Association of Baseline Subject Characteristics with Changes in Coronary Calcification Assessed by 18F-Sodium Fluoride PET/CT

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Introduction

Plaque macrocalcification and microcalcification are associated with atherosclerosis. Atherosclerosis often does not have symptoms, but when severe it can lead to a heart attack or stroke. Macrocalcification can lead to plaque vulnerability and increase the potential for the rupture that causes cardiovascular events [1-3].

While CT imaging is capable of identifying macrocalcification, it cannot detect microcalcification [1]. 18F-Sodium Fluoride (NaF) is a radiopharmaceutical with affinity for fluoride to hydroxypatite. For this reason, it is appealing for bone imaging. Recent studies have shown that NaF could also be used to detect calcified micro-deposits within coronary plaque [1, 2, 4-8]. NaF PET/CT is the only noninvasive imaging technique currently capable of distinguishing between macro- and microcalcification [2]. NaF is able to distinguish between areas of macro and microcalcification because the extent of fluoride absorption depends on surface area, making it more likely to bind to microcalcification but unable to penetrate deeper into areas of macrocalcification [2]. The method of using NaF PET/CT scans to detect microcalcification has been shown to be repeatable and reproducible [8].

Fluoride uptake has been shown to correlate with cardiovascular disease risk and have a direct link to myocardial infarction [4, 5, 9]. Many individuals with coronary artery disease are asymptomatic. One study of middle aged Western asymptomatic subjects found that a majority had scans indicating coronary artery disease [10]. NaF imaging has been shown to be feasible even in healthy patients [11]. The disease is often a silent killer, leading to abrupt deaths due to myocardial infarction, but NaF is associated with such events. In a study of 40 patients with myocardial infarction, the highest coronary NaF uptake was seen on culprit plaque [5], revealing the power of the radiotracer to indicate potential risk areas. In addition to being able to identify areas of myocardial infarction, NaF has been shown to be able to provide an independent prediction of whether myocardial infarction will be fatal or nonfatal [6].

With NaF being a reliable indicator of microcalcification, progression of atherosclerosis, and the possibility of coronary events, it becomes a powerful tool to study what impacts these occurrences and how to prevent them. Prior studies have examined the factors that uptake of NaF correlates with, including age, BMI, hypertension, and male sex [7, 12, 13]. Our study examined the rate of change of calcification over a two year period in individuals. Understanding what factors relate to increase in microcalcification can help improve the predictive power of NaF imaging in healthy patients. The primary purpose of our study was to test which baseline subject characteristics are associated with the changes in coronary microcalcification over a two year period as assessed by NaF PET/CT standard uptake values (SUV).

Methods and Materials

The participants of this prospective study were taken from a larger prospective Cardiovascular Molecular Calcification Assessed by NaF PET/CT (CAMONA) study. The study was conducted and approved by the Danish National Committee on Health Research Ethics. Our study included healthy patients from the CAMONA study that came in for PET/CT scans two years apart. 23 individuals (female, N = 8, 52 ± 10 years, BMI 24 ± 1.7 kg/m²; male, N = 15, 50 ± 10 years, BMI 27 ± 2.9 kg/m²) in the study had two year follow-up data with consistent dosages, and were used to test correlation of SUV in 18FNaF MZ and HU in 18FNaF MZ over time, as well as the relationship between these changes and age, BMI, cardiovascular risk factors, and blood chemistry. We used the following correlations:

Hybrid PET/CT machines were used to create NaF PET imaging.

All participants had BMI, age, coronary calcium score, cardiovascular risk factors, blood chemistry, and Framingham HeartSCORE determined at the time of their baseline scan.

The operator guided software POMOD (POMOD Technologies LLC, Switzerland) was used to calculate SUV using existing video frames of interest around subjects’ hearts.

Nonparametric statistical analyses were performed to determine significant results.

Results

Percentage change in SUV mean over the two year period correlated BMI and systolic blood pressure. When stratified by gender, males had significant correlations of percent change in SUV mean with BMI (r = 0.85, P < 0.0001) and systolic blood pressure (r = 0.65, P = 0.0082) (Figure 1). However, there were no significant correlations between any baseline characteristics and percent change in SUV mean with BMI.

Paired t-tests in all subjects showed no significant difference between baseline and follow-up values for SUVmean (P = 0.0770) and SUVmax (P = 0.0491). The paired t-test in all subjects for HU showed a significant decrease (P = 0.0126). A box plot was derived of the baseline and follow-up values for SUVmean, SUVmax, and HU of all subjects (Figure 2).

The change in SUV mean and the change in HU over the two year period for each individual were not correlated (r = 0.31, P = 0.0027). The change in SUV mean was significantly greater than the change in HU for an individual as determined by a paired t-test (P = 0.0019).

Discussion

Previous studies have shown associations between SUV mean and BMI [7-11]. However, this is the first longitudinal study to show the significant correlation between the percent change in SUV mean over the short term and BMI. This illustrates that not only does the quantity of microcalcification correlate with BMI, but so does the rate of microcalcification. High BMI is a known risk factor for cardiovascular disease [12, 13], and obesity is associated with a shorter lifespan as well as a greater proportion of life lived with cardiovascular disease [14]. Our study included patients whose BMI remained relatively the same, follow-up studies could be done in patients in targeted weight loss programs to see if rate of microcalcification correlates with a change in BMI.

With the strength of the association between change in SUVmean and BMI it is unsurprising that blood pressure significantly correlated with change in SUVmean. NaF emission tomography could be used in the future to see if the use of blood pressure lowering medications or diets could slow the rate of microcalcification.

The correlations in our study were only significant for males. This may be due to the small sample size of females (n = 8). However, an examination of numerous studies provides a conflicting view of how sex impacts NaF uptake, which some suggesting males have more significant uptake and some suggesting females do.

Before analyzing the data for this study, we expected that SUV and HU would have a significant increase over the two year interval as microcalcification progressed but this was not the case. This was likely because subjects had both increases and decreases of SUV over the two year interval, suggesting the possibility of the occurrence of both atherosclerosis progression and regression.

This study was limited by a small sample size (n = 23), especially for females (n = 8). Furthermore, the CAMONA study only had healthy subjects with follow-ups, so there were no high risk subjects to compare to.

Further longitudinal studies should be done with larger sample sizes to determine the ability of predicting microcalcification progression using baseline characteristics, as well as to determine the best ways to prevent progression and promote regression of atherosclerosis using this methodology.