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Optimizing ^{18}F-FDG PET/CT Imaging of Vessel Wall Inflammation –The Impact of ^{18}F-FDG Circulation Time, Injected Dose, Uptake Parameters, and Fasting Blood Glucose Levels

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Abstract

Purpose—^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is increasingly used for imaging of vessel wall inflammation. However, limited data is available regarding the impact of methodological variables, i. e. patient's pre-scan fasting glucose, the FDG circulation time, the injected FDG dose, and of different FDG uptake parameters, in vascular FDG-PET imaging.

Methods—195 patients underwent vascular FDG-PET/CT of the aorta and the carotids. Arterial standard uptake values ($_{mean}SUV_{max}$) as well as target-to-background-ratios ($_{mean}TBR_{max}$) and the FDG blood pool activity in the superior vein cava (SVC) and the jugular veins (JV) were quantified. Vascular FDG uptake classified according to tertiles of patient's pre-scan fasting glucose levels, the FDG circulation time, and the injected FDG dose was compared using

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ANOVA. Multivariate regression analyses were performed to identify the potential impact of all variables described on the arterial and blood pool FDG uptake.

Results—Tertile analyses revealed FDG circulation times of about 2.5 h and prescan glucose levels of less than 7.0 mmol/l showing favorable relations between the arterial and blood pool FDG uptake. FDG circulation times showed negative associations with the aortic $_{mean}SUV_{max}$ values as well as SVC- and JV FDG blood pool activity but a positive correlation with the aortic- and carotid $_{mean}TBR_{max}$ values. Pre-scan glucose was negatively associated with aortic- and carotid $_{mean}TBR_{max}$ and carotid $_{mean}SUV_{max}$ values, but correlated positively with the SVC blood pool uptake. Injected FDG dose failed to show any significant association with the vascular FDG uptake.

Conclusion—FDG circulation times and pre-scan blood glucose levels significantly impact FDG uptake within the aortic and carotid wall and may bias the results of image interpretation in patients undergoing vascular FDG-PET/CT. FDG dose injected was less critical. Therefore, circulation times of about 2.5 h and pre-scan glucose levels less than 7.0 mmol/l should be preferred in this setting.

Keywords

FDG-PET; FDG Dose; FDG Circulation Time; Pre-scan Glucose; Vessel Wall Inflammation

INTRODUCTION

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) arterial imaging has been shown to be capable of imaging metabolic activity within human carotid atherosclerosis, and hence provide a marker for plaque inflammation [1]. It has also been used in several trials of novel anti-atherosclerosis therapies as a surrogate marker of treatment efficacy [2,3]. The basis for the FDG uptake in the arterial wall is attributed to its preferential uptake by plaque macrophages over other cells within the vessel wall [4].

Despite the increased acceptance of FDG-PET as a marker of vessel wall inflammation, the optimal vascular FDG-PET acquisition protocol and image analysis methodologies are still debated [5,6]. Among these, appropriate FDG circulation time (the time interval between FDG injection and starting time of data acquisition) the patient's pre-scan fasting glucose levels, and the minimum FDG dose injected are deemed critical [1,4,7–18].

Optimizing these factors will also help minimize study patient radiation exposure an important consideration especially when follow-up studies are required as part of drug trials.

Standardization of data analysis is essential to facilitate comparison between different trials [5]. While most previously published studies have used target (plaque, arterial wall)-to-background (blood) ratios (TBR) to quantify plaque FDG uptake, some have used vessel SUV without correction for blood pool FDG activity [1,4,10,11,19].

This study aims to address the impact of the above methodological variables on in a large, prospectively imaged study population of patients with established or suspected cardiovascular disease.

PATIENTS AND METHODS

Study Design

The study was conducted at the Mount Sinai School of Medicine, New York, U.S.A. All subjects gave written informed consent. It was fully approved by our institutional review board.

Criteria for inclusion in the study were as follows: Males and females with a diagnosis of CVD or with multiple CVD risk factors were recruited. Definition of CVD was previous myocardial infarction, stroke, transient ischemic attack (TIA), history of peripheral artery disease, or a history of a coronary revascularization procedure. In fact we chose deliberately heterogeneous population of patients to study. This allows us to examine the effect of the methodology on a wide range of SUV values, to ensure maximum applicability to routine practice. None of the subjects were oncological subjects. Patients with fasting glucose levels ≥11.1 mmol/l or previous carotid surgery were excluded from the study.

Questionnaire, Biometric and Biochemical Measurements

We assessed the presence of cardiovascular risk factors, use of medication, and family history of CVD by using a questionnaire. Presence of hypertension was defined as a history systolic blood pressure > 140 mmHg, or a diastolic blood pressure > 90 mmHg. Diabetes was defined as documented diagnosis of type 1- or -2 diabetic disease and the use of anti-diabetic treatment (diet, oral- or insulin treatment). Weight and height were measured to calculate body mass index (BMI). Smoking was defined as smoking at least one cigarette on a daily basis. Fasting glucose levels were obtained by finger stick blood glucose measurements (Accu-Chek™ Advantage™, Roche Diagnostics; Indianapolis, Indiana) prior to FDG administration.

FDG-PET/CT Imaging

FDG-PET/CT was performed after an overnight fast using a General Electric Healthcare (Milwaukee, Wisconsin) Lightspeed discovery™ ST 16-slice PET/CT scanner. FDG was administered intravenously (562.4 ± 92.5 MBq) and patients rested comfortably for approximately 90 to 120 min.

Imaging of the ascending aorta was performed first and covered the area from the heart to the aortic arch as the upper limit, over 15–30 min (1 or 2 bed positions) acquisition time depending on the patient's anatomy. Afterwards, subjects were placed into a head holder for imaging of the carotids. Images from one bed position (15.5 cm) with coverage extending inferior to the internal auditory meatus were acquired for 15 minutes. We chose two separate acquisitions so we could improve the image quality with arms up for the aorta acquisition and arms down for the carotid acquisition.

A low dose CT scan (140 kV, 80 mA, and 4.25 mm slice thickness) was performed for attenuation correction and co-registration. No CT contrast agent was administered. The absence of CT contrast was deliberate, to allow those with renal impairment to be imaged.

The main studies of reproducibility also did not use contrast CT, but nevertheless reported excellent reproducibility [20,21].

Image Analysis of the Vessels

Image analysis was performed on a dedicated commercially available workstation (Extended Brilliance™ Workspace V4.0.0.3206; Philips Medical Systems Inc.; Cleveland, Ohio). An experienced reader (J. B.) analyzed all scans [19]. Arterial FDG-uptake was quantified by manually drawing a region of interest (ROI) around each common carotid artery and the ascending aorta, including the vessel lumen, on every slice of co-registered transaxial PET/CT images. Next, the maximum arterial standardized uptake value (SUV) (highest pixel activity within the region of interest) was determined. The SUV is the decay-corrected tissue concentration of FDG in kBq/ml, adjusted for the injected FDG dose and the body weight of the patient. By averaging the maximum SUV values of all arterial slices of the left and right carotid artery and the ascending aorta, respectively, a $_{mean}SUV_{max}$ value was derived for all arteries.

The arterial target-to-background ratio (TBR) was calculated by normalizing the arterial SUV for blood pool activity by dividing the SUV values in the arteries by the average blood mean SUV ($_{mean}SUV_{mean}$) estimated from both jugular veins (JV, to achieve carotid TBR values) or the superior vena cava (SVC, to achieve aortic TBR values). The TBR is a blood-normalized arterial SUV, considered to be a reflection of arterial FDG uptake and reflective of underlying macrophage activity [22]. For evaluation of the FDG blood pool activity, at least six 3–4 mm ROIs were placed in consecutive slices of both JVs and the SVC and averaged.

The arterial TBR values obtained were then averaged in order to derive a $_{mean}TBR$ for both carotid arteries and the ascending aorta.

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation and categorical data as absolute numbers and percentages throughout this manuscript. In general, normal distribution of data was tested for all of the different statistical calculations using the Kolmogorov-Smirnov-Test. Depending on normal distribution, comparisons between continuous variables were performed with the student's t test or the Mann-Whitney U test. To assess the relationship between classified pre-scan glucose values and tertiles of the respective FDG circulation time for the chest and neck data acquisition as well as the injected FDG dose on one hand and the FDG uptake parameters in the aorta and carotids on the other, a 1-way analysis of variance (ANOVA) with appropriate testing for multiple comparisons was performed (to test for between-group differences). The Tukey test was used for post-hoc testing. Classification of the pre-scan glucose values was performed according to the recommendations by The International Diabetes Federation IGF/IGT consensus statement [normal: < 6.1 mmol/l (< 110 mg/dl), impaired glucose tolerance: ≥6.1 mmol/l (≥110 mg/dl) and < 7.0 mmol/l (< 126 mg/dl), and diabetic disease: ≥7.0 mmol/l (≥ 126 mg/dl)] [23].

MULTIPLE REGRESSION WITH BACKWARD ELIMINATION AND LINEAR REGRESSION WITH ENTER METHOD

In order to look at the relationship between each of more than one independent variable on one dependent variable, multiple regression analyses with backward elimination were used to assess the association between variables potentially impacting the vascular aortic and carotid FDG uptake parameters ($_{mean}SUV_{max}$ and $_{mean}TBR_{max}$). Vascular FDG-uptake parameters were treated as the response variables ($_{mean}SUV_{max}$ or $_{mean}TBR_{max}$, dependent) and the methodological, biological and demographic variables as the explanatory (independent) variables for the regression analysis. The explanatory variables included were as follows: body mass index (BMI), statin medication, diabetes, oral anti-diabetic medication, injected FDG dose, fasting pre-scan glucose levels, and FDG circulation time (either time interval between injection of the tracer and starting time of the chest (aortic) or neck (carotid) data acquisition, depending on the respective response variable). For pre-scan fasting glucose levels, we used both, the continuous, as well as the classified glucose values in separate multivariate regression models. Following the backward analysis, the ENTER regression was used to determine independent predictors of the response variables. For this method, all of the explanatory variables of the backward elimination model that showed a significant association with the FDG uptake value were retained and entered the regression model as a block in a single step. This entry method was preferred over the forward selection of variables since after excluding all of the explanatory variables without a significant association with the different aortic- and carotid wall FDG uptake values, only few significant variables were left for a relatively low number of cases. Throughout the manuscript, all results of the multiregression models were given with the standardized regression coefficient (β), the 95% confidence interval, and the p-value for the estimate of the statistical significance.

All statistical analyses were performed using SPSS™ statistical package 16.0 (SPSS Inc.; Chicago, Illinois).

RESULTS

Population Characteristics

All 195 patients rendered sufficient clinical data and entered further analyses (Table 1). In five out of the 195 patients included in the study, analysis of the carotids could not be performed due to high FDG uptake in the thyroid, affecting the visualization and analysis of FDG uptake within the vessel. In two patients, the aortic images could not be analyzed due to poor image quality making assessment of the FDG uptake within the vessel impossible. In 17 patients, no aortic scans were available for analysis as the study protocol did not include the aortic scans at that time. Therefore, a total of 176 aortic scans were available for further analysis.

Image Parameters

PET-related methodological data as well as results of the image analyses for the ascending aorta and the common carotids as well as the FDG blood pool activity in the SVC and JV are given in Table 1.

Comparing the aortic and carotid FDG uptake parameters, no significant differences were found with regard to the $_{mean}SUV_{max}$ values ($p = 0.261$). In contrast, $_{mean}TBR_{max}$ values were significantly higher in the carotids as compared to the aorta ($p < 0.0001$). FDG blood pool activity was significantly higher in the SVC as compared to the JV ($p < 0.0001$; Table 1).

Aortic FDG Uptake

Results of the multivariate regression analyses for the aortic FDG uptake are shown in Table 2. BMI and statin medication showed a significantly positive association with both, the aortic $_{mean}SUV_{max}$ and $_{mean}TBR_{max}$. FDG circulation $time_{Chest}$ showed a negative association with the $_{mean}SUV_{max}$ but correlated positively with the $_{mean}TBR_{max}$ values (Table 2). These associations were also seen in the ANOVA of the three different tertiles of the FDG circulation $time_{Chest}$ showing significantly higher aortic $_{mean}SUV_{max}$ values at the earliest tertile (≥78 min ≤111 min between FDG injection and starting time of the chest acquisition) compared to the second tertile (> 111 min < 145 min, Figure 3a; Appendix). Reflecting the positive correlation between the circulation $time_{Chest}$ and the aortic $_{mean}TBR_{max}$ values seen in the multivariate regression model, ANOVA revealed significantly lower $_{mean}TBR_{max}$ values in the earliest time tertile compared to both, the second as well as the third tertile (≥145 min), respectively (Figure 3).

The continuous pre-scan glucose values as well as the classified glucose values ≥7.0 mmol/l were negatively associated with the $_{mean}TBR_{max}$ but showed no association with the $_{mean}SUV_{max}$ values (Table 2, Figures 1 and 1a; Appendix). ANOVA revealed significant differences for the aortic $_{mean}TBR_{max}$ according to the different groups of classified pre-scan glucose values with significantly lower $_{mean}TBR_{max}$ values in patients with pre-scan glucose values ≥7.0 mmol/l compared to those with values < 6.1 mmol/l (Figure 1).

The multivariate regression model did not show a significant association between the injected FDG dose and any of the aortic FDG uptake parameters (Table 2). Accordingly, no statistically significant differences were found for both the aortic $_{mean}SUV_{max}$ as well as the $_{mean}TBR_{max}$ values according to the three different tertiles of the injected FDG dose (Figure 2 and Figure 2a; Appendix).

Carotid FDG Uptake

Continuous- and classified pre-scan glucose values ≥7.0 mmol/l were negatively associated with the carotid $_{mean}SUV_{max}$- and $_{mean}TBR_{max}$ values in the multivariate regression models but ANOVA failed to show any significant difference for both carotid FDG uptake parameters according to the three different classes of pre-scan glucose values (Table 2, Figures 1 and 1a; Appendix).

Contrarily, FDG circulation $time_{Neck}$ was positively associated with the $_{mean}TBR_{max}$ values (Table 2). However, ANOVA did not reveal any significant difference between the three different tertiles of the FDG circulation $time_{Neck}$ with either the carotid $_{mean}SUV_{max}$ or $_{mean}TBR_{max}$ values (Figures 3 and 3a; Appendix).

BMI ($_{mean}SUV_{max}$) and statin medication ($_{mean}TBR_{max}$) were positively associated with either one of the carotid FDG uptake parameters (Table 2).

As with the aortic FDG uptake parameters, injected FDG dose failed to show any significant association with one of the carotid FDG uptake values in the multivariate regression models (Table 2). Accordingly, no significant differences were shown for both carotid uptake parameters in the ANOVA of the FDG dose tertiles (Table 2, Figures 2 and 2a; Appendix).

FDG Blood Pool Activity in the SVC and JV

Multivariate regression analysis revealed FDG circulation $time_{Chest}$ or $_{-Neck}$ to be significantly negatively associated with both, the FDG blood pool activity in the SVC and JV, respectively (Table 3). In contrast, continuous pre-scan glucose values correlated significantly with the FDG activity in the blood of the SVC only. BMI showed a significant positive correlation with the blood pool activity in the SVC as well as in the JV (Table 3).

Neither the FDG blood pool activity in the SVC nor in the JV showed significant differences related to the classified pre-scan glucose values or the tertiles of the injected FDG dose (Figures 1 and 2). In contrast, the FDG blood pool activity in the SVC was significantly higher in the earliest tertile of the FDG circulation $time_{Chest}$ compared to the two later tertiles (second: $p < 0.0001$; third: $p = 0.002$). This was also due for the first tertile of the FDG circulation $time_{Neck}$ showing a significantly higher FDG blood activity in the JV compared to the second later tertile ($p = 0.01$; Figure 3).

DISCUSSION

FDG-PET/CT is increasingly used for non-invasive imaging of vascular inflammation [1,4–6,10,11,19,22,24,25]. However, standardized scan protocols to achieve the best optimal imaging quality accompanied by the lowest possible radiation exposure for the patients on the one hand and comparability between different trials from different groups on the other hand, are still missing. We therefore prospectively evaluated several variables, already known or suspected to potentially influence the FDG uptake in target tissues like cancer or inflammation, for their impact on the vascular FDG uptake pattern. A special focus was set on the FDG circulation time, the patient's fasting pre-scan blood glucose levels as well as the injected FDG dose. A cross sectional study design in a large sample population with known cardiovascular disease or multiple risk factors for it was applied.

FDG Circulation Time

The FDG circulation time is critical as a sufficient contrast between the target (plaque, arterial wall) and the background (blood) is essential to ensure proper region of interest (ROI) placement and thus accurate quantification of plaque FDG uptake [1,4,7–12]. Therefore, a longer FDG circulation time than that for oncology PET is advised in order to

allow sufficient FDG accumulation in the arterial wall and to permit blood levels of FDG to become reduced by decay and wash-out.

Based on the results of the multivariate regression models, we found increasing aortic and carotid $_{mean}TBR_{max}$ values with increasing FDG circulation times. Whereas the circulation time did not show any impact on the $_{mean}SUV_{max}$ values in the carotids, at the earlier acquisition times of the chest scan, $_{mean}SUV_{max}$ values indeed decreased with increasing FDG circulation times. This was also due to the FDG blood pool activity in the SVC as well as in the JV. Most likely, the later finding mainly accounts for the decreasing aortic $_{mean}SUV_{max}$ values with increasing circulation times as, in contrast to the TBR values, no correction for the underlying FDG blood pool activity is applied to the SUV values. In contrast, the increasing $_{mean}TBR_{max}$ values seem more or less to reflect the increasing FDG uptake in the arterial wall only as these values are indeed corrected for the FDG blood pool uptake and should therefore not be influenced by the background activity.

Our results are in line with previous studies showing that a circulation time for FDG in excess of 2 h gives a much higher TBR [1,4,10]. In order to further maximize the contrast between plaque and background, other groups have used even longer time intervals with imaging around 3 h after FDG injection [1,4,10]. This later time point was derived from dynamic PET studies in both patients with carotid disease and animal models of atherosclerosis [1,4,10,22]. At one hour after injection, there is little FDG uptake with poor plaque/background ratio. However, after 3 h the plaque/background uptake ratio becomes optimized for lesion visualization and quantification. Using this 3 h time point in an animal model that more closely mimics human atheroma, Tawakol et al. demonstrated that, compared to control aortas, atherosclerotic aortas accumulates 19 times as much FDG, translating into SUV values up to 10 times greater when imaged using PET [4]. Contrarily, one hour after injection, little FDG uptake with poor plaque/background ratio was found. With increasing FDG circulation times, this ratio should increase due to an increased specific FDG uptake into inflammatory cells on the one hand, and, additionally, due to a decreased FDG activity within the blood pool. Our results seem to confirm an optimal acquisition time point of approximately 2.5 h after injection of the tracer. At this time point, the blood pool activity in both the SVC and the JV was lowest compared to the activity in both venous vessels at the earliest circulation time. This goes along with significantly lower $_{mean}SUV_{max}$ and significantly higher $_{mean}TBR_{max}$ values in the aorta in the second tertile, reflecting circulation times between 111 min and 145 min, compared to the earliest time tertile. An optimal acquisition time point of 2.5 h as seen in our study is further supported by the study of Tawakol et. al. in which an acquisition time point of 3 h was used leading to still excellent correlations of the FDG-uptake with histology [4]. This indeed argues against a relevant cellular FDG washout in the target tissue. Starting data acquisition as early as 60 min after FDG injection as recommended by some seems not to be appropriate, as based on our results, blood pool activity showed highest and $_{mean}TBR_{max}$ lowest values, respectively, at the earliest circulation time tertile which, for the chest scan, even starts later at 60 min with times of about 78 min post injection [7,26]. In contrast, prolonging the circulation time to above 145 min did not lead to a further relevant improvement of the aortic FDG uptake, even though the $_{mean}TBR_{max}$ values were significantly higher for the third compared to the second time tertile. At longer FDG

circulation times, as generally seen for the neck (carotid) scan in our study, the impact of the circulation time seems of less relevance as no significant difference between the three tertiles of the FDG circulation $time_{Neck}$ was found for both, the $_{mean}SUV_{max}$ and $_{mean}TBR_{max}$ values in the carotids.

Pre-scan Fasting Glucose Values

Previously published studies strongly suggest an impact of patient's pre-scan glucose levels on the FDG uptake at least in oncologic imaging [13,15,16]. The observed reduction of the FDG uptake is most likely due to competition between glucose and FDG as facilitative transport via the glucose transporter protein (GLUT) system is the most important way for either glucose or FDG to enter human cells [27]. Additionally, it was shown that uptake of FDG in macrophages in culture depends not only on the culture duration and the degree of macrophage activation but also on the prevailing glucose concentration which is associated with a decreasing FDG uptake with increments of the glucose load in the culture medium [27]. As diabetes is strongly associated with atherosclerotic disease, the problem of elevated pre-scan glucose levels occurs frequently in patients scheduled for FDG-PET imaging of vessel wall inflammation.

The impact of glucose on FDG uptake in inflammatory lesions is less well investigated. Cell culture experiments suggest that moderate hyperglycemia, up to 250 mg/dl (14 mmol/l), does not adversely affect FDG uptake in inflammatory cells [14]. In contrast, data from experimental studies in rats not only showed a significantly reduced FDG uptake in the lesions of infectious and non-infectious inflammatory models with moderate hyperglycemia [(150–180 mg/dl (8.3–10.0 mmol/l)] but also decreased GLUT-1 and GLUT-3 levels by glucose loading in lesions of infectious origin [29,30].

Therefore, the reproducibility of atheroma imaging with FDG might be expected to be worse in those with high blood sugar at the time of imaging compared with normoglycemic subjects. Our data support this. We found a negative association between pre-scan glucose levels on FDG uptake in the aortic and carotid arteries $_{mean}TBR_{max}$ but also the $_{mean}SUV_{max}$ values in the carotids. In contrast, we observed an increased FDG blood pool activity in the SVC with elevated pre-scan glucose values. As the FDG activity in the SVC is used to calculate the aortic TBRs this finding might at least partly explain the lower TBRs in patients with high pre-scan glucose values. Furthermore, the results of the present study seem also to confirm that even moderate hyperglycemia lowers FDG uptake into inflammatory cells, as we found pre-scan glucose levels at any level higher than 7.0 mmol/l to be negatively associated with the vascular FDG uptake. Glucose values below that level failed to have any impact on FDG accumulation. Patients with pre-scan glucose levels higher than 7.0 mmol/l should therefore be excluded from vascular FDG imaging studies if possible or, if not and also in the clinical setting, data analysis should be performed by using an appropriate mathematical glucose correction for the vascular FDG uptake [31].

Injected FDG Dose

Looking at the injected FDG dose, neither a significant impact on any of the vascular FDG uptake parameters nor a significant difference in the vascular FDG uptake according to the

different tertiles of the injected dose was observed. Therefore, injection of a rather small FDG dose of between 307 and 458 MBq seems to be justified. This dose seems applicable even for over-weight patients, as in the multivariate regression model, injected FDG dose was adjusted for BMI and BMI values failed to show a negative association with the vascular FDG uptake. Indeed, a significantly positive association between BMI and the arterial and blood pool FDG uptake was seen. This finding gains importance with regard to radiation protection issues for the patients, mainly as an increasing number of clinical trials with one or more follow-up PET scans requested have to be more frequently expected in the future [24,25]. This might have been expected, as we note that some studies have successfully used doses of FDG as low as 185 MBq without undue degradation of either image quality or lesion quantification [10].

FDG Uptake Parameters

Our results are highly consistent for the two applied FDG uptake parameters except of the impact of shorter FDG circulation times on the aortic FDG uptake. As we performed the chest scan first in the current trial, the, compared to the neck scan, shorter circulation times led to a negative association with the aortic $_{mean}SUV_{max}$ but a positive impact on the $_{mean}TBR_{max}$ values. This is most likely due to the increased FDG blood activity at this time for which the $_{mean}SUV_{max}$ values are not corrected. The impact of mainly the shorter circulation times on the vascular FDG uptake is confirmed by the fact, that at the later acquisition times for the neck scans, no significant association with the carotid $_{mean}SUV_{max}$ values was observed at all. We also found significantly higher carotid $_{mean}TBR_{max}$ values as compared to the respective aortic FDG uptake parameter, which might also be related to the longer circulation time for the neck data acquisition leading to a lesser impact of the FDG blood pool activity on the arterial FDG uptake. This is indeed reflected by favorable TBRs but seems in fact also to be due for the carotid $_{mean}SUV_{max}$ values, which are slightly higher as the aortic $_{mean}SUV_{max}$ values. However, this difference failed to be statistically significant.

Limitations

In the present study image analyses was performed by only one reader. This might reduce statistical noise related to inter-observer variation but might raise concerns regarding intra-observer bias. However, previous reports demonstrated that this method has good inter- and intra-observer reproducibility [19,21].

As we did not use contrast-enhanced CT in the current study, soft plaques in the vessels could not be detected. The absence of CT contrast was deliberate, to allow those with renal impairment to be imaged. However, by intention, we chose a population either with defined atherosclerosis (e. g. known CAD, carotid artery disease, etc.) or multiple risk factors for it, and we included all evaluable slices of the arterial wall. Thereby, both focal and diffuse areas of FDG uptake have been included in the analysis. Furthermore, subjects with known vasculitis were excluded, and we made the assumption that any FDG signal within the vessel wall was likely to be due to accumulation of the tracer within atherosclerotic plaque. Others have previously demonstrated co-localization between lipid-rich plaque and FDG uptake [32].

Finally, some of the correlations we found were modest. However, being statistically significant they still provide important and relevant insights about factors impacting the vascular FDG uptake, which need to be taken into account in future prospective trials using dedicated vascular PET imaging protocols.

CONCLUSION

FDG circulation time and pre-scan fasting glucose values are prone to impact the vascular FDG uptake. This has to be taken into account when designing FDG-PET protocols. FDG circulation times of about 2.5 h should be preferred and pre-scan glucose values ≥7.0 mmol/l should be avoided. An FDG dose of between 307 and 458 MBq seems to be justified to achieve an appropriate quality of the scans and likely to be best optimal for repeated scans in clinical trials. Keeping the impact of the FDG circulation time on the $_{mean}SUV_{max}$ values, mainly at shorter circulation times, in mind, $_{mean}SUV_{max}$ and $_{mean}TBR_{max}$ values provide comparable results for quantification of the vascular FDG uptake.

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Appendix

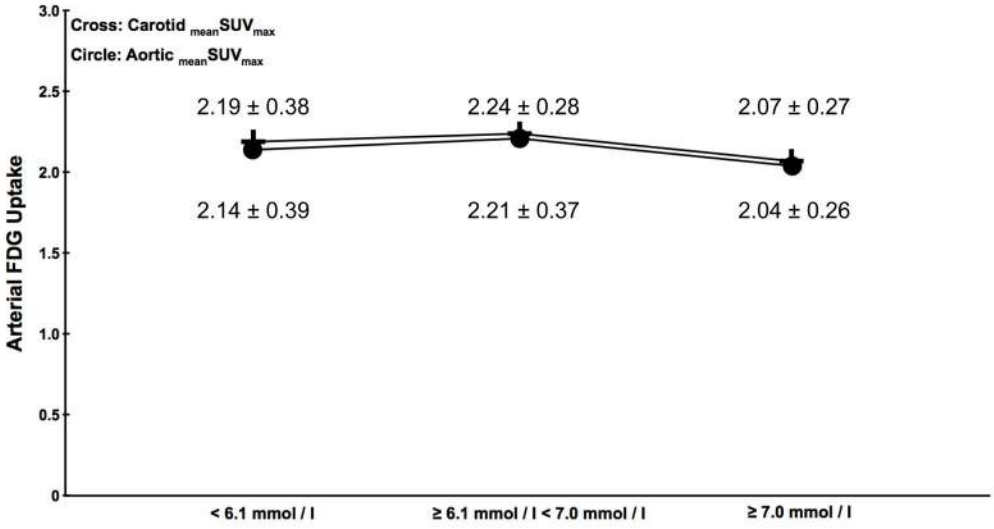

Figure 1a.

Relation Between the Classified Pre-scan Glucose Values and the Arterial FDG Uptake in the Aorta and the Carotids.

The FDG uptake is given as mean standardized uptake value ($_{mean}SUV_{max}$). All values are given as mean. A one-way ANOVA was performed to test for between group differences.

Aorta:	$_{mean}SUV_{max}$: p = 0.216
Carotid:	$_{mean}SUV_{max}$: p = 0.170

Mean values ± standard deviation are given in the figures

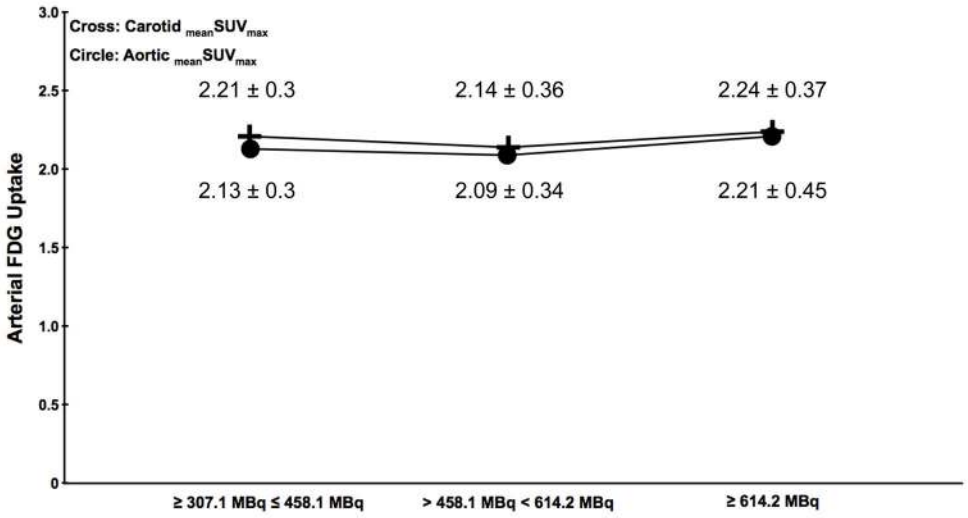

Figure 2a.

Relation Between Tertiles of the Injected FDG Dose and the Arterial FDG Uptake in the Aorta and the Carotids.

The FDG uptake is given as mean standardized uptake value ($_{mean}SUV_{max}$). All values are given as mean. A one-way ANOVA was performed to test for between group differences.

Aorta:	$_{mean}SUV_{max}$: p = 0.166
Carotid:	$_{mean}SUV_{max}$: p = 0.229

Mean values ± standard deviation are given in the figures

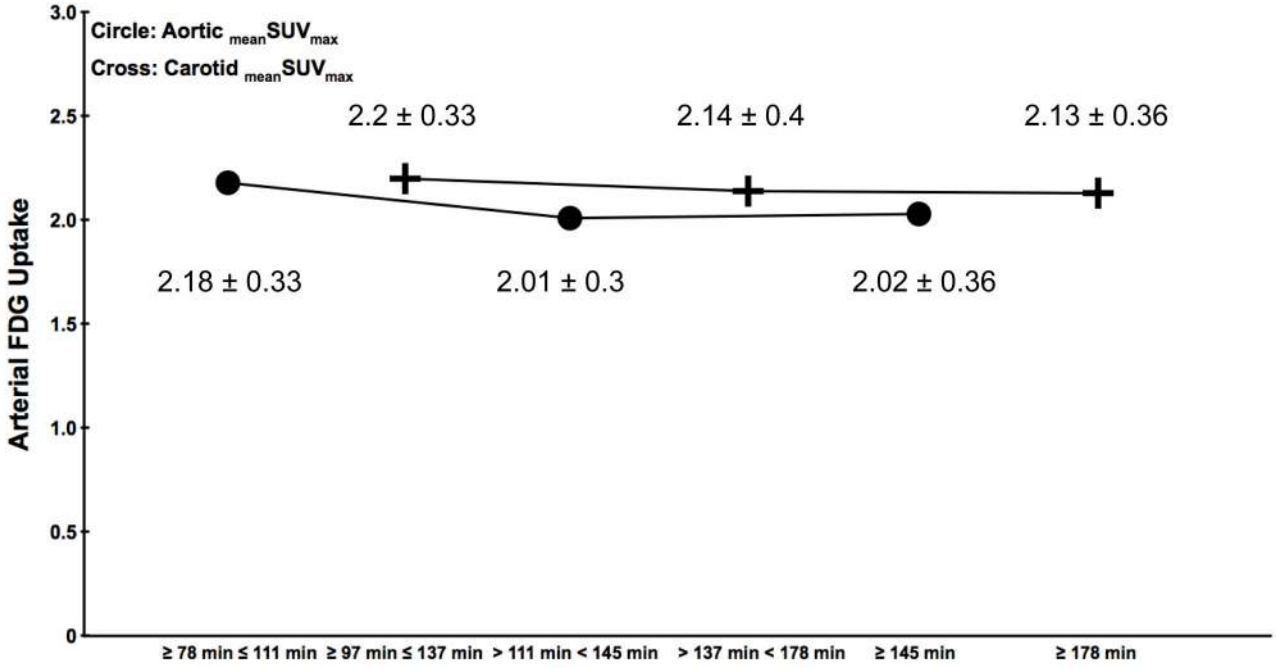

Figure 3a.

Relation Between Tertiles of the FDG Circulation Time for the Chest and Neck Scan and the FDG Uptake in the Aorta and the Carotids.

The FDG uptake is given as mean standardized uptake value ($_{mean}SUV_{max}$). All values are given as mean. A one-way ANOVA was performed to test for between group differences.

Aorta:	$_{mean}SUV_{max}$: p = 0.031	≥78 min ≤111 min vs. > 111 < 145 min: p = 0.034
Carotid:	$_{mean}SUV_{max}$: p = 0.524	

Mean values ± standard deviation are given in the figures

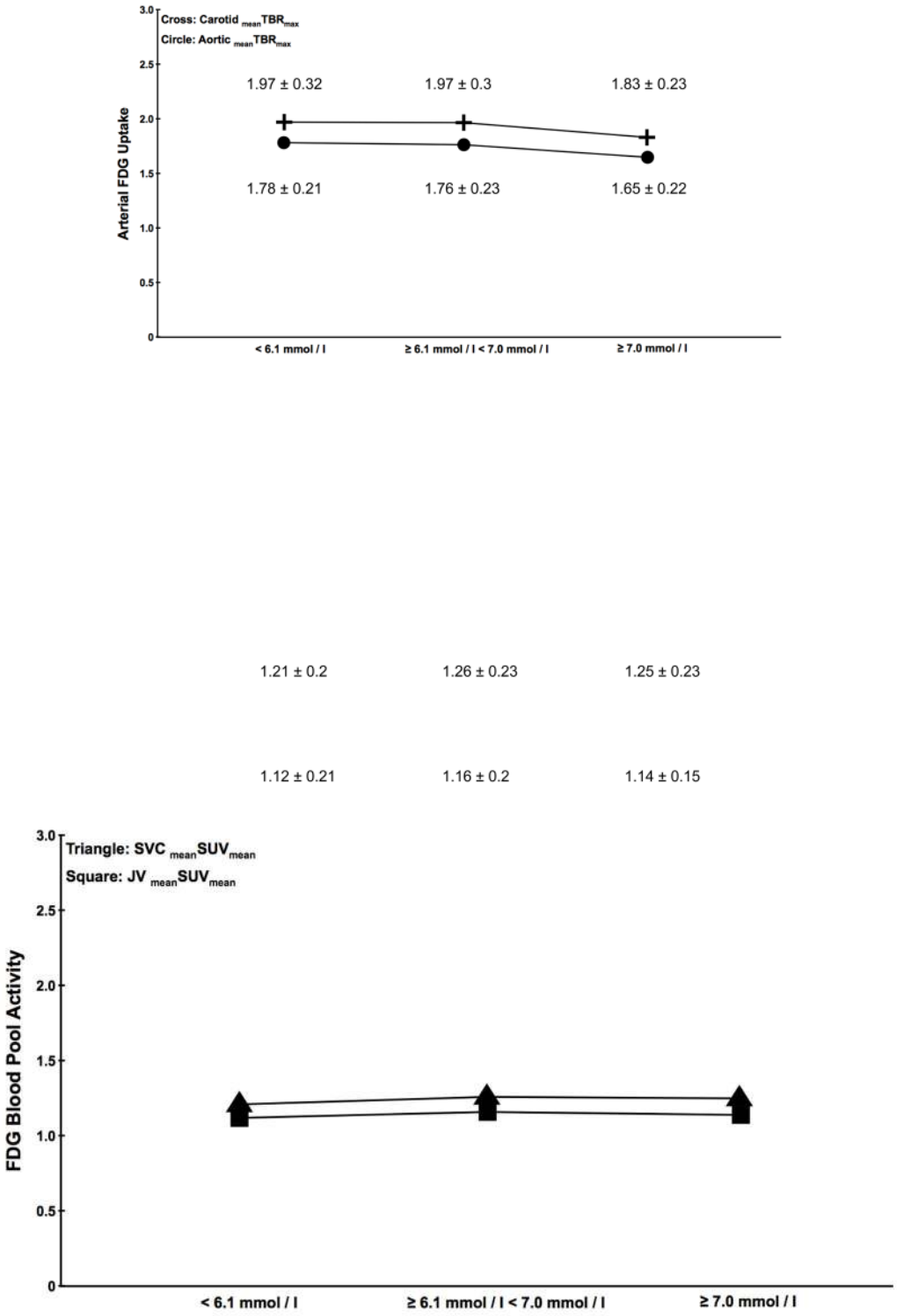

Figure 1. Relation Between the Classified Pre-scan Glucose Values and the Arterial FDG Uptake in the Aorta and the Carotids (upper) and the FDG Blood Pool Activity in the SVC and JV (lower)

The FDG uptake is given as mean Target-to-Background Ratio ($_{mean}TBR_{max}$). FDG blood pool activity is given as $_{mean}SUV_{mean}$. All values are given as mean. A one-way ANOVA was performed to test for between group differences.

Aorta:	$_{mean}TBR_{max}$: p = 0.013	< 6.1 mmol/l vs. ≥7.0 mmol/l: p = 0.009
Carotid:	$_{mean}TBR_{max}$: p = 0.082	
SVC:	$_{mean}SUV_{mean}$: p = 0.303	
JV:	$_{mean}SUV_{mean}$: p = 0.661	

Mean values ± standard deviation are given in the figures

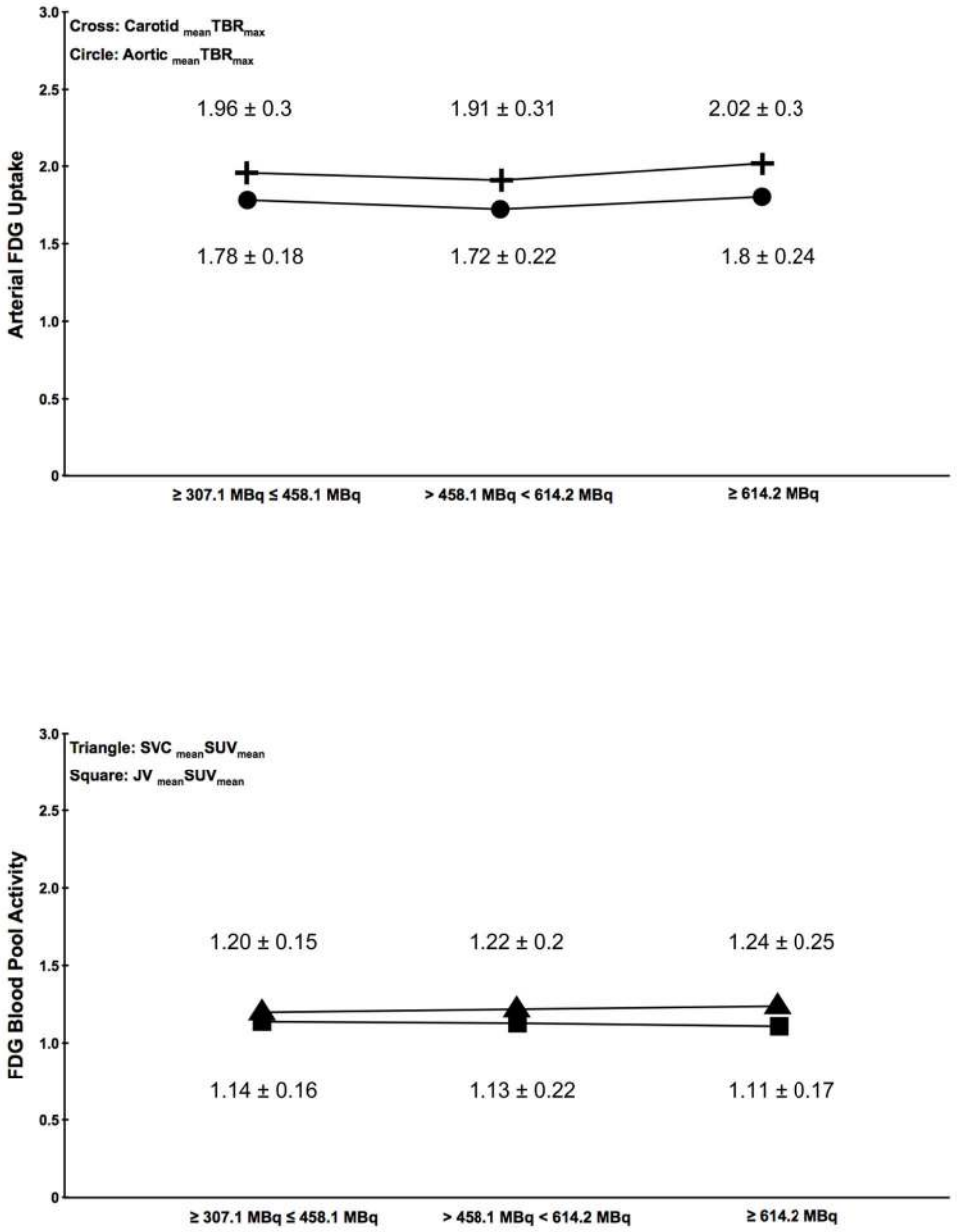

Figure 2. Relation Between Tertiles of the Injected FDG Dose and the Arterial FDG Uptake in the Aorta and the Carotids (upper), and the FDG Blood Pool Activity in the SVC and JV (lower)

The FDG uptake is given as mean Target-to-Background Ratio ($_{mean}TBR_{max}$). FDG blood pool activity is given as $_{mean}SUV_{mean}$. All values are given as mean. A one-way ANOVA was performed to test for between group differences.

Aorta:	$_{mean}TBR_{max}$: p = 0.083
Carotid:	$_{mean}TBR_{max}$: p = 0.103
SVC:	$_{mean}SUV_{mean}$: p = 0.691

JV: $_{mean}SUV_{mean}$: p = 0.805

Mean values ± standard deviation are given in the figures

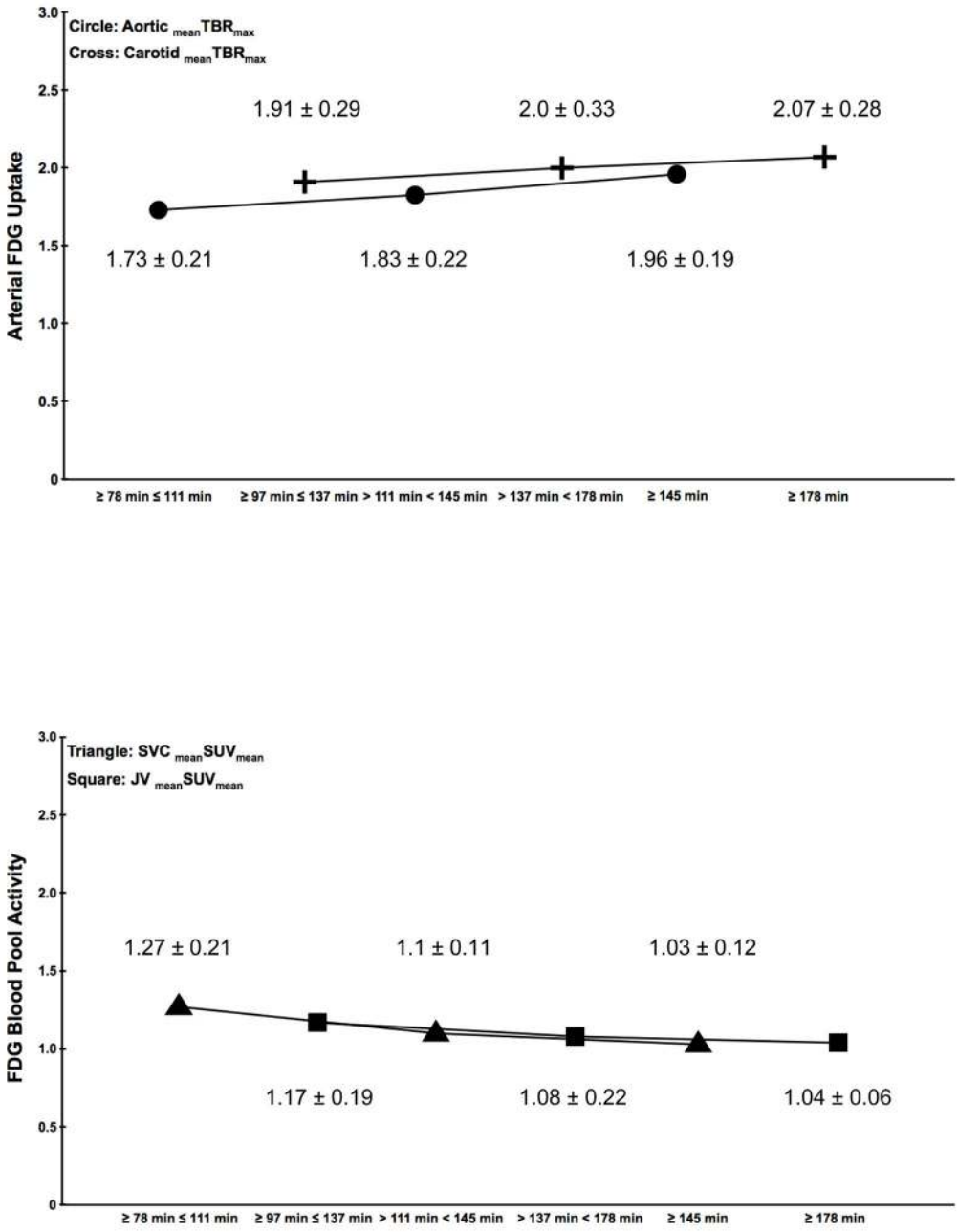

Figure 3. Relation Between Tertiles of the FDG Circulation Time for the Chest and Neck Scan and the FDG Uptake in the Aorta and the Carotids (upper) and the FDG Blood Pool Activity in the SVC and JV (lower)

The FDG uptake is given as mean Target-to-Background Ratio ($_{mean}TBR_{max}$). FDG blood pool activity is given as $_{mean}SUV_{mean}$. All values are given as mean. A one-way ANOVA was performed to test for between group differences.

Aorta:	$_{mean}TBR_{max}$: p = 0.001	≥78 min ≤111 min vs. > 111 < 145 min: p = 0.03 ≥78 min ≤111 min vs. ≥145 min: p = 0.008

Carotid:	$_{mean}TBR_{max}$: p = 0.059	
SVC:	$_{mean}SUV_{mean}$: p < 0.0001	≥78 min ≤111 min vs. > 111 < 145 min: p < 0.0001 ≥78 min ≤111 min vs. ≥145 min: p = 0.002
JV:	$_{mean}SUV_{mean}$: p = 0.006	≥97 min ≤137 min vs. > 137 < 178 min: p = 0.01

Mean values ± standard deviation are given in the figures

Table 1
Characteristics and PET-related Data of the Study Population

Characteristics	**n = 195**
Age (years)	57.7 ± 11.6
• Age > 65 years	53 (27.2)
Gender	
• Male	131 (67.2)
• Female	64 (32.8)
Body Mass Index (BMI; kg/m^2)	29.1 ± 5.7
• BMI < 25	45 (23.1)
• BMI ≥25 < 30	78 (40.0)
• BMI ≥30	72 (36.9)
Lifestyle	
Smoking	
• Never	92 (47.2)
• Former	71 (36.4)
• Current	32 (16.4)
Alcohol Users	84 (43.1)
Exercisers	112 (57.4)
Cardiovascular Disease	
• Myocardial Infarction	34 (17.4)
• Percutaneous Coronary Intervention	79 (40.5)
• Coronary Artery Bypass Surgery	25 (12.8)
• Stroke/Transient Ischemic Attack (TIA)	13 (6.7)
• Peripheral Artery Disease	7 (3.6)
Family History of Cardiovascular Disease	110 (56.4)
Hypertension	116 (59.5)
Diabetes	64 (32.8)
• Diabetes Type I	6 (3.1)
• Diabetes Type II	58 (29.7)
Medication	
Statin	121 (62.1)
Beta-blockers	75 (38.5)
Calcium Channel Blockers	29 (14.9)
Angiotensin Converting Enzyme Inhibitors	53 (27.2)
Angiotensin II Blockers	27 (13.8)
Nitrates	9 (4.6)
Diuretics	29 (14.9)
Aspirin	109 (55.9)
Clopidrogrel	78 (40.0)
Oral Anti-Diabetics	50 (25.6)
PET-related Data	

Characteristics	**n = 195**
Pre-scan Glucose Values (mmol/l)	5.8 ± 1.3
Classified Pre-scan Glucose Values*	
• < 6.1 mmol/l	134 (69.0)
• ≥6.1 mmol/l–< 7.0 mmol/l	30 (15.5)
• ≥7.0 mmol/l	30 (15.5)
Injected FDG Dose (MBq; corrected for decay and residual activity in syringe after injection of the FDG dose)	562.4 ± 92.5
Tertiles Injected FDG Dose	
• > 307.1 ≤458.1	31 (15.9)
• > 458.1 < 614.2	109 (55.9)
• ≥614.2	55 (28.2)

	Chest Scan (n = 178) Aorta: 176 (90.3)	**Neck Scan (n = 195) Carotids: 190 (97.4)**	***p - value***
FDG Circulation Time (Time difference between FDG injection and starting time of chest- or neck scan, respectively; min)	101.3 ± 19.1	137.1 ± 20.5	< 0.0001
	Tertiles FDG Circulation Time		
	≥78 ≤111 min: 132 (74.2)	≥97 ≤137 min: 112 (57.4)	
	> 111 < 145 min: 38 (21.3)	> 137 < 178 min: 74 (38.0)	
	≥145 min: 8 (4.5)	≥178 min: 9 (4.6)	
Acquired Counts (kcps)	29.0 ± 10.7	291.0 ± 96.3	< 0.0001
FDG Blood Pool Activity (SVC or JV, respectively; $_{mean}SUV_{mean}$)	1.22 ± 0.21	1.13 ± 0.20	< 0.0001
Vascular FDG Uptake Parameters	Aorta	Carotids	
• $_{mean}SUV_{max}$	2.13 ± 0.37	2.18 ± 0.36	0.261
• $_{mean}TBR_{max}$	1.76 ± 0.22	1.95 ± 0.31	< 0.0001

Values are mean ± SD or n (%).

• One value missed during follow-up

MBq: Megabecquerel

kcps: kilo counts per second

SVC: Superior Vein Cava

JV: Jugular Vein

Table 2

Multiple Linear Regression Analyses with Backward Elimination and Enter Analysis to Identify Variables Potentially Impacting the Aortic and Carotid Vessel Wall FDG Uptake

$_{mean}SUV_{max}$ and mean Target-to-Background Ratio ($_{mean}TBR_{max}$), respectively, were the response variables and BMI, statin medication, diabetes, anti-diabetic drugs, injected FDG dose, FDG circulation time (Chest or Neck, respectively), and continuous- or classified pre-scan fasting glucose values were the explanatory variables. Variables were retained in the model when $p < 0.10$ and entered afterwards the Enter Analysis. In that model, variables were judged to be statistically significant when $p < 0.05$. β is the standardized regression coefficient.

Aorta (Continuous Pre-scan Fasting Glucose Values)

Backward Analysis

Explanatory Variables ($_{mean}SUV_{max}$ or $_{mean}TBR_{max}$, respectively):
BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation $Time_{Chest}$, Pre-scan Fasting Glucose

Enter Analysis $_{mean}SUV_{max}$

Explanatory Variables: BMI, FDG Circulation $Time_{Chest}$, Statin Medication, Anti-diabetic Drugs

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.186	< 0.0001	
BMI	0.294	0.010 – 0.028			< 0.0001
FDG Circulation $Time_{Chest}$	−0.255	−0.008 – −0.002			< 0.0001
Statin Medication	0.279	0.101 – 0.318			< 0.0001
Anti-diabetic Drugs	−0.238	−0.324 – −0.083			0.001

Enter Analysis $_{mean}TBR_{max}$

Explanatory Variables: FDG Circulation $Time_{Chest}$, BMI, Pre-scan Fasting Glucose, Statin Medication

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.186	< 0.0001	
FDG Circulation $Time_{Chest}$	0.326	0.002 – 0.005			< 0.0001
BMI	0.243	0.004 – 0.015			0.001
Pre-scan Fasting Glucose	−0.218	−0.003 – 0.000			0.002
Statin Medication	0.146	0.002 – 0.128			0.042

Aorta (Classified Pre-scan Fasting Glucose Values)

Backward Analysis

Explanatory Variables ($_{mean}SUV_{max}$ or $_{mean}TBR_{max}$, respectively):
BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation $Time_{Chest}$, Pre-scan Fasting Glucose < 6.1 mmol/l, Pre-scan Fasting Glucose ≥6.1 mmol/l < 7.0 mmol/l, Pre-scan Fasting Glucose ≥7.0 mmol/l

Enter Analysis $_{mean}SUV_{max}$

Explanatory Variables: BMI, FDG Circulation Time$_{Chest}$, Statin Medication, Anti-diabetic Drugs

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.186	< 0.0001	
BMI	0.294	0.010 – 0.028			< 0.0001
FDG Circulation Time$_{Chest}$	−0.255	−0.008 – −0.002			< 0.0001
Statin Medication	0.279	0.101 – 0.318			< 0.0001
Anti-diabetic Drugs	−0.238	−0.324 – −0.083			0.001

Enter Analysis $_{mean}TBR_{max}$

Explanatory Variables: FDG Circulation Time$_{Chest}$, Pre-scan Fasting Glucose ≥7.0 mmol/l, BMI, Statin Medication

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.205	< 0.0001	
FDG Circulation Time$_{Chest}$	0.327	0.002 – 0.005			< 0.0001
Pre-scan Fasting Glucose ≥7.0 mmol/l	−0.255	−0.231 – −0.071			< 0.0001
BMI	0.227	0.003 – 0.014			0.001
Statin Medication	0.141	0.001 – 0.124			0.046

Carotid (Continuous Pre-scan Fasting Glucose Values)

Backward Analysis

Explanatory Variables ($_{mean}SUV_{max}$ or $_{mean}TBR_{max}$, respectively):
BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation Time$_{Neck}$, Pre-scan Fasting Glucose

Enter Analysis $_{mean}SUV_{max}$

Explanatory Variables: BMI

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.149	< 0.0001	
BMI	0.392	0.016 – 0.032			< 0.0001

Enter Analysis $_{mean}TBR_{max}$

Explanatory Variables: Statin Medication, Pre-scan Fasting Glucose, FDG Circulation Time$_{Neck}$, BMI

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.083	< 0.0001	
Statin Medication	0.209	0.041 – 0.223			0.005
Pre-scan Fasting Glucose	−0.190	−0.004 – 0.000			0.009
FDG Circulation Time$_{Neck}$	0.175	0.001 – 0.005			0.014

Eur J Nucl Med Mol Imaging. Author manuscript; available in PMC 2014 May 17.

Carotid (Classified Pre-scan Fasting Glucose Values)

Backward Analysis

Explanatory Variables ($_{mean}SUV_{max}$ or $_{mean}TBR_{max}$, respectively):
BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation $Time_{Neck}$, Pre-scan Fasting Glucose < 6.1 mmol/l, Pre-scan Fasting Glucose ≥6.1 mmol/l < 7.0 mmol/l, Pre-scan Fasting Glucose ≥7.0 mmol/l

Enter Analysis $_{mean}SUV_{max}$

Explanatory Variables: Pre-scan Fasting Glucose ≥7.0 mmol/l, BMI

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.163	< 0.0001	
BMI	0.395	0.016 – 0.032			< 0.0001
Pre-scan Fasting Glucose ≥7.0 mmol/l	−0.136	−0.264 – −0.005			0.042

Enter Analysis $_{mean}TBR_{max}$

Explanatory Variables: Pre-scan Fasting Glucose ≥7.0 mmol/l, FDG Circulation $Time_{Neck}$, Statin Medication

	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.076	0.001	
Pre-scan Fasting Glucose ≥7.0 mmol/l	−0.185	−0.276 – −0.038			0.010
FDG Circulation $Time_{Neck}$	0.175	0.001 – 0.005			0.014
Statin Medication	0.170	0.019 – 0.196			0.017

Table 3

Multiple Linear Regression Analyses with Backward Elimination and Enter Analysis to Identify Variables Potentially Impacting the FDG Blood Pool Activity in the SVC and JV

$_{mean}SUV_{mean}$ was the response variables and body mass index (BMI), statin medication, diabetes, anti-diabetic drugs, injected FDG dose, FDG circulation $time_{Chest}$ or FDG circulation $time_{Neck}$, respectively, and continuous- or classified pre-scan fasting glucose values, respectively, were the explanatory variables. Variables were retained in the model when $p < 0.10$ and entered afterwards the Enter Analysis. In that model, variables were judged to be statistically significant when $p < 0.05$. β is the standardized regression coefficient.

SVC (Continuous Pre-scan Fasting Glucose Values)					
Backward Analysis $_{mean}SUV_{mean}$					
Explanatory Variables: BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation $Time_{Chest}$, Pre-scan Fasting Glucose					
Enter Analysis $_{mean}SUV_{mean}$					
Explanatory Variables: FDG Circulation $Time_{Chest}$, Pre-scan Fasting Glucose, Anti-diabetic Drugs, Statin Medication, BMI					
	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.268	< 0.0001	
FDG Circulation $Time_{Chest}$	–0.501	–0.007 – –0.004			< 0.0001
Pre-scan Fasting Glucose	0.174	0.000 – 0.003			0.021
Anti-diabetic Drugs	–0.173	–0.156 – –0.011			0.024
SVC (Classified Pre-scan Fasting Glucose Values)					
Backward Analysis $_{mean}SUV_{mean}$					
Explanatory Variables: BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation $Time_{Chest}$, Pre-scan Fasting Glucose < 6.1 mmol/l, Pre-scan Fasting Glucose ≥6.1 mmol/l < 7.0 mmol/l, Pre-scan Fasting Glucose ≥7.0 mmol/l					
Enter Analysis $_{mean}SUV_{mean}$					
Explanatory Variables: FDG Circulation $Time_{Chest}$, Statin Medication, Anti-diabetic Drugs, BMI, Pre-scan Fasting Glucose ≥7.0 mmol/l					
	Standardized Coefficient β	**95 % Confidence Interval**	**Adjusted R^2**	**Significance**	***p - value***
			0.260	< 0.0001	
FDG Circulation $Time_{Chest}$	–0.499	–0.007 – –0.004			< 0.0001
Statin Medication	0.152	0.005 – 0.124			0.033
Anti-diabetic Drugs	–0.169	–0.157 – –0.007			0.033
BMI	0.139	0.000 – 0.010			0.042
JV (Continuous Pre-scan Fasting Glucose Values)					
Backward Analysis $_{mean}SUV_{mean}$					

Explanatory Variables: BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation Time$_{Neck}$, Pre-scan Fasting Glucose

Enter Analysis $_{mean}SUV_{mean}$

Explanatory Variables: BMI, FDG Circulation Time$_{Neck}$

	Standardized Coefficient β	95 % Confidence Interval	Adjusted R^2	Significance	*p - value*
			0.179	< 0.0001	
BMI	0.371	0.008 – 0.017			< 0.0001
FDG Circulation Time$_{Neck}$	−0.210	−0.003 – 0.000			0.002

JV (Classified Pre-scan Fasting Glucose Values)

Backward Analysis $_{mean}SUV_{mean}$

Explanatory Variables: BMI, Statin Medication, Diabetes, Anti-diabetic Drugs, Injected FDG Dose, FDG Circulation Time$_{Neck}$, Pre-scan Fasting Glucose < 6.1 mmol/l, Pre-scan Fasting Glucose ≥6.1 mmol/l < 7.0 mmol/l, Pre-scan Fasting Glucose ≥7.0 mmol/l

Enter Analysis $_{mean}SUV_{mean}$

Explanatory Variables: BMI, FDG Circulation Time$_{Neck}$

	Standardized Coefficient β	95 % Confidence Interval	Adjusted R^2	Significance	*p - value*
			0.179	< 0.0001	
BMI	0.371	0.008 – 0.017			< 0.0001
FDG Circulation Time$_{Neck}$	−0.210	−0.003 – 0.000			0.002