A quick glance at selected topics in this issue

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Received Mar 25, 2019; accepted Mar 25, 2019
doi:10.1007/s12350-019-01703-1

''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;26:696–700.)

Key Words: CAD • Myocarditis • Atherosclerosis • MRI • PET • Myocardial blood flow • Tests

Abbreviations

CAD	Coronary artery disease
MPI	Myocardial perfusion imaging
SPECT	Single photon emission computed tomography
PET	Positron emission tomography
CMR	Cardiac magnetic resonance
LV	Left ventricle
FDG	^{18}F-fluorodeoxyglucose
CZT	Cadmium-zinc-telluride
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. Recently, we have started to provide the quick glance write up in an audio format as well via the JNC/ASNC Podcast, which can be accessed on iTunes, Spotify, and most podcast manager applications. We realize that many of us do not have time to read all journals or attend all national meetings. For that reason, every issue of the JNC includes 2 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/s12350-019-01690-3), while the second outlines select publications in the general cardiovascular disease literature that have relevance to our field (https://doi.org/10.1007/s12350-019-01696-x).

Another entry is the historical corner that looks at the career and scientific contributions of a pioneer in Cardiac and Endocrine Nuclear Medicine, Joseph Pinkus Kriss, MD (https://doi.org/10.1007/s12350-018-1403-8). He was an internationally recognized authority on the pathogenesis and treatment of thyroid disorders and is credited with performing the first comprehensive series of radionuclide angiocardiography studies in more than 100 cardiac patients. 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 Nudi et al. from Italy (https://doi.org/10.1007/s12350-018-01562-2) that discusses the 'Hybrid Anatomic-Functional Imaging of Coronary Artery Disease.' Reviewed are combinations of various available anatomic and functional imaging modalities including CMR, CT angiography, CT perfusion, CT-FFR, Echo, PET MPI, and SPECT MPI. Many of the original articles also have accompanying PowerPoint slides. The

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J Nucl Cardiol 2019;26:696–700.
1071-3581/$34.00

abstract of the lead original article 'Impact of regadenoson-induced myocardial creep on dynamic Rubidium-82 PET myocardial blood flow quantification' by Koenders and colleagues from The Netherlands 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 https://doi.org/10.1007/s12350-019-01649-4. The review article by Lanza et al. from Washington University Medical School, St. Louis, MO (https://doi.org/10.1007/s12350-017-0942-8) looks at the 'The history of thrombus imaging,' while the theme article by Petretta and colleagues from Italy (https://doi.org/10.1007/s12350-017-1154-y) provokes deeper thinking into the seemingly reassuring concept of the 'Warranty Period' after a normal MPI. Also included is the ASNC information statement on 'Aminophylline shortage and current recommendations for reversal of vasodilator stress' by Abidov et al. (https://doi.org/10.1007/s12350-018-01548-0). The 'Case Presentation Corner' in this issue discusses 'Challenges in Medical Management of a Patient with Coexisting Cardiac Amyloidosis and Coronary Artery Disease' (https://doi.org/10.1007/s12350-019-01644-9).

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.

Stress PET MPI with myocardial blood flow (MBF) quantification is known to provide valuable diagnostic and prognostic information in CAD patients. Pharmacologic vasodilators (e.g., adenosine, dipyridamole, and regadenoson) are generally used to induce stress. These vasodilators can induce short-term side effects such as chest pain and shortness of breath causing increased respiratory rate and lung volumes which lead to repositioning of the heart, referred to as myocardial creep which in turn may result in erroneous MBF measurements and affect diagnostic accuracy of PET MPI. Koenders and colleagues from The Netherlands (https://doi.org/10.1007/s12350-019-01649-4) study the incidence of myocardial creep and its effect on MBF values before and after correction in 104 patients undergoing rest-regadenoson stress Rb-82 PET MPI. Upon analysis, 54 (52%) patients showed myocardial creep during the stress scan, of which 45 (83%) had a change $> 10\%$ in MBF and MFR (myocardial flow reserve) in one of the territories or the whole myocardium. The largest differences were found in the RCA territory where the mean MBF values decreased after correction from 4.0 to 2.7 mL/min/g ($P < 0.001$). Thus the authors demonstrate that myocardial creep is a frequent phenomenon during regadenoson stress Rb-82 PET MPI and has a significant impact on MBF values, especially in the RCA territory. As this may affect diagnostic accuracy, detection and correction of myocardial creep is necessary for reliable quantification.

PET MPI is an excellent and well-established tool for relative myocardial perfusion imaging and for measuring MBF and CFR in CAD patients. However its use has been curtailed due to need for costly resources such as PET imaging equipment, cyclotrons (for ^{13}NH3) and generators (for ^{82}Rb). SPECT is the most commonly used MPI tool with over 7 million scans performed in the United States annually. Thus there is a lot of interest in looking at improved SPECT methods to perform both visual assessment of myocardial perfusion and flow quantification as part of standard MPI. Sciammarella and colleagues from the University of California, San Francisco, CA (https://doi.org/10.1007/s12350-017-1016-7) conduct a preliminary feasibility study in a sample of 15 patients comparing combined dynamic with static conventional SPECT MPI with CT-based attenuation correction in a one-day visit for the diagnosis of CAD. Dynamically acquired data were also used to estimate the MBF and CFR. Imaging began with a dynamic study followed by the static clinical study, first at rest, followed by pharmacologic stress. Both visual inspection of static and dynamic images and quantitative estimation of flow were tested against selective coronary angiography to find the validity of the methods. Relative perfusion assessment with static conventional and dynamic SPECT MPI had a similar accuracy (64% for both), sensitivity (40% for both), and specificity (83% vs 100%). Addition of CFR improved the diagnostic performance with an overall accuracy of 91%, sensitivity of 80%, and specificity of 100%. Thus the authors demonstrate the feasibility and make a case for incorporating dynamic SPECT MPI with CFR measurement in the clinical setting for improved CAD diagnosis.

Given multiple comorbidities, end-stage renal disease (ESRD) patients are at increased risk for cardiovascular events and therefore often undergo pharmacologic stress MPI as part of their renal transplant (RT) evaluation to rule out significant ischemic heart disease. Additionally it is well documented that blunted heart rate response (HRR) to vasodilator stress agents during MPI is independently associated with worse outcomes in patients with chronic kidney disease and ESRD. Thus HRR has an incremental prognostic value and can improve risk stratification beyond clinical and MPI data. In a retrospective analysis, AlJaroudi and colleagues (https://doi.org/10.1007/s12350-017-1061-2) assess whether HRR in asymptomatic ESRD patients ($n = 352$) undergoing pre-RT vasodilator stress MPI can predict post-RT outcomes. They note that blunted

HRR was prevalent (> 40%) among ESRD patients selected for RT. During a mean follow-up of 3.2 ± 2.0 years, 85 (24%) MACEs were observed. Blunted HRR was associated with a significant increase in 30-day post-operative MACE risk (17.9% vs 8.5%; $P = 0.009$) defined as cardiac death or myocardial infarction even after adjusting for relevant clinical and imaging covariates. It is noteworthy that blunted HRR was predictive of MACE risk even in patients with normal MPI and those with low clinical risk, suggesting that HRR can be particularly helpful in patients who otherwise seem to be at low risk. In conclusion, HRR may be a valuable tool in the risk assessment of renal transplant candidates.

Implementation of Protecting Access to Medicare Act (PAMA) is upon us. The new Act directs the Centers for Medicare and Medicaid (CMS) to promote the use of appropriate use criteria for advanced imaging services. Thus, in an effort to respond to the need for the rational use of myocardial perfusion imaging, the American College of Cardiology Foundation (ACCF) and the American College of Radiology (ACR) have proposed Appropriate Use Criteria (AUC) also called as Appropriateness Criteria (AC) in 2013 and 2010, respectively. Bagrova et al. (https://doi.org/10.1007/s12350-017-0965-1) perform a retrospective analysis of 451 patients who had undergone nuclear MPI between June 2011 and September 2014 to assess the agreement in appropriateness category using the ACCF and ACR criteria. Interestingly, they find poor agreement between the ACCF and ACR appropriateness ratings (kappa correlation coefficient 0.32, $P < 0.0001$). When using ACCF AUC, the investigators found that 73.4% of MPI studies fell under ''appropriate'' category, 8% under ''maybe appropriate,'' and 18.6% were ''rarely appropriate.'' Applying the ACR criteria, 73% of studies were classified as ''usually appropriate,'' 20.2% as ''may be appropriate,'' and 6.8% as ''usually not appropriate.'' The greatest disagreement occurred within categorization of indications classified as 'maybe appropriate' or 'usually not appropriate.' The authors bring attention to discordance between the respective appropriate criteria which can create disagreement and conflicts between payers (e.g., CMS) and healthcare providers if only one set of criteria is used for reimbursement purposes.

LV myocardial stunning is a well-known phenomenon of transient acute systolic dysfunction secondary to myocardial ischemia. Normally LV myocardial contractility increases during exercise or pharmacologic stress testing, with correspondent increase in LV ejection fraction. Difference in LVEF between stress and rest is referred to as LVEF reserve, which normally is > 5%. In patients with significant CAD, demand-supply mismatch during stress testing results in myocardial perfusion abnormalities resulting in transient stunning of the myocytes and decrease in myocardial contractility. Thus stress-induced new wall motion abnormality is highly specific for CAD. Bestetti and colleagues from the University of Milan, Milan, Italy (https://doi.org/10.1007/s12350-017-1115-5) evaluate the value of systolic wall thickening in addition to other metrics of MPI in diagnosing myocardial stunning in 91 patients with angiography proven CAD. Maximal treadmill exercise tests were performed on all patients. The investigators scored LV wall thickening on a four-point scale (0 = normal, 1 = mildly impaired, 2 = moderately impaired, 3 = severely impaired to absent thickening) based on the visual assessment of myocardial wall brightening from diastole to systole in 20 segments and quantified the summed stress, rest, and wall thickening difference scores. The stress LVEF was significantly lower than rest LVEF (48.1% ± 10.3% vs 50.3% ± 10.7%; $P = .0001$). The wall thickening summed difference score (WT-SDS) was 4.44 ± 4.13 ($P = .0001$) which, on multivariate regression analysis, was the only independent variable that significantly correlated with myocardial ischemia (summed difference score, SDS). While both WT-SDS and LVEF reserve indicate the presence of myocardial stunning, WT-SDS showed greater correlation with the severity of ischemia, and was altered even in the absence of a major reduction in LVEF reserve (i.e., $\Delta < 5\%$). Thus the authors suggest that WT-SDS should be considered as the best parameter to identify myocardial stunning.

A common cardiac adaptive mechanism in the setting of hemodynamic overload is the compensatory increase in LV mass. However, this compensatory increase in ventricular wall thickness/hypertrophy (LVH) is detrimental in the long run and a predictor of increased risk of cardiovascular morbidity and mortality. Due to the high image quality, cardiac magnetic resonance (CMR) is considered the gold standard for the non-invasive measurement of LV mass and diagnosis of LVH. Gimelli et al. from Italy (https://doi.org/10.1007/s12350-017-1086-6) compare the estimates of LV mass on Cadmium-Zinc-Telluride (CZT) SPECT MPI using 2 different software packages [Corridor 4DM (4DM) and Emory Cardiac Toolbox (ECTb)] and compare it with CMR. Rest CZT images were used for LV perfusion and functional analyses. The investigators noted that there was an excellent correlation between LV mass values between CMR and both 4DM ($R^2 = .95$; $P < .001$) and ECTb ($R^2 = .98$; $P < .001$) with narrow limits of agreement. Thus the authors show that quantification of LV mass is feasible during routine SPECT MPI using modern CZT cameras and commercially available software with comparable results to CMR, the reference standard.

CMR is frequently used as the first-line non-invasive diagnostic imaging exam for the diagnosis of acute myocarditis, given its good sensitivity and specificity. The recommended CMR diagnostic criteria for acute myocarditis also called as ''Lake Louise Criteria'' (LLC) requires at least two of three qualitative findings of abnormal T2 signal suggesting myocardial edema, early gadolinium enhancement suggesting hyperemia, and late gadolinium enhancement suggesting myocardial injury in a non-ischemic pattern. However, these criteria have been limited by marked variation in sensitivity and negative predictive value. Imbriaco and colleagues from Italy (https://doi.org/10.1007/s12350-017-1109-3) compare CMR qualitative (LLC) and quantitative analysis methods for the non-invasive assessment of myocardial inflammation in 61 patients with suspected acute myocarditis. The quantitative analysis methods include evaluation of edema ratio (ER) and global relative enhancement (RE); both are significantly higher in patients with acute myocarditis compared to those without. ER is derived from the short time inversion recovery (STIR) T2-weighted sequence and global RE from the pre- and post-contrast T1-weighted images. No significant differences were found between the LLC, i.e., T2-weighted STIR, EGE, and LGE sequences for the diagnosis of acute myocarditis. Also there were no significant differences among qualitative and quantitative methods in the identification of acute myocarditis patients. Given a similar diagnostic accuracy, the investigators suggest consideration of a simplified and shortened CMR protocol that includes only T2-weighted STIR sequences without the need of contrast administration as a screening exam for the diagnosis of suspected acute myocarditis in patients with normal coronary angiography.

Heart transplantation (HTx) is the first choice in treatment of patients with end-stage heart failure. However, the long-term outcomes are often limited by cardiac allograft vasculopathy (CAV), occurring in up to 50% of the patients and is associated with an increased risk of mortality. As a result of denervation of the transplanted heart, CAV-related anginal symptoms are usually absent and the first clinical sign of CAV can be heart failure, myocardial infarction, ventricular arrhythmias, or sudden death. Veenis et al. from Erasmus Medical Center, Rotterdam, The Netherlands (https://doi.org/10.1007/s12350-017-1089-3) evaluated the long-term prognostic value of stress 99mTc-tetrofosmin SPECT MPI for predicting all-cause mortality and cardiac events in 166 HTx recipients. During a median follow-up of 12.8 years (range 0 to 15, mean follow-up 9.5 years), 109 (66%) patients died (all-cause mortality), of which 67 (40%) were due to cardiac causes. 5 (3%) patients experienced a non-fatal MI. HTx recipients with a normal stress SPECT MPI had a significantly better prognosis as compared with those with an abnormal study, up to 5 years after the initial test. A reversible perfusion defect was a significant predictor of all-cause mortality, cardiac mortality, and major cardiac events, during the follow-up period. Thus stress SPECT MPI can provide valuable prognostic information for the prediction of long-term outcome in HTx recipients.

Multiple studies have shown the association of ^{18}F-FDG uptake and the inflammatory burden of carotid plaques and its ability to retrospectively identify culprit lesions after strokes or transient ischemic attacks. Other FDG PET applications include tracking the effect of therapeutic interventions on plaque biology and cardiovascular risk stratification. Currently there is no consensus on the methodology for quantification of ^{18}F-FDG uptake in inflammation in atherosclerosis. Johnsrud and colleagues from Oslo University Hospital, Oslo, Norway (https://doi.org/10.1007/s12350-017-1121-7) explore different methods for quantification of ^{18}F-FDG uptake in carotid atherosclerotic plaques and correlate the uptake values to histologic assessments of inflammation. 44 patients with atherosclerotic stenosis $\geq$ 70% of the internal carotid artery underwent ^{18}F-FDG PET/CT. Maximum standardized uptake values (SUVmax) from all plaque-containing slices were collected. SUVmax for the single highest and the mean SUVmax of multiple slices with and without blood background correction [by subtraction (cSUV) or by division (target-to-background ratio (TBR)] were calculated. Following endarterectomy, 30 plaques were assessed histologically. The length of the carotid plaques in the craniocaudal direction was 6 to 32 mm (mean 19 mm). There were significant moderate (0.44 to 0.59) correlations between the amount of histologic inflammation and all the different ^{18}F-FDG quantification methods. The highest correlations were found for mean SUVmax, and the lowest for max SUVmax independent of background correction. Thus the authors suggest that SUVs without background correction from large carotid artery plaques can be used as an inflammatory parameter in atherosclerosis.

Infective endocarditis (IE) is associated with considerable morbidity and mortality, from local damage to cardiac structures, metastatic infection, embolic phenomenon, or immune-mediated damage. ^{18}F-FDG PET/CT is an adjunctive diagnostic tool in the evaluation of IE, with high diagnostic accuracy reported in small studies. Mahmood et al. at Mayo Clinic, Rochester, MN (https://doi.org/10.1007/s12350-017-1092-8) perform a meta-analysis of 13 studies involving 537 patients evaluating the use of PET/CT in the diagnosis of IE to establish a more precise estimate of diagnostic accuracy. In this meta-analysis, the pooled sensitivity of PET/CT

for diagnosis of IE was 76.8% and the pooled specificity was 77.9%. Diagnostic accuracy was better for prosthetic valve IE with sensitivity of 80.5% and specificity of 73.1%. The authors conclude that PET/CT is a useful adjunctive diagnostic tool in the evaluation of diagnostically challenging cases of IE, particularly in prosthetic valve endocarditis. Given the whole body image acquisition, PET/CT also has the potential to detect clinically relevant extracardiac foci of infection, and other sources of inflammation leading to more appropriate treatment regimens, including avoidance of unnecessary antibiotic therapy or surgical intervention for presumed IE. The rapid turnaround time of around 2 hours combined with an excellent spatial resolution that allows for precise definition of valvular infection and associated complications are added benefits.

We encourage the readers to read 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.