Aortic Valve 18F-Fluoride Positron Emission Tomography 
Can the Skeleton Key Be Copied?

Ian C.Y. Chang, MD; Panithaya Chareonthaitawee, MD

Calcific aortic valve disease (CAVD) is the most common valvular disease in the developed world.\(^1,2\) The disease prevalence is projected to reach 4.5 billion worldwide in 2030, underscoring its significance as a worldwide public health burden. Valve replacement is the only established therapy, but despite recent advances, both surgical and transcatheter approaches still have substantial morbidity and mortality and remain reserved for those with significant hemodynamic complications from severe aortic stenosis.\(^2,3\) For ineligible patients, no proven medical therapy exists to prevent, reverse, or delay the progression of CAVD. The ability to identify individuals who are at risk for CAVD progression and to provide disease-modifying treatment would substantially transform the field.

The study by Pawade et al\(^4\) in this issue of *Circulation: Cardiovascular Imaging* exemplifies the ongoing efforts to use multimodality imaging not only for the diagnosis and management of CAVD but also for greater understanding of the underlying cellular mechanisms and pathogenesis of the disease, which are potential pharmacological targets for CAVD.\(^5,6\) These efforts have their basis in evidence that CAVD is not only a degenerative condition but also the result of complex and tightly regulated processes of inflammation and calcification.\(^1,7,8\) The pathophysiology begins with an early initiation phase, which resembles atherosclerosis, and is characterized by valvular lipid deposition, injury, and inflammation. Because activated macrophages produce pro-ostecogenic factors, a transition to the propagation phase occurs, whereby valvular interstitial myofibroblasts become osteoblast-like cells. The propagation phase is also characterized by severe proinflammatory conditions, which further enhance inflammation and microcalcifications, contributing to greater calcium deposition and leaflet stiffening. In the later stages, calcification seems to be irreversible and unresponsive to medical therapy, in contrast to the early stages when both inflammation and calcification are present and medical therapy might slow the progression of osteogenic changes.\(^1\)

Current clinical imaging techniques, echocardiography, computed tomography (CT), and cardiac magnetic resonance imaging are all outstanding tools for evaluation and management of CAVD but have limitations in quantifying and monitoring early valve calcification and measuring active inflammatory processes.\(^9\) These limitations have been cited as a possible explanation for the negative pharmacological intervention trials in CAVD to date. Several studies have evaluated the effect of statin therapy on the progression of CAVD.\(^8\) The RAAVE trial (Rosuvastatin Affecting Aortic Valve Endothelium) was an open-label prospective trial of rosuvastatin in asymptomatic aortic stenosis with versus without hyperlipidemia. The results suggested that statin therapy might slow CAVD progression in patients with elevated cholesterol. However, 4 double-blinded randomized control trials (ASTRONOMER [Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin], SALTIRE [Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression], SEAS [Simvastatin and Ezetimibe in Aortic Stenosis], and TASS [Tyrolean Aortic Stenosis Study]) and a systematic review of 10 studies totaling 3822 patients failed to replicate this promising finding.\(^10\) Other potential pharmacological interventions of CAVD include bisphosphonates, which are osteoclast inhibitors, and denosumab, a monoclonal antibody targeting the osteoblast-generated calcification pathway. From observational and animal studies, these medications may halt CAVD progression before clinically significant stenosis occurs. The development of these promising disease-modifying targets requires reliable high-resolution and high-sensitivity imaging modalities to identify early CAVD and to measure therapeutic efficacy.

In the past few years, a few groups have developed and validated highly novel positron emission tomography (PET) techniques for imaging CAVD.\(^11,12\) In particular, Dweck et al\(^12\) have used PET with CT and 2 tracers, 18F-fluorodeoxyglucose (18F-FDG) and 18F sodium fluoride (18F-NaF) to target inflammation and calcification, respectively. 18F-FDG is a glucose analogue that allows visualization and measurement of macrophages and proinflammatory cells with high metabolic requirements.\(^8,13,14\) 18F-NaF is a bone tracer that is directly incorporated into hydroxyapatite via an exchange mechanism with hydroxyl groups, thus serving as a potential marker of active tissue calcification. The first demonstration that 18F-NaF PET may detect early valve calcification in CAVD was published by Dweck et al\(^12\) on 121 adults with a range of CAVD severity, from normal to aortic sclerosis to severe stenosis. They reported not only increased uptake of 18F-NaF but also of 18F-FDG in the early stages of CAVD, reflecting both active calcification and inflammation, respectively. In agreement with background studies, they also noted a progressive increase in uptake of both tracers with increasing stenosis severity but greater calcification than

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From the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN.

Correspondence to Panithaya Chareonthaitawee, MD, Department of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail chareonthaitawee.panithaya@mayo.edu


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inflammation in the later stages. Furthermore, 18F-NaF uptake was observed in regions remote from advanced calcification, implying that 18F-NaF may detect microcalcifications.

Although Dweck et al.12 have previously demonstrated excellent repeatability in quantifying 18F-FDG and 18F-NaF uptake in the valve leaflets, these PET techniques remain highly novel and require additional protocol optimization and assessment of clinical use in larger prospective studies. As such, Pawade et al.14 take the necessary steps to refine, optimize, and test their aortic valve 18F-NaF PET technique. In the current study, they examined their protocol performance with different PET/CT acquisitions and image analytical methods in a stepwise approach in 15 male patients with mild-to-severe aortic stenosis. They reported that ECG-gated PET and contrast-enhanced CT permitted adequate spatial resolution to localize the 18F-NaF signal to individual aortic leaflets that was not achieved with previous approaches. This is especially relevant when the calcification process on nearby coronary arteries could conceivably interfere with the valvular interpretation.7 Furthermore, they noted increased tracer uptake at the leaflet tips and commissures, where mechanical stress would be the greatest. By adopting the right atrium blood-pool correction and most diseased segment approach, they showed a significant reduction in relative error of the mean tissue to background ratio. Their scan–rescan results were reproducible with high intra- and interobserver variability. These results set the stage for 18F-NaF PET/CT to be the potential method of choice for detecting early calcification in CAVD and for its promising use in clinical trials of efficacy.

Despite the promising findings, the current study and the literature on human aortic valve 18F-NaF PET/CT imaging have their limitations. First, the current study reported on only 15 patients with aortic stenosis of varying severity in a single tertiary center. Second, the scan–rescan reproducibility in this study included data analyzed only by 2 highly experienced operators who developed the technique. Third, even though the right atrium blood pool-correction and the most diseased segment approach have reduced the number of steps for image analysis, the final approach still involves significant operator interaction that could affect repeatability and reproducibility when performed by less experienced operators. Fourth, the severity of aortic stenosis in this study was ascertained by transthoracic echocardiography, which has its own limitations including inconsistent grading of the severity of the stenosis15 and the inability to accurately detect calcification.13,16 These limitations extend to the current literature on human aortic valve 18F-NaF PET/CT imaging which has, thus far, been conducted almost exclusively by a single group, thus possibly reporting on a more homogenous population and on data analyzed by a few highly experienced operators.11,12,17–19 To date, only one study has been published by a different group of investigators.13 Hyafil et al.11 conducted a feasibility study of ongated, nonenhanced 18F-NaF PET/CT scans using the right atrium for blood-pool correction in 5 patients with severe aortic stenosis and 20 controls without aortic stenosis. Their study also demonstrated significantly higher 18F-NaF uptake in patients with aortic stenosis compared with those without CT evidence of valve calcification and high intra- and interobserver reproducibility of 18F-NaF PET/CT measurements. Another important aspect of aortic valve 18F-NaF PET/CT imaging to consider is its ability to predict disease progression and clinical events. Thus far, 2 longitudinal studies have been published in this regard.17,19 A study of 30 aortic stenosis patients found that baseline 18F-NaF uptake correlated with increased aortic valve calcification on CT calcium scoring at 1 year.17 Another study of 121 volunteers with and without aortic valve disease (20 controls, 20 with aortic sclerosis, and 25 with mild, 33 with moderate, and 23 with severe aortic stenosis) reported the emergence of 18F-NaF PET as a predictor of clinical outcome after age and sex adjustments.19 A retrospective analysis in that study also demonstrated that patients with aortic stenosis and higher than expected 18F-NaF uptake for a given CT calcium score experienced 3 times faster disease progression than those with lower than expected uptake. However, 18F-NaF PET did not offer independent prediction of clinical outcomes after correction for CT calcium scoring, likely reflecting the small number of events and the collinearity between CT calcium scoring and 18F-NaF uptake in the valve.

Although Pawade et al. have successfully demonstrated that additional refinements to their aortic valve 18F-NaF PET/CT imaging are associated with a high degree of reproducibility in the current study, further investigations are clearly needed. The next steps should include further optimization of aortic valve 18F-NaF PET/CT imaging analysis routines, perhaps by incorporating computer algorithms to increase automation and reduce operator interaction; larger studies to confirm the high level of reproducibility and applicability of these techniques in multiple settings, with less experienced operators, and in different populations; addition of validated high-resolution invasive imaging modalities not only to ascertain the severity of aortic stenosis but also to understand the mechanisms at various stages of CAVD; assessment of the role of multimodality imaging, not only with CT for its use in providing detailed valve anatomy and quantification of established valve calcification but also with cardiac magnetic resonance imaging, for its detection and quantification of fibrosis and other tissue characteristics; development of more specific tracers and imaging protocols for specific bone cell phenotypes and matrices; and larger prospective studies to examine the incremental use of 18F-NaF for prediction of disease progression and adverse cardiovascular outcome.

Disclosures
None.

References


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