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Aortic valve and coronary 18F-sodium fluoride activity: a common cause?

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THE SETTING

An understanding of the pathophysiology of a disease is crucial for the development and application of interventions. This is particularly salient for diseases which lack preventative therapies. Degenerative aortic stenosis is one such condition. Interest in improving our understanding of the biological processes governing aortic stenosis is therefore intense. This has become even more relevant in the current era of transcatheter heart valves, with the increasing number of potential candidates for intervention sharpening focus on the healthcare burden posed by this chronic disease.[1]

Degenerative aortic stenosis is the prototypical calcific valve disease, with complex biological processes occurring over years before manifesting as a clinical entity. Cellular injury, lipid deposition, and inflammation lead to valve interstitial cell differentiation and expression of pro-osteogenic factors that drive calcium deposition, ultimately resulting in outflow obstruction due to valvular stenosis.[2] Similarities have been drawn between the early pathology of aortic stenosis and atherosclerosis,[3] yet seminal randomized controlled trials of statin therapy failed to demonstrate benefit with regard to aortic stenosis progression.[4-6] Although early calcification of the valve and coronary arteries may be a common response to injury and inflammation, the ultimate clinical effects are divergent. Progressive calcification is the predominant pathological process driving valve obstruction in aortic stenosis. In contrast, coronary macrocalcification is associated with stable atherosclerotic plaques that are less prone to rupture and appears to be accelerated by statin therapy.[7] Further work is therefore required to understand the governing mechanisms and interactions of valvular and coronary calcification.

THE STUDY

In this issue of the *Journal of Nuclear Cardiology,* Nakamoto *et al* explore this relationship with a post hoc analysis from their previously published prospective 18F-sodium fluoride (18F-NaF) positron emission tomography-computed tomography (PET-CT) study.[8,9] 18F-NaF is the current focus of multiple cardiac imaging studies, having previously been used as a bone tracer in oncology. The radiotracer binds to hydroxyapatite and serves as a marker of calcification activity in multiple cardiovascular disease states. In particular, increased 18F-NaF uptake has been demonstrated in high-risk and culprit coronary and carotid plaques.[9-12] It is also associated with faster aortic stenosis disease progression[13,14] and bioprosthetic aortic valve degeneration.[15] As such, there is appeal in using this imaging biomarker to investigate calcification activity in both aortic stenosis and coronary atherosclerosis.

The overall study cohort was comprised of 44 patients with known/suspected coronary artery disease, recruited between June 2014 and December 2018, who underwent computed tomography coronary angiography (CTCA) and were found to have at least one coronary atherosclerotic lesion. 18F-NaF PET-CT was performed within 1 month of the CTCA. For this substudy, the investigators retrospectively identified 25 patients with evidence of early aortic valve calcification on CT ($\geq$ 130 Hounsfield units) who did not have aortic stenosis on echocardiography (peak aortic valve velocity $<$ 2m/s). CTCA analysis included qualitative assessment for high-risk coronary artery plaque, defined by the

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Table 1. Clinical studies investigating 18F-NaF PET in valvular heart disease

	Year	Design and population	Imaging	Main findings
Hyafil *et al*[22]	2012	Retrospective 5 severe AS 10 controls	Aortic valve PET-CT	Higher 18F-NaF activity in AS compared to controls
Dweck *et al*[23]	2012 2013	Prospectively recruited	Aortic valve, mitral valve,	Higher 18F-NaF and 18F-FDG activity in aortic stenosis compared to controls
Dweck *et al*[24]	2015 2019	20 controls 20 aortic sclerosis 25 mild AS 33 moderate AS 23 severe AS	coronary, aortic and bone PET-CT	Greater progressive increase in 18F-NaF with increasing disease severity compared to 18F-FDG Severity of aortic stenosis correlated more strongly with valvular 18F-NaF than extra-valvular 18F-NaF 18F-NaF correlated with progression in aortic valve calcium score at 2 years. Mitral annular calcium score associated with local 18F-NaF activity
Jenkins *et al*[14] Massera *et al*[25]				
Dweck *et al*[13]	2014	Prospective (including some from above cohort) 12 AS undergoing AVR 6 Aortic sclerosis 5 Mild AS 7 Moderate AS	Aortic valve PET-CT and calcium score	18F-NaF co-localized with tissue staining for calcification, including regions free of macroscopic calcification 18F-NaF correlated with progression in aortic valve calcium score at 1 year
Pawade *et al*[21]	2016	Prospective 7 Mild AS 4 Moderate AS 4 Severe AS	Aortic valve PET-CT	Optimized 18F-NaF PET-CT analysis reproducibility using a most diseased segment methodology
Cartlidge *et al*[15]	2019	Prospective 80 patients with bioprosthetic AVR 7 Degenerated bioprosthetic AVR 15 Explanted aortic valve bioprostheses	Aortic valve PET-CT	18F-NaF independently associated with more rapid bioprosthetic valve deterioration over 2 years. All patients who developed new bioprosthetic dysfunction had 18F-NaF uptake at baseline

presence of low-density plaque (<30 Hounsfield units) or positive remodeling (remodeling index > 1.1). Aortic valve calcium score, density, and 18F-NaF uptake were quantified. Of the 25 patients, 11 underwent repeat cardiac CT (35 ± 9 months) for assessment of aortic valve disease progression.

At baseline, the mean aortic valve velocity was 1.4 ± 0.3 m/s, while the median aortic valve calcium score was 101 (11-171) Agatston units. The maximum aortic valve tissue-to-background ratio (TBR_{max}) was 1.52 ± 0.18. At the patient level, 14 of 25 had at least one high-risk plaque. At the lesion level, 20 of 90 plaques had at least one high-risk feature. The median coronary calcium score was 314 (28-1147) Agatston units.

The main finding was an independent association between aortic valve TBR_{max} and the presence of high-risk coronary plaque on multivariable linear regression ($\beta = 0.56$, $P = .029$) after adjusting for age, sex, coronary risk factors, statin use, and obstructive coronary stenosis; aortic valve calcium score was the only other

independently associated covariable. Aortic valve TBR_{max} was 1.60 ± 0.18 in patients with high-risk coronary plaque and 1.42 ± 0.13 in those without. Aortic valve TBR_{max} had a modest correlation with baseline aortic valve calcium score ($r = 0.54$, $P = .005$). In the 11 patients who had follow-up CT scans, aortic valve TBR_{max} correlated strongly with change in aortic valve calcium score ($r = 0.74$, $P = .009$).

COMMENTS

In this interesting imaging substudy of patients with coronary plaque and subclinical aortic valve calcification, the investigators have demonstrated a modest correlation between aortic valve 18F-NaF and the presence of high-risk coronary atherosclerosis. In the context of this small post hoc analysis, the pathophysiological implications of this observation are uncertain. It may reflect similarities between the early stages of aortic stenosis and coronary atherosclerosis. However, both conditions are common and become more prevalent with increasing age, while high-risk plaque features on CTCA are frequently seen in patients with coronary atherosclerosis (e.g., 676/2890 and 608/1123 patients in the PROMISE and SCOT-HEART randomized controlled trials, respectively).[16,17] Although calcium metabolism is a key process in both aortic stenosis and coronary artery disease, its role in the complex mechanisms governing these processes may differ. Therefore, while the present study demonstrates the co-existence of aortic valve microcalcification and high-risk coronary plaque, further inferences remain speculative at this stage.

Importantly, the authors do provide further evidence that baseline aortic valve 18F-NaF PET activity predicts progression of valve calcification. Notably, this correlation was observed in a cohort of patients without aortic stenosis, albeit in a subset of the study cohort. These results are in keeping with the existing body of observational data to date (Table 1) and suggest that 18F-NaF PET may be helpful in identifying the minority of patients with aortic sclerosis who go on to develop obstructive stenosis. Larger studies are required to consolidate this finding, while the implications of radiation exposure in this otherwise healthy patient group need to be considered.

This was a retrospective analysis of a small cohort, and the usual caveats apply. Additionally, there was also a preponderance of males (80%), which leaves open the question as to whether findings would be reproducible in both men and women—an important point, given the increasing appreciation of gender disparities in the pathophysiology and clinical presentation of aortic stenosis.[18,19]

Several points should be noted about the imaging analysis undertaken. The authors did not include the presence of spotty calcification or the napkin-ring sign, well-described adverse coronary plaque characteristics,[20] in their analysis. Furthermore, aortic valve 18F-NaF uptake was measured only in regions of visual valve calcification on CT; the highest maximum standardized uptake value of these regions of interest was used to calculate the TBR_{max}. This method may miss 18F-NaF uptake in regions of the valve that do not have visually apparent calcification.[13,14] Previous data have explored the optimum method of quantifying aortic valve 18F-NaF, demonstrating a most diseased segment technique that incorporates regions of interest around the entire valve area in *en face* slices to be the most reproducible, correlating strongly with native and bioprosthetic valve disease progression.[14,15,21] Here, the authors demonstrate a similarly good level of interobserver agreement with their technique. Ultimately, validation against clinical outcomes will be required to demonstrate the incremental benefit of this imaging modality and the various image analysis techniques.

CONCLUSION

Nakamoto *et al* have added to the growing body of literature investigating the associations between baseline vascular 18F-NaF uptake and calcification progression and highlighted a potential association with high-risk coronary plaque. The mechanisms and clinical implications of these correlations require further prospective research, interest in which is rightly engendered by these early observational studies.

Disclosures

All authors declare that they have no conflict of interest.

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