

Invited Perspective

Ready for prime time? Dual tracer PET and SPECT imaging

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Abstract: Dual isotope single photon emission computed tomography (SPECT) and dual tracer positron emission tomography (PET) imaging have great potential in clinical and molecular applications in the pediatric as well as the adult populations in many areas of brain, cardiac, and oncologic imaging as it allows the exploration of different physiological and molecular functions (e.g., perfusion, neurotransmission, metabolism, apoptosis, angiogenesis) under the same physiological and physical conditions. This is crucial when the physiological functions studied depend on each other (e.g., perfusion and metabolism) hence requiring simultaneous assessment under identical conditions, and can reduce greatly the quantitation errors associated with physical factors that can change between acquisitions (e.g., human subject or animal motion, change in the attenuation map as a function of time) as is detailed in this editorial. The clinical potential of simultaneous dual isotope SPECT, dual tracer PET and dual SPECT/PET imaging are explored and summarized. In this issue of AJNMMI (<http://www.ajnmml.us>), Chapman et al. explore the feasibility of simultaneous and sequential SPECT/PET imaging and conclude that down-scatter and crosstalk from 511 keV photons preclude obtaining useful SPECT information in the presence of PET radio-tracers. They report on an alternative strategy that consists of performing sequential SPECT and PET studies in hybrid microPET/SPECT/CT scanners, now widely available for molecular imaging. They validate their approach in a phantom consisting of a 96-well plate with variable ^{99m}Tc and ¹⁸F concentrations and illustrate the utility of such approaches in two sequential SPECT-PET/CT studies that include ^{99m}Tc-MAA/¹⁸F-NaF and ^{99m}Tc-Pentetate/¹⁸F-NaF. These approaches will need to be proven reproducible, accurate and robust to variations in the experimental conditions before they can be accepted by the molecular imaging community and be implemented in routine molecular microPET and microSPECT explorations. Although currently not accepted as standard procedures in the molecular imaging community, such approaches have the potential to open the way to new SPECT/PET explorations that allow studying molecular mechanisms and pathways in the living animal under similar physiological conditions. Although still premature for the clinical setting, these approaches can be extended to clinical research once proven accurate and precise *in vivo* in small and large animal models.

Keywords: Dualisotope, dual tracer, positron emission tomography (PET), single photon emission tomography (SPECT), quantitative imaging

Dual tracer imaging has potential clinical and molecular applications in many areas of brain, cardiac, and oncologic imaging as it allows the exploration of different physiological and molecular functions (e.g., perfusion, neurotransmission, metabolism, apoptosis, angiogenesis) under the same physiological and physical conditions. This is crucial when the physiological functions studied depend on each other (e.g., perfusion and metabolism) hence requiring simultaneous assessment under identical conditions, and can reduce greatly the quantitation errors associated with physical

factors that can change between acquisitions (e.g., human subject or animal motion, change in the attenuation map as a function of time).

In SPECT, energy-based discrimination takes advantage of the differences in gamma photon emission energies associated with different radionuclides to identify the underlying radio-tracer distributions. Identification of simultaneously present activity distributions is feasible and can yield quantitative simultaneous dual isotope imaging when cross-talk and down scatter are corrected accurately, in addition to

other physical factors affecting single isotope SPECT imaging [1, 2]. Furthermore, accuracy of discrimination of the two (or several) radioisotopes can be improved by performing spectro-temporal discrimination to take advantage of both the radionuclide emission energy information as well as the differences in dynamic behavior (time activity curves and underlying kinetic models) of each radiotracer [3]. For example, the simultaneous assessment of pre-synaptic dopamine transporter (e.g., ^{123}I -b-CIT [4]), and/or postsynaptic phases of dopaminergic neurotransmission (e.g., IBZM [5]) as well as brain perfusion (e.g., $^{99\text{m}}\text{Tc}$ -HMPAO or $^{99\text{m}}\text{Tc}$ -ECD) can be achieved with SPECT tracers and has great potential clinical utility in various movement disorders including Parkinson's disease, Huntington's disease, progressive supranuclear palsy, multiple system atrophy and Wilson disease (for a review see [6]). We have previously demonstrated the feasibility in the clinical setting of dual isotope SPECT for differential diagnosis of idiopathic Parkinson disease (IPD) and multiple system atrophy (MSA) using simultaneous $^{99\text{m}}\text{Tc}$ -ECD/ ^{123}I -FP-CIT SPECT imaging [7].

Unlike dual-tracer SPECT which relies on a physical spectral property, independent of the state of the subject, simultaneous dual-tracer PET can not use photon energy information to differentiate between radiotracers because all photons resulting from a positron-electron annihilation have an energy of 511 keV. Therefore, simultaneous dual-tracer PET must rely on differences in the kinetics and/or spatial distributions of the tracers, which are physiological or biochemical properties of the system. One previously reported technique consists of determining kinetic parameters from two ^{11}C tracers acquired semi-simultaneously by fitting the total concentration curve measured by PET to the sum of two kinetic models [8]. This approach is promising, but does not address simultaneous co-injection of the two tracers. One way around this limitation is to include a delay between the two injections. Using a 100 min delay with dual ^{18}F -fallypride and ^{18}F -fluoromethane yielded accurate estimates of both binding potential and rCBF in primates [9]. Similar work based on simulated data yielded accurate estimates of hypoxia, perfusion and metabolism using ^{62}Cu -ATSM, ^{62}Cu -PTSM and ^{18}F -FDG [10]. Another work has

successfully reported on quantitative assessment of rest and stress myocardial blood flow with ^{13}N ammonia [11].

In SPECT/PET, there are several clinical applications that would greatly benefit from simultaneous assessment of SPECT and PET radiotracers. To cite a few, the capacity to perform ^{123}I -MIBG and ^{18}NaF would have immediate benefits in pediatric neuroblastoma imaging and would allow to avoid one additional sedation to children while ensuring that the ^{123}I -MIBG and ^{18}NaF distributions are temporally registered and directly comparable. Another example of great potential utility in the pediatric population, although of significant logistical challenge, is ictal $^{99\text{m}}\text{Tc}$ -ECD or HMPAO brain perfusion SPECT followed by inter-ictal ^{18}F -FDG PET. In the adult population, performing rest-stress $^{99\text{m}}\text{Tc}$ -sestamibi cardiac SPECT followed by ^{18}F -FDG viability PET would assess myocardial blood flow at rest and stress to determine areas of ischemic mismatch between rest and stress, whether myocardial tissue is viable and the patient a good candidate for coronary artery bypass graft or percutaneous transluminal coronary angioplasty.

In this issue of the American Journal of Nuclear Medicine and Molecular Imaging (<http://www.ajnmj.us>), Chapman et al. explored the feasibility of simultaneous and sequential SPECT/PET imaging and concluded that down-scatter and crosstalk from 511 keV photons preclude obtaining useful SPECT information in the presence of PET radiotracers [12]. This conclusion is to be expected given the cross-sections for photon interactions in the 50-1000 keV range and holds for any detector resolution given that many scattered 511 keV photons can be detected in any narrow window around the lower energy SPECT radionuclide photopeak. Since simultaneous SPECT/PET imaging becomes unachievable, the investigators explore, evaluate and report on an alternative strategy that consists of performing sequential SPECT and PET studies where the SPECT radiotracer is injected and imaged first, and then the PET radiotracer is injected and imaged in the presence of the SPECT tracer. This approach is logical and straightforward given that the energies of most SPECT radiotracers are well below 511 keV. Even in the event of a SPECT radionuclide with emission energies approaching 511 keV (e.g., ^{131}I , ^{123}I), the coincidence rates asso-

ciated with random coincidences of two such events emitted simultaneously is negligible.

With the advent of hybrid microPET/SPECT/CT scanners and their increasing availability in molecular imaging centers, the proposed approach becomes an attractive way to allow imaging two functions, one with SPECT and one with PET. The authors validate their approach in a phantom consisting of a 96-well plate with variable ^{99m}Tc and ^{18}F concentrations with increasing concentrations of ^{99m}Tc and decreasing concentrations of ^{18}F and report accurate measurement of ^{18}F concentrations in the presence of ^{99m}Tc . The utility of this approach is illustrated in two sequential SPECT-PET/CT studies that include ^{99m}Tc -MAA/ ^{18}F -NaF and ^{99m}Tc -Penteta-te/ ^{18}F -NaF. Unfortunately, the *in vivo* animal studies are qualitative and it would have been very interesting to confirm that constant rates measured using full kinetic models of the dynamic PET data are not significantly different in the presence and absence of ^{99m}Tc -MAA and ^{99m}Tc -Pentetate. This is a key validation that will be needed for these approaches to be proven reproducible, accurate and robust to variations in the experimental conditions before they can be accepted by the molecular imaging community and be implemented in routine molecular microPET and microSPECT explorations. Despite the lack of widespread acceptance of dual tracer approaches in the molecular imaging community, such approaches have the potential to open the way to new SPECT/PET explorations that allow studying molecular mechanisms and pathways in the living animal under similar physiological conditions. Such studies are currently performed sequentially, therefore another potential advantage is reduction of imaging time. Although still premature for the clinical setting, these approaches can be extended to the clinical research setting once proven robust, accurate and reproducible *in vivo* in small and large animal models.

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