# REVIEW ARTICLE

# A quick glance at selected topics in this issue

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''A quick glance at selected topics in this issue'' aims to highlight contents of the *Journal* and
provide a quick review to the readers. (J Nucl Cardiol 2019;26:1792–5.)

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| Abbreviations | | | |
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| CAD | Coronary artery disease | MRI | Magnetic resonance imaging |
| MPI | Myocardial perfusion imaging | Rb-82 | Rubidium-82 |
| SPECT | Single-photon-emission-computed-tomography | LV | Left ventricle |
| | | CZT | Cadmium zinc telluride |
| PET | Positron emission tomography | MACE | Major adverse cardiac events |

''A quick glance at selected topics in this issue'' aims to highlight contents of the *Journal* and provide a quick review to the readers. In the last year, we have also started to provide the quick glance write up in an audio format via the JNC/ASNC Podcast, which can be accessed on iTunes, Spotify, and most podcast manager applications. We realize that many of you do not have time to read all journals or attend all national meetings. For that reason, every issue of the JNC includes two types of literature reviews: One summarizing recent key nuclear cardiology articles that have been published in journals other than ours (https://doi.org/10.1007/s12350-019-01910-w), while the second outlining select publications in the general cardiovascular disease literature that have relevance to our field (https://doi.org/10.1007/s12350-019-01909-3). Another entry is the historical corner that looks at the career and scientific contributions of a pioneer in coronary physiology research and Cardiac PET imaging, K. Lance Gould, MD, Professor of Medicine at McGovern Medical School at The University of Texas Health Science Center at Houston (https://doi.org/10.1007/s12350-019-01822-9). The international corner manuscript by Gutierrez-Villamil et al (https://doi.org/10.1007/s12350-019-01805-w) from looks at the positive impacts that the International Atomic Energy Agency has had in the development of the practice and research in the field of nuclear cardiology in low-and-middle-income countries, specifically Latin America and the Caribbean. These manuscripts are complimented by a great selection of original articles with accompanying editorials, brief reports, 'What is this image' and 'Images that Teach' and a CME review paper by Juarez-Orozco and

colleagues, (https://doi.org/10.1007/s12350-019-01670-7) on 'Phase analysis of gated PET in the evaluation of mechanical ventricular synchrony'. Many of the original articles also have accompanying PowerPoint slides. The abstract of the lead original article 'Long-term prognostic value of quantitative myocardial perfusion in patients with chest pain and normal coronary arteries' by Monroy-Gonzalez and colleagues has also been translated into Spanish, Chinese, and French in response to requests from the international readership. PowerPoint slides from this paper can be found by searching DOI: https://doi.org/10.1007/s12350-018-1448-8. Also included by Dorbala and colleagues, (https://doi.org/10.1007/s12350-019-01760-6) is the Part 1 of 2 ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis. The Case Presentation Corner discusses hybrid imaging with PET/MRI for the diagnosis and management of cardiac sarcoidosis (https://doi.org/10.1007/s12350-019-01770-4).

Our comments on a few selected papers noted below are therefore only the tip of the iceberg. These manuscripts were selected at random and we sincerely believe all original articles serve a purpose, provide great value and have undergone an intense peer review.

Patients with chest pain and no obstructive coronary artery disease are known to have a high incidence of major adverse cardiovascular events (MACE) compared to an asymptomatic reference population. It has been suggested that in at least half of these patients microvascular dysfunction is accountable for the symptoms. Monroy-Gonzalez and colleagues (https://doi.org/10.1007/s12350-018-1448-8) demonstrate the value of absolute myocardial perfusion quantification using Nitrogen-13 ammonia PET in predicting all-cause mortality and MACE during long-term follow-up in 79 patients who presented with chest pain with normal or near-normal coronary arteries as demonstrated by invasive coronary angiography and/or coronary computed tomography angiography, and suspected impaired relative myocardial perfusion. Median follow-up was 8 years. Univariate Cox regression analysis showed that myocardial flow reserve (MFR, $P = 0.01$) was a predictor of all-cause mortality, whereas both MFR and stress myocardial blood flow (MBF) were predictors of MACE ($P < 0.001$ and $P = 0.01$, respectively). Thus the investigators demonstrate that microvascular dysfunction-related angina is related to all-cause mortality and MACE during long-term follow-up and PET-derived absolute myocardial perfusion quantification (MBF and MFR) can help clinicians identify these patients who would benefit from therapies aimed at relieving angina symptoms and preventing future cardiovascular events.

Rubidium-82 (Rb-82) is the most commonly used PET tracer for stress myocardial perfusion imaging (MPI) and is increasingly used for quantification of myocardial blood flow and stress/rest myocardial flow reserve. Renaud et al from University of Ottawa Heart Institute, ON, Canada (https://doi.org/10.1007/s12350-018-1261-4), as part of a clinical quality improvement program, investigate if an additional 26-mL saline-push following the Rb-82 elution and injection improves PET image quality. Rb-82 PET scans were acquired with and without the 26-mL saline-push in six patients. Similar eluted activity was measured with/without the saline-push. The investigators noted that the activity delivered to the heart and retained in the myocardium was consistently increased more than twofold ($P < 0.001$) with the saline-push technique. Image quality was also improved in all patients, with lower background noise ($P \leq 0.01$). The saline-push flushes the Rb-82 activity out of the infuser tubing, patient injection, and intravenous access lines and thus increases the activity delivered to the heart and hence is recommended to maximize image quality with Rb-82 PET MPI.

Splenic response (i.e., decreased flow to the spleen during stress compared to rest) is a physiologic response to dipyridamole or adenosine infusion and likely indicates adequacy of chemical stress during Rb-82 PET MPI. Consequently, a failure of this response may be an indicator of insufficient pharmacologic stress and thus a marker of false-negative stress MPI. Bami et al (https://doi.org/10.1007/s12350-018-1269-9) investigate the incremental prognostic impact of splenic response ratio (SRR) in 653 patients with normal Rb-82 PET Dipyridamole Rest-Stress MPI results. SRR was calculated by placing spherical volumes of interest (VOI) in the spleen and liver and then using the formula, (spleen stress/liver stress)/(spleen rest/liver rest). Patients with SRR <0.71 were classified as splenic responders (normal SRR) and those above this value as non-responders (abnormal SRR). This threshold was derived from an initial normal cohort of 50 patients. There was significantly higher MACE observed in splenic non-responders vs splenic responders in both the normal summed stress score—SSS (7.8% vs 2.9%, $P = .027$) and the normal summed difference score-SDS groups (7.4% vs 2.2%, $P = .014$). On multivariate analysis in patients with normal SDS, splenic response was a significant, independent predictor of MACE (HR 2.97, 95% CI 1.10 to 8.04, $P = .033$). Interestingly, 17% of patients that had a full hemodynamic response (i.e., HR increase of $\geq 10$ bpm and SBP decrease of $\geq 10$ mmHg) were splenic non-responders, which suggest that splenic switch-off may provide incremental information to aid the interpretation of a negative dipyridamole PET MPI. Thus splenic response represents a simple and reproducible marker of adequate

pharmacologic stress during Rb-82 PET MPI and in addition to abnormal myocardial flow reserve may be used to identify patients at risk of false-negative results and increased MACE.

Rb-82 PET MPI is prone to subdiaphragmatic activity-related imaging artifacts similar to single-photon-emission-computed-tomography MPI. Rasmussen and colleagues from University of Copenhagen, Copenhagen, Denmark (https://doi.org/10.1007/s12350-018-1359-8) study the association between clinical parameters and MPI interference from subdiaphragmatic activity including any potential correlation between interference severity and stomach volume in 200 patients. The authors find that interference with the left ventricle myocardium Rb-82 activity is mainly caused by excessive radiotracer activity in the stomach. Weight and BMI were inversely correlated with MPI interference and BMI was the strongest predictor of MPI interference. Patients with larger stomach volumes also tended to have higher degree of interference from subdiaphragmatic activity, suggesting a potential benefit from longer fasting (greater than the 2 hours used in this study) prior to examination, especially in smaller patients.

Depressed left ventricular ejection fraction (LVEF), LV mechanical dyssynchrony (LVMD), and prolonged QTc interval are known predictors of poor outcomes in end-stage renal disease (ESRD) patients. Crosland et al from the University of Alabama at Birmingham, Alabama (https://doi.org/10.1007/s12350-018-1411-8) studied the before and after effects of renal transplantation on these indices in 32 ESRD patients with normal SPECT-MPI and compared with a similar size control group with normal perfusion who have had two MPI's at least 3 years apart, but not separated by renal transplantation. The investigators note that LVEF and QTc improved after renal transplantation ($P < 0.001$ for both) but LVMD indices and QRS ($P = 0.9$ for both) did not change, which suggests that LV electrical and mechanical dyssynchrony, unlike LV systolic dysfunction and prolonged repolarization, may be irreversible in ESRD.

Soft-tissue attenuation artifacts from the abdomen, breasts, and lateral chest wall are known to mimic true perfusion defects and thus potentially limit the diagnostic performance of SPECT-MPI. Oddstig et al from Lund, Sweden (https://doi.org/10.1007/s12350-018-1296-6), compare the localization, extent, and depth of attenuation artifacts in SPECT-MPI for a multi-pinhole cadmium zinc telluride (CZT) camera vs a conventional gamma camera using phantom measurements and 22 patients with suspected stable ischemic heart disease. All images were attenuation corrected with externally acquired low-dose computed tomography. Attenuation artifacts were quantified by comparing attenuation-corrected and non-attenuation-corrected images. The attenuation artifacts were noted to shift counter-clockwise from the inferolateral wall to the lateral wall using the CZT camera compared to a conventional camera in both patients and the phantom. The results also show that the extent of attenuation artifacts was significantly larger for the CZT camera compared to the conventional camera ($P < .001$) for both patients and the phantom. Furthermore, the depth of the attenuation artifact (percent of maximum counts) was less pronounced for the CZT camera than for the conventional camera, both for phantom measurements and patients ($P < .001$). In conclusion, the authors note that attenuation artifacts are found in different locations and to different extents and depths when using a CZT camera vs. a conventional gamma camera for MPI SPECT. These differences should be taken into consideration when evaluating MPI SPECT studies without attenuation correction to avoid misinterpretation of myocardial perfusion.

Rb-82 PET MPI is increasingly utilized in the evaluation of patients with suspected or known coronary artery disease. Apart from providing attenuation-corrected perfusion and gated information, it also provides a quantitative assessment of myocardial blood flow, which has added prognostic value over perfusion data alone. Multiple software packages for data processing have been developed with conflicting data regarding reproducibility between various software packages. In this study, Oliveira et al (https://doi.org/10.1007/s12350-018-1444-z) compared the quantitative results of myocardial perfusion and exam classification (normal vs. abnormal) from three different available commercial software programs, i.e., Corridor 4DM (Invia, Ann Arbor, Michigan, USA), QPET (Cedars-Sinai, Los Angeles, California, USA), and SyngoMBF (Siemens Healthineers, Erlangen, Germany) from 55 patient exams. The results showed that mean values of myocardial blood flow (MBF) and myocardial perfusion reserve (MFR) were statistically significantly different among the 3 software programs ($P < 0.05$). Corridor4DM had consistently lower values of MFR and classified a larger number of exams as abnormal. SyngoMBF and QPET results were overall comparable. Thus users should be cautious when using different software interchangeably as differences may introduce quantitative variation which could be clinically significant.

F-18 Flurpiridaz binds to mitochondrial complex 1 in the cardiac myocyte with high affinity and has the potential to yield steady-state myocardial imaging along with the improved resolution and quantitation afforded by PET. Maddahi and colleagues (https://doi.org/10.1007/s12350-018-01484-z) study the dosimetry, biodistribution, and safety of F-18 flurpiridaz in 12 healthy

subjects undergoing rest and exercise or adenosine pharmacological stress PET myocardial perfusion imaging. The heart wall received the largest mean absorbed dose with both exercise and adenosine stress, a desirable feature for a myocardial perfusion imaging tracer. The maximum dose that could be administered without exceeding 1 rem (10 mSv) effective dose threshold was 19 mCi (685 MBq) for exercise and 15 mCi (539 MBq) for adenosine pharmacologic stress. There were no drug-related adverse events, and the tracer was well tolerated in all subjects. Thus the investigators demonstrate the feasibility of PET myocardial perfusion imaging with F-18-labeled flurpiridaz in conjunction with either treadmill exercise or pharmacological stress testing in a small group of normal subjects. Tracer dosimetry was within the clinically acceptable range and F-18 flurpiridaz was found to be safe and well tolerated.

We encourage the readers to look at the several other articles in the Journal with accompanying scholarly and informative editorials that not only put the findings in perspectives but also outline future directions. We would like to hear your comments as we strive to gain knowledge and in the process, improve patient care.

## Disclosure

*There are no COI with this work.*