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^{18}F-FDG PET and Vascular Inflammation; Time to Refine the Paradigm?

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The recognition of the significance of atherosclerotic plaque biology and more specifically, inflammation in determining the propensity of plaque to rupture has led to efforts aimed at detecting vessel wall inflammation through molecular imaging [1]. Given their high sensitivity and non-invasive nature, nuclear imaging modalities are particularly suitable for vascular molecular imaging. This is especially true when they are combined with CT or MRI to localize the target vessel. Following several reports on incidental observations of ^{18}F-FDG uptake in large arteries on PET studies performed for cancer staging and other applications [2], a landmark study by Rudd et al more than a decade ago linked carotid artery ^{18}F-FDG signal to symptomatic carotid artery disease [3]. Since then a large number of studies have been performed to evaluate ^{18}F-FDG PET as a tool for vessel wall characterization. To date, arterial ^{18}F-FDG PET signal has been linked to age [4], gender [5], diabetes [6], metabolic syndrome [7], history of coronary artery disease [5], Framingham risk score [8], symptomatic carotid disease [3, 9], distal microembolization [10], atherosclerotic plaque structure and morphology [5, 11, 12], systemic inflammatory disease [13], and risk of future cardiovascular events, as reported by several groups of investigators, including Blomberg et al in an earlier issue of the journal [14, 15]. The proposed applications of vascular ^{18}F-FDG PET include retrospective identification of culprit lesions after transient ischemic attack [9], tracking the effect of therapeutic interventions on plaque biology [16–18] and cardiovascular risk stratification [14, 15].

While vascular ^{18}F-FDG PET is promising, there are a number of biological and technical issues that need further clarification prior to its use as a reliable clinical diagnostic tool (Table 1). As a glucose homologue, ^{18}F-FDG is trapped in the cell upon uptake via glucose transporters and irreversible phosphorylation. Thus, any glucose-dependent, metabolically active cell can retain ^{18}F-FDG. While macrophages are believed to be a major contributor to ^{18}F-FDG uptake in atherosclerosis, vascular smooth muscle cells and endothelial cells can also retain ^{18}F-FDG [19]. Macrophages are a heterogeneous population of cells with distinct roles in inflammation and there is debate on which subset of macrophages, e.g., pro-inflammatory M1 or regulatory M2 macrophages, retains ^{18}F-FDG the most [20, 21]. Likewise,

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the triggers of enhanced glucose metabolism by vascular cells in vivo remain to be fully identified, as pro-inflammatory cytokines as well as hypoxia can each promote ^{18}F-FDG uptake by vascular cells in culture [19, 22, 23]. Like for any other tracer, ^{18}F-FDG signal is the product of both specific and non-specific uptake in the target tissue. In the case of arteries, enhanced endothelial permeability associated with inflammation and non-specific binding to atherosclerotic plaque components can contribute to tracer accumulation in the vessel wall [24]. Given major differences in the composition of atherosclerotic and non-atherosclerotic vessel wall, it seems unreasonable to assume that the data obtained and validated in atherosclerosis are directly extrapolatable to non-atherosclerotic arteries.

The interpretation of vascular ^{18}F-FDG PET studies is complicated by the magnitude of partial volume and scatter effects, in part due to the small size of the vessel wall and its close proximity to blood. Other factors to consider include the imaging protocol (e.g., patient preparation and timing of imaging), quantification methodology, inherent variability of the results [25], and potential biological and mechanistic contributors to ^{18}F-FDG uptake in the vessel wall. The importance of patient preparation, diet and blood glucose level is well-recognized in cardiac ^{18}F-FDG PET studies [26]. Less is known about the effect of these variables on ^{18}F-FDG uptake in the vessel wall, but it is prudent to consider them in interpreting vascular PET studies [27, 28]. The optimal timing of imaging (between 60 to 180 minutes after tracer administration) remains a subject of debate [29]. In line with the conclusions of Blomberg et al published in an earlier issue of the Journal [15], many investigators (but not all) recommend delayed imaging (at 2 to 3 hours) to reduce residual blood pool activity [27, 29, 30]. The importance of the quantification methodology which can potentially introduce major errors in the results cannot be neglected. Differences in this respect often preclude the extrapolation of the results from one study to another (Table 2).

In the absence of an in vivo “gold standard” for measuring inflammation, validation of ^{18}F-FDG PET as indicator of vessel wall inflammation would require tissue inflammation to be quantified ex vivo in surgical or post-mortem samples and correlated with ^{18}F-FDG signal. A more stringent criterion would be the demonstration of a change in in vivo signal upon modulation of vessel wall inflammation. Given major differences in spatial resolution between imaging and histology, inaccuracy in co-registering these two techniques can potentially introduce considerable error in such validation studies. The same potential for error exists in correlating in vivo and ex vivo quantification of tracer uptake. ^{18}F-FDG uptake in perivascular structures such as brown fat [31] further complicates the interpretation of PET studies. Similarly, a potential direct inhibitory effect of therapeutic interventions such as statins on glycolytic metabolism and ^{18}F-FDG uptake by macrophages [19], which could reduce ^{18}F-FDG signal independent of macrophage content of the vessel wall, is another reasonable possibility to consider.

The link between vessel wall inflammation and ^{18}F-FDG signal on vascular PET studies has been investigated in a small number of preclinical and clinical studies (Table 3). On the surface, the results predominantly support a linkage. However, further inquiry into these studies brings up a number of questions. Rudd et al [3] attributed ^{18}F-FDG signal to vessel wall inflammation based on ex vivo uptake of tritiated deoxyglucose in CD68 (macrophage)-rich segments of three carotid endarterectomy samples [3]. Ogawa et al [32]

reported a correlation between aortic wall macrophage content and ^{18}F-FDG accumulation assessed by gamma-well counting in atherosclerotic rabbits. The correlation between aortic ^{18}F-FDG uptake and macrophage content in atherosclerotic rabbits was confirmed in other studies [33, 34]. A clinical study in 17 human subjects linked ^{18}F-FDG signal (expressed as target-to-background ratio, TBR) on PET images acquired at 3 hours and co-registered with separately-acquired CT or MR images, to CD68 content of endarterectomy samples obtained within a month of imaging studies [35]. The authors noted a weaker correlation between SUVmean and CD68 staining, while they found no correlation between ^{18}F-FDG signal and high sensitivity CRP in this study [35]. The correlation between ^{18}F-FDG signal and atherosclerotic plaque macrophage content was confirmed in a subset of these subjects (n=10) [12]. Other investigators reported a correlation between ^{18}F-FDG signal on PET images acquired within 30–45 minutes and CD68 staining of endarterectomy samples [36]. Interestingly, in this study the authors noticed a better correlation in ^{18}F-FDG signal between the two carotid arteries [36]. Graebe at al[37] reported a correlation between CD68 mRNA expression in endarterectomy samples and ^{18}F-FDG signal on PET images (acquired at 3 hours) performed 1 day prior to endarterectomy for symptomatic carotid disease. Another report from the same group of investigators found a modest correlation between CD68 mRNA expression and ^{18}F-FDG signal in 17 patients in a similar setting [38]. It is unclear if any of these 17 patients were included in their original cohort of subjects. Menezes at al [39] reported a modest correlation between SUVmax and CD68 immunostaining in endarterectomy samples obtained from 21 consecutive symptomatic or asymptomatic subjects who underwent ^{18}F-FDG PET (acquired at 90 minutes) prior to endarterectomy. However, in multivariable regression analysis ^{18}F-FDG signal was not identified as a predictor of CD68 expression. Also, while in this study there was a statistically significant 10% difference between ipsi- and conra-lateral carotid artery SUVmax, the TBR was not different between the two carotids. In line with these findings, a multicenter trial of ^{18}F-FDG PET (acquired 90 minutes after tracer administration), performed within 2 weeks of atherectomy for peripheral arterial disease in 30 patients with claudication, found no correlation between ^{18}F-FDG signal and plaque macrophage content[40]. A strong correlation between right and left superficial femoral artery TBR in this study raises the possibility that a systemic factor, such as blood pool activity, could have been the main determinant of vascular ^{18}F-FDG signal.

The conflicting results of these studies, combined with their small size and methodological differences introduce some ambiguity regarding the biological basis of ^{18}F-FDG signal in atherosclerotic arteries. While a few studies have linked ^{18}F-FDG uptake to macrophage density in human carotid plaque, there is no such data regarding other vascular beds. Furthermore, even if inflammation were found to be unequivocally the main determinant of ^{18}F-FDG uptake in atherosclerosis, the same could not be assumed regarding ^{18}F-FDG signal in non-atherosclerotic arteries. The variability in relative uptake of ^{18}F-FDG in different vascular beds is another potential confounding factor to be considered [5]. There is no clear basis for assuming that ^{18}F-FDG uptake in any specific arterial bed (beyond carotid and coronary arteries) should reflect the risk for future cardiovascular events better than other vascular beds. As the imaging protocol and quantification methodology vary widely between different studies, the most appropriate methodology may depend on the specific

question to be addressed [41]. To focus on imaging vascular inflammation, it is prudent to rely on protocols that have established a link between ^{18}F-FDG signal and tissue inflammation. Ultimately, one cannot equate unequivocally any ^{18}F-FDG signal in blood vessels with vessel wall inflammation.

Like any good body of scientific work, these initial studies on vascular ^{18}F-FDG PET have raised promise along with many questions. While it is appealing to assume a direct association between ^{18}F-FDG signal and vascular inflammation, there is a need for further sound validation studies before the paradigm passes to dogma. The major promise of molecular imaging is in addressing some of the existing diagnostic gaps in the management of cardiovascular patients. Focusing imaging on assessing biology rather than anatomy and/or physiology can be transformative. Like any new concept or technology, the success of molecular imaging is dependent on carefully designed, sound studies. As imaging investigators and cardiovascular practitioners we stride for maintaining and reinforcing the high standards our field is grounded upon.

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Table 1

Unresolved issues in vascular ^{18}F-FDG PET imaging

- Biological
  - Relative contribution of various vascular cell types to the signal
  - Triggers of vascular cell glucose metabolism
  - Role of endothelial hyper-permeability
  - Uptake in perivascular structures
  - Non-specific binding to plaque components
  - Influence of hyperglycemia
  - Effect of therapeutic interventions on glucose metabolism
- Technical
  - Histological validation
  - Subject preparation
  - Timing of imaging
  - Co-registration methodology
  - Quantification methodology
  - Scatter and partial volume effect
- Uncertain basis
  - Variable uptake in different vascular beds
  - Uptake variability over time

Table 2

Examples of quantification methodologies used in vascular ^{18}F-FDG PET studies

- Accumulation rate (mean decay-corrected plaque ^{18}F-FDG concentration divided by the integral of the decay-corrected input function, expressed in units of sec^{-1}) [3]
- SUV (decay-corrected tissue concentration in KBq per milliliter, divided by the injected dose per body weight in KBq per gram) [33]
- SUVmean [38]
- SUVmax for each plaque divided by the "average of the normal vessel wall values" [36]
- TBR (plaque SUVmean divided by venous blood SUVmean) [35, 41]
- TBR (mean of SUVmax measured at regular intervals divided by venous blood SUVmean) [12, 37, 40, 41]

SUV: standardized uptake value, TBR: target-to-background ratio

Table 3

Studies evaluating the link between ^{18}F-FDG PET and vascular inflammation

	Type of study	Timing of analysis	Quantification methodology	Validation technique
Rudd et al [3]	Clinical carotid (n=3)		Ex vivo: descriptive	Ex vivo ^{3}H-deoxy glucose uptake detected by autoradiography in CD68-rich sections of carotid endarterectomy samples
Ogawa et al [32]	Pre-clinical aorta (Rabbit)	4 hours	Ex vivo: differential Uptake Ratio: (tissue activity/tissue weight)/(injected radiotracer activity/animal body weight)	Ex vivo gamma- well counting vs number of macrophages on histological sections
Tawakol et al [33]	Pre-clinical aorta (Rabbit)	3 hours	In vivo: SUV(mean?) (decay-corrected tissue concentration in KBq per milliliter, divided by the injected dose per body weight in KBq per gram) Ex vivo: % injected dose/gram	In vivo imaging or ex vivo gamma-well counting vs % area of macrophage immunostaining on histological sections
Hyafil et al [34]	Pre-clinical aorta (Rabbit)	3 hours	In vivo: SUV mean	In vivo imaging vs % area of macrophage immunostaining on histological sections
Tawakol et al [35]	Clinical carotid (n=17)	3 hours	In vivo: TBR (SUV mean divided by venous blood SUV mean)	In vivo imaging vs % area of macrophage immunostaining on histological sections
Figueroa et al [12]	Clinical carotid (n=10 from a previous study)	1.5–3 hours	In vivo: TBR (SUV max measured at 5 mm intervals along the long axis of the carotid artery divided by venous blood SUV mean)	In vivo imaging vs % or total area of macrophage immunostaining on histological sections
Font et al [36]	Clinical carotid (n=15)	30–45 minutes	In vivo: SUVmax for each plaque divided by the “average of the normal vessel wall values”	In vivo imaging vs % area of macrophage immunostaining on histological sections
Graebe et al [37]	Clinical carotid (n=10)	3 hours	In vivo: TBR (mean SUVmax of the carotid artery divided by venous blood SUV mean) or SUV max	In vivo imaging vs CD68 mRNA level
Menezes at al [39]	Clinical carotid (n=21)	90 minutes	In vivo: SUVmax	In vivo imaging vs % area of macrophage immunostaining on histological sections
Myers et al [40]	Multicenter clinical PAD (n=30)	90 minutes	In vivo: mean of max TBR (mean of SUVmax divided by venous blood SUV mean)	In vivo imaging vs CD68 immunoassay