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¹⁸F-FDG PET Imaging of Atherosclerosis—A New Approach to Detect Inflamed, High-Risk Coronary Plaques?

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Rating

- Of importance.

Introduction

Inflammation is a significant component of plaques that cause acute myocardial infarction. Positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) can visualize metabolically active tissues, including atherosclerosis, and high ¹⁸F-FDG signal correlates with plaque macrophages (inflammation). However, ¹⁸F-FDG PET imaging of the coronary arteries remains challenging because of background uptake of FDG in metabolically active myocardium, cardiac and respiratory motion, and the lower spatial resolution of PET (3–5 mm). In this study, Rogers et al. addressed many of these challenges and investigated ¹⁸F-FDG uptake in coronary arteries in patients with acute coronary syndrome (ACS) or stable angina.

Aims

To compare ¹⁸F-FDG uptake in the ascending aorta and coronary arteries in patients with ACS or stable angina, using PET and co-registered coronary CT angiography.

Methods

PET imaging with ¹⁸F-FDG and coronary CT angiography were performed in a total of 25 patients: 10 with ACS requiring coronary stenting of culprit lesions and 15 with stable angina (including 5 requiring stent placement). Exclusion criteria included diabetes mellitus,

Disclosure

No potential conflicts of interest relevant to this article were reported.

contrast allergies, renal dysfunction, significant arrhythmias, and decompensated heart failure.

Imaging with cardiac CT angiography and cardiac ^{18}F -FDG PET was performed on the same day, 3 to 22 days after stent placement. To suppress background myocardial ^{18}F -FDG uptake that would obscure coronary plaque ^{18}F -FDG signal, a specialized diet was initiated 1 day prior to imaging. Patients consumed a high-fat, low-carbohydrate diet for 1 day, followed by an overnight fast, and then imbibed a high-fat, low-carbohydrate beverage 45 min before ^{18}F -FDG PET imaging.

PET imaging was performed 3 h after an intravenous injection of 13 mCi of ^{18}F -FDG. The dedicated PET imaging system had 4.2-mm intrinsic resolution at the center of the image. PET images were acquired in 2D mode over 25 min of free breathing. The same day, 64-slice cardiac CT angiography was performed with inspiratory breath hold, retrospective electrocardiogram (ECG) gating, and reconstruction at 65% of the R-R interval. Patients received intravenous metoprolol and sublingual nitroglycerin to enhance coronary CT angiography.

The PET and CT images were manually co-registered by a blinded observer and the interobserver variability was measured. The ascending aorta was prioritized in registration, as it is relatively fixed and is readily discernible on ^{18}F -FDG PET and CT. Furthermore, as the ascending aorta is tethered to the ostium of the left main coronary artery (LM), this approach optimizes LM co-registration. Uptake of ^{18}F -FDG was measured as the maximal standardized uptake value (SUV) from several 5-mm² regions of interest (ROIs) defined using CT images. ROIs were placed over the LM, proximal and mid segments of the left anterior descending artery (LAD), left circumflex artery (LCx), right coronary artery (RCA), culprit coronary lesions, and remotely stented lesions (identified by stent location on CT). Background ^{18}F -FDG signal was defined as the mean SUV of arterial blood within the left atrium. Results were reported as median target-to-background ratios (TBRs) and interquartile range (IQR). Suppression of myocardial ^{18}F -FDG uptake was assessed qualitatively on a scale of 0 to 3 (0 = minimal uptake, 3 = intense uptake). In addition, several inflammatory biomarkers were acquired before imaging: high-sensitivity C-reactive protein (hs-CRP), CD40 ligand, intercellular adhesion molecule-1 (ICAM1), IL-12 p70, tumor necrosis factor- α (TNF α), immunoglobulin M (IgM), and vascular cell adhesion molecule 1 (VCAM-1).

Results

In this cross-sectional study, the study groups shared similar demographics, but the stable angina group had more patients with a history of coronary artery disease and a larger body mass index (BMI). The high-fat diet protocol was effective in suppressing background myocardial ^{18}F -FDG uptake: only 4 of 25 patients had high myocardial ^{18}F -FDG uptake of grade 2 or 3. Of 175 coronary segments investigated, only 4% had uninterpretable signals due to myocardial interference. The blinded interobserver variability for the PET/CT co-registration process was highest for the LM (interclass coefficient (ICC)=0.97) and proximal LCx (ICC=0.99), followed by the ascending aorta (ICC=0.92) and proximal LAD (ICC=0.94). The ICC for the proximal RCA was low at 0.29.

Of 10 culprit, stented lesions in ACS, 8 could be evaluated. The maximum ^{18}F -FDG TBR signal within these lesions in ACS patients was 2.61, significantly higher than culprit, stented lesions in patients with stable angina (1.74, $P=0.02$). Culprit lesions in ACS also had a higher TBR than the proximal vessels of the same patients (2.61 vs 1.88, $P=0.04$).

Interestingly, in patients with stable angina, there was no difference in the culprit plaque TBR between newly stented plaques and remotely stented plaques ($P=0.49$).

Other maximum vessel TBRs were also higher in the ACS group than in the stable angina group: 3.30 versus 2.43 ($P=0.02$) for the ascending aorta and 2.48 versus 2.00 ($P=0.03$) for the LM. Compared with stable angina patients, the ^{18}F -FDG signals for ACS patients were significantly greater in the proximal and mid LAD, but not in the circumflex and RCA. The ACS group had higher hs-CRP and IL-12 p70 values than the stable angina group ($P=0.02$ for each).

Discussion

This study presents novel human coronary imaging data. Uptake of ^{18}F -FDG, or arterial inflammation, is increased in the aorta, LM, and LAD of ACS patients compared with stable angina patients, consistent with the hypothesis that ACS induces a systemic inflammatory state. The study also reveals that ^{18}F -FDG uptake is higher in culprit stented lesions of ACS patients than in those of stable angina patients.

The self-described study limitations include the fact that RCA and distal coronary artery co-registration was less reproducible, and that the co-registration process was time-consuming. It is also important to note that the PET images were collected days after initial presentation, and therefore the ^{18}F -FDG signal may have been different when measured than it was before the patient's ACS presentation.

Comment

Abundant basic and clinical evidence indicates that inflammation is a key component of plaques that induce ACS. This important paper by Rogers et al. advances the capabilities of ^{18}F -FDG PET imaging to visualize arterial metabolism and inflammation in human coronary arteries, a target vascular bed historically elusive for molecular imaging. Several technical approaches were employed to achieve reproducible ^{18}F -FDG imaging of the coronary arteries: (1) use of the ascending aorta to enable reliable co-registration of PET and CT datasets and excellent co-registration of the anchored left main coronary artery; (2) a low-carbohydrate, high-fat diet approach similar to the one used by Wykrzykowska et al. [1], which suppresses background myocardial ^{18}F -FDG uptake; and (3) tailored PET/CT co-registration via highly conspicuous stents on coronary CTA to enhance accurate detection of culprit plaque ^{18}F -FDG signals.

Importantly, recently stented culprit plaques in ACS patients had higher ^{18}F -FDG TBRs than those in stable angina patients. This finding suggests that stent-induced vascular inflammation is unlikely to underlie the observed higher ^{18}F -FDG signal in plaques of ACS patients. Rather, the finding suggests greater intrinsic culprit plaque inflammation in ACS patients. A limitation here is that the pre-stent culprit plaque volume was not reported; it would be interesting to know whether plaque inflammation per unit volume of plaque is greater in ACS patients. Additionally, as stated by the authors, this observation is limited in that ^{18}F -FDG PET imaging occurred after clinical presentation. The observed increase in inflammation in ACS plaques may in part be a consequence of plaque rupture and erosion, rather than being wholly due to pre-existing plaque inflammation. The applicability of this method to patients with diabetes is also unknown, as such patients were excluded, likely because of the potential of inferior ^{18}F -FDG plaque imaging in the setting of hyperglycemia [2].

It therefore remains to be seen how useful ^{18}F -FDG PET coronary imaging will be in predicting plaque complications in patients at risk of developing an ACS. For this

application, most patients will not have a pre-existing coronary stent to optimize co-registration, as in the current paper. As the average volume of a plaque is about 0.1 mL and the volume resolution of ^{18}F -FDG PET imaging is about 0.125 mL [3], PET detection of coronary plaques will typically span 1 voxel. Further improvements in integrated PET/CT imaging, such as cardiac and respiratory gating, partial volume correction, and attenuation correction, are likely to be necessary in order to accurately identify coronary plaque inflammation in the average patient. Finally, the risks of radiation and contrast exposure will need to be considered in a prevention-based approach.

Nonetheless, the promise of ^{18}F -FDG PET to image coronary plaque inflammation remains exciting. Alternative noninvasive molecular imaging approaches, such as macrophage-targeted agents for CT [4], are emerging but are still in the preclinical domain. Though ^{18}F -FDG PET imaging of the coronary arteries is not yet ready for natural history studies, it is likely to allow some assessment of the effects of anti-inflammatory pharmaceuticals [5].

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