Original article

**Contribution of** $^{18}$F-sodium fluoride PET/CT to the study of the carotid atheroma calcification

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**A R T I C L E   I N F O**

Article history:
Received 1 August 2012
Accepted 24 August 2012
Available online 12 October 2012

Keywords:
Carotid atheroma
$^{18}$F-sodium fluoride PET/CT
Calcification
Atherosclerosis
Stroke
Molecular imaging

**A B S T R A C T**

Aim: To assess the calcification process of the carotid plaque by $^{18}$F-sodium fluoride PET/CT imaging.

Material and methods: A prospectively designed study including 15 patients in whom an atheroma plaque was detected by contrast enhanced CT scan during a neurological work-up was performed. A total of 29 plaques, 19 asymptomatic and 10 symptomatic, were studied. An $^{18}$F-sodium fluoride PET/CT scan was acquired 180 min after the i.v. injection of 370 MBq of $^{18}$F-sodium fluoride in all the patients. The images obtained were analyzed visually according to the intensity of the uptake.

Results: All the plaques showed $^{18}$F-sodium fluoride uptake, regardless of the intensity. However, the plaques of the symptomatic group showed a level of 2 or greater intensity while the intensity in 6 of the 19 in the asymptomatic group was lower than 2.

Conclusions: Although the study is limited by the small number of cases, the results show the feasibility of the technique to study the calcification of the atheroma using $^{18}$F-sodium fluoride and suggest an association between symptomatology and higher uptake of $^{18}$-sodium fluoride. Thus, these results encourage us to continue this study, with the inclusion of a larger number of patients.

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**Caracterizacion de la calcificacion del ateroma carotideo mediante $^{18}$F-fluoruro PET/TAC**

**RESUMEN**

Objetivo: Estudiar el proceso de calcificación de la placa de ateroma carotideo mediante $^{18}$F-fluoruro sódico PET/TAC.

Material y métodos: Estudio prospectivo en 15 pacientes con ateromatosis carotidea detectada por angio-TAC durante su estudio neurológico. El total de placas de ateroma estudiadas fue de 29, 19 asintomáticas y 10 sintomáticas. En todos los pacientes se adquirió un estudio PET/TAC a los 180 min de la administración intravenosa de 370 MBq de $^{18}$F-fluoruro sódico. Las imágenes se analizaron visualmente considerando la intensidad de captación.

Resultados: Todas las placas captaron $^{18}$F-fluoruro sódico, con independencia de la intensidad. Sin embargo las placas del grupo sintomático mostraron una intensidad de 2 o mayor mientras que 6 de las 19 del grupo asintomático mostraron una intensidad inferior a 2.

Conclusiones: Aunque el estudio está limitado por el pequeño número de casos, los resultados muestran la aplicabilidad de la técnica al estudio de la calcificación del ateroma con $^{18}$F-fluoruro sódico y sugieren una asociación entre la sintomatología y una mayor captación de $^{18}$F-fluoruro sódico. Por ello, estos resultados nos animan a continuar este estudio incluyendo un mayor número de pacientes.

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**Introduction**

The indication of invasive procedures such as endarterectomy or angioplasty in patients with carotid atheromatosis is still unclear and, therefore, new markers to identify the vulnerable plaques are needed, so that the appropriate invasive technique, which involves high risk of morbidity, is indicated.1,2 The pathophysiological mechanisms involved in the development of symptoms include changes in the blood flow secondary to the stenosis or the embolic events caused by the rupture of the plaque; the latter associated with vulnerability of the plaque. Therefore, if the composition of the plaque could be determined “in vivo”, the criteria to select the patients under risk of developing these neurovascular events would be the candidates for those invasive therapies. This is the key of the “in vivo” metabolic imaging of the atheroma plaque as, potentially, they could help to characterize the different phases of the atherogenesis to select the appropriate therapy and to monitor and measure the response to it.

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Atheromatosis is considered nowadays an immune inflammatory process characterized by accumulation of lipids, monocytes and macrophages, and by the calcification of vessels. This led to the evaluation of different radiotracers to image the inflammation associated with the atheroma. As result, $^{18}$F-FDG PET an PET/CT became the accepted technique for the assessment of the inflammatory process and for monitoring and measuring the response to new therapies.

However, there are other mechanisms which can be involved in the development of the plaque and could not be investigated until now. Thus, the most recent guidelines for the management of patients with extracranial carotid disease, published in 2011, emphasize on the need for identifying new data related with the vulnerability of the plaque.

Arterial calcification is an active process regulated in a similar way as bone formation, and although it is considered as the final phase of the plaque development, which would be in accordance with the absence of $^{18}$F-FDG uptake, it also can be seen in the early phases. In this sense, it seems justified to study in depth this physiological process in the atherogenesis.

Recently, Derlin et al. from The University Medical Center Hamburg-Eppendorf have reported the uptake of $^{18}$F-sodium fluoride by the plaques that are found incidentally in a retrospective review of oncologic patients in whom the scan was done for the study of bone metastasis.

Calcification may be one of the processes involved in the growth progression of the arterial wall which is in accordance with the new pathophysiological theories of the atherogenesis and vascular calcification. It opens new lines of research for molecular imaging not only to study the atherogenesis in depth but also to evaluate the introduction of new therapies and to monitor and measure the efficacy of the response.

In this setting, we designed a prospective study to evaluate the role of molecular imaging in a selected population with carotid stenosis detected by contrast enhanced CT by assessing the calcification process using $^{18}$F-sodium fluoride PET/CT scan.

**Material and methods**

A prospective study was designed to evaluate the calcification process in the carotid plaques detected by CT in patients investigated for first time by Vascular Unit of the Neurology Department. The study was approved by the Ethics Committee of our hospital and informed consent was signed by all the patients.

**Patients and carotid atheroma plaques**

The study included 15 patients, 10 men and 5 women. The age ranged from 52 to 82 years, and the mean age was 69 years. All patients showed at least one carotid plaque detected by contrast enhanced CT. Of the 15, 8 had neurovascular symptoms: transient ischemic attack (TIA) in 3, cerebrovascular accident (CVA) in 3, CVA and contralateral TIA in 1 and retinal ischaemia in 1. The other 7 have no neurovascular symptoms or signs.

The 8 symptomatic patients had 16 plaques, 10 of them ipsilateral to the cerebral hemisphere of the vascular event and the other 6 asymptomatic. The 7 asymptomatic patients had 13 plaques in total. Altogether there were 29 carotid plaques, 10 in the 8 symptomatic patients and potentially related with the ipsilateral vascular event and 19 in the 7 asymptomatic patients.

**Acquisition and processing of $^{18}$F-sodium fluoride PET/CT scan**

All patients underwent a PET/CT examination using a Siemens Biograph PICO 3D LSO. Images of chest and neck were acquired during 3 minutes per bed 180 minutes after the i.v. injection of 370 MBq of $^{18}$F-sodium fluoride. For image reconstruction, attenuation correction was applied and an iterative algorithm including 2 iterations and 16 subsets was employed.

**Interpretation of the PET/CT scans**

A visual reading of each examination was done and an intensity grading was applied according to a scale ranging from 0 (absence of uptake) to 5 (uptake the same or higher than cervical spine) (Figs. 1 and 2).

**Analysis of the results**

The $^{18}$F-sodium fluoride uptake by each plaque in the symptomatic population was compared with the asymptomatic populations.

**Results**

Fig. 3 shows the distribution of the plaques according to the intensity of the uptake and for each of the 2 groups, symptomatic and asymptomatic. It can be seen that all the plaques in the group of patients with symptomatology showed an intensity of uptake of 2 or higher, whereas in the asymptomatic group the distribution was more heterogeneous 6 plaques showing an uptake lower than 2.

In a more detailed analysis of the data, Table 1 shows the number and the percentage of plaques according to the thresholds of intensity of the uptake rating. All plaques, symptomatic or not, revealed some degree of uptake; however, the percentage of symptomatic plaques with uptake above 2 was higher than in the asymptomatic group, although the difference was not significant.

**Discussion**

This is the first study prospectively designed to assess the metabolism of the carotid atheroma plaque using the $^{18}$F-sodium...
fluoride as a marker of calcification. While $^{18}$F-FDG can be already considered an established technique to evaluate the atheroma inflammation and to monitor anti-inflammatory therapies,\(^5\) the introduction of $^{18}$F-fluoride offers a new approach based on the previous and recent retrospective reports on findings of systemic atheromatosis in oncologic population.\(^9\) From the publication of the first article, several authors have approached this topic\(^10,11,13,14\) but none of them focused on the carotid atheromatosis in a prospective way.\(^10,13\) These results correspond to a preliminary evaluation of the designed study and although it includes a small number of patients and some lax criteria of inclusion (carotid plaque by CT) the findings are relevant enough to be reported so that they can encourage future research in this direction. This is especially true if the results are considered within the new paradigms of the origin and development of the vascular atherosclerosis.\(^12\) This new approach to the identification “in vivo” of the calcification process involved in the atheroma plaque opens new possibilities for the development and monitoring of new therapies.\(^15\)

Previous retrospective studies have reported that the association between calcification and $^{18}$F-sodium fluoride uptake may vary depending on the vascular territory. According to Dweck et al.,\(^14\) it could be explained by the low resolution of the PET technology and by the heterogeneity of the populations included in the studies. In our study, as reported in Table 1, all the plaques showed $^{18}$F-sodium fluoride uptake which should not be unexpected as all of them where detected already by CT deserving to be referred to the Neurovascular Unit because of carotid atheromatosis. This could be also in agreement with Dweck et al. who reported a correlation between the degree of calcification and the $^{18}$F-sodium fluoride uptake although it was lower for the high degrees of calcification due, perhaps, to the stability result of an old process.\(^14\) The different uptake time for $^{18}$F-sodium fluoride, before the PET/CT acquisition, 180 min compared with the 60 min used by other groups can also explain the different results obtained.\(^9–11,13,14\) The long uptake

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Asymptomatic $n = 19$</th>
<th>Symptomatic $n = 10$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1$</td>
<td>19 (100%)</td>
<td>10 (100%)</td>
<td>ns</td>
</tr>
<tr>
<td>$\geq 2$</td>
<td>13 (68%)</td>
<td>10 (100%)</td>
<td>ns</td>
</tr>
<tr>
<td>$\geq 3$</td>
<td>8 (42%)</td>
<td>5 (50%)</td>
<td>ns</td>
</tr>
<tr>
<td>$\geq 4$</td>
<td>2 (11%)</td>
<td>2 (20%)</td>
<td>ns</td>
</tr>
<tr>
<td>$\geq 5$</td>
<td>0</td>
<td>0</td>
<td>–</td>
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time used in our protocol is the result of our research comparing early and delayed acquisitions to avoid the overlap of blood pool activity when applying 18F-FDG PET/CT to the study of vasculitis and atheroma. The delayed acquisition provides a higher plaque/background contrast.16–18

Taking into account the symptomatology of the plaque and its correlation with the 18F-sodium fluoride uptake is crucial for the potential application of the technique as biomarker of the stability of the plaque. In this sense, an association between the intensity of 18F-FDG uptake and instability has been reported.19 Also, Li et al.13 and Dweck et al.14 have reported, an association between the intensity of 18F-sodium fluoride uptake and the development of cardiovascular events.

Although plaques, regardless symptomatology, took up 18F-sodium fluoride, it is interesting that in all the plaques corresponding to symptomatic patients the uptake intensity was 2 or more. Therefore, we can hypothesize a correlation between neurovascular symptomatology and the active calcification. The metabolic pattern described here cannot be taken, until now, as a specific biomarker of the instability of the plaque as 18F-sodium fluoride has been shown in our study to be taken up also by the asymptomatic plaques (Fig. 3). However, this can only be clarified by the follow-up of these patients and the corresponding plaques.

Other limitations of the study, in addition to the small number of patients, are the difficulty to accurately determine the cause of the cerebrovascular event, and the clinical heterogeneity of the symptomatic group, a limitation, which could be overcome by increasing the patient population.

Conclusions

Although the number of patients is small, the results allow us to report the feasibility of 18F-sodium fluoride PET/CT to image the carotid plaque. The study showed that all the plaques took up the 18F-sodium fluoride, regardless the intensity. The study also showed an association between the intensity of uptake and symptomatology. This allows us to hypothesize a relationship between active calcification and the instability of the plaque associated or not to the effect of inflammation. Therefore, the results of this preliminary work are encouraging to include the number of patients to clarify the real meaning of these findings in order to contribute to the knowledge of the atherogenesis by in vivo imaging molecular techniques.

Conflict of interest

No conflict of interests.