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Issue "noninvasive molecular imaging and theranostic probes": New concepts in myocardial imaging

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ABSTRACT

Cardiovascular applications continue to be a driving force for new developments in radionuclide imaging. Recent years have seen an evolution of myocardial perfusion imaging systems towards optimized radiation detection sensitivity, leading to fast and low dose studies with high image quality. Additional advances in hard- and software facilitated the integration of computed tomography and nuclear imaging, and enabled absolute quantification of myocardial blood flow. Finally, non-perfusion tracers and clinical indications outside of coronary artery disease (e.g. in endocarditis, infiltrative cardiomyopathies or regenerative medicine) have resulted in a growth of molecular-targeted myocardial imaging, aiming at improved guidance of increasingly specific therapies – in a manner similar to current oncologic applications of nuclear imaging.

Contents

1. Introduction

Ever since their introduction in the early seventies [1,2], cardiac radionuclide imaging techniques have been a centerpiece of clinical nuclear medicine and a strong contributor to advances in the field. Despite the broadening spectrum of available noninvasive diagnostic techniques, both in the field of cardiovascular medicine as well as in the field of imaging in general, this continues to be the case today [3,4]. Radionuclide imaging of the myocardium has seen recent developments in imaging technology, tracers and clinical application, which are driven by three major trends in clinical cardiology:

First, pressure resulting from the increasing success of alternative techniques for the detection of myocardial ischemia, such as echocardiography, cardiac computed tomography or cardiac magnetic resonance imaging, has triggered an evolution of camera systems for radionuclide-based perfusion imaging – with the goal of maximizing sensitivity for reduction of dose and acquisition time [5]. Second, the increasing availability and utilization of implantable devices such as cardioverter-defibrillators (ICDs), valvular prostheses, or left-ventricular assist devices (LVAD) has emphasized the need for diagnostic tools to identify appropriate candidates for such expensive therapies and to manage complications such as infection [6]. And third, there is an increasing awareness towards non-ischemic heart disease and molecular mechanisms contributing to organ failure, which translates into increasing efforts to develop molecular-targeted therapies and thus, also translates into an increasing demand of molecular-targeted diagnostic testing [7,8].

Accordingly, new methods in myocardial imaging using nuclear medicine techniques include new imaging technology, new clinical applications and new radiopharmaceutical imaging agents (Table 1), which are reviewed in more detail in the following.

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Table 1
New Trends in Nuclear Cardiology.

Trend	Facilitated by	Result
Imaging Technology:		
PET perfusion imaging	Success in oncology; availability of rubidium generators	Increased accuracy, faster and lower dose protocols, absolute flow quantification
Hybrid PET/CT and SPECT/CT	Advances in camera manufacturing	Robust attenuation correction, integration of morphology and function, stepwise diagnostic algorithms
Hybrid PET/MR	Magnetic field resistant PET detectors	Multimodal molecular tissue characterization
Solid-state detector SPECT	CZT technology	Fast and low dose SPECT, absolute floow quantification, simultaneous multi-isotope imaging
Clinical Applications:		
ICD implantation	Sympathetic innervation imaging	Prediction of outcome, improved selection of candidates
CRT	Dyssynchrony assessment software	Improved selection of candidates, monitoring of success
Device infection	FDG PET/CT, leukocyte SPECT/CT	Accurate diagnosis in cases with equivocal clinics/conventional imaging
Infiltrative cardiomyopathies	New, specific molecular imaging agents	Early detection of cardiac involvement in systemic sarcoidosis and amyloidosis
Plaque vulnerability	Improved resolution, new radiotracers	Guidance of therapy, drug development
Myocardial regeneration	New radiotracers, trends in molecular cardiology	Guidance of therapy, drug development
Imaging Agents:		
F-18 perfusion tracers	Advances in radiopharma-ceutical chemistry	Broader availability, improved accuracy
PET innervation tracers	Advances in radiopharma-ceutical chemistry	Improved accuracy, quantitative assessment
Various molecular imaging agents	Advances in radiopharma-ceutical chemistry, overlap with oncology/neurology	Personalized guidance of molecular therapy

2. New imaging technology

The current spectrum of camera systems used for nuclear cardiology is characterized by 3 major trends:

First, there is an increasing implementation of positron emission tomography (PET). This is supported by the increasing availability of PET, owing to its success as a diagnostic tool in clinical oncology [9]. It is also supported by the robust and accurate nature of PET imaging, and by the increasing availability of positron-emitting perfusion tracers which generally have superior extraction fraction and flow characteristics when compared to perfusion agents used for standard single photon emission computed tomography (SPECT) [10]. Strontium/rubidium generators are commercially available and yield Rb-82 as a very short-lived perfusion tracer at sites without access to an on-site cyclotron (which is needed for production of the alternative short-lived perfusion agents N-13 ammonia and O-15 water). New F-18 labelled perfusion agents are on the horizon and those may lead to further penetration of PET-based perfusion imaging [11].

Second, the advent of hybrid imaging devices has changed the field of nuclear cardiology [12]. Today, PET cameras are often integrated with multi-slice computed tomography (CT) systems, enabling hybrid cardiac PET/CT. The CT is a necessary ingredient for attenuation correction and quantification of PET studies [13]. It may, however, also be used diagnostically to determine coronary calcium or to perform contract-enhanced coronary CT angiography. This has resulted in stepwise algorithms for a comprehensive workup of the morphologic and functional aspects of coronary artery disease [14], and it has led to the introduction of dedicated software for integrated analysis of vascular integrity and tissue perfusion in the precise territory of the respective diseased vessel [15] (Fig. 1). Such multi-modality information has been shown to influence and refine targeted interventional therapy. More recently, PET has also been integrated with magnetic resonance (MR) scanners [16]. The resulting PET-MR systems may offer even broader options for non-invasive characterization of myocardial tissue, by e.g. combining molecular-targeted PET tracers with MR-based measures of tissue integrity and function. But their clinical usefulness remains to be established in larger trials. Finally, SPECT as the widely used conventional technology for radionuclide-based myocardial perfusion imaging has also benefited from the introduction of hybrid SPECT-CT devices. CT-based attenuation correction improves the diagnostic accuracy of SPECT [17], and coronary calcium scores are often routinely obtained in SPECT-CT sessions for improved risk-stratification of patients with coronary artery disease [18].

Third, new solid-state detector technology has resulted in a revolution of cardiac SPECT imaging [19]. Cadmium-Zinc-Telluride (CZT) crystals are semiconductors, which enable the construction of small photon-detecting units. Unlike in standard cameras, which use light-emitting scintillating crystals, no large photomultipliers are needed because the semiconductors translate the energy of incoming photons directly into electric charge. Accordingly, CZT detectors can be packed together more tightly and enable smaller camera designs [20,21]. For dedicated cardiac imaging, new CZT cameras include the semiconductor detectors in a semi-circular design, which focuses on the heart and acquires all projections for tomographic image reconstruction simultaneously. This is in contrast to standard scintillator-crystal equipped SPECT cameras, which need to rotate around the patient. Accordingly, the sensitivity of CZT systems is 4- to 10-fold higher than for regular SPECT [22]. Because CZT detectors can also be positioned closer to the cardiac region of interest, an additional increase of spatial resolution is achieved. Accordingly, high quality images are obtained with shorter acquisition times and/or lower injected dose [23]. Several multi-center studies support the usefulness and the diagnostic as well as prognostic value of CZT-based myocardial perfusion SPECT. While early work with those novel systems focused on the reduction of imaging time (from 15 to 30 min for standard SPECT down to 2–3 min for CZT SPECT using a standard amount of injected radioactivity) [24,25], subsequent work focused on reducing the injected radioactivity to reduce patient dose. A recent multi-center trial has e.g. suggested that CZT imaging may be completed with a very low effective dose of one millisievert (mSv), at an image quality that is still superior to standard SPECT imaging [26]. But CZT SPECT does not only make standard myocardial perfusion SPECT faster and less radiation-exposing. The high energy resolution of semiconductor crystals also facilitates the simultaneous acquisition of multiple radioisotopes and thus multiple tracers at the same time [20]. This can be used to design unique multi-tracer protocols that cannot be achieved with any other radionuclide imaging system. First attempts have e.g. been made