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Early aortic valve inflammation precedes calcification: A longitudinal FDG-PET/CT study

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ABSTRACT

Objectives: Recent data shows a relationship between aortic valve (AV) inflammation and calcification. However, direct evidence linking early valve inflammation (prior to hemodynamic compromise) to subsequent calcium (Ca) deposition is lacking in humans. We sought to test the hypothesis whether local AV inflammation predisposes to subsequent AV Ca deposition. **Methods**: We identified 111 individuals (age 60[49, 68], 50.5% male) without active cancer or aortic stenosis who underwent 2 PET/CT studies 1–5 years apart for cancer surveillance. AV inflammation was determined by measuring FDG uptake (maximum standardized uptake value, SUVmax) within the AV on baseline PET/CT. Subsequent deposition of AV Ca was determined by comparing baseline and follow-up CT scans, determined as an increase in AV Ca volume score (CaVS). Patients were classified as "non-progressors" or "progressors" based on Square Root difference in CaVS (using a pre-determined cut-off value of 2.5). CT and PET measurements were conducted by 2 mutually blinded laboratories. **Results**: During follow-up, AV Ca increased in 23 patients (20.2%) classified as "progressors", of whom 9 (9.2%) demonstrated subsequent 'incident' AV Ca. The AV SUVmax (mean ± SD) was higher in progressors vs. non-progressors (2.03 ± 0.52 vs.1.74 ± 0.36, $p = 0.02$) and especially in patients with-vs. without-incident AV Ca (2.28 ± 0.42 vs. 1.73 ± 0.36, $p < 0.001$). Moreover, AV inflammation (AV SUVmax) independently predicted subsequent calcification after adjusting for cardiovascular risk factors [OR (95%CI): 4.99 (1.30–19.15), $p = 0.02$]. **Conclusion**: The findings suggest that early AV inflammation may predispose to AV sclerosis. The evaluation of valvular metabolic activity may prove useful for developing a better understanding of calcific valve disease.

1. Introduction

Calcific aortic valve disease (CAVD) is a slowly progressive pathological process manifesting as a spectrum of clinical disease, ranging from early mild valve thickening (aortic sclerosis), to severe calcification with impaired leaflet motion and obstruction of blood flow (aortic stenosis) [1]. CAVD has been established as an active inflammatory process with lipid accumulation, upregulation of angiotensin converting enzyme activity and infiltration of macrophages and T-lymphocytes [1–4]. Inflammatory cellular infiltration was demonstrated early on in the disease process in histological specimens [3] and in animal models using non-invasive molecular imaging techniques [5].

^{18}F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) has been validated for measurement of arterial inflammation [6] and FDG uptake has been shown to correlate with macrophage concentration in atherosclerotic plaques in animals [7,8] and humans [9,10]. Recently, PET/CT imaging of the aortic valve has been reported, and AV FDG uptake was shown to be higher in mild to moderate AV stenosis, and an elevated AV FDG signal has been shown to be predictive of subsequent progression of hemodynamic abnormality associated with AV stenosis [11,12]. Given that FDG

Abbreviation: AV, aortic valve; Ca, calcium; CAVD, calcific aortic valve disease; CT, computerized tomography; CaVS, calcium volume score; FDG, 18F-flourodeoxyglucose; PET, positron emission tomography; ROI, region of interest; SUVmax, maximum standard uptake value; TBR, target to background ratio.

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uptake in the arterial wall is associated with subsequent deposition of calcification in the same location [13], it was hypothesized that in AV as well, a similar relationship between FDG uptake and subsequent calcification would be observed. However, a recent study failed to observe a relationship between baseline ^{18}F-FDG and future valvular calcification [14]. Nonetheless, that was a small study of 18 patients (12 of whom had established AV stenosis). Additionally, preclinical models suggest that valve inflammation may play a more important role in earlier forms of CAVD [5].

Accordingly, the goal of this study was to test the hypothesis that early AV inflammation (prior to hemodynamic compromise), predisposes to AV calcification. To do so, we assessed the relationship between initial AV PET signal and subsequent AV calcium (Ca) deposition in a relatively large cohort of individuals without AV stenosis who underwent FDG-PET/CT imaging. Thereafter, AV Ca deposition was evaluated using serial Computed Tomography (CT).

2. Methods

2.1. Design and subjects

We identified 1410 unique patients who previously underwent at least 2 PET/CT examination spaced 1–5 years apart for clinical indications, between years 2004–2011 at the Massachusetts General Hospital in a prior study to evaluate the effect of local vascular inflammation and subsequent calcification [13]. We have selected same population for our current study and excluded any patient that had one or more of the pre-defined exclusion criteria: age <35 years, diagnosis of Aortic Stenosis on Transthoracic Echocardiography, presence of chronic inflammatory disease, use of chronic anti-inflammatory medications, or presence of active malignant cancer (defined as any radiological or pathological evidence of malignant cancer disease or undergoing chemotherapy or radiation therapy within 1 year prior to initial PET/CT and throughout the inter-scan duration). Accordingly, 111 unique patients meeting the above criteria were identified. Thereafter, their image sets were prepared for blinded analysis of the PET and CT images by two geographically distinct investigative groups who were blinded to the clinical data (see Fig. 1). The group performing analysis of AV FDG uptake was provided the baseline fused FDG-PET/CT imaging studies, but not the subsequent PET or CT images in order to ensure that they would remain blinded to changes in AV Ca. The group measuring AV Ca was provided the baseline and follow-up attenuation correction CT scans (but not the PET imaging data). Accordingly, complete mutual blinding between the two groups was achieved.

2.2. Imaging acquisition and analysis

FDG-PET imaging was performed on a hybrid PET/CT scanner (Biograph 64, Siemens, Forcheim, Germany, or similar system). Briefly, FDG was administered (~10 mCi) intravenously after an overnight fast, and PET images were acquired 45–60 min later (mean = 51 min) in 3-dimensional mode. Patients were imaged in the supine position, and images were obtained over 15–20 min per bed position.

A nongated, non contrast-enhanced CT was obtained for attenuation correction of PET images. CT imaging was performed using a pitch 1.0, tube voltage 120 kVp, tube current of 40 mA s, and slice thickness of 5 mm. Prior studies have demonstrated that calcium scores measured on CT images obtained from a hybrid PET/CT scanner is comparable to that obtained on a dedicated CT scanner [15]. Additionally, all patients underwent contrast enhanced CT as a part of the protocol for FDG-PET imaging for cancer patients.

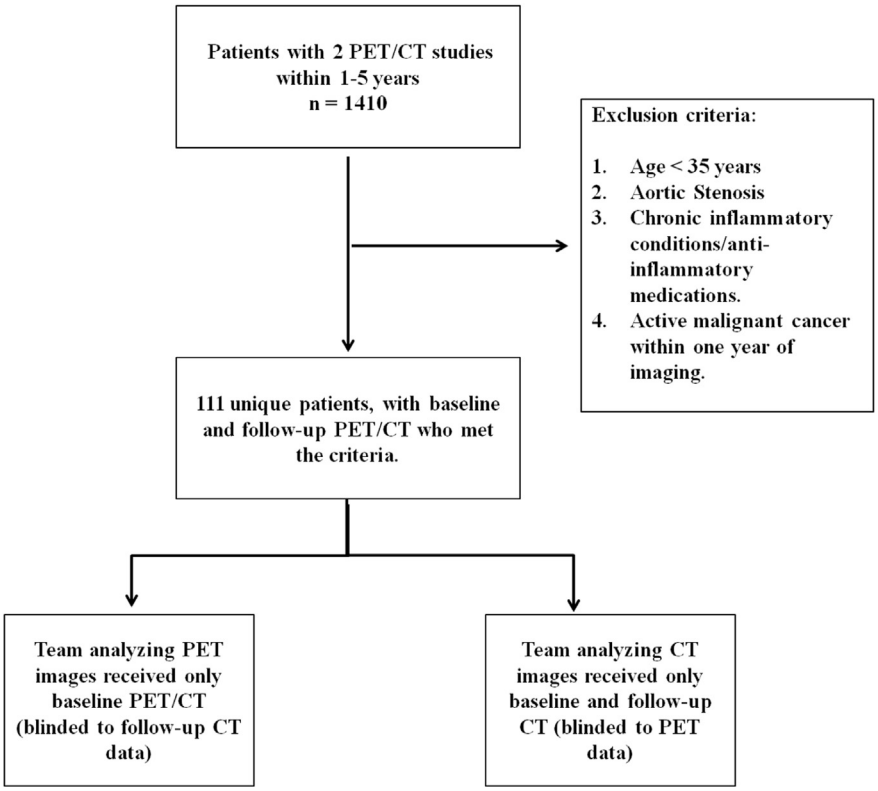

Fig. 1. Study flow chart. CT = Computed Tomography, PET = Positron Emission Tomography.