Selection of abstracts from the scientific sessions of The Society Of Nuclear Medicine and Molecular Imaging annual meeting Anaheim CA

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This mini-review highlights cardiovascular studies that were presented during the Society of Nuclear Medicine and Molecular Imaging (SNMMI) 2019 annual meeting in Anaheim, California. The aim is to provide the readers insight to noteworthy studies related to the fields of nuclear cardiology presented during the conference. Although cardiovascular applications of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are not the primary focus of the SNMMI, several scientific teams working in this field presented their latest findings in Anaheim. While this review is directed to the benefit of those who were not able to attend the annual meeting, we believe that a general overview may also be useful for those who did attend as it is often difficult to get exposure to all the high-quality abstracts presented at this large conference.

Key Words: Preclinical imaging • image reconstruction • PET • SPECT • MPI

Abbreviations

SPECT	Single Photon Emission Computed Tomography
PET	Positron Emission Tomography
CT	Computed Tomography
PIB	Pittsburgh Compound B
18F-TTP	18F-triphenylphosphonium
MRI	Magnetic Resonance Imaging
TBR	Target to Background Ratio
MPI	Myocardial Perfusion Imaging

INTRODUCTION

The journal has previously published selected abstracts from the American College of Cardiology, American Heart Association, and European Society of Cardiology Scientific Sessions as a service to our readers who could not attend these meetings.[1–3] Here we present noteworthy abstracts on nuclear cardiac imaging that were presented at the SNMMI 2019 annual meeting.

At SNMMI 2019, held in Anaheim, a grand total of 747 oral abstracts and 1189 posters were presented. Of

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these, 101 abstracts (64 oral contributions and 37 posters) were presented in the Cardiovascular track. Several contributions of great interest to the nuclear cardiology community have also been presented in the instrumentation and data analysis track. Below we provide an overview of selected studies, which in our view, are arguably the most significant. The abstracts presented focused on newly developed tracers, technical refinement of recently introduced approaches, and preclinical models.

NEW CARDIOVASCULAR TRACERS

Among the newly developed tracers presented at the meeting, we witnessed further encouraging data supporting the feasibility of utilizing ^{68}Ga-pentixafor for imaging coronary artery disease and three novel developments: ^{18}F-triphenylphosphonium (^{18}F-TPP+) for in vivo assessment of cardiac mitochondrial potential, ^{11}C-Pittsburgh compound B (PIB) for diagnosing cardiac amyloidosis, and ^{18}F-Flurobenguan for imaging cardiac innervation. Additionally, further data demonstrating the clinical applications of ^{18}F-Flurpiridaz were also presented at the annual meeting.

The CXC-motif chemokine receptor 4 (CXCR4) and its ligand, CXCL12, play an important role in trafficking of progenitor and inflammatory cells.[4] ^{68}Ga-pentixafor is the first PET agent that exhibits high affinity and selectivity for CXCR4.[5] Previously, Hyafil et al [6] showed that this tracer allows for the non-invasive detection of CXCR4 expression in the vessel wall with PET and concluded that it emerges as a potential alternative to ^{18}F- fluorodeoxyglucose (FDG) for the assessment of macrophage infiltration in atherosclerotic plaques.

During the meeting, Kircher et al presented further data supporting the use of ^{68}Ga-Pentixafor for atherosclerotic plaque imaging (J Nucl Med 2019;60:668). The authors aimed to investigate the performance of ^{68}Ga-Pentixafor PET/computed tomography (CT) for imaging atherosclerosis in comparison to ^{18}F-FDG PET/CT. The study cohort comprised 92 patients (37 females and 55 males; mean age 62 ± 10 years) who underwent ^{68}Ga-pentixafor and ^{18}F-FDG PET/CT examinations for staging of oncologic diseases. In a total of 652 corresponding atherosclerotic lesions, respective tracer uptakes were measured and arterial target to background ratios (TBRs) calculated. Uptake values were then correlated and compared to the degree of arterial calcification, as quantified on CT. Kircher et al showed that the TBR of both PET tracers showed a moderate positive correlation ($r = 0.28$; $P < 0.01$), but ^{68}Ga-Pentixafor demonstrated a significantly higher TBR than ^{18}F-FDG (1.8 ± 0.5 vs. 1.4 ± 0.4; $P <$ 0.01). The authors concluded that non-invasive PET/CT imaging of atherosclerotic plaques using ^{68}Ga-Pentixafor is associated with a better target to background contrast than ^{18}F-FDG. Given that ^{68}Ga-Pentixafor uptake is lowest in severely calcified plaques that are considered less susceptible to rupture, CXCR4-directed PET/CT might prove a useful tool for identification and monitoring of high-risk patients.

Myocardial mitochondrial dysfunction plays a key role in many pathologic processes such as cellular apoptosis, heart failure, and ventricular arrhythmia. Under normal conditions, mitochondrial membrane potential ($\Delta\Psi m$) is maintained within narrow limits. During the Cardiovascular Young Investigator Award Symposium, Matthieu Pelletier-Galarneau et al. (J Nucl Med 2019;60:99) reported the first assessment of $\Delta\Psi m$ in patients. This group has previously validated a method for the ''in vivo'' assessment of cardiac $\Delta\Psi m$ in a porcine model using a fluorine-18-labeled compound ^{18}F-triphenylphosphonium (^{18}F-TPP+).[7] In the study, seven healthy subjects were imaged using ^{18}F-TPP+ on a Siemens Biograph PET/MR scanner. Patients were administered with a bolus injection of 300 MBq followed by a 120-min infusion of 0.6 MBq/min. A 60-min dynamic PET acquisition was started 1 hour after the bolus injection. The $\Delta\Psi T$ was calculated from the fraction of the extracellular space (which was simultaneously measured using MR T1-mapping images acquired at baseline and 15 minutes after gadolinium injection with correction for the subject's hematocrit level) and the myocardial and plasma tracer concentration at secular equilibrium. The authors were able to calculate the mitochondrial membrane potential in all patients whom achieved a tracer concentration equilibrium. With an average $\Delta\Psi m$ of – 157 ± 4 mV (absolute range of values: − 151 to − 163 mV), Pelletier-Galarneau et al. demonstrated the feasibility of non-invasive, in vivo, quantitative assessment of cardiac $\Delta\Psi T$ in humans. In their study, the quantitative values of $\Delta\Psi T$ were in good agreement with bench top measurements in isolated mitochondria, cells, and Langendorff-perfused rat hearts.[7] If successfully implemented in the clinical setting, in vivo quantification of the mitochondrial function could provide new diagnostic and prognostic information for several cardiac diseases as well as allow for therapy monitoring. Further investigations exploring the potential of the mitochondrial membrane potential will undoubtedly be of great interest to the nuclear imaging community.

Xiao Bi et al (J Nucl Med 2019;60:103) investigated the potential of ^{11}C-PIB for cardiac amyloidosis PET/MR imaging. This novel tracer has been successfully used for Alzheimer's disease imaging as it binds to the β-amyloid protein deposit in the central nervous

system. Additionally, it was also shown that in patients with serum monoclonal gammopathy, ^{11}C-PIB helps to differentiate subjects who underwent chemotherapy from those with untreated cardiac amyloidosis.[8] To explore the potential of this new tracer in diagnosing cardiac amyloidosis among heart failure patients, the authors performed cardiac ^{11}C-PIB PET/MR and non-cardiac biopsies. The MRI protocol included cine, late gadolinium enhancement (LGE), and native T1 mapping sequences. The PET scan was performed 40 minutes after ^{11}C-PIB administration in a single bed position for 20 minutes. Cardiac volumetric assessment along with native T1 values and maximum myocardial target to background ratios (TBRmax) were measured. On a cohort of 12 patients, the authors showed that all the cardiac amyloidosis positive subjects had diffused transmural LGE pattern and that the diagnostic sensitivity and specificity of TBRmax were 75% and 100%, respectively. Importantly, there was a significant difference between the cardiac amyloidosis patients and normal controls in terms of both the MRI-derived volumetric parameters: left ventricular (LV) ejection fraction (44.43 ± 12.69 vs 65.15 ± 1.86, P = 0.005), interventricular septum thickness at end-diastole (13.38 ± 3.21 vs 8.32 ± 0.53, P = 0.001), LV posterior wall thickness (11.41 ± 3.12 vs 7.62 ± 0.81, P = 0.043), Native T1 value (1550.5 ± 31.29 vs 1233.51 ± 46.73, P = 0.001), and TBRmax (2.44 ± 1.90 vs 0.85 ± 0.06, P = 0.001). The study suggests that ^{11}C-PIB PET/MR may be valuable in the non-invasive diagnosis of cardiac amyloidosis in heart failure patients. Importantly, it appears that by utilizing PET/MR establishing a final differential diagnosis (rather than just ruling in or out cardiac amyloidosis) at a single imaging session would be feasible.[9,10]

Another intriguing study presented at the annual meeting related to cardiac innervation imaging with ^{18}F-Flurobenguan (J Nucl Med 2019;60:32) by Zelt et al. To date, it was shown that cardiac autonomic innervation is integral to the regulation of perfusion, heart rate, and contractile function.[11,12] Importantly, abnormal cardiac innervation has been documented and may contribute to the pathogenesis of various heart diseases including heart failure, myocardial ischemia, infarction, and arrhythmias. Zelt et al. validated a new PET tracer ^{18}F-Flurobenguan as a marker of presynaptic neuronal function in humans with and without the concomitant heart disease, by comparing myocardial ^{18}F-Flurobenguan PET imaging versus ^{11}C-hydroxyephedrine PET imaging. While the latter tracer is the most commonly used PET tracer in humans, its widespread clinical utility is limited because of the short half-life of ^{11}C. In the study, sixteen participants underwent two separate PET imaging visits within one week. The group from Ottawa showed that the retention index of flurobenguan and hydroxyephedrine are strongly correlated (r = 0.87; $P < 0.0001$) and that there are no regional differences in the retention index between the two PET tracers in patients with or without ischemic cardiomyopathy. The study suggests ^{18}F-Flurobenguan can serve as an alternative for ^{11}C-hydroxyephedrine facilitating a more dissemination of cardiac innervation PET imaging.

PRECLINICAL IMAGING

In the past decade, cardio-oncology has emerged as an important area of research and clinical practice. With anthracyclines, such as doxorubicin remaining as a highly utilized class of chemotherapeutic agents, more and more cancer patients are exposed to cumulative dose-dependent cardiotoxic effects of chemotherapy.[13,14] Advanced cardiac imaging approaches such as cardiovascular magnetic resonance imaging and dynamic SPECT imaging with ^{123}I-MIBG can elucidate doxorubicin-induced cardiotoxicity.[15,16]

In a canine model of cardiotoxicity, Luyao Shi et al. (J Nucl Med 2019 60:237) have non-invasively investigated the intramyocardial blood volume using ^{99m}Tc-red blood cells (RBC) and SPECT. To provide accurate quantification of microvasculature, the group employed respiratory and cardiac motion correction. In the study, seven dogs were treated weekly with doxorubicin (1 mg/kg) for 12 to 14 weeks. Four serial SPECT ^{99m}Tc-RBC scans, attenuation CT scans and contrast-enhanced CT scans were performed on anesthetized animals under rest conditions using a GE Discovery 570c SPECT/CT at baseline and at cumulative doxorubicin doses of 3 to 5, 7 to 9, and 12 to 14 mg/kg. The SPECT list-mode data were rebinned into 5 respiratory and 8 cardiac gates using an offline rebinning algorithm. Cardiorespiratory motion correction was performed by summing the end-expiration respiratory gates for each cardiac phase. The study focused on the end-diastolic and end-systolic cardiac phases. SPECT images were reconstructed using the maximum likelihood expected-maximization algorithm with attenuation and scatter corrections. A body-contour was delineated from the CT attenuation map and used as an image-prior to constrain image reconstruction. The authors found that both the end-diastolic and end-systolic intramyocardial blood volume decreased in a step-wise fashion with increasing cumulative doses of doxorubicin. While the LV ejection fraction also decreased under exposure to chemotherapy, the fall in systolic function became significant only with prolonged anthracycline exposure suggesting that microvascular disease precedes LV decompensation. The authors concluded that serial SPECT/CT imaging with ^{99m}Tc-RBC can detect step-wise decrements in the

intramyocardial blood volume. Additionally, they acknowledged that to fully characterize the potential of this method it should be applied to other cardiovascular diseases—and particularly to models with exposure to chemotherapy agents that primarily influence the microvasculature, such as trastuzumab.

IMAGING PROTOCOLS

For cardiac ^{18}F-FDG PET imaging, suppression of myocardial tracer uptake is essential. In everyday clinical practice, this can be achieved by a low-carbohydrate diet, yet successful suppression is highly dependent on patient compliance.[17] In order to improve the image quality, a single-dose heparin administration before ^{18}F-FDG PET can be considered, aside from reduction in the patient's carbohydrate intake.[18] Masao Miyagawa et al. (J Nucl Med. 2019;60:380) evaluated the effects of prolonged fasting prior to PET imaging with and without an additional unfractionated heparin injection. In a cohort of 30 healthy controls, the authors showed that all participants tolerated well the 18-hour-long carbohydrate fasting diet and that the additional pre-imaging heparin injection was not beneficial. When the prolonged-fasting diet, no-heparin protocol was applied in the clinical setting for diagnosing cardiac sarcoidosis, it had a sensitivity of 90% (18/20) and a specificity of 95.7% (44/46) for detecting active disease. Two patients with false-negative findings were under immunosuppressive therapies for proven cardiac sarcoidosis. False-positive findings were reported in diabetic patients with glycohemoglobin $>$ 7.0. The authors concluded that complete suppression of physiological ^{18}F-FDG uptake in the myocardium can be achieved by 18 hours of low-carbohydrate diet. Under such circumstances, heparin administration does not bring added value to the suppression. In the clinical setting, special attention needs to be paid to severe diabetic patients on insulin therapy with glycohemoglobin values exceeding 7.0. The study supports the findings of previously published original article in the *Journal of Nuclear Cardiology,*[19] providing further evidence that a prolonged diet protocol is feasible and has a favorable diagnostic accuracy.

One of the challenges associated with SPECT myocardial perfusion imaging (MPI) is the imaging artifacts.[20] In particular, sometimes observed abnormality is a curvilinear activity in the stomach wall. This activity is mostly inferior or inferolateral to the heart and can be responsible for false-positive or false-negative artifacts in the inferior wall of the left ventricle after image reconstruction. At the clinical poster session, Ashwani Sood et al (J Nucl Med 2019 60:1423) presented an informative study on the association of gastric wall tracer uptake with proton pump inhibitors and H2 receptor antagonists use in patients undergoing ^{99m}Tc-sestamibi MPI SPECT. In a cohort of 156 patients, the authors showed that the use of proton pump inhibitors and not H2 receptor antagonists is associated with a higher incidence of clinically relevant gastric wall tracer uptake, which leads to imaging artifacts. They also demonstrated that activity in the stomach is associated with pharmacologic stress and not with exercise stress. The authors concluded that it is imperative that patients scheduled for pharmacologic vasodilator stress should be advised to discontinue proton pump inhibitors for at least one week prior to imaging or alternatively replace them with H2 antagonists. Such an approach can significantly reduce the incidence of gastric wall uptake and improve the detection of perfusion defects on MPI SPECT.

IMAGE QUANTIFICATION

Several studies reported improvements in cardiovascular quantification techniques. In a study by Lassen et al (J Nucl Med 2019 60:451), the authors investigated the feasibility of correcting for the variations in the injection-to-scan delays and its relative impact on the test-retest reproducibility of TBR values for ^{18}F-NaF coronary PET imaging protocols. In a prior study, the group demonstrated that while lesion uptake remains stable, the blood pool activity, which is used to calculate the TBR, continually decreases over time.[21] In order to account for these differences, Lassen et al normalized the tracer administration to image acquisition intervals to 60 minutes post injection according to an equation which was derived from their work: SUV (background corrected) = SUV(Background) $\times$ $e^{-0.004*(60-t)}$, where t represents the injection-to-scan delay in minutes. By applying this simple formula in a test-retest setup, the reproducibility of TBR values improved by 19.7% (Coefficient of reproducibility: Non-corrected = 0.437, corrected= 0.365, $P < 0.001$). Importantly, in a subanalysis of lesions which presented with uptake exceeding the widely utilized 1.25 TBR threshold for positive ^{18}F-NaF uptake, the test-retest reproducibility was improved by 25.3% (Coefficient of reproducibility: Non-corrected = 0.628, corrected = 0.501, $P < 0.001$).

^{18}F-Flurpiridaz PET MPI has been of key interest to the nuclear cardiology community with advanced clinical studies ongoing.[22,23] During the meeting, intriguing data regarding ^{18}F-Flurpiridaz PET imaging were presented. Rene Packard (J Nucl Med. 2019;60:102) sought to adapt a previously developed automated relative perfusion quantitation method to ^{18}F-Flurpiridaz PET MPI. The group aimed to determine the normal limits, criteria for abnormality and compare performance

metrics of an automated method with that of expert visual reads. In a study of 678 patients, the authors showed that both the automated and visual analysis methods yield similar, modest accuracies for detection of obstructive coronary artery disease (71% and 72% for detecting $\geq$ 70% stenosis, respectively).

In another work related to the ^{18}F-Flurpiridaz tracer, Moody et al (J Nucl Med 2019;60:667) validated the 2-compartment myocardial blood flow (MBF) kinetic model in patients undergoing ^{18}F-Flurpiridaz PET, previously developed in preclinical studies by Nekolla et al.[24] In the work presented at the SNMMI 2019, dynamic PET was evaluated in 125 patients for whom invasive coronary angiography data were also available. According to the study, MBF and flow reserve estimation is feasible in patients by dynamic ^{18}F-Flurpiridaz PET. The authors showed that global rest and stress MBF and flow reserve are progressively lower in coronary arteries with greater disease severity. Both global and vascular stress MBF were highly sensitive to disease severity across all subgroups. The authors noted that overall, mean MBF estimates are similar or slightly lower than those of comparable patient groups as shown in a recent literature review.[25] Of interest in the study, flow reserve estimates were larger due to progressively lower rest MBF with greater disease severity.

RECONSTRUCTION

During the SNMMI 2019 meeting, several groups presented projects focused on optimizing image reconstruction and image denoising by novel deep learning approaches typically utilizing convolutional neural networks (CNN). These studies promise to tailor the algorithms to the specific imaging tasks. In cardiovascular applications, a study by Ladefoged et al (J Nucl Med. 2019;60:573) evaluated the potential of denoising cardiovascular FDG PET images, following count reductions in the acquired data, using only 1% of the injected dose (simulation of low-dose imaging). The authors propose to use a deep learning approach (3D U-Net), to achieve this goal. The group from Copenhagen included a total of 146 patients for training of their deep learning model, while they tested the model on 20 patients. The 20 patients used for validation were evaluated in a clinical toolbox, where the authors reported similar findings using all the data acquired and in image reconstructions using 1% of the acquired data. Through such implementation, it may be possible to either reduce the injected dose to the patient or to significantly reduce the acquisition time.

MOTION CORRECTION

Previous studies showed that attenuation correction improves the specificity and the accuracy of SPECT MPI in the diagnosis of coronary artery disease.[26] The co-registration of attenuation correction maps with perfusion data is critical for diagnostic accuracy, yet to date, automatic methods for performing such alignment are not clinically available. In a study utilizing advanced artificial intelligence methods, Ko et al (J Nucl Med. 2019;60:570) aimed to develop a CNN-based algorithm to achieve automatic translational co-registration of imaging data. In a total of 502 pairs of manually co-registered and verified solid-state SPECT MPI and non-contrast CT images, the group from Taiwan trained (402 cases) and tested (100 cases) the CNN to predict the true offset between the images in 3-dimensions. For training, a total of two million image pairs were generated during the 500 rounds. In the study, there was no significant difference of the iteration number needed between training and testing datasets (3.52 vs. 3.58, $P = 0.27$). Importantly, the mean residual misalignment between image pairs was 1.71 ± 1.32 mm for the training dataset and 2.38 ± 2.00 mm for the testing dataset. The elegant approach proposed by the group holds great clinical potential for optimizing postprocessing of SPECT MPI.

Coronary ^{18}F-NaF PET plaque imaging is a promising application for the identification of vulnerable plaques.[27] Cardiorespiratory and gross body motion have detrimental effect on coronary PET imaging and have been shown to translate the heart by up to 3 cm.[28–30] During the SNNMI 2019 meeting, novel motion correction approaches for ^{18}F-NaF plaque imaging have been presented. Building upon their prior work,[28] Lassen et al (J Nucl Med 2019 60:104) demonstrated how triple motion correction (cardiac, respiratory, and body motion) can improve the reproducibility of test-retest uptake assessments. The authors evaluated the coronary PET quantitative test-retest reproducibility with and without triple motion correction. The proposed method utilized 4 ECG, 4 respiratory, and an acquisition-dependent number of body motion gates. Both respiratory and body motion were detected using data-driven techniques using only raw PET list data with motion detected from center-of-mass evaluations (in 3D) at each 200 ms from single-slice rebinned sinograms. In a cohort of 20 patients who underwent ^{18}F-NaF PET twice within 3 weeks, they showed that the triple motion correction increases signal-to-noise ratios for all coronary lesions (10.95 ± 6.00 vs. 13.23 ± 9.51, $P < 0.001$). Crucially, in the study the TBR test-retest reproducibility improved for all lesions following triple motion correction (46% improvement), $P < 0.001$. Even greater gains in

reproducibility were observed in coronary plaque presenting with increased tracer activity (49% improvement).

NEW HARDWARE

In the previously published studies evaluating the impact of motion during image acquisition, it was demonstrated that motion during imaging has detrimental impact on visual and quantitative evaluation of the patients. Motion compensation is anticipated to be increasingly important, with the improved spatial resolution of the PET systems where even small shifts during the acquisition might lead to blurring of the high-resolution PET images obtained with new hardware. During the conference, results from two recent developed PET systems were reported: the whole-body PET/MR system from United imaging (uExplorer) and high-resolution PET/CT Siemens (Biograph Vision). Related to the cardiovascular applications—in a study considered for the Physics, Instrumentation and Data Science Young Investigator Award Session—Van Sluis and colleagues (J Nucl Med 2019: 60:109) presented an interesting comparison study between Siemens Biograph mCT system and the new Siemens Biograph Vision PET/CT system. The authors evaluated the effect of the enhanced time-of-flight resolution (reported in the range of 210 to 215 ps) as well as the increase in the overall image contrast in clinical oncology patients. The study comprised 20 patients who underwent a single-injection, dual time-point imaging protocol with altering scan order in the two systems. Van Sluis et al reported significantly improved image quality for the images acquired on the Vision system. Although no cardiac scans were evaluated, this study is of significant interest due to potential applications in high-resolution PET plaque imaging. The use of Silicon Photomultiplier (SiPM) technology and digital electronics (implemented in the Vision system)—with the improved time-of-flight precision and smaller crystal size—permits increased sensitivity, reduced noise, and spatial resolution. Such new hardware coupled with motion correction methods might ease identification and improve the quantification of the plaques in the cardiovascular system.

NEW KNOWLEDGE GAINED

Several noteworthy abstracts were presented at the SNMMI 2019 annual conference, covering topics from preclinical imaging, new tracer developments, improvements in imaging protocols to technical developments. The presented studies indicate the novel trends in nuclear cardiology, which will be interesting to follow in the years to come.

Disclosures

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