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EDITORIAL COMMENT

Penile Artery ^{18}F-NaF Uptake and Erectile Dysfunction

Off-Target Molecular Insights*

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Molecular imaging serves as a powerful tool for cardiovascular clinical care and research. These techniques, especially those using positron emission tomography (PET) integrated with computed tomography (CT) or magnetic resonance imaging, have become integral in the care of individuals with suspected or known coronary and systemic atherosclerosis, cardiac sarcoidosis, and cardiac amyloidosis, among others (1-4). Concurrently, basic and clinical research continues to yield novel applications of molecular imaging to study the biology underlying cardiovascular pathologies, to assess response to therapy, and to identify findings with important clinical implications.

Multimodality imaging with PET/CT provides a unique opportunity to measure tracer activity and structural features simultaneously within distinct tissues. Leveraging the multitissue imaging afforded by this technique, a growing body of research has generated novel insights by evaluating tracer activity outside of the original tissues of interest. Within this paradigm, ^{18}F-florbetapir, a PET tracer initially used to identify protein deposition in Alzheimer disease, has been implemented in cardiac and extracardiac amyloidosis (3,5). Similarly, uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a radioactive glucose analog used to assess for malignancy, myocardial viability, systemic inflammatory diseases, and infection, has additionally been used to evaluate atherosclerotic inflammation (6). Assessment of ^{18}F-FDG uptake can also be leveraged to elucidate multiorgan disease mechanisms. For example, ^{18}F-FDG activity measured in the amygdala, a neural center involved in the neurobiological response to psychosocial stress, was recently found to robustly predict the risk of subsequent cardiovascular disease (CVD) through a serial pathway:

↑amygdalar activity → ↑bone marrow activity → ↑arterial inflammation → ↑CVD risk (7)

Hence, multitissue, multimodality molecular imaging provides a trove of valuable information beyond the initial target tissue alone.

In this vein, investigators have derived important insights into CVD by studying off-target ^{18}F-sodium fluoride (^{18}F-NaF) uptake. ^{18}F-NaF is a PET tracer that binds to hydroxyapatite and has been used for decades to identify bone formation and pathologies (e.g., metastatic disease) (8). Importantly, ^{18}F-NaF-PET/CT imaging localizes to biologically active microcalcifications (<50 μm) that are far below the detection threshold of CT (9). Previously, observant imagers noticed incidentally that ^{18}F-NaF frequently accumulated in cardiovascular tissues. Subsequent studies showed that ^{18}F-NaF uptake is greater within rupture-prone or symptomatic atheroma, and can predict CVD events (9-11). Accordingly, measurement of ^{18}F-NaF activity within larger arteries has developed into an exciting technique for imaging atherosclerosis.

The study by Nakahara et al. (12) in this issue of the *Journal* takes advantage of many of the aforementioned strengths of ^{18}F-NaF and of multimodality molecular imaging to derive its innovative finding.

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The researchers astutely made the observation that penile arterial ^{18}F-NaF uptake was frequently heightened in patients with prostate cancer who also had erectile dysfunction (ED). Given that endothelial dysfunction plays an important role in ED (13), the investigators hypothesized that penile arterial ^{18}F-NaF uptake may serve as a marker of vasculogenic ED. To test that hypothesis, they retrospectively analyzed penile arterial ^{18}F-NaF uptake on PET/CT images that were initially acquired to assess for bone metastasis in 437 prostate cancer patients. They found that individuals with prevalent ED (i.e., diagnosed before scanning) or incident ED (i.e., diagnosed within 1 year of follow-up) had significantly higher penile ^{18}F-NaF uptake than those without ED. Further, higher ^{18}F-NaF uptake associated with a greater likelihood of developing ED after adjustment for covariables including cancer treatment, vascular macrocalcifications, and pharmacotherapies associated with ED.

Additionally, the investigators harnessed structural data from the CT images to measure arterial macrocalcification. Interestingly, unlike the substantially larger Multiethnic Study of Atherosclerosis, the current study found no significant relationship between CT-detected large-vessel atherosclerotic macrocalcification and ED (14). It is possible that the current study was underpowered to observe a significant association between macrocalcification and ED, or perhaps the pathobiology of ED in prostate cancer differs from the general population. However, the investigators convincingly showed that ^{18}F-NaF measures of penile arterial microcalcification predict ED substantially more robustly when compared with CT measures of large-vessel macrocalcification in this study's population.

This study's findings have near-term implications. First, they raise the possibility that the process of penile arterial microcalcification may contribute to the development of ED. Future studies should evaluate whether antagonism of penile artery microcalcification may be effective in ED (perhaps using drugs that reduce calcification activity, including those that are currently being investigated in the context of aortic valve calcification). Second, the study highlights ^{18}F-NaF imaging as a novel tool that could be used to study vasculogenic ED: to enrich ED trials by identifying individuals at highest risk for ED or to be used as a surrogate marker for predicting treatment response. Third, ^{18}F-NaF PET/CT imaging continues to be used routinely for assessment of possible bone pathology; thus, high penile arterial ^{18}F-NaF activity will no doubt be recognized incidentally. The question of what to do for such individuals with incidentally observed high penile arterial ^{18}NaF uptake will certainly arise. Although further work is still needed to define the clinical utility of this imaging approach, in the meantime, it may be reasonable to consider individuals with high penile ^{18}NaF uptake to be at increased risk for ED and to contemplate referral to a urologist for interventions that may ameliorate or prevent ED.

This study is not without limitations. Its cohort was derived retrospectively, and all individuals had prostate cancer, so broad generalization of the findings should be avoided. Additionally, the number of individuals without ED in this cohort was small but was consistent with the high prevalence of ED in a treated prostate cancer population. Therefore, the reported accuracy of this approach for predicting ED should be interpreted cautiously. Prospective studies of larger populations of subjects with and without cancer are needed to evaluate the utility of ^{18}F-NaF imaging for assessment of ED risk. Furthermore, the observation of an association between microcalcification and ED risk, while intriguing, does not denote causation.

Despite these limitations, the study by Nakahara et al. (12) is noteworthy. It represents an initial innovative use of ^{18}F-NaF imaging to evaluate penile artery atherosclerosis and shows that penile arterial ^{18}F-NaF uptake may predict the subsequent development of ED. Should these findings be confirmed in prospective studies, then penile ^{18}F-NaF uptake could be evaluated routinely in clinically obtained ^{18}F-NaF scans, providing an opportunity to initiate interventions aimed at forestalling the development of ED.

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