Correlation between 18-fluorodeoxyglucose accumulation in large vessels and serological markers of inflammation in polymyalgia rheumatica: a quantitative PET study

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Objective: To quantify 18-fluorodeoxyglucose (FDG) accumulation in large vessels in patients with polymyalgia rheumatica by positron emission tomography (PET), and to compare these data with serological markers of inflammation.

Methods: 13 untreated patients with active polymyalgia rheumatica underwent FDG positron emission tomography; eight were analysed in a second PET when in clinical remission. Six patients with other highly inflammatory conditions served as controls. For quantitative analysis, FDG uptake over nine defined vascular regions, divided by an individual background value, was expressed as a region of interest (ROI) index. These data were compared with the clinical status of the patient and with erythrocyte sedimentation rate (ESR), C reactive protein, haemoglobin, and platelet and leucocyte counts.

Results: By visual evaluation, 12 of the 13 patients showed an increased tracer uptake of the aorta or its major branches. By quantitative analysis, FDG uptake was significantly increased in polymyalgia rheumatica. In patients with active disease, the mean ROI index for all vascular regions exceeded that of controls by 70% (mean [SD]: 1.58 [0.37] v 0.93 [0.12]; p<0.001). In the eight patients who underwent follow up PET, the index declined substantially. In active polymyalgia rheumatica, FDG uptake was significantly correlated with C reactive protein (r=0.8), ESR (r=0.79), and platelet counts (r=0.68).

Conclusions: The observed FDG accumulation in the aorta and its branches and a strong correlation between tracer uptake and markers of inflammation is suggestive of large vessel arteritis. Quantitative ROI analysis appears to be a sensitive tool for detecting such inflammation.
significant differences between patients with active polymyalgia rheumatica and the controls with regard to C reactive protein levels, erythrocyte sedimentation rate (ESR), or platelet counts. Their characteristics are also given in table 1. All patients gave their informed consent to the studies.

FDG imaging
After at least six hours of fasting, 450 MBq of FDG were injected intravenously; 90 minutes after the injection, images of the torso including the carotid arteries and in some cases the iliac arteries were obtained with a field of view of 54 cm using a PET scanner (CTI, 951–31).

The PET scans were analysed visually in a descriptive manner, as well as by a quantitative computed method. For quantitative evaluation, regions of interest (ROI) were placed over nine defined vascular areas (ascending thoracic aorta, descending thoracic aorta, abdominal aorta, right and left subclavian arteries, right and left external carotid arteries, right and left common iliac arteries). A peripheral region of the lung served as the background region and an ROI index was calculated by dividing the respective vascular ROI scores by the individual background values.

Statistics
We used the GraphPad™ software package for the statistical analyses. Where applicable the Wilcoxon matched pairs test was used. Other analysis were done using the Mann–Whitney test. For the calculation of correlations we used the Spearman rank order test.

RESULTS
Visual examination
In 12 of the 13 patients, visual examination of the PET scans showed an increased tracer uptake of the aorta or its major branches compared with the controls. In one patient (patient 3) the PET could not be evaluated because of technical problems.

Quantitative PET analysis
Patients with active disease had significantly greater FDG uptake than control patients, the mean (SD) ROI index for all nine regions evaluated being 1.58 (0.37), v 0.93 (0.12) in controls (p, 0.001). Among the various vascular areas evaluated, the regions best discriminating between active polymyalgia rheumatica and controls were the subclavian and external carotid arteries.

PET re-evaluation after clinical remission
Eight patients underwent re-PET after achieving a complete or partial remission with corticosteroid treatment, as judged by the clinical and laboratory findings. The laboratory data are given in table 1. In this group of patients, tracer uptake was reduced from a mean index of 1.50 (0.16) in the initial PET to 1.09 (0.08) in the follow up PET (p, 0.001). In three patients, re-PET was completely normalised according to visual analysis. An example is given in fig 1.

When comparing these patients with the controls, the mean ROI index for all regions and the values obtained for the subclavian region were higher in patients who were in clinical remission than in the controls (0.74 (0.15) v 0.47 (0.11) for the right subclavian artery; 0.72 (0.17) v 0.51 (0.10) for the left; p<0.001 for both comparisons). There were no significant differences in other vascular regions. The results for the subclavian region are shown in fig 2.

Correlations between quantitative PET measures and laboratory data
In the patients with polymyalgia rheumatica the ESR was strongly correlated with PET values obtained for all
individual vascular regions except for those over the iliac arteries, for which only eight sets of data were available. The mean FDG uptake for all regions showed the best correlation ($r = 0.79; p < 0.0001$).

The C reactive protein concentration correlated significantly with the PET values obtained for each vascular region as well as with the mean value ($r = 0.80; p < 0.001$).

There was also a significant correlation between tracer uptake for all vascular regions and the platelet count, the strongest correlation being for the mean values of all vascular regions ($r = 0.68; p = 0.001$).

The haemoglobin concentration was inversely correlated with the FDG uptake detected in the abdominal aorta and with the mean value of all regions ($r = -0.47; p = 0.037$), but not with values obtained for other regions.

**DISCUSSION**

Our study shows increased FDG accumulation in the aorta and its proximal branches in all except one of 13 patients with polymyalgia rheumatica. Furthermore, the tracer uptake quantified by computer based evaluation showed a strong correlation with laboratory markers of disease activity. Hence the data presented here confirm and extend the studies undertaken by Blockmans et al.78

According to our hypothesis it might be concluded that PET evidence of large vessel vasculitis may be found in many patients with polymyalgia rheumatica without direct clinical signs of vasculitis such as stenosis or aneurysm. However, as these blood vessels are not suitable for routine histological examination, direct proof of vascular inflammation is not possible. Nonetheless, there is considerable indirect evidence:

First, there is an established close association between polymyalgia rheumatica and giant cell arteritis.2 In the patients with giant cell arteritis—about 50% of whom also present with the symptoms of polymyalgia rheumatica—late sequelae of vasculitis such as stenosis, aneurysm, or dissection predominantly occur in the vessels showing pathological changes in our PET series.3 Second, earlier necropsy studies showed involvement of the aorta and other arteries not only in patients with coexisting giant cell arteritis, but also in those with polymyalgia rheumatica in whom a temporal biopsy was negative or clinical signs of vasculitis were absent.10 Turkalow et al recently reported a patient with the typical manifestations of polymyalgia rheumatica in whom PET was done because of a mediastinal mass suspicious of malignancy. The PET images were very similar to the ones we have obtained in active polymyalgia rheumatica, and a biopsy taken from the mediastinal mass proved the vasculitic nature of the process and excluded malignancy.11

Third, there are striking similarities in the pathobiology of giant cell arteritis and polymyalgia rheumatica. As demonstrated by Weyand et al, cytokine mRNA levels (mainly IL-2) are almost identical in temporal artery specimens.12 13

There are some limitations to our study: The control group was relatively small and the average age of the controls was significantly lower than in the patients. Thus age related conditions such as atherosclerosis cannot completely be ruled out as confounding factors. For that reason we analysed a further eight patients (two women and six men, median age 64 years) with different types of neoplasia without serological signs of inflammation. In these patients no increased tracer uptake into vessel walls was observed (data not shown).

Overall, our data support the assumption that polymyalgia rheumatica is often accompanied by subclinical vasculitis of the aorta and its branches. Quantitative ROI analysis appears to be a sensitive tool for detecting vascular inflammation.

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**Figure 1** Normalisation of tracer uptake in a patient with polymyalgia rheumatica (PMR) on steroid treatment.

**Figure 2** Mean region of interest (ROI) index for the subclavian arteries in patients with polymyalgia rheumatica and controls; a, active disease; c, control; r, remission. *p < 0.01; **p < 0.001.
REFERENCES


