EDITORIAL

Novel application of ^{18}F-sodium fluoride an old tracer to a clinically neglected condition

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Janssen and co-investigators report the results of a retrospective study of 409 oncology patients who underwent ^{18}F-sodium fluoride PET/CT for evaluation for bone metastases. The scans from these patients were read for the presence of linear uptake of the tracer in the femoral arteries as a molecular signal for calcification of the media of these large arteries and marker for increased vascular stiffness associated with increasing age and risk factors for diffuse atherosclerosis particularly hypertension and diabetes. This same group has published several papers where they reported focal uptake of ^{18}F-sodium fluoride in atheroma in the carotid arteries, abdominal aorta, and ascending aorta identified by CT and/or F-18 FDG uptake.[1-3] This report extends findings into a different pathological but related entity: arterial medial calcification.

Targeting bone formation with ^{18}F fluoride ion was first reported in 1962[4] and was a standard bone scanning agent until the 1970s when it was supplanted by ^{99m}Tc diphosphonate compounds because of the more widely available gamma scintillation cameras. Since PET imaging has advanced technologically and become more widely available the use of ^{18}F-sodium fluoride for bone imaging has returned.[5] In addition to the skeleton, calcification also occurs in vascular tissue. There are two major types of arterial calcification: atherosclerotic plaque calcification involving the intimal layer of the vascular wall and calcification of the media tunica layer referred in the older literature as Monckeberg's sclerosis and more commonly as medial elastocalcinosis (MEC). While these two conditions share some molecular mechanisms they are considered as two distinctly different pathological entities with different sites in the vascular wall and distributions in the vascular tree with different appearances on imaging studies. Atherosclerotic plaque calcification is more focal in appearance and localized to the common sites of atherogenesis such as the coronary arteries, carotids aorta, and iliofemoral arteries with predilection to more proximal locations and branching. Atherosclerotic plaque calcification is localized to the intima with similarities to osteogenesis and involvement of bone morphogenic protein (BNP) signaling,[6,7] while MEC is localized to the media and arises from an interplay of both biological (hormonal) and physical factors.

Molecular imaging approaches to atherosclerotic plaque imaging using radionuclides target biological sites involved in the initiation, evolution, and development of vulnerability and numerous sites and probes have been investigated.[8] The soft (non-calcified) plaques are at greater risk for rupture.[9] Plaque calcification is seen in more advanced and complex lesions. Coronary calcification on CT indicates that coronary atherosclerosis is present but does not identify flow limiting coronary lesions nor lesions that are prone to rupture. When combined with a targeting probe such as FDG, hybrid PET/CT imaging can provide information on components of disease advancement (calcium) and activity (inflammation) in the same scan.[10,11]

In contrast to the appearance of calcification in atherosclerotic plaques, MEC involving the media of larger arteries is linear in appearance described as resembling ''railroad tracks,'' and seen in the aorta and vessels supplying the lower limbs with higher wave velocities. It can occur in the absence of atherosclerotic plaques and is increased with age, hypertension, and metabolic diseases such as chronic renal insufficiency and diabetes.[12,13] Experimental evidence supports the interplay of both passive and active processes in its development. Hemodynamic consequences of MEC include rises in systolic BP and widening in the pulse pressure which is observed with advancing age and represent the physiological consequences of increases in arterial stiffness and reduction in arterial elasticity and compliance. These physiological manifestations affect the heart by increasing afterload and contributing to left ventricular hypertrophy. Understanding causative mechanisms for MEC can lead toward finding applications for this imaging tool.

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J Nucl Cardiol 2013;20:506–9.
1071-3581/$34.00

doi:10.1007/s12350-013-9724-0

The media of large arteries includes vascular smooth muscle cells (VSMC) and extracellular matrix (ECM) composed of elastic lamellae and collagen fibrils. The structure and cross-linking of the ECM and VSMCs provide the mechanical properties needed for stretching and recoil to accommodate pulsatile flow. VSVC's comprise 30%-50% of the tissue volume, elastic lamellae 25% providing elasticity, and collagen 35% providing stiffness and tensile strength.[12] The mechanical properties of arteries are altered as a result of changes in these component parts. An interplay of mechanical and biological factors leads to MEC but central in many of these contributing pathways is degradation and fragmentation of elastin which is the most abundant protein in the vascular wall.[14] This protein is largely produced in early life with little turn-over and capacity for repair. In experimental animal studies, characteristic pathological features of vascular aging are thinning, splitting, and fraying of the elastic lamellae with matrix metalloproteinases playing a role in this process.[15] An interesting early observation that implicated elastin as central to MEC is the notable absence of MEC in syphilitic aortitis in which elastic elements of the media are destroyed.

Both mechanical (passive) and biological (active) factors have been identified as contributing to degradation of elastin and these include mechanical strain, oxidative stress, changes in local tissue polarity, and inflammation.[12,13] There is a direct correlation between elastin degradation and MEC. Among the biological factors identified as contributing to the development of MEC is advanced glycated endproducts (AGEs) in which glucose binds to the slow turn-over proteins in the vascular wall by a non-enzymatic process.[16] These AGEs are ligands for receptor for advanced glycated endproducts (RAGE) and are expressed on smooth muscle cells. The ligand/receptor binding initiates downstream pathways for inflammation which contributes to elastin degradation. This mechanism is particularly important in diabetes. Elastin degradation products are polar molecules that create a local environment promoting calcium binding.[17] The polar environment created by elastin degradation has also been postulated to attract cholesterol and there are similar rises in both cholesterol content and calcium in artery walls with aging. In addition to elastin, VSMC also play a role in initiating MEC.[18-20] They express RAGE and are the likely source for promoting inflammation. In addition, there is experimental evidence showing the presence of matrix vesicles similar to those seen in foci of calcification of cartilage, bone, and dentin and it has been suggested that these vesicles are extruded from VSMCs undergoing apoptosis in the vascular media.[19,20]

Cigarette smoking is recognized as an important clinical risk factor for vascular disease. Vitamin D3 plus nicotine administration to experimental animals produces calcium overload and the animal model is characterized by elastocalcinosis in elastic large arteries.[21] Two metabolic diseases that are characteristically associated with MEC are diabetes renal disease. Both these conditions are associated with diffuse medial calcification and atherosclerotic plaque calcification. In renal failure, all of the pathways to MEC described above are stimulated by uremic toxins and high phosphates and bone matrix protein plays a role in MEC in renal failure as well as in atherosclerotic plaque calcification.[22,23] In patients with end stage renal disease, diffuse arterial calcification produces arterial wall stiffening and the consequent adverse hemodynamic effects of this calcification leads to further reduction in renal blood flow and increases in afterload on the heart and reduction in coronary perfusion pressure. Hyperglycemia is a strong and independent risk factor for diffuse vascular calcification.[24] Similar to renal insufficiency the metabolic derangements in diabetes contribute to many of the known pathways to elastin degradation and VSMC apoptosis, oxidative stress, and mechanical stress with the additional contribution of increases in AGEs. The physiological consequence is similar to that described above with deleterious effects on regional perfusion and cardiac function.

These mechanical and biological factors contributing to MEC in the aging process and in common diseases such as diabetes and renal insufficiency, and the adverse consequences of diffuse vascular calcification on hemodynamics tie in well with observations from clinical studies showing correlations between MEC and risk for CV events. An imaging test that can sensitively diagnose and quantify MEC could serve as a CVR marker and as a biomarker to follow in pharmacological therapy to regress vascular calcification. Successfully accomplishing this latter goal to regress MEC would improve vascular compliance, reduce systolic hypertension, and reduce afterload on the heart and improve the health of the CV system.

There are advantages of bone avid nuclear imaging agents to diagnose and quantify vascular calcification compared to x-ray studies. Uptake of the bone avid agents depends on the active process of bone metabolism. Hawkins et al[25] investigated the skeletal kinetics of ^{18}F-sodium fluoride with dynamic PET imaging and tested a three-compartment model and Patlak graphical analysis to quantify regional and diffuse metabolic bone disease and imaging. In this study, Janssen and co-investigators used a semi-quantitative approach based on target to background to measure tracer uptake. Vascular locations were analyzed both for calcification by CT and

uptake of the bone avid PET agent. They distinguished focal calcification as representing calcified atherosclerotic plaque and linear calcification representing MEC. About 46% of the 159 patients with linear femoral uptake showed medial-type linear calcifications on CT. This indicates that ^{18}F-sodium fluoride accumulation is more sensitive for detecting MEC than x-ray. This is predictable when one considers that identification of calcium on CT is based on the purely physical density of bone with reduced x-ray attenuation compared to soft tissue and air, while uptake of the bone avid agent represents an active metabolic process.

Janssen et al. found a significant correlation of their measurements of femoral artery calcification with age, hypertension, hypercholesterolemia, diabetes, and history of cigarette smoking. Patients with renal disease were excluded. They also found a significant correlation between linear calcification in the femoral arteries and number of calcified plaques per patient. This is not unexpected as the risk factors for both processes are similar. It would be of interest to know if there were any patients with isolated femoral artery linear calcification in the absence of calcified atherosclerotic plaque in patients with isolated hypertension or heavy cigarette smokers to document by this imaging method the separate nature of these two types of vascular calcification.

Importantly, this imaging agent has been approved for clinical use for many years and PET imaging is now widely available and performed commonly with CT allowing assessment of both vascular calcification by CT and active bone metabolic activity. The authors suggest potential use of this imaging approach to assess CV risk. A more focused application would be to consider the opportunity to use semi-quantitative or quantitative measures of ^{18}F-sodium fluoride uptake in the large arteries of the lower extremities to evaluate drugs that have the potential to regress MEC. The process of vascular wall stiffening that increases with age and is accelerated by physical and biological factors changes the biology of the vascular wall with loss of VSMC and fragmentation of elastin and increase in collagen and finally with calcification of the media. Calcification makes a poorly compliant vessel into a structure resembling a rigid pipe which cannot change its capacitance to accommodate pulsative flow which produces adverse upstream and downstream effects on CV hemodynamics. Reversing these structural changes in the vascular wall would reduce SBP and reduce afterload on the heart, improve renal perfusion and drop LVEDP. Antihypertensive therapy has been designed primarily to reduce diastolic pressure but the detrimental effects of systolic hypertension especially in older patients are recognized.[26-29] In experimental animal models, hydrochlorthiazide and irbesartan when given to animals prospectively prevented MEC but did not regress it.[30] However, the endothelin receptor antagonist darusentan when given to experimental animals not only prevented but also regressed MEC.[30] These important observations point toward the need for a clinical marker for MEC regression to evaluate the effects of antihypertensive drug therapy targeting the vascular wall. By applying an old radiopharmaceutical developed to image bone metabolic activity to a vascular application, Janssen and colleagues have provided us with such a potential marker.

There are limitations to this study. The patient cohort comprised oncology patients referred to the nuclear medicine department for skeletal imaging. As the authors point out in their ''Limitations'' section the imaging approach needs to be applied prospectively to a group of non-cancer patients at risk for MEC and the imaging protocol optimized for vascular imaging.

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