Editorial: ^{18}F -Fluoride PET/MR in cardiac amyloid; simple addition versus synergy?

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Hybrid imaging with positron emission tomography–magnetic resonance (PET-MR) combines two valuable imaging modalities, with the expectation of synergy; a combined effect greater than the sum of the separate effects. Simultaneous acquisition of magnetic resonance imaging (MRI) and positron emission tomography (PET) brings together anatomical detail and tissue characterization with metabolic data. The challenges associated with PET-MR imaging; expense, proximity to a cyclotron, specialist staff trained in PET and MRI for patient preparation, image acquisition, attenuation correction, post-processing, analysis and reporting; need to be outweighed by the incremental value of simultaneous PET-MR imaging over sequential imaging.

Cardiac amyloidosis (CA) has benefited from adopting imaging technologies used in other pathologies. The utility of bone scintigraphy radiotracers $^{99\text{m}}\text{Tc}$ PYP, DPD, HMDP, in CA has already been proven in a large multi-center study.¹ This demonstrated that cardiac scintigraphy with bone avid radiotracers can diagnose transthyretin amyloidosis (ATTR) cardiomyopathy in the absence of a monoclonal gammopathy with a specificity of close to 100%. Fluorine-18-labeled sodium fluoride (also known as ^{18}F -NaF

or sodium fluoride, or in this paper just ^{18}F -fluoride) is a PET radiotracer. This has already been adopted from skeletal imaging, where its predominant use is the imaging of bone metastases, for use in cardiovascular disease.^{2–4} It has been used for imaging of vulnerable plaques in coronary disease; Joshi et al showed that culprit lesions accumulate ^{18}F -fluoride avidly during an acute coronary syndrome.² ^{18}F -fluoride has been shown to selectively deposit in atherosclerotic plaques where microcalcifications accumulate in crystals of calcium apatite.³ In recent years, there is growing evidence for its use in cardiac amyloidosis, with a similar calcium binding mechanistic hypothesis as the other bone avid radiotracers.^{5–7} Amyloid-specific PET tracers were initially developed for the imaging of cerebral A β -amyloid in Alzheimer's disease. They are thioflavin T analogues that bind directly to the amyloid fibrils, which include 11C-Pittsburgh compound B (PIB), ^{18}F -florbetapir, ^{18}F -florbetaben and ^{18}F -flutemetamol; all are being evaluated in CA, especially for their ability to monitor disease progression and response to therapy.^{8–11}

Akin to the imaging of cardiac amyloidosis, we are still in a phase of discovery for effective therapies for ATTR cardiac amyloidosis. Just one therapy is FDA-approved, tafamidis, and multiple agents are undergoing phase III evaluations, including gene silencers, approved for familial amyloid polyneuropathy.^{12–14} The cost of tafamidis and the gene silencers are prohibitively expensive for some healthcare systems, underlining the importance of evaluation of the effectiveness of these therapies.^{15,16} A biomarker, or combination of biomarkers that can monitor therapeutic response to allow the most effective use of a growing armamentarium of therapies will be close to priceless given the current price tag on therapies. With the advent of treatments, there is further urgency to diagnose this disease earlier; in the ATTR-ACT study of tafamidis

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those with lower NYHA class had better outcomes on sub-group analysis. As well as an ability to track and quantify disease burden, criteria for novel imaging biomarkers in CA include the ability to detect early infiltration.

Amyloid infiltration has a distinct biosignature on MRI due to the extracellular deposition of the amyloid fibrils, which makes the disease process highly suitable for evaluation with novel imaging biomarkers, such as pre- and post-contrast T1 mapping with quantification of extracellular volume (ECV).¹⁷ These MRI imaging biomarkers have both diagnostic and prognostic value in CA, and there is a lot of optimism for their ability to track response to therapy. Our group has also shown elevation in ECV in early infiltration, before abnormalities in wall thickness and cardiac biomarkers are apparent.⁸ However, a limitation of MRI in cardiac amyloidosis is the inability to distinguish amyloid-type. Cardiac amyloidosis is predominantly caused by the transthyretin protein (ATTR) or by light chains produced for an abnormal plasma cell clone in the bone marrow (AL).¹⁸ Although MRI is sensitive and specific for cardiac amyloidosis, to distinguish the type additional imaging is required. The need for sequential imaging may delay access to therapies, which cannot be delayed in AL amyloidosis due to its rapid course and poor prognosis if untreated.¹⁹ An additional benefit of combining PET with MRI is the combination of a quantifiable metrics to potentially aid prognosis and track disease progression.

In this edition of the Journal of Nuclear Cardiology, Andrews et al describe ^{18}F -fluoride PET/MRI in 53 patients, showing its ability to differentiate ATTR ($n = 10$) from AL ($n = 8$), aortic stenosis (AS) ($n = 22$) and healthy controls ($n = 8$). They employed two approaches for myocardial analysis. First, standardized uptake values (SUV_{MEAN} and SUV_{MAX}) were calculated for septal VOIs and corrected for blood pool activity to provide tissue-to-background ratio (TBR_{MEAN} and TBR_{MAX}). Second, in patients with cardiac amyloid, ^{18}F -fluoride uptake was assessed in areas of myocardial late gadolinium enhancement (LGE). Equal sized volumes of interest (VOI) were placed within areas of LGE demonstrating the greatest visual uptake on short axis slices with SUV_{MEAN} and TBR_{MEAN} values recorded. Increased septal ^{18}F -fluoride activity was observed in patients with ATTR amyloid ($\text{TBR}_{\text{MEAN}} 1.13 \pm 0.16$) compared to healthy volunteers (0.86 ± 0.10 , $P = 0.0002$) and patients with both AL amyloid (0.95 ± 0.08 , $P = 0.01$) and aortic stenosis (0.73 ± 0.12 , $P < 0.0001$).

The authors have experience with ^{18}F -fluoride PET-MR in CA;⁶ in a prior single center study they evaluated its use in 4 subjects with ATTR, 3 with AL amyloid, and 7 control subjects. Focusing on TBR_{MAX} , versus

TBR_{MEAN} in the current analysis, they found that myocardial TBR_{MAX} values in patients with ATTR (1.14 ± 0.24) were 68% higher than control subjects and 48% higher than patients with AL amyloid (0.77 ± 0.06). A TBR_{MAX} threshold of > 0.84 appeared to differentiate ATTR from AL and control subjects. This highlights an important weakness of this tracer, a tissue to blood pool ratio less than 1 is considered a diagnostic threshold. It goes against logic that more activity in the blood pool than myocardial uptake could still indicate a positive scan. In the current paper, the TBR values were 35% higher in the LGE regions compared to other areas of 'normal' myocardium in the same ATTR patients ($\text{TBR}_{\text{MEAN}} 1.39 \pm 0.23$ vs 0.90 ± 0.23 , $P < 0.0002$). It was only in these areas of LGE that the ^{18}F -fluoride TBR values discriminated between patients with ATTR and AL amyloid, with a TBR_{MEAN} threshold > 1.14 providing 100% sensitivity (C.I. 72.25-100%) and 100% specificity (C.I. 67.56-100%) for TTR amyloid (AUC 1, $P = 0.0004$). This brings us back to the original question regarding the benefit of hybrid imaging; simultaneous MRI imaging is clearly necessary here, co-localization with areas LGE enhances the quantification of the tracer increasing the yield of metabolic information. However, LGE is evidence of definitive disease, this seems to rule out the potential for this tracer to detect early disease, before there is markedly elevated ECV and obvious LGE.

Other groups experience on the utility of ^{18}F -fluoride PET in CA is similar. Morgenstern et al evaluated ^{18}F fluorine-labeled sodium fluoride PET in a pilot study in which they enrolled 7 patients with biopsy-proven CA (2 with AL, 5 with ATTR).⁵ They found greater uptake in patients with ATTR vs AL and controls, when comparing standard uptake values in the entire myocardium (SUV_m), which were 1.5 (1.4-1.7) in ATTR subjects, and 0.8(0.4-0.9) and 0.95(0.9-1.0), in AL and control subjects, respectively. Abulizi et al looked at ^{18}F -fluoride in 16 patients with ATTR, 7 with AL and 4 control subjects.⁷ They measured ^{18}F -fluoride uptake visually and semi-quantitatively by calculating myocardium-to-blood pool (M/B) ratios. M/B ratios were statistically higher in ATTR CA (1.00 ± 0.12) than in AL (0.81 ± 0.06 , $P = 0.001$) or in control subjects (0.73 ± 0.16 , $P = 0.006$). Yet again, this shows the tracer uptake is similar to blood pool, with differentiation by visual assessment limited by low contrast.

This study also set out to evaluate ^{18}F -fluoride PET/MR to distinguish ATTR from AS. These conditions commonly co-exist, demonstrated in data from multiple centers using DPD or PYP imaging.^{20,21} ATTR and AS have distinct LGE patterns on MRI, as acknowledged by the authors. The additional benefit of PET over MRI alone in this cohort is not clear. For this group of

patients with AS and ATTR, PYP and DPD have already shown their utility; they can be visually interpreted and widely performed, without the need for major investment in establishing a PET/MR program.

In their earlier publication, this group noted that there is potential for ^{18}F -fluoride PET/MR to aid in the diagnosis of cardiac amyloidosis, identify characteristic LGE, establish systolic function, and differentiate AL and ATTR all within a single scan.⁶ They added the caveat that further confirmatory studies were still required, and the technology was limited by generalizability in clinical practice. The current analysis has helped address the need for further confirmatory studies, especially as the findings were comparable across the two centers. Yet, the limitations are replicated; low myocardial uptake with poor contrast to blood pool activity. The authors did not evaluate the full potential of MRI in conjunction with ^{18}F -F PET, and we await further work from this group looking at T1 mapping and ECV in this cohort. Exciting progress is being made in this field of PET imaging of CA, we anticipate longitudinal studies evaluating many of the tracers. If ^{18}F -fluoride PET/MR is shown to be the most accurate marker of response to therapy in ATTR, discussions over the cost and complexities of a PET/MR program maybe a moot point if it brings about more appropriate use of million-dollar medicines, and simple subtraction may be all it takes.

Disclosures

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