General discussion

The introduction of modern imaging techniques, particularly molecular imaging such as $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT), enabled us to increase our knowledge regarding inflammatory diseases that affect the arterial wall. In this thesis we describe several aspects of imaging large artery inflammation with $^{18}$F-FDG PET, comprising methodological considerations, clinical applications and directions for further research. The focus of this thesis was on Giant Cell Arteritis (GCA)/large-vessel vasculitis (LVV) and atherosclerosis, the primary etiologies of large-artery inflammation. (1–3)

GCA is classified as a vasculitis affecting medium- and large sized vessels. Together with Takayasu arteritis (TA) it has been classified as large-vessel vasculitis. (4) The major difference between these two types of large-vessel vasculitis is the age of disease presentation with TA patients generally being younger. (5) In addition, it was previously believed that the distribution of vascular involvement in TA primarily consisted of the aorta and its’ proximal tributaries, whereas GCA would be more restricted to the medium sized/cranial arteries. (6) Nevertheless, the incidence of large artery involvement is currently considered to be much higher (50-75%) than previously thought (approximately 15%). Large artery involvement is mostly assessed by imaging and in some cases when patients present with specific clinical signs or symptoms. Large artery involvement could already be implicated by the observation that GCA patients have an increased relative risk of developing thoracic and abdominal aortic aneurysms. (7) GCA is most often suspected when patients present with cranial symptoms (new onset headache in the temporal artery region), jaw claudication or visual disturbances in combination with
elevated inflammatory parameters (either erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP)). However, these ‘typical’ signs and symptoms may be absent when cranial arteries are not involved. This ‘atypical’ phenotype of GCA has been referred to as ‘silent’, ‘occult’ or ‘extracranial’ GCA.\textsuperscript{(8,9)} To investigate whether extracranial GCA may represent a distinct clinical entity compared to cranial GCA, we systematically searched for articles that described characteristics (epidemiologic, histopathologic, clinical (signs/symptoms, treatment, complications) and diagnostic) of extracranial GCA and summarized current knowledge.

In \textbf{chapter 1} we conclude that literature on extracranial GCA is scarce. Moreover, there is a lack of studies that directly compare properties of both phenotypes, including diagnosis, pathophysiology, treatment and complications. Epidemiologically, patients with extracranial GCA seem to be characterized by a higher proportion of women, a younger age at disease onset, and a longer diagnostic delay (probably due to less specific complaints) when compared to cranial GCA patients. Extracranial GCA is more difficult to diagnose resulting in longer delay. The diagnosis often depends on imaging results. As a result, the last decade, during which the results of this thesis were gathered, there has been a shift towards defining GCA as a spectrum of a disease with overlapping clinical manifestations.\textsuperscript{(12)} Accordingly, experts in the field have suggested to expand classification criteria for GCA. Abnormal imaging results (ultrasound, MRI or PET/CT) are proposed to be included in the criteria, not necessitating temporal artery biopsy (gold standard for GCA) in patients without typical cranial symptoms. Based on the current knowledge derived from this review and our own clinical experience we proposed a flow-chart to aid in choosing which diagnostic (imaging) modality is indicated, depending on the presenting clinical scenario that suggests possible large-vessel GCA. Our review also
revealed controversy regarding whether or not to treat patients with large-vessel GCA (LV-GCA) and whether the same treatment protocol applies as in cranial GCA (c-GCA). This issue is further explored in chapter 5 and will be discussed subsequently.

Methodological considerations

Several methodological issues regarding the assessment of vascular wall inflammation on PET/CT existed, both in the field of vasculitis and atherosclerosis. In clinical practice, visual assessment of linearly enhanced vascular wall $^{18}$F-FDG uptake was often used to diagnose large-vessel vasculitis. (13–15) Nevertheless, observer agreement between observers with mixed experience (working in academic and non-academic medical centers), comparable to the diversity of observers assessing $^{18}$F-FDG PET/CT images in general daily practice, had not been assessed. In addition, as mentioned above, standardized criteria for assessment of large-vessel vasculitis are absent. We showed (in chapter 2) that interobserver agreement was higher when using standardized criteria compared to the general first impression (sometimes referred to as ‘gestalt’) of the observer. Among dedicated and experienced observers, agreement was highest when vascular wall $^{18}$F-FDG uptake was higher than liver uptake. These results could, however, not be corroborated among somewhat less experienced observers in whom agreement between ‘gestalt’ and standardized criteria were equal. These results suggest that a minimum level of experience is required for optimal assessment of large-vessel vasculitis on $^{18}$F-FDG PET/CT. These minimum requirements (e.g. supervised assessment of at least 100 scans by a dedicated observer) should be discussed among certified nuclear medicine specialists.
In atherosclerosis, plaque inflammation can be quantified using $^{18}$F-FDG PET/CT. In chapter 6 it is illustrated that various protocols have previously been used for this purpose. Since variation in methodology might lead to variation in quantitative outcome measures, e.g. maximal standardized uptake value or target-to-background ration (SUVmax or TBRmax), we performed a study in a small group of patients with increased risk of cardiovascular disease to establish whether variation of a set of data acquisition or image analysis parameters affects these outcome measures. In this dynamic $^{18}$F-FDG PET/CT study we observed, as may be expected, that late imaging (i.e. 90 minutes after intravenous injection of $^{18}$F-FDG, as compared to 60 minutes) significantly decreases vascular wall SUVmax and increases vascular wall TBRmax. In addition, the applied type of SUV normalisation significantly affected SUVmax. Interobserver agreement for the ‘hot-spot’ method was only acceptable for a limited amount of vascular segments as opposed to the ‘whole-segment’ method which showed high interobserver agreement for all vascular segments. The results of our study emphasize the need of standardized protocols, especially in the case of a multi-center study, but also to compare results between studies. In daily practice, standardization of acquisition parameters should not be too difficult. However, with regards to the data analysis, this may prove to be more challenging, particularly since the ‘whole-segment’ method is extremely time-consuming. For that purpose, development of computerized models with agreement comparable to the ‘whole-segment’ method may be of particular interest. Alternatively, analyses are performed using the ‘hot-spot’ method in those particular vascular segments in which high agreement is observed. At present, however, there is still a lack of data concerning the prognostic value of increased $^{18}$F-FDG uptake in a specific vascular segment compared to that in other segments. This may also be a subject of future studies.
Vascular wall calcification is a well-established independent predictor of cardiovascular morbidity and mortality. (16,17) It is considered to be a marker of global atherosclerotic burden. Vascular wall $^{18}$F-FDG uptake has been used as a surrogate marker for plaque inflammation and anecdotal reports (mainly retrospective research) have shown that it may independently predict cardiovascular disease (morbidity and/or mortality). Previous publications showed inconsistent results regarding the correlation between vascular wall calcification and $^{18}$F-FDG uptake within distinct vascular segments. In addition, none of these studies have investigated whether these markers may represent the same entity (i.e. global atherosclerotic burden) or 2 distinct features of atherosclerosis (i.e. inflammatory vs structural damage).

In chapter 7 our prospective study on the association between vascular wall $^{18}$F-FDG uptake and calcification is presented. We showed that there was a positive association between vascular wall $^{18}$F-FDG uptake and calcification in several segments. More importantly, we assessed that vascular calcification, when used as an independent predictor in multivariate regression, did not affect other determinants of vascular wall $^{18}$F-FDG uptake. Therefore, we conclude that vascular wall $^{18}$F-FDG uptake represents more than just global atherosclerotic burden. This has implications for future research, e.g. in trials investigating the effect of therapy on the inflammatory component of atherosclerotic plaque development assessed by change in vascular wall $^{18}$F-FDG uptake. Several studies have already shown a relationship between vascular wall $^{18}$F-FDG uptake and cardiovascular events. (18–20) However, whether decrease in vascular wall $^{18}$F-FDG uptake results in decreased risk of cardiovascular morbidity has not been proven at present. Although this may be hampered by the natural history of inflammatory lesions in atherosclerosis as it has been shown, by assessment of serial $^{18}$F-
FDG PET/CT scans, that these lesions will also resolve spontaneously. (21)

**Clinical implications**

In Chapter 2 we demonstrated that $^{18}$F-FDG PET/CT results may be highly specific for a diagnosis of large-vessel GCA, depending upon the criteria used. The absence of a gold standard, i.e. histological proof of giant cell arteritis, was an important drawback of this study in which circular reasoning may have biased the positive results. We are, however, inclined to believe that a combination of elevated inflammatory parameters, $^{18}$F-FDG PET/CT images compatible with large-vessel GCA, rapid response (both clinically and biochemically) to treatment (glucocorticoids) and no alternative diagnosis during adequately long follow-up minimizes this potential bias. Therefore, these specific criteria (diffuse $^{18}$F-FDG vascular wall uptake higher than liver uptake or higher than $^{18}$F-FDG vascular wall uptake in the femoral artery) need to be incorporated in daily clinical practice by nuclear medicine physicians.

Another important clinical implication of the results of this thesis is the study on the value of $^{18}$F-FDG PET/CT in patients presenting with inflammation of unknown origin, expressed as a persistently elevated ESR (in the absence of fever) and no cause determined after simple laboratory tests (including paraproteinemia), a chest X-ray and abdominal ultrasound. The results of this study are illustrated in chapter 3. $^{18}$F-FDG PET/CT contributed in the diagnostic work-up (and more importantly successful treatment) in 38-40% of patients. This was assessed both prospectively and retrospectively. The final diagnosis included infection (3.3-3.4%), auto-immune/inflammation (16.7-31%) or malignancy (2-3.3%). These results are somehow comparable to results of patients presenting with fever of unknown origin. However, the relative contribution of auto-immune disease
(including large-vessel GCA) was higher in our study.\(^{22}\) This was mainly observed in our prospective study and may partially be explained by the standardized work-up. Also, as shown in chapter 2, observer variability may have played a role in the lower degree of large-vessel GCA in the retrospective part of this study. \(^{18}\)F-FDG PET/CT should therefore be considered by clinicians in elderly patients with elevation of inflammatory markers without clinical clues and after a simple diagnostic work-up. Moreover, it may be argued that \(^{18}\)F-FDG PET/CT should be performed even earlier in the diagnostic work-up as it shows similarities with fever of unknown origin in which such an approach is cost-effective.\(^{23}\) Nevertheless, this needs to be ascertained in patients with inflammation of unknown origin.

**Future directions**

Despite the previously described progress regarding the value of \(^{18}\)F-FDG PET/CT in vascular inflammation there still remain some challenges that need to be assessed in future studies. With regards to large-vessel GCA several issues concerning both imaging and treatment can be addressed.

First, the most optimal strategy in the work up of suspected extracranial GCA or large artery involvement in cranial GCA is not known yet. Prospective, comparative studies are required to establish whether any of the potential imaging modalities could be superior. These studies should also incorporate strategies to improve cost-effectiveness of this approach. In addition, standardized criteria for the assessment of LV-GCA need to be established for all imaging modalities prior to the initiation of such a comparative study.

Second, there are no standardized assessment/imaging criteria at present for patients presenting with relapse while still using
immunosuppressive therapy. Prospective studies need to establish the value of $^{18}$F-FDG PET/CT in these patients. In addition, alternative strategies, e.g. other imaging modalities should be studied as well (perhaps incorporating biomarkers such as IL-6 or SAA) in order to assess the most effective approach in patients presenting with a possible disease relapse.

Third, $^{18}$F-FDG PET/CT imaging has shown great potential, but also has some drawbacks such as high cost and radiation exposure. Therefore, we explored whether the use of biomarkers to differentiate between patients with and without large artery involvement in GCA may be of benefit.

In chapter 4 we describe that several markers appear to be associated with LV-GCA/intensity of large-artery inflammation. IL-6 and SAA were the ones showing the most potential. Due to the low number of patients in this study we were not able to determine cut-off values to exclude or establish LV-GCA. If these cut-off values can be determined in a larger study, $^{18}$F-FDG PET/CT will be indicated/required less frequently.

On the other hand, the treatment of LV-GCA also remains a matter of debate. In this thesis we did not investigate whether establishing LV-GCA would require a different management, i.e. we did not determine whether these patients have a different prognosis would therefore perhaps require different management, either in treatment or follow-up. Regardless, we explored whether Dutch clinicians are inclined to manage GCA patients differently depending upon the presence or absence of large artery involvement (cranial vs large-vessel GCA). The results of this survey are discussed in chapter 5. Surprisingly, there was a trend towards a less aggressive approach in patients with LV-GCA. These results are not in line with the development of new guidelines.(24) The rationale behind a less
aggressive approach can only be hypothesized. Presumably, the perceived risk of (complications of) undertreatment of LV-GCA was lower than in c-GCA. Future studies should compare clinically relevant outcome measures (e.g. development of clinically important aortic aneurysm, major cardiovascular events, overall mortality) between GCA patients with and without large vessel involvement. These results may indicate the need for additional studies comparing different treatment strategies, i.e. treatment duration, alternative (biological) treatment. Due to the low incidence of GCA a multi-center study would be preferable.

Considering atherosclerosis, future studies investigating the value of a decrease of $^{18}$F-FDG vascular wall uptake as an endpoint still need to be interpreted with caution. At present, the evidence for the relation between enhanced vascular wall $^{18}$F-FDG uptake and future cardiovascular events is still limited. First of all, a large prospective study is warranted to establish vascular wall $^{18}$F-FDG uptake as an independent predictor. In addition, therapies that decrease uptake need to be placebo-controlled (given the aforementioned natural history of vascular wall $^{18}$F-FDG uptake in atherosclerotic lesions) and need to be related to important cardiovascular endpoints.

**Conclusion**

The knowledge base regarding large artery inflammation and the value of $^{18}$F-FDG PET/CT has increased dramatically the last decades. The work of this thesis adds to this base and provides information that is useful in daily clinical practice (i.e. use of $^{18}$F-FDG PET/CT in patients with inflammation of unknown origin and use of standardized criteria for the assessment of LV-GCA using $^{18}$F-FDG PET/CT), for research purposes (i.e. resolving methodological issues regarding quantification of vascular wall inflammation), and in generating hypotheses (i.e. by determining potential serological
biomarkers for the assessment of LV-GCA and by exploring the current practice of treatment of LV-GCA among a heterogenous group of clinicians).
References


