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Original Article

Positron emission tomography imaging for vascular inflammation evaluation in elderly subjects with different risk factors for cardiovascular diseases

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Abstract: This study was aimed to investigate the usefulness of ^{18}F-FDG-PET to differentiate vascular inflammation and to determine the effect of rosuvastatin. Eight subjects were recruited and were divided according to their health status in three groups; 3 healthy subjects, 3 patients with hypercholesterolemia and 2 patients with stable angina pectoris. Hypercholesterolemic patients were submitted immediately after their recruitment to rosuvastatin treatment (20 mg/d). Two PET/CT measurements were made throughout the course of the study, one at baseline and the second 12 months later. Our results showed that the ratio of calcified arteries to total analyzed arteries segments were 23%, 36% and 44% for healthy, hypercholesterolemic and stable angina patients respectively. Healthy subjects present, at baseline, a high level of vascular inflammation as measured by ^{18}F-FDG uptake in both calcified and non-calcified segments of the arteries. This vascular inflammation increases as a function of the cardiovascular risk factors. After the 12-month follow-up period, non-calcified arteries showed a significant increase of ^{18}F-FDG uptake in both healthy, hypercholesterolemic and stable angina patients. However, the highest increase was noted for the healthy subjects; (50% increase, $p<0.0001$), while hypercholesterolemic patients under rosuvastatin showed only 25% increase of ^{18}F-FDG uptake ($p<0.0001$). This study confirms the usefulness of ^{18}F-FDG measurement to localize and quantify arterial inflammation in each artery segments and as a function of the CVD risk factors. Rosuvastatin may have a protective effect against arterial inflammation however; other studies with higher rosuvastatin doses (>20 mg/d) are needed to confirm this beneficial effect.

Keywords: Atherosclerosis, positron emission tomography, ^{18}F-FDG, vascular inflammation, aging, rosuvastatin

Introduction

Atherosclerosis and its clinical manifestations such as stroke and myocardial infarction are the most frequent diseases associated with aging [1]. Indeed, the rupture of the atherosclerotic plaque is involved in approximately 70% of fatal myocardial infarction and/or sudden death and this is especially common in elderly population [2, 3]. Interestingly, over half of the acute myocardial infarctions or the sudden cardiac death occur in previously asymptomatic individuals [4].

Coronary atherosclerosis is present in almost all subjects from the age of 50 years. Advances in the basic and clinical understanding of the process of atherosclerosis have identified inflammation as the key phenomenon, contributing to lesion initiation, progression, and complication [5]. One of the aims of the preventive cardiology is to determine whether atherosclerosis has evolved to a point where the inflammation of the arteries can progress to the rupture of the atherosclerotic plaque [6, 7]. Although current diagnostic techniques for cardiovascular diseases (CVD) are used to assess the extent of atherosclerotic plaques and the level of arterial stenosis, these techniques do not allow to accurately assess the stability of the plaque in order to anticipate and prevent the acute events and avoid the irreversible con-

sequences of the disease [8]. Angiography is the most common technique used to assess cardiovascular risk in determining the level of arterial stenosis. However, its limitation is that it cannot assess the risk of rupture [9]. Furthermore, it has been shown that 50% of ruptures occur in plaques that cause less than 50% stenosis [10].

The vulnerability of atherosclerotic plaques is manifested by its high instability [6, 7]. It differs metabolically from stable atherosclerotic plaques [11]. Inflammation plays an important role in the development, the progression and the rupture of the plaques with the concomitant thrombus formation and therefore constitutes a target for the detection and characterization of vulnerable plaque [12-16].

During the last 10 years, the positron emission tomography (PET) imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has emerged as a promising method for the estimation of plaque inflammation and therefore in the determination of plaque vulnerability. ^{18}F-FDG is a glucose analogue that is taken up by cells at the same rate as glucose. However, phosphorylated ^{18}F-FDG does not undergo glycolysis and therefore accumulates within the cells. This ^{18}F-FDG accumulation is interpreted as a marker for metabolic activity. Studies have shown that ^{18}F-FDG is taken up by macrophages in the atherosclerotic plaque; as a result, ^{18}F-FDG-PET imaging can detect and delimit inflammatory changes as well as quantify the degree of atherosclerotic activity in the arterial wall [17]. This type of quantitative tomographic imaging has the potential to non-invasively determine the site and the characteristics of the vascular inflammation.

Statins (3-hydroxy-3-methylglutaryl coenzyme A HMG-CoA reductase inhibitors) are a class of drugs mainly used to treat hypercholesterolemia and to prevent cardiovascular events. Several clinical trials have demonstrated that statins are gaining widespread acceptance as a principal therapy for the primary and secondary prevention of atherosclerosis and CVD [18]. In addition to their lipid-lowering effect, statins also possess pleiotropic anti-inflammatory properties and reduce systemic inflammation [19-21]. The Jupiter study suggested that rosuvastatin has not only a direct effect on the cholesterol synthesis by the liver but it may have other pleiotropic effects among which, its capacity to improve endothelial function and to decrease inflammation [22]. Other studies have demonstrated that statins might reduce inflammation within the atherosclerotic plaque, which prevent its rupture. Tahara *et al.* showed that three months treatment with simvastatin, one of the statins family members, beyond its lipid lowering effect, reduces inflammation within the atherosclerotic plaque as measured by ^{18}F-FDG-PET [23]. Another study of Ishii *et al.* investigated the effect of 6 months treatment with 2 doses of atorvastatin for the reduction of ^{18}F-FDG uptake in atherosclerotic plaque and showed a significant effect of atorvastatin at 20 mg/d dose [24]. However, the study of Tahara *et al*. used data of ^{18}F-FDG-PET imaging of voluntary cancer screening [23] and the study of Ishii *et al.* [24] reported only on patients with dyslipidemia and who were scheduled to undergo percutaneous coronary intervention for stable angina. Our prospective study was conducted in healthy elderly subjects compared to hypercholesterolemic and stable angina patients after coronary percutaneous intervention in the aim to investigate the usefulness of ^{18}F-FDG-PET to differentiate vascular inflammation as a function of the cardiovascular risk factor during 12 months follow up. Moreover our study also investigated the effect of a relatively new member of the statin family (rosuvastatin) on vascular inflammation in elderly hypercholesterolemic patients.

Materials and methods

Study population

Eight subjects aged between 65 and 85 years were recruited for this study: 3 healthy subjects (69.5 ± 4.5 years), 3 hypercholesterolemic subjects (i.e. with elevated blood cholesterol) (68.75 ± 4.57 years) and 2 subjects with stable angina (69.5 ± 2.12 years). The hypercholesterolemic subjects were newly diagnosed with this condition and were not under any cholesterol-lowering medications and have not been diagnosed for any disease at the time of the recruitment.

The healthy and hypercholesterolemic patients had no clinical or physical signs of atherosclerosis and were not consuming any type of prescribed and non-prescribed medications. At the time of recruitment, the hypercholesterolemic

Table 1. The clinical characteristics of participants at baseline (T0) and after 12 months (T12)

	Healthy subjects		Hypercholesterolemic patients		Stable Angina patients	
	T0	T12	T0	T12	T0	T12
N	3	3	3	3	2	2
Age (years)	69.5 ± 3.91	70.5 ± 3.91	68.75 ± 3.96	69.75 ± 3.96	69.5 ± 1.5	70.5 ± 1.5
Weight (kgs)	67.0 ± 3.52	67.8 ± 4.42	78.3 ± 8.91	77.7 ± 9.85	87.6 ± 22.9	86.9 ± 23.1
Total cholesterol (mmol/L)	5.38 ± 0.41	5.75 ± 0.40	6.56 ± 0.62	4.38 ± 0.39•	3.59 ± 0.49**	3.29 ± 0.8
HDL (mmol/L)	1.34 ± 0.30	1.38 ± 0.11	1.33 ± 0.23	1.31 ± 0.16	1.22 ± 0.16	1.18 ± 0.32
LDL (mmol/L)	3.43 ± 0.53	3.64 ± 0.47	4.54 ± 0.53	2.39 ± 0.41••	1.91 ± 0.42#,**	1.59 ± 0.48
Triglycerides (mmol/L)	1.22 ± 0.15	1.61 ± 0.58	1.52 ± 0.72	1.49 ± 0.41	1.02 ± 0.20	1.16 ± 0.02
Glucose (mmol/L)	4.18 ± 0.19	4.73 ± 0.80	4.82 ± 0.08	4.98 ± 0.26	4.85 ± 0.35	5.35 ± 0.25
CRP (mg/L)	<3	3.05 ± 0.09	3.00 ± 0	3.12 ± 0.15	3.8 ± 0.8	11.9 ± 8.9
Type of medication	none		Rosuvastatin 20 mg during the 12-months follow-up		Aspirin 280 mg, Lipitor 90 mg, apo-Ramipril 10 mg, Apo-Hydro 12.5 mg, Mavik 4 mg, Apo-Metropolol 5 mg, Plavix 75 mg	

Values are mean SD, unless otherwise specified. •p<001 and ••p<0.0007 when compared to hypercholesterolemia at T0. **p<0.01 for stable angina patients when compared to hypercholesterolemia at T0. #p<0.05 for stable angina patients when compared to healthy subject at T0. •p<0.0001 for hypercholesterolemic patients when compared between T0 and T12.

patients were diagnosed with high levels of total and LDL cholesterol. After recruitment, hypercholesterolemic subjects were treated with rosuvastatin (20 mg/d) during 12 months.

The stable angina patients had an established cardiovascular disease and antecedents of arterial structural modifications (2 stent placements). These subjects had a previously diagnosed and treated stable angina (<6 months) with a background of two different stent placements as a consequence of coronary stenosis. These patients followed their proper treatment that mainly consisted of beta-blockers, antihypertensive drugs, statins and antiaggregant drugs (**Table 1**). All subjects were non-smokers, not taking antioxidants, vitamin supplements or hormonal replacement for women, and not having excessive alcohol consumption. The Ethical committee of the Geriatric University Institute of Sherbrooke approved the study and all patients signed a written informed consent prior their enrollment in the study.

Of the 24 subjects enrolled, only 14 completed the study with the two ^{18}F-FDG-PET measurements. From the 10 patients that did not completed the study, 3 patients forsaken the study for personal reasons, 2 patients presented adverse events following rosuvastatin treatment, 2 subjects suffered from osteoarthritis therefore they could not raise their arms during the PET scanning. The other 3 patients who completed the study, however, were excluded from the study due to their constant movements during the PET measurements. Details for the 14 patients that completed the study are presented in **Table 1**.

Laboratory measurements

After an overnight fasting, peripheral blood samples were collected for the measurements of blood glucose, lipid profiles (LDL, HDL, total cholesterol and triglycerides) and C-reactive protein (CRP).

Imaging techniques

The subjects were measured with a PET/CT (Philips Gemini TF). Two PET/CT measurements were made throughout the course of the study, one at T0 (baseline) and the second at T12 (12 months later). For each PET/CT measurement, patients were invited to respect an overnight fast, at least 6 hours prior the imaging to assure a normal glucose level. The CT scan was conducted first then the subjects received, by intravenous injection, a bolus of 140 to 400 MBq (adjusted by the subjects' weight) of ^{18}F-FDG and the PET scan was initiated in dynamic mode for 30 min. The arteries scanned were the abdominal aorta, and left and right iliac.

The CT and PET images were co-registered. The 30 min dynamic scans were divided into 26 image frames of 12 x 10 sec; 8 x 30 sec; 6 x 240 sec. The images were examined slice by slice on the transaxial image views to detect and include several portions of the arteries.

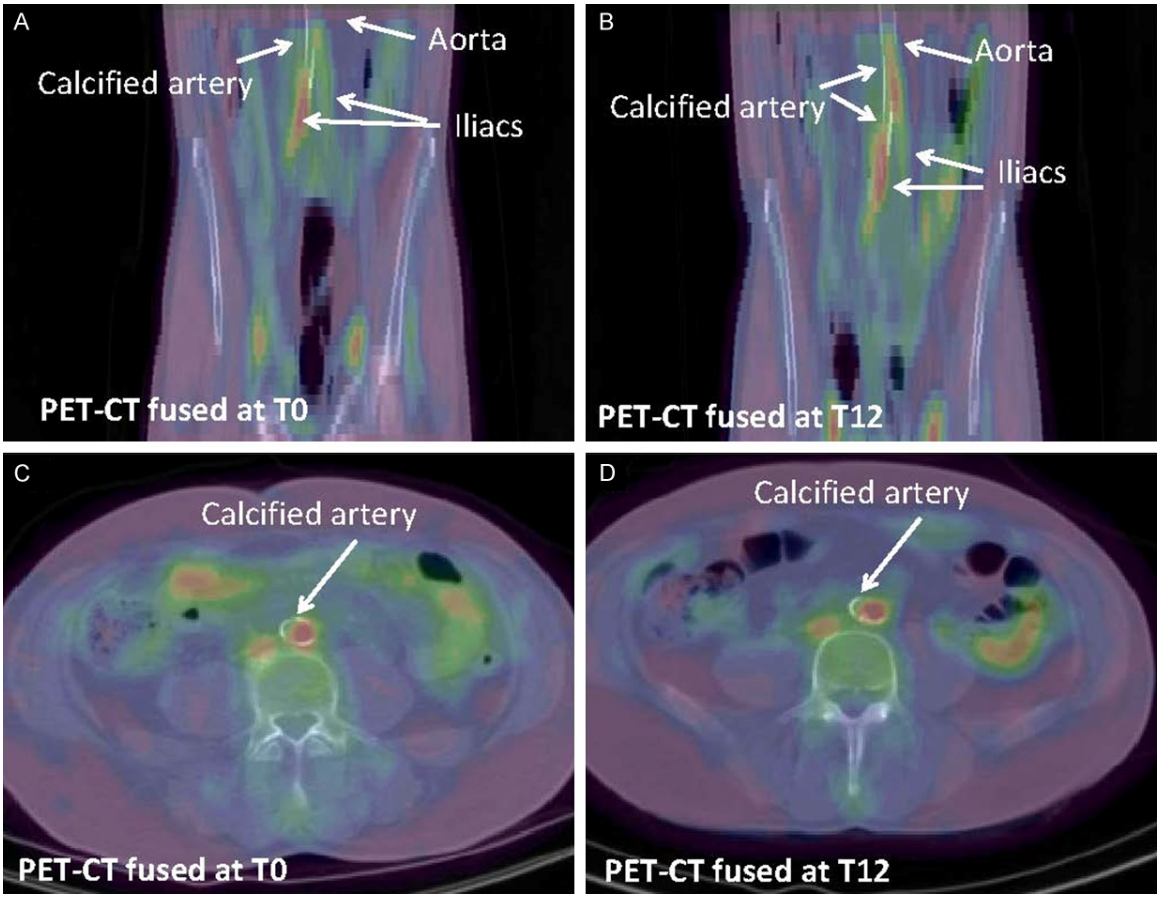

Figure 1. Coronal and transaxial PET-CT images at T0 (A, C) and at T12 (B, D). Arrows indicate calcified segments of the aorta. Fusion of PET and CT shows that ^{18}F-FDG uptake is mostly located in the calcified segments of the arteries suggesting inflammation in the atherosclerotic plaque. (A) Coronal fused PET-CT at T0, (B) Coronal fused PET-CT at T12, (C) Transaxial fused PET-CT at T0 and (D) Transaxial fused PET-CT at T12.

Since atherosclerosis has a heterogeneous progression in the abdominal aorta, iliac and femoral arteries, a number of 53 artery segments in normal, 45 in hypercholesterolemic and 34 in subjects with stable angina were examined. The CT images were used as references for the delimitation of the regions of interest (ROI) in the transaxial slices of the artery images. Each specific ROI produced its time-activity curve (TAC). The CT images were also used to localize calcified plaques. These sections were then classified in two main groups: calcified and non-calcified. The standard uptake values (SUV) were calculated using the mean of the last four data points in the time activity curve of each region of interest on the artery, corresponding to 8 min scan acquired 22 min after radiotracer injection, divided by the injected radiotracer activity and normalized to the subjects' body surface area. The body surface area was quantified according to the following formula [25].

Statistical analyses

All variables were presented with the minimum and maximum values. A one-way analysis of variance was used for multiple comparisons and student's t-test was used for comparison of differences between 2 groups. These statistical analyses were performed using Prism 5.0 version software. A p value <0.05 was considered statistically significant.

Results

The clinical characteristics of all the patients are reported in **Table 1**. At baseline, the healthy individuals presented high cholesterol levels but not sufficiently elevated to require treatment. Hypercholesterolemic patients had significant high total and LDL cholesterol levels

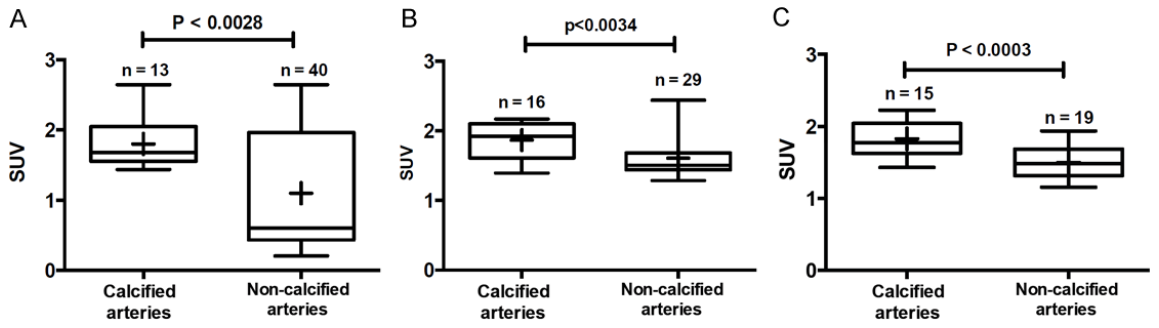

Figure 2. Comparison of the SUV values of calcified and non-calcified segments of arteries of healthy, hypercholesterolemic and stable angina patients. SUV values were determined at baseline (T0) for the three groups. Panels A-C correspond to healthy, hypercholesterolemic and stable angina patients respectively. The data were obtained from transaxial image slices. Student-t test was used to determine whether there is a significant difference between the means. P<0.05 was considered significant. n: represents the number of arteries segments evaluated for ^{18}F-FDG uptake.

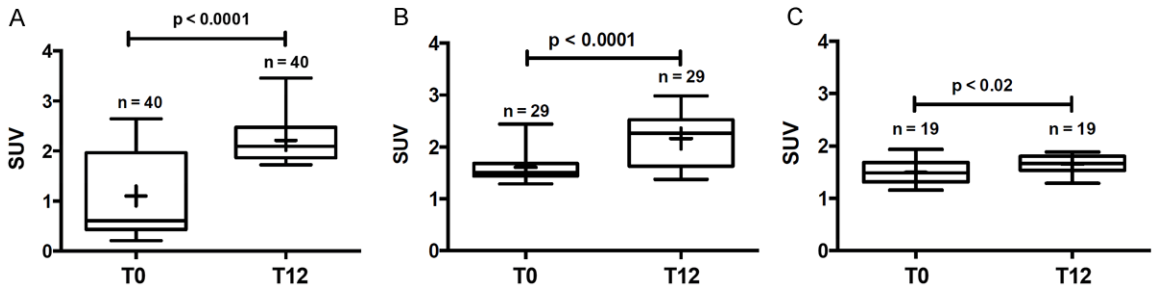

Figure 3. Comparison of the SUV of non-calcified arteries between baseline and after 12 months of follow-up of healthy, hypercholesterolemic and stable angina patients SUV values were determined at baseline and after 12 months for non-calcified segments of the arteries of the same patient in each group. The data were obtained from transaxial image slices. Statistical analyses were performed using GraphPad Prism. A student-t test was used to compare values at T0 and T12. P<0.05 was considered significant. n: represents the number of arteries segments evaluated for ^{18}F-FDG uptakes.

particularly when compared to stable angina patients (p<0.01). These patients were submitted immediately after their recruitment to rosuvastatin treatment (20 mg/d).

Throughout the 12 months of follow-up period, there were no significant changes in the overall clinical and biochemical parameters for the healthy and stable angina patients. However, the hypercholesterolemic patients showed significant decrease of both total and LDL cholesterol (p<0.001 and p<0.0007, respectively) as a response to the rosuvastatin treatment (20 mg/d).

Figure 1 presents coronal and transaxial PET-CT images at T0 and at T12. Co-registration of PET and CT shows that ^{18}F-FDG uptake is located in the calcified segments of the arteries suggesting inflammation in the atherosclerotic plaque. The ratio of calcified arteries to total analyzed arteries segments were 23%, 36% and 44% for healthy, hypercholesterolemic and stable angina patients respectively.

Interestingly ^{18}F-FDG uptake was observed in both calcified and non-calcified arteries with significantly a higher ^{18}F-FDG uptake in the former (**Figure 2**). Calcified arteries presenting high ^{18}F-FDG uptake correspond to atherosclerotic plaques, while non-calcified arteries with significant ^{18}F-FDG uptake may be attributed to arterial inflammation at early atherosclerotic lesions.

^{18}F-FDG uptake by the calcified arteries does not change significantly between baseline and after 12 months for the three studied groups and despite rosuvastatin intake by hypercholesterolemic patients (results not shown).

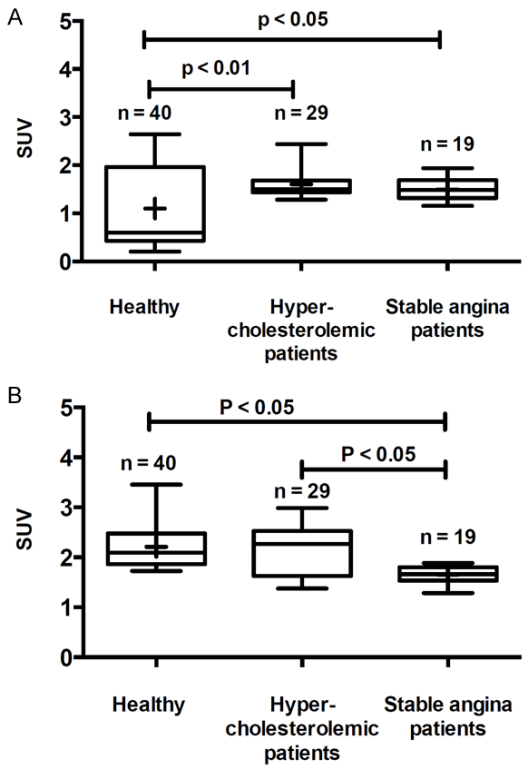

Figure 4. Measurement of SUV of non-calcified segments of the arteries of healthy, hypercholesterolemic and stable angina patients at baseline (A) and after 12 months (B). SUV values were determined at baseline and after 12 months for non-calcified segments of the arteries of the same patient in each group. The data were obtained from transaxial image slices. Statistical analyses were performed using GraphPad Prism. A one-way analysis of variance (ANOVA) was used for multiple comparisons, followed by Bonferonni's multiple comparison tests. P<0.05 was considered significant. n: represents the number of arteries segments evaluated for ^{18}F-FDG uptake. Non-significant statistical differences between the groups are not indicated in the figure.

However, non-calcified arteries showed a significant increase of ^{18}F-FDG uptake in both healthy and hypercholesterolemic and stable angina patients, with a significant high increase for the former; 50% increase of ^{18}F-FDG uptake (p<0.0001) for healthy subjects and 25% increase (p<0.0001) for the hypercholesterolemic patients (**Figure 3**). Stable angina patients present the lowest increase of ^{18}F-FDG uptake after 12 months (12%, p<0.02). The comparison of ^{18}F-FDG uptake by non-calcified arteries of the three patient groups, at baseline and at T12, showed that hypercholesterolemic and stable angina patients present high ^{18}F-FDG uptake when compared to healthy patients at T0 (p<0.01 and p<0.05 respectively) (**Figure 4A**). Interestingly, 12 months of rosuvastatin intake limited the ^{18}F-FDG uptake in non-calcified arteries of hypercholesterolemic patients to values comparable to healthy subjects (**Figure 4B**).

Discussion

The measurement of ^{18}F-FDG uptake by the arterial wall is suggested as a non-invasive technique to determine vascular inflammation and the risk of atherosclerotic plaque rupture [26]. Our prospective study aimed to evaluate the use of ^{18}F-FDG to compare vascular inflammation as a cardiovascular risk factor and to determine how the level of inflammation may change during a 12-month follow-up. The study was conducted in an elderly population with various cardiovascular risk factors, specifically, in healthy, in hypercholesterolemic and in stable angina elderly patients.

Our results showed a significant ^{18}F-FDG uptake in the calcified segments of the arteries of healthy subjects when compared to non-calcified segments. In accordance with the results in the literature, the ^{18}F-FDG uptake in the calcified segments of arteries suggests an inflammatory process at the atherosclerotic plaques [27-29]. Nevertheless, non-calcified segments of the studied arteries may also present a significant ^{18}F-FDG uptake. Mochizuki et al. and Yun et al. have attributed this uptake either to physiological accumulation or to age-related changes such as senescence or atherosclerosis [30, 31]. It is thus not surprising, that in our conditions, ^{18}F-FDG uptake might be due to an inflammatory process within these non-calcified segments of the arteries. Indeed, a systemic low-grade inflammation, called inflammaaging [32] is one of the patho-physiological processes that occur in the elderly, which may be further increased in the presence of an additional risk factor such as hypercholesterolemia. In accordance with this assumption, our results showed, at baseline, a highly significant ^{18}F-FDG uptake in non-calcified arteries of hypercholesterolemic and stable angina patients when compared to healthy subjects.

It is well known that hypercholesterolemia induces phenotypic changes in the microcircu-

lation that are consistent with an inflammatory response [33]. Yun *et al*. demonstrated that age and hypercholesterolemia are the only parameters significantly correlating with vascular-wall ^{18}F-FDG uptake of large arteries (abdominal aorta, iliac and proximal femoral arteries) [29, 31]. Moreover, recent evidence suggests that high plasma cholesterol levels enhance the expression of pro-inflammatory genes, of cellular adhesion molecules and of cytokine production, thus promoting a pro-inflammatory status [34, 35], which in turn expose hypercholesterolemic patients to additive risk for cardiovascular events [36]. The hypercholesterolemic patients enrolled in this study were newly diagnosed with this condition and had no previous or current treatment for it. Therefore, the age-associated low-grade inflammation could be exacerbated in these patients, which explains the high ^{18}F-FDG intake by the arteries of these patients. Although the link between systemic inflammation associated to the inflamma-aging and arterial inflammation is not yet established, Bural *et al.* demonstrated a linear correlation between mean age and SUV [37]. However, the study of Bural *et al.* was a retrospective design including patients who underwent whole-body PET scans for the assessment of non-cardiovascular disorders that may exacerbate the age-related inflammation [37]. In the present study, the results obtained with healthy elderly subjects confirm the highly significant ^{18}F-FDG uptake by arteries of elderly patients and this is enhanced in the presence of hypercholesterolemia.

Non-calcified segments of arteries of patients with stable angina also present a high ^{18}F-FDG uptake when compared to healthy subjects possibly resulting from the endothelial activation and the pro-inflammatory state that develops long term after coronary stenting [38, 39]. This observation is another confirmation that arterial ^{18}F-FDG uptake is more than just an age-related physiologic change in the arteries. The levels of ^{18}F-FDG uptake in non-calcified arteries parallels the percentage of calcified arteries in each group (calcified to total analyzed artery segments), which are 23%, 36% and 44% for healthy, hypercholesterolemic and stable angina patients, respectively. Thus, ^{18}F-FDG uptakes in non-calcified segments of the arteries may represent an inflammation state at an early stage of the atherosclerotic lesion formation (that precedes calcification) [40], which may increase with cardiovascular risk factors or complications (**Figure 4**).

Interestingly, our data showed that ^{18}F-FDG uptake in non-calcified arteries increased between baseline and after a 12 months period for the three patients groups. Surprisingly, ^{18}F-FDG uptake increased in hypercholesterolemic patients despite the administration of rosuvastatin 20 mg/d throughout the 12 months duration of the study. Nevertheless, this increase was 2-fold lower than the increase measured for the healthy elderly subjects (respectively 26% and 50% increase of ^{18}F-FDG uptake between baseline and 12 months). Moreover, treatment of hypercholesterolemic patients with rosuvastatin limited the ^{18}F-FDG uptake in non-calcified arteries to values comparable in healthy subject. This suggests that rosuvastatin may have beneficial effects against arterial inflammation, particularly at the early atherosclerotic lesions. In accordance, stable angina patients present the lowest increase of ^{18}F-FDG uptake between baseline and 12 months (12%), which could be explained by the effectiveness of their prescribed medication (beta-blockers, antihypertensives, statins and antiaggregant drugs). The increase of ^{18}F-FDG uptake after 12 months of follow-up particularly in healthy elderly subjects demonstrates that atherosclerosis is a chronic progressive inflammatory process involving the vascular walls of arteries and constantly modulated by the aging process. We notice that despite the increase of ^{18}F-FDG uptake in the healthy subjects after 12 months, these subjects did not present any clinical manifestation, and thus this was considered as a normal aging process.

Inversely, ^{18}F-FDG uptake in calcified segments of arteries does not change significantly during the 12-month of follow-up for both healthy, hypercholesterolemic and stable angina patients. While the absence of change in stable angina patient could be attributed to the prescribed medication, the stabilization of the ^{18}F-FDG uptake in hypercholesterolemic patient may be due to rosuvastatin intake. This member of statin family induced a significant reduction of total and LDL cholesterol in these patients, however it is not surprising that the used dose (20 mg/d) might not be enough high to regress inflammation within atherosclerotic plaque. Indeed, Nicholls and colleagues

observed that rosuvastatin induces atherosclerotic plaque regression (reduction of the plaques' volume) when used at dose 40 mg/d [41]. However, these higher doses should be avoided because of the expected side effects.

It is noteworthy that our study is among the few ones that have focused on monitoring the ^{18}F-FDG uptake over such a long period of time (12 months) and in subjects recruited specifically for this purpose. Moreover, our data distinguishes ^{18}F-FDG uptake in calcified and non-calcified segments of the arteries. Most of the other data measuring ^{18}F-FDG uptakes were obtained from retrospective analysis and from cancer patients, which for the most part had no risk factors for CVD. Nevertheless, Meirelles *et al*. measured ^{18}F-FDG uptake retrospectively on PET/CT scans performed at mean interval of 7 months [42] and showed an increase of ^{18}F-FDG uptake in more than half of the studied patients (100 patients) [42].

Conclusions

The present study allowed us to confirm the usefulness of ^{18}F-FDG measurement to localize and quantify arterial inflammation in each artery segments and as a biomarker of the CVD risk factor. Our results showed a high level of vascular inflammation in elderly healthy subjects while the treated angina group showed lesser variation during the 12 months period of the study. They also showed that the level of arterial inflammation increased significantly during the 12-month follow-up period. While this increment could be inhibited by medication including statins for hypercholesterolemic patients, dietary interventions could help to reduce arterial inflammation in healthy individuals [43].

Nevertheless, our study presents some limitations that should be addressed in a large study. Technically, it was not possible to compare ^{18}F-FDG uptake at baseline and after 12 months for the same vascular segment. This difficulty was due to inherent misplacement of subjects in the same position for the two scans. The other limitations are related to the number of participants and the need of an alternative quantitative analysis besides that of the SUV measurements. Finally, no systemic inflammatory markers except CRP were measured in our subjects.

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Disclosure of conflict of interest

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