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INVITED EDITORIAL

Challenging Nuclear Cardiology Research:

Stimulating Discovery, Validation and Clinical Relevance

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Historical Perspective

Most of what we know of nuclear cardiology has been discovered in the past, nearly 50 years. In tracing the history of nuclear cardiology research, it attracted early the attention of some of the best minds in nuclear medicine and cardiology working closely with highly talented, skilled and academically engaged radiochemists, physicists and technologists. This successful blueprint of integrated approach of scientific discovery in order to address clinically relevant issue of the past remains true today, and should remain so in the future.

Nuclear imaging expands the traditional imaging of anatomic structures to physiologic and biochemical structures or biological processes. A key attribute of nuclear molecular imaging is that it allows clinicians to visualize cellular functions that influence progression of disease, therapeutic responsiveness, and ultimately patient outcome. Such molecular targeted imaging has the potential to direct new drug development, gene- and cell-based therapies, and determine the subset of patients who are most likely to respond to such therapies. Since the introduction of myocardial perfusion (1) and metabolic agents (2), there has been explosive growth in the literature and National Institutes of Health funding of experimental studies in cardiovascular molecular imaging. Unfortunately, such advances in basic sciences have not translated into clinically approved diagnostic or therapeutic agents. Important challenges that have limited the progression to clinical reality include cost, scalability and regulatory burden (3).

How to Increase its Relevance?

For a productive pursuit of scientific investigation, it is essential that a lead or idea is clinically relevant and that it addresses an unmet need. Next, there must be adequate methodological and imaging procedures that enable the specific biological process of interest, such as metabolic pathway, receptor biology or enzyme regulation, to be captured either visually or quantitatively. For example, the ability to image the metabolic shift of energy production from fatty acids to glucose in the setting of reduced myocardial blood flow at rest has helped explain the pathophysiology of viable, hibernating myocardium, and critical patient management decisions regarding coronary artery revascularization, left ventricular assist device placement, cardiac transplantation, or continued medical therapy (4,5).

In medicine, we must try to infer the nature of the biological system from measured dynamic function, and derive information about their causes and interrelations in order to understand normal and abnormal disease conditions. Dynamic and quantitative analysis is a key virtue of nuclear radiotracer-based imaging. It allows assessment of changes in enzymatic or receptor activity as a function of disease severity and time. Creation of time profile of the change in disease process is critical in following progression or regression of disease and the therapeutic effect of medications over a long period of time, such as days, weeks or months. The latter also

has implications for decreasing the number of animals sacrificed for the purposes of scientific investigation.

In this context, it is important to identify the best tools for investigation (radiotracers and imaging systems) which will detect and localize the most complex physiological processes. Radiotracer-based approaches of noninvasive cardiovascular imaging have the advantage of targeting small and sparse biologically relevant processes with high selectivity and sensitivity. When coupled with the favorable high resolution of CT and MRI, it allows anatomic co-localization of the underlying pathophysiological mechanisms responsible for diseases of the myocardium and vasculature (6). The development of such hybrid or multimodality imaging has facilitated validation of specific molecular signals and optimized targeted imaging.

Novel Findings and Novel Applications: A Tale of Three Radiotracers

The greatest interest in the field lies in the unique and original discoveries or in the novel applications of previously approved radiotracers. Below are representative radiotracers that fulfill the innovation criterion.

Iodine-123 meta-iodobenzylguanidine, a sympathetic neurotransmitter analogue of norepinephrine, represents one of the few molecular imaging agents that can serve as a model for enduring the scientific journey of bench-to-bedside of receiving US Food and Drug Administration (FDA) approval for imaging neuroendocrine tumors and subsequently fulfilling the criterion of novel application for cardiac neuronal imaging for risk evaluation in heart failure (7,8). Current multicenter clinical trial is investigating whether iodine-123 meta-iodobenzylguanidine may also help identify patients who are at highest risk for sudden death and in whom automatic implantable cardiac devices will have the greatest cost effectiveness and clinical impact.

Tc-99m pyrophosphate, an FDA approved bone seeking radiotracer, which has been used by nuclear cardiologists for cardiac infarction imaging now provides the opportunity to diagnose cardiac amyloidosis and to differentiate light-chain amyloidosis from transthyretin related cardiac amyloidosis (9). The diagnosis of cardiac amyloidosis is challenging as the clinical manifestations of cardiac amyloidosis overlap with other heart diseases, such as heart failure with preserved ejection fraction, and is often not recognized until late stages of the disease. The gold standard for diagnosing cardiac amyloidosis is an endomyocardial biopsy, which is invasive and carries a low but substantial risk of heart perforation. Tc-99m pyrophosphate imaging provides the opportunity for early noninvasive diagnosis of cardiac amyloidosis, differentiating light-chain amyloidosis from transthyretin related cardiac amyloidosis, monitoring disease progression, and assessing treatment response.

Another potentially unique radiotracer with novel clinical application is a methyl branched-chain fatty acid β-Methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP). Delayed recovery of regional fatty acid metabolism, as an imprint of a prior ischemic event, has been shown with

BMIPP, and termed “ischemic memory” (10,11). In an open-label phase IIA clinical trial, the utility of fatty acid metabolism with BMIPP to detect myocardial ischemic memory was shown up to 30 h following exercise-induced ischemia (10). In a subsequent phase III clinical trial, the safety and efficacy of BMIPP were evaluated in patients presenting to an emergency department with symptoms suggestive of acute coronary syndrome (12). When the BMIPP data were added to the initial clinical diagnosis alone, the sensitivity for the acute coronary syndrome diagnosis nearly doubled without sacrificing specificity. Not only the use of BMIPP imaging added incremental value toward early diagnosis of acute coronary syndrome but it substantially extended the “time window” within which noninvasive imaging may assist in the evaluation of patients with antecedent ischemia and suspected acute coronary syndrome beyond the resolution of symptoms. However, despite the salutary phase II and III clinical trial results, BMIPP is not FDA approved in the US, because the parent company who had the US patent for BMIPP was acquired by another pharmaceutical company whose focus and priority was to expand their oncology pipeline rather than cardiology. BMIPP has been commercially available and clinically used in Japan for over 20 years.

Possibilities for Future Discoveries

Nuclear cardiology research offers possibly the clearest insight into the unsolved mechanisms for disease processes, areas of controversy, and promising areas of future investigation on molecular imaging. Disagreement and controversy in the literature often gains rather than loses interest in the field. Certain areas of investigations may not necessarily be controversial but rather a blank canvas in the sense that explanations are needed through experimental and translational research.

Judging by the rich history of the field of nuclear cardiology and its present status, many future discoveries, that is even more exciting than the past ones, will emerge from the experimental and translational employment of these radiotracers. However, innovative mechanisms would need to be worked out to facilitate more cost-effective and rapid translation from experimental animals to large animals and humans, with the support of the National Institutes of Health and FDA as potential partners in this translational journey. This impasse also requires academia-industry partnerships, where the industry partner has to be confident that the investment in time and resources for the potential diagnostic imaging agent is justifiable.

Challenges and Barriers of Academic Pursuit for Early Career Physicians

Another barrier for innovative nuclear cardiology research is the limited number of training programs that have the expertise and requisite facilities to perform high-quality, molecular-based and translational imaging studies, and train the next generation of investigators. There is a need for concerted effort to promote mentoring and establish philanthropic foundations that will fund research. Although NIH has increased funding of career development grants, unfortunately, only a small number of early career physicians have benefited as funding of the entire cohort has decreased (13). Academic centers and institutions need to embrace such early career physicians

and decrease the pressure to meet clinical Relative Value Unit goals and provide credit for academic pursuits of writing grants, research and teaching.

Finally, we cannot forget that outreach and partnering with professional societies, such as the American College of Cardiology, American Heart Association, and the American Society of Nuclear Cardiology, along with education and awareness of radiotracer-based targeted molecular imaging through imaging journals (e.g. The Journal of Nuclear Medicine and Journal of Nuclear Cardiology) and annual scientific sessions are all requisites for stimulating discovery, validation and clinical relevance of nuclear cardiology research.

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