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F-18-Fluoride Imaging for Atherosclerosis Reply

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molecular calcification with ^{18}F -fluoride PET/CT: will this become a clinical reality and a challenge to CT calcification scoring?" (3), published earlier on the same topic.

In addition, we take issue with a number of points made by the authors (1). Although we agree with them that it is feasible to detect cardiac calcifications using ^{18}F -sodium fluoride far in advance of visualizing this phenomenon with x-ray computed tomography (CT), attempts to image coronary artery calcification by visualizing the artery on CT scan are challenging for a variety of reasons. First, it is extremely difficult to localize the coronary arteries without the assistance of contrast dye. The administration of x-ray contrast agent is not practical for screening of individuals at risk, given the potential toxicity of these agents. As noted by the investigators (1), it is necessary to assign regions of interest on clearly visualized calcifications on CT scan for detecting the ongoing calcification. Because the power of ^{18}F -sodium fluoride technology lies in its early ability to detect molecular calcification in advance of structural abnormalities observed on CT scan, assigning a region of interest based on coronary artery calcification is not feasible in early disease in younger patients. Second, the authors (1) failed to address the need for partial volume correction, which is of importance in such small structures as coronary arteries because loss of signal or spillover from adjacent signal may occur when a relatively small region of interest is evaluated. Particularly, motion artifacts due to the cardiac cycle further degrades the spatial resolution and necessitates partial volume correction. Third, the blood pool correction for background activity of tracer adds further complexity and potential error.

We believe that a methodology independent of recognition of vascular distribution, a global assessment, will be of great value in detecting early disease before calcification is apparent on electron beam CT imaging. The methodology that we presented in publications predating the recent article by Dweck et al. (1) describes a global assessment of molecular calcification detected with ^{18}F -sodium fluoride. Although the methodology described in this article (1) appears to be reproducible by the investigators involved, this may not be the case for inexperienced practitioners. A global assessment of cardiac calcification obviates the need for partial volume correction and therefore is essential in assessing overall calcification in the heart. In addition, a global approach allows for delayed imaging of 2 to 3 h after the administration of sodium fluoride, which would obviate the need for blood pool correction.

There is certainly a dire need for visualizing atherosclerotic disease in early stages and ^{18}F -sodium fluoride imaging may realize this objective. Prospective, randomized clinical trials are needed to determine the feasibility and clinical benefit of ^{18}F -sodium fluoride imaging for early atherosclerotic disease.

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Reply

We thank Dr. Mohler and colleagues for their interest in our study and for their communication. We agree that prospective randomized clinical trials are now required to assess the clinical benefit of cardiovascular ^{18}F -sodium fluoride (^{18}F -NaF) scanning.

Our paper was the first prospective description of ^{18}F -NaF uptake in the coronary arteries of patients specifically studied to assess the heart (1). The highlighted paper by Behshti et al. (2) described ^{18}F -NaF activity within the heart in a small retrospective cohort of patients with cancer that did not localize ^{18}F -NaF uptake to the coronary arteries. Their approach was to draw ellipsoid regions of interest around the cardiac silhouette on noncontrast axial images. We previously demonstrated that ^{18}F -NaF activity also occurs within noncoronary structures in the heart, most notably the aortic valve and mitral valve annulus (1). As such, cardiac and coronary ^{18}F -NaF uptake cannot be considered synonymous.

There is the further question of whether it is possible to measure ^{18}F -NaF uptake only in the coronary vessels. We demonstrated that this is the case and is evidenced in the images and the excellent measures of reproducibility we obtained and reported in our paper. Most of our population with aortic stenosis had high calcium scores, and so it was readily possible to determine the course of the coronary arteries on both the electrocardiogram-gated and non-gated scans. We accept that in patients with less advanced disease, computed tomography coronary angiography will be required to better visualize the lesions displaying increased ^{18}F -NaF uptake. Indeed we are currently conducting such a study and can localize ^{18}F -NaF uptake not only to individual coronary arteries but also individual plaques and their components.

We recognize that the issue of partial volume averaging is important in positron emission tomography (PET) imaging. However, the spatial resolution of PET is approximately 3 mm. We are interested in localizing ^{18}F -NaF activity to individual plaques, which are commonly 20 to 30 mm long in vessels with a diameter of 3 to 4 mm. Therefore, our approach is well within the spatial resolution of PET, especially given the very high signal-to-background ratio observed with ^{18}F -NaF in the heart. Quantifying the maximum uptake value is straightforward as reflected by our excellent measures of reproducibility, and we are confident that our approach will be reproduced by other groups. Indeed, several studies have confirmed the feasibility of this approach using ^{18}F -fluorodeoxyglucose in the coronary arteries (2,3).

Given the above, we do not believe that a volume of interest approach to the measurement of ^{18}F -NaF uptake in the heart is warranted. This would result in coronary arterial ^{18}F -NaF measures being conflated with valvular uptake. In addition, that approach would fail to harness the high sensitivity and spatial

resolution of PET to define the precise locations of ^{18}F -NaF uptake in coronary arteries.

Finally, we do agree with Dr. Mohler and colleagues that, after further validation, ^{18}F -NaF PET of the coronary arteries may give unique insights into the pathophysiology of calcium deposition and perhaps its dispersal with appropriate therapy.

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Efficiently Doing the Wrong Thing

We would like to commend Felker and Mentz (1) for their comprehensive review of volume removal therapy for patients with acute decompensated heart failure (ADHF). However, we also would like to challenge their most basic assertion that “fluid retention and congestion are responsible for 90% of HF hospitalizations.” Neither of the references they cite (2,3) provide data to support that fluid retention occurs before the onset of ADHF in most patients. In fact, more recent studies that have measured weight gain (as a surrogate for fluid retention) show clearly that most patients gain either no, or minimal, weight before hospitalization for ADHF (4,5) despite increased cardiac filling pressures (5).

To account for increased cardiac filling pressures in the absence of weight gain, volume shifts rather than volume gains must occur. In a recent manuscript (6), we elucidate the likely mechanisms underlying these shifts, which involve a normally compliant splanchnic venous system that becomes noncompliant and results in redistribution of volume to the cardiopulmonary circulation, a process that can occur rapidly. We also point out that even in the minority of patients who do experience weight gain, little of the excess fluid resides within the effective circulatory volume (approximately 2.5%). The majority of patients presenting with congestion

likely have a syndrome of sympathetically mediated redistribution of volume and diuretic resistance.

Fluid retention and congestion do not necessarily represent the same phenomenon, and congestion most often is not due to fluid overload. Thus, strategies aimed at removing salt and water will necessarily be fraught with complications, including intravascular volume depletion, activation of the renin-angiotensin system, worsening renal function, and iatrogenically induced cardiorenal syndrome. Therefore, we caution readers to reconsider volume removal as the prime target of therapy for patients with ADHF. Diagnosing the contribution of redistribution versus total body salt and water gain emerges as the primary decision point, followed by therapy directed at the underlying etiology of congestion.

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Reply

We thank Drs. Dunlap and Sobotka for their interest in our recent review on volume removal in patients with acute decompensated heart failure (ADHF). We agree with them that redistribution of volume (rather than increase in total body volume) may be an important and underappreciated mechanism in patients with acute decompensated heart failure, as our group has suggested previously (1).

Although we welcome “outside the box” thinking in a field that clearly would benefit from new ideas, we also suggest that the results from recent clinical trials might dampen the enthusiasm for