Challenges and opportunities for nuclear cardiology

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Over the last decade, we have witnessed an explosive expansion in the armamentarium of imaging technologies capable of providing detailed information about the structure and function of the heart and vasculature resulting in unprecedented improvements to our ability to diagnose disease, improve patient care, and advance biomedical research.[1] Cardiovascular imaging approaches are powerful as they are non-invasive, targeted to the specific biology, and highly quantitative. Along with clinical, molecular, and genome-wide association studies, structural and functional quantitative imaging already plays a critical role in phenotyping cardiovascular disease. There is virtually no cardiovascular condition in which imaging does not play a significant role in diagnosis, risk stratification, or management decisions. The role of imaging continues to evolve and now encompasses the entire continuum of biomedical research and clinical practice.

We are also witnessing a paradigm shift in what is being required from imaging and how we measure its effectiveness in a manner that is moving away from simple diagnosis of disease to its role in integrated disease management.[2] In addition, the effective management of many complex diseases now necessitates the use of multi-modality imaging approaches with complementary strengths. This rapidly changing landscape presents significant challenges but also unique opportunities. Thus, this may be a good time for us to pause and carefully assess new knowledge and how it is affecting clinical practice, and then thoughtfully re-examine and embrace the changes that may be necessary to enhance the role of nuclear cardiology in patient care and biomedical research.

CHANGING PARADIGM IN CORONARY ARTERY DISEASE EVALUATION

Cardiovascular disease remains the number one cause of death and disability, but clinical presentations of this disease are changing. Indeed, the incidence of acute presentations of atherothrombotic plaque rupture causing ST-segment elevation myocardial infarction (MI) has decreased.[3] Meanwhile, the rates of hospitalizations with a secondary MI diagnosis and heart failure with preserved ejection fraction (HFpEF) have risen sharply.[4] These observations follow other epidemiological shifts in the prevalence of cardiovascular risk factors in the population, including the growth of obesity, diabetes, and prediabetes and its complications (especially chronic kidney disease), and older age.[5] This changing epidemiology of coronary heart disease is likely going to affect both the anatomic and functional substrates of clinical presentations from predominantly focal coronary artery disease to the expected high prevalence of diffuse atherosclerosis[6] and coronary microvascular dysfunction.[7]

Furthermore, the emergence of CT coronary angiography as a useful tool to rule out coronary artery disease and guide management in low-intermediate risk patients[8] is likely going to shift utilization of myocardial perfusion imaging to intermediate-high-risk patients with a higher burden of cardiometabolic risk factors.

In this context, our traditional approach to diagnosis and risk stratification with semi-quantitative myocardial

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perfusion imaging will likely be insufficient for accurate diagnosis and risk assessment and, ultimately, for effective disease management. Indeed, there is consistent evidence that the use myocardial perfusion SPECT imaging has resulted in sub-optimal risk stratification among high-risk patients including those with diabetes mellitus and chronic kidney disease.[9,10] This suggests that our semi-quantitative perfusion approach may be insensitive for delineating the extent and severity of diffuse atherosclerosis and myocardial ischemia, thereby resulting in sub-optimal identification of clinical risk and, potentially, patient management.

Consequently, the tools needed to evaluate the growing segment of intermediate/high cardiometabolic risk patients with myocardial perfusion imaging will have to evolve to be able to effectively assess the burden of diffuse atherosclerosis and its functional consequences in the myocardium. This will require the use of advanced quantitative tools to assess atherosclerotic burden and myocardial tissue perfusion.[7] There are emerging, consistent data using quantitative PET demonstrating the utility of blood flow quantification for effective risk reclassification among high-risk cohorts. Indeed, the inclusion of the quantitative myocardial blood flow information into risk prediction models allows precise risk reclassification in a number of high-risk cohorts including patients with diabetes,[11] metabolic syndrome,[12] obesity,[13] chronic kidney disease,[14] heart failure,[15] and cardiomyopathy.[16,17] In addition, the quantitative PET approach promises to provide detailed information to accurately phenotype patients' risk in a manner that may allow and more individualized approach to patient management. There are also emerging data that the use of quantitative myocardial blood flow data can help identify patients with coronary artery disease who may benefit most from revascularization.[18,19] This evidence suggests that accurate and reproducible absolute quantification of myocardial perfusion, a unique advantage of nuclear cardiology, will become an indispensable tool in clinical practice.

THE RISE OF MOLECULAR IMAGING

We are also beginning to realize the promise of targeted molecular imaging for diagnosis and management of complex cardiovascular disease. Cardiac amyloidosis offers a perfect case in point of how molecular imaging can become a key component of cardiovascular disease management. The importance of targeted molecular imaging is highlighted by the fact that over the last 12 months we have seen new approved therapies in this disease.[20,21]

Since the original description by Perugini et al documenting the value of bone scintigraphy for diagnosis and phenotyping patients with known or suspected cardiac amyloidosis,[22] we have seen a growing number of publications from multiple laboratories around the world confirming those initial observations.[23,24] A multi society consensus document now confirms the prime place for bone scintigraphy in the workup of patients with suspected cardiac amyloidosis.

It is important to recognize that the newly approved drugs for transthyretin-related amyloidosis are designed to reduce production of the amyloid protein in the liver or stabilizing the circulating transthyretin protein, thereby reducing protein deposition in the heart. Consequently, early detection of amyloid cardiomyopathy may become key to maximize the benefits of these new therapies. It is possible that bone scintigraphy and/or targeted molecular imaging approaches with PET may show amyloid deposits in the heart before structural changes are evident on echocardiography or cardiac MRI. Ongoing clinical research will provide the necessary evidence to support future implementation of screening strategies using molecular imaging for early identification and to guide management in patients with preclinical evidence of amyloid cardiomyopathy.

INFLAMMATION IMAGING: A GROWTH AREA FOR NUCLEAR CARDIOLOGY

Inflammation imaging is another key application of nuclear cardiology for complex disease management that will likely see significant growth. Indeed, nuclear imaging approaches to imaging of immune cell activation have become critical in the diagnosis and management of cardiac sarcoidosis,[25,26] infective endocarditis,[27,28] and vasculitis.[29] In the future, it is possible that the list will also include diagnosis and management of myocarditis.

A current challenge of nuclear medicine based inflammation imaging is the low specificity of the currently available imaging probes (e.g., FDG). As we move forward, this field will require the development of targeted agents that that can help us improve specificity for both diagnosis and monitoring response to therapy. In this regard, it will be important to follow and learn from the rapid developments in molecular imaging of immune response in cancer. For example, the development of single-domain antibodies targeting specific groups of cell surface antigens is emerging as an attractive approach to tracking immune responses in cancer patients.[30,31] Single-domain antibodies are small molecules (nanobodies) that have high specificity and penetration into tissue, and rapid clearance from circulation, thereby allowing radiolabeling with relative short lived radioisotopes (e.g., ^{18}F). The similarity of the biology of the immune response in the heart will

facilitate adoption of these technologies in the not too distant future.

In summary, we are entering a transformative time in cardiovascular imaging. The next few years will likely witness rapid changes in the way we use nuclear cardiology procedures for guiding patient management. Innovation has been a central theme in our field over the last three decades and will continue to play a key role in the future. Our tools will need to adapt to the changing epidemiology and pathobiology of cardiovascular disease. I believe that we can and should transform the challenges ahead into opportunities to shape the future of imaging-based management of cardiovascular disease.

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