes and 38% have chronic kidney disease.

There is also emerging evidence that the frequency of obstructive CAD as a key manifestation of the disease is declining. Over the last two decades, diagnostic yields have fallen; not only for invasive coronary angiography,^{5, 6} but also for noninvasive stress testing.^{7, 8} In one large registry from Denmark, the rate of nonobstructive atherosclerosis in patients with angina referred for invasive coronary angiography increased by 20% to 40% over a 10-year period in women and men, respectively.⁵ This suggests that nonobstructive CAD now accounts for at least 33% and 65% of angiographic findings among symptomatic men and women, respectively. Moreover, recent data from Olmstead County, MN also documented a steady decline in angiographically obstructive CAD over the last two decades.⁹ At the same time, the epidemic of cardiometabolic risk factors has been associated with an anatomic phenotype dominated by 'diffuse atherosclerosis' and 'microvascular remodeling'.¹⁰ The latter includes microvascular obstruction with luminal narrowing of the intramural arterioles and capillaries, and capillary rarefaction, often in the context of increased LV mass.¹¹ These changes help explain, at least in part, the significant temporal decline in the rate of abnormal SPECT MPI studies⁸ with a marked reduction in the proportion of high-risk scans and a proportional increase in low-risk tests.⁷ Indeed, the presence of extensive structural abnormalities characterized by diffuse epicardial atherosclerosis and microvascular disease would be relatively invisible for our traditional radionuclide semi-quantitative MPI approach designed to uncover focal obstructive CAD. Although the observations described above may be perceived as 'good news', the emerging evidence suggest that the rise in diffuse atherosclerosis and microvascular disease are also associated with significant adverse outcomes.⁴ Indeed, the incidence of acute presentations of atherothrombotic plaque rupture causing myocardial infarction (MI), particularly with ST-segment elevation, has decreased¹² while the rates of hospitalizations with a secondary MI diagnosis¹³ and heart failure with preserved ejection fraction¹⁴ have risen sharply. These secondary causes of MI have been associated with heart failure, atrial fibrillation, diabetes and chronic kidney disease. Similar findings have been reported in patients suffering an MI before 50 years of age.¹⁵

The need for new tools: Advantages of quantitative PET imaging

The pioneering work of Schelbert and Gould introducing the possibility of quantitative myocardial blood flow imaging noninvasively with PET in the early 1980s provided the field of nuclear cardiology with a powerful tool that now - nearly 40 years later- will prove to be indispensable in the evaluation of

ischemic heart disease. As outlined below, the emerging evidence supports the notion that quantitative PET MPI is a superior approach to diagnosis and risk prediction, and to possibly to guide patient management.

A recent meta-analysis,¹⁶ a prospective European multicenter study,¹⁷ and a prospective comparative effectiveness study¹⁸ support the notion that PET MPI is one of the most accurate noninvasive techniques for detecting flow-limiting CAD. These quantitative measures of myocardial perfusion improve the sensitivity and negative predictive value of PET for ruling out high-risk obstructive CAD. Equally important is the fact that quantitative measures of myocardial blood flow and flow reserve by PET are now recognized as the test of choice for the evaluation of patients with angina or angina equivalents without obstructive CAD.²

As mentioned above, radionuclide MPI provides robust prognostic assessments of patients with suspected stable CAD and forms the basis of its widespread use and clinical utility. A normal or low risk radionuclide MPI with SPECT or PET has been associated with an annual risk of major adverse cardiac events (MACE) <1%.¹⁹ However, the risk associated with a normal semi-quantitative radionuclide MPI has not necessarily been low (<1%) in higher risk cohorts including those with diabetes, chronic kidney impairment, and the elderly.²⁰ The reasons for the observed increased adverse event rate in higher risk cohorts despite a visually normal radionuclide MPI are likely multifactorial. First, coexisting co-morbidities including cardiometabolic risk factors increase clinical risk, even in the absence of obstructive CAD. Second, and notwithstanding the clinical utility of SPECT MPI, it is a somewhat insensitive test to uncover diffuse obstructive and nonobstructive atherosclerosis and/or coronary microvascular dysfunction associated with myocardial ischemia and increased risk of adverse events. Consequently, absolute quantification of myocardial blood flow and flow reserve by PET—an integrated marker of epicardial stenosis, diffuse atherosclerosis and microvascular dysfunction—offers a definite advantage in higher risk patients, which is precisely the group of patients that will become the primary target of radionuclide MPI. In such patients, a relatively preserved myocardial flow reserve identifies truly low risk individuals among high risk patients.²¹⁻²⁴ For example, patients with diabetes without known CAD but abnormal MFR had a cardiac mortality risk similar to that of patients without diabetes who have known CAD.²⁵ Conversely, patients with diabetes without overt CAD with relatively preserved MFR had an annual risk <1% that was comparable to subjects without diabetes or CAD. Similar findings have been shown in patients with chronic kidney disease.²⁶

Furthermore, the quantitative regional and global myocardial blood flow and flow reserve information obtained with PET MPI provides incremental risk stratification. Indeed, for any amount of ischemic

and/or scarred myocardium, as assessed semi-quantitatively, having severely reduced global MFR is associated with a higher risk of death or MI when compared with having preserved flow reserve.²¹ The increased risk of adverse events in patients with reduced MFR (< 2.0) also applies to patients with visually normal radionuclide MPI, in whom the reduced MFR reflects a combination of diffuse nonobstructive atherosclerosis and coronary microvascular dysfunction and is found in half of symptomatic men and women without overt obstructive CAD.²⁷ Importantly, the noninvasive PET measure of MFR has been able to improve risk re-classification, especially among high risk cohorts (e.g., diabetics, NSTEMI, non-ST elevation myocardial infarction, in patients with chronic renal impairment, and in those with high coronary calcium scores). Thus, the ability to quantify MFR allows a level of risk assessment well beyond that achieved thus far using semi-quantitative analysis of regional perfusion defects, by incorporating measures of endothelial function and vascular health status into routine patient evaluations.

Opening new opportunities for nuclear cardiology in disease management

Radionuclide MPI has been traditionally used to identify symptomatic patients for myocardial revascularization. While this will likely continue to be one of its uses in the future, the ability to accurately quantify the extent and severity of coronary vascular dysfunction may offer an opportunity for identification of high risk individuals who may benefit most from novel therapies. Such approach may prove to be beneficial in clinical trials by identifying patients who have sufficient risk to benefit from these therapies many of which are expensive and not without risk. In so doing, this test may be able to offer a cost-effective approach to patient selection for life-long therapies and to assess response to treatment both in the clinical setting and in drug development.

Conclusions

Coronary artery disease continues to be the leading cause of death and disability in the US and worldwide. As described above, however, the epidemiology and pathobiology of the disease is changing with the rise of cardiometabolic disease. This poses significant challenges to the efficacy of our conventional imaging tools used in diagnosis, risk assessment, and patient management. Quantitative PET offers a powerful opportunity to tackle these challenges effectively and we need to quickly embrace such changes to maintain the transformative role of nuclear cardiology in patient care and research.

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