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Cardiovascular Molecular imaging: Expanding the Paradigms and Parameters

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Advances in Cardiovascular (CV) imaging in the past two decades have significantly contributed to the improvement in CV care and the reduction in CV mortality in recent years. The main focus of CV imaging has been and remains the detection and quantification of cardiac anatomy and physiology (e.g., ejection fraction and valvular function), myocardial blood flow and ischemia, and vascular size and structure (e.g., aortic aneurysm diameter). While a few other indications for imaging do exist, these areas continue to constitute the great majority of imaging studies performed.

The emphasis on cost-containment and focus on outcome have put tremendous pressure on the imaging community to avoid inappropriate studies, and to demonstrate incremental value on patient management and outcome. In parallel, advances in cardiovascular pathophysiology and medicine mandate continuous adaptation and modernization of imaging concepts. In the field of nuclear cardiology, two concurrent processes impede the growth of nuclear cardiology: 1) emergence of competing tests at lower or comparable cost without radiation exposure, and 2) evolving clinical data that may restrict appropriate indications. As such, stress echo is now equally indicated or is the first recommended test in a subset of (lower risk) patients. MRI, while costly, can provide complementary information on cardiac function and structure. The quantitative nature of nuclear imaging and the large number of studies that support its effectiveness for diagnostic and prognostic purposes in cardiology are unmatched. However, technical and technological advances and emerging clinical trials based on other modalities are rapidly filling this gap. A reduction in myocardial perfusion imaging (MPI) studies is foreseeable if an ongoing trial could demonstrate that in patients with stable CAD (and no left main or proximal left anterior descending artery stenosis), medical therapy is as effective as an initial invasive strategy independent of MPI results (ref: <https://clinicaltrials.gov/ct2/show/NCT01471522>, accessed 02/19/15).

The improvement in CV care in developing countries has led to a surge in nuclear cardiology utilization globally. This expansion is welcome, but not sustainable. Current trends indicate that the future for cardiovascular imaging lies in multimodality imaging practiced by imaging consultants with expertise in and access to multiple technologies for addressing specific clinical questions. The shift from office-based to hospital-based imaging services facilitates the implementation of this model. Meanwhile, incremental advances in nuclear cardiology are getting smaller and one may argue that LV function and perfusion have reached their limits. Ultimately, like any other field, nuclear cardiology needs to adapt to the changing landscape and evolve with science, and new diagnostic parameters and paradigms are needed for the field to remain relevant.

For our field to thrive, we need to identify existing and emerging diagnostic gaps as CV biology and medicine evolve, and to focus on those gaps that may be best addressed by nuclear imaging. Examples of such diagnostic gaps include the characterization of vessel wall biology in atherosclerosis and substrates for arrhythmia. Other potentially high impact areas of expansion are better risk stratification of aortic aneurysm and identification of patients with moderate valvular disease who are at high risk for disease progression and who might benefit from medical therapy. The ability to assess the need for intervention and to track the effect of therapeutic interventions on ventricular remodeling process may significantly improve patient care. Reliable techniques for detection of implanted device thrombosis and infection are needed. Moreover, with the recent growth of cardio-oncology, better parameters are necessary for early detection of chemotherapy-induced CV damage. Lastly, combining (nuclear) imaging and therapeutics (theranostics) can be transformative.

Molecular imaging extends detection (and quantification) capabilities beyond anatomy and physiology to biology. Given the intrinsic strengths of nuclear imaging in terms of sensitivity and quantifiability, nuclear imaging (in combination with high resolution structural imaging) is particularly suitable for CV molecular imaging. Over the past two decades, the feasibility of CV molecular imaging in the preclinical and some clinical settings has been established and the field is now on the verge of more widespread clinical implementation. However, this preclinical to clinical transition may not be going as fast and smooth as expected. Some of the barriers to clinical translation include economics, research funding, and, more importantly, the paradigm shift that is coupled to the implementation of molecular imaging concepts in the clinic. Given the huge costs of tracer development, the introduction of any novel tracer can only be supported by a potentially large market. This would indicate that the focus should be on developing tracers that target common biological processes, such as inflammation and remodeling, or testing existing tracers for new applications. These challenges have led the industry to limit its involvement in probe development. To address this barrier, federal funding is needed to advance this transformative field. The current structure of NIH grant review process focuses on novelty, which places translational research aimed at late stage preclinical validation and first-stage human studies at a relative disadvantage. One way to address this is to set up new study sections and dedicated funding focused on clinical translation of molecular imaging.

A major challenge to clinical implementation of CV molecular imaging may lie in the inherent transformative nature of the field. While the implementation of molecular imaging

in oncology may be achievable within the current cancer management paradigms, in CV medicine this would require a paradigm shift in patient management. In the case of atherosclerotic diseases, for instance, this would mean a shift of focus from the degree of stenosis to vessel wall characterization. This paradigm shift can only be implemented if emerging diagnostic capabilities are coupled with specific treatments. To complicate matters, the development and validation of such novel therapies (and potentially the demonstration of their effect on a surrogate) would most likely depend on CV molecular imaging.

These problems can be addressed by concerted effort of all stakeholders, including the professional societies, industry, and funding and regulatory agencies. To this end, the American Society of Nuclear Cardiology and the Society of Nuclear Medicine and Molecular Imaging have spearheaded a multi-societal think tank on CV molecular imaging. The goals of this effort are to define major diagnostic gaps in CV medicine, and devise strategies to bridge this translational divide. The *Society* and the *Journal* play an important role in leading such efforts. For our field to thrive and contribute to advancement of cardiovascular medicine, a continuing effort is necessary to re-evaluate the state-of-the-art as well as to expand to new territories and applications.

Ref

1. [accessed 02/19/15] <https://clinicaltrials.gov/ct2/show/NCT01471522>