Concise Report

Myocardial ischaemia in patients with primary APS: a $^{13}$N-ammonia PET assessment

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Objective. Evaluate the presence and severity of myocardial ischaemia in a population of asymptomatic patients with primary APS (PAPS) using $^{13}$N-ammonia PET.

Methods. We studied 36 patients, 18 with a diagnosis of PAPS and 18 healthy volunteers. All patients underwent a two-phase (rest–stress) $^{13}$N-ammonia PET. Myocardial perfusion images were acquired and then analysed by two experts in the field.

Results. We found ischaemia in 7/18 asymptomatic PAPS patients (38.8%). The anterolateral wall was the most commonly affected cardiac territory [5/7 PAPS patients (71.4%)]. In a severity analysis, we found that five patients (71.4%) had mild ischaemia, one patient (14.2%) had moderate ischaemia and another one (14.2%) had severe defects. All the healthy volunteers studied showed normal myocardial perfusion images.

Conclusion. An important proportion of PAPS patients, even when asymptomatic, showed myocardial perfusion defects assessed with PET. Most of the ischaemic patients had mild defects and the anterolateral wall was the territory mainly affected.

Key words: Primary anti-phospholipid syndrome, Ischaemia, Positron emission tomography, $^{13}$N-ammonia, Thrombosis, Coronary disease, Ischaemic heart disease, Autoimmune diseases, Heart, Cardiovascular imaging.

Introduction

Primary Antiphospholipid Syndrome (PAPS) describes patients with thrombocytopenia, recurrent arterial and/or venous thrombosis, and in the case of women spontaneous abortions, with the presence of serum antiphospholipid antibodies aPL [1, 2]. Preliminary classification criteria for the APS were formulated during a workshop in 1998 [3]. When patients fulfil these criteria but do not otherwise have serological or clinical evidence of other autoimmune disorders, they are diagnosed as having PAPS [1, 2].

Cardiac manifestations are found in 40% of patients with APS, and significant morbidity appears in 4–6% of these patients. Most of them are thrombotic lesions either in the coronary circulation or on the valves, and they may mimic other cardiovascular conditions, such as infective endocarditis.

Clinical and experimental data indicate that aPL predispose APS patients to thrombosis [4–7]. This thrombotic tendency shares several pathways with atherosclerosis [8–11] since it is also a chronic inflammatory disease [12, 13]. The current consensus is that a pro-inflammatory Th1 response favours plaque formation whereas a humoral Th2 response inhibits atherogenesis [9]. The immune response targeted against GPI, the cofactor recognized by some autoantibodies in APS patients, favours the development of atherosclerotic plaques [14].

Increased levels of aPL, including aCL, have also been detected in the sera of young patients who develop accelerated atherosclerotic disease [15, 16]. Vascular injury due to direct binding of aPL to vascular endothelial cells or the deposition of circulating immune complexes may contribute to the cardiovascular disease burden of these patients [17].

The thrombotic microangiopathy may present as an acute disease, or may follow a chronic course and be identified as proliferative intimal changes. These changes can induce myocardial ischaemia.

PET is a non-invasive technique that allows the assessment of myocardial perfusion with the use of different radiotracers such as ammonia ($^{13}$N-ammonia), $^{82}$rubidium or oxygen ($H_2^{15}$O) [3]. In addition, it is possible to quantify the coronary blood flow in millilitres/gram/minute, using $^{13}$N-ammonia [18] and therefore study endothelial function by means of the cold pressor test (CPT) [19].

The goal of this study was to evaluate the presence and severity of myocardial ischaemia in an asymptomatic population of PAPS patients from our institution using $^{13}$N-ammonia PET.

Patients and methods

A transverse, observational, comparative study was developed. We studied 18 asymptomatic patients with a diagnosis of PAPS and 18 healthy volunteers. The PAPS group met the Sapporo Classification criteria for APS [3]. Exclusion criteria included: previous myocardial infarction demonstrated by electrocardiogram, fasting glucose levels over 100 mg/dl, known hypersensitivity to any of the substances used during the study, pregnancy or lactation at the time of the study, as well as technical problems during PET scanning acquisition. Main demographic and clinical information of healthy volunteers and PAPS patients are summarized in Table 1. All patients gave their informed consent to participate in this study. Ethics approval for the study was obtained from the local ethics committee. Statistical analyses were performed using SPSS 15.0 for Windows (2006).

PET protocol

All patients underwent a two-phase (rest–stress) PET protocol using a total of 40 mCi of $^{15}$O-ammonia radiotracer [20] (20 mCi for each phase), which was synthesized in the Cyclotron of the PET-Cyclotron Unit of the Universidad Nacional Autónoma de México (UNAM). The stress test was performed using an infusion of adenosine at 140 µg/kg/min for 6 min, injecting 20 mCi of the ammonia radiotracer at the end of the third minute. Dynamic image acquisition was performed immediately after injection of a
bolus of radiotracer. A transmission scan was obtained to correct emission images for photon attenuation. Imaging was performed on a full ring, whole-body system, ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN, USA). The heart was divided into 17 segments to evaluate myocardial perfusion and it was scored using a scale ranging from 0, which reflected a normal perfusion, to 4 when there was an absence of uptake of the tracer. Myocardial ischaemia was considered with a normal rest scan and the presence of a reversible change during stress.

Results

A total of 36 patients were studied, 18 asymptomatic PAPS patients and 18 healthy volunteers. Patient characteristics and comparison of both groups are summarized in Table 1. All patients with PAPS were taking oral anticoagulants.

In the PAPS group, we detected the presence of myocardial ischaemia in 7/18 patients (38.8%). In the rest of the patients, a normal myocardial perfusion was obtained. The magnitude of the ischaemia was graded severe in one patient (14.2%), moderate in another patient (14.2%) and mild in the rest of them (71.4%) and the localization of the perfusion defects as follows: anterolateral in five patients (one with severe ischaemia and four with mild ischaemia), anterosetal in another patient (the one with moderate ischaemia) and inferolateral in the last patient. In the healthy volunteer group, all myocardial perfusion images were normal. There were no complications during the PET study among both groups.

Discussion

In a previous study from our institution, myocardial infarction occurred in 37.5% of PAPS patients. Coronary angiograms showed normal coronary arteries in the majority of PAPS patients, suggesting the possibility of embolic events. In the remaining cases, the cause of the infarction was probably mixed, because these patients had traditional coronary risk factors and the coronary angiogram showed significant coronary artery obstruction [21].

The presence of the aPL is now considered as a novel risk factor for the presence of atherosclerotic disease as it was confirmed by the analysis of the Hopkins Lupus Cohort performed by Petri [22]. Recently, 9% of the cohort has had clinical evidence (myocardial infarction or angina) of coronary artery disease. In the Euro-Phospholipid Cohort, which includes 1000 European patients with APS, myocardial infarction was the presenting manifestation in 2.8% of the patients, and it appeared during the evolution of the disease in 5.5% of the cohort [23]. In this same study, angina was reported in 2.7% of the entire population. Conversely, Diaz and Becker [24] found aCL in 8 out of 22 (36.4%) patients with unstable angina. The prevalence of aPL in patients with myocardial infarction seems to be between 5% and 15% [25].

Although the previous numbers are only estimations among different populations and different moments within the natural evolution of the disease (also influenced by the effect of medications) it is rather clear that the atherosclerotic process is a constant phenomenon between 3% and 10% of the patients studied. What is more interesting is that we do not know which proportion of patients among the asymptomatic group suffers from the disease since this group of patients will only be apparent when they present with a life-threatening thrombotic event.

In a previous study from our group, we reported that the prevalence of ischaemic alterations found in a myocardial perfusion with sestamibi SPECT in PAPS patients was 27%. The prevalence of defects in myocardial perfusion in autoimmune diseases (such as SLE, RA and PAPS) assessed globally was 30% [26].

In comparison with SPECT, PET has several technical advantages that make it an excellent method for functional evaluation of many tissues. The use of positron emission radiotracers avoids attenuation due to soft tissues, reduces acquisition time and improves the accuracy of the study. Also positron emission radiotracers have short or ultra-short half-lives, turning them into a very useful method for the study of dynamic processes such as coronary blood flow quantification and myocardial perfusion imaging. There are many positron emission radiotracers that can follow physiological pathways more closely; these radiotracers make PET capable for evaluation of tissue metabolism, perfusion, inflammation and blood flow. Temporal and spatial resolution are also very important differences between PET and SPECT. Better spatial and temporal resolution of PET make this method more accurate than SPECT, which explains the difference in sensitivity and specificity between both techniques, and the greater number of ischaemic patients detected by PET in this study [27].

Myocardial ischaemia in PAPS patients was observed asymptotically (from the cardiovascular point of view), which gives us a glimpse of what could be happening in this particular group of patients in an early disease course. These findings support the hypothesis that the presence of aCL per se is the major cause of endothelial damage in PAPS patients and suggests the possibility that this dysfunction may be the initial step in the pathogenic process that leads to overt clinical ischaemic events in this particular group of patients. In the present study, we found ischaemia demonstrated by PET in nearly 40% of the patients and its localization was predominantly anterolateral and anterosetal. The ischaemia was graded as mild in the majority of cases and all the patients, even those who showed myocardial ischaemia, were clinically asymptomatic.

In addition, APS is recognized as an endotheliopathy with thrombotic microangiopathy, which results from a variety of causal mechanisms, suggesting that aPL might induce expression of intracellular adhesion molecules on endothelial cells and activate platelets. Such events would have a pro-coagulant effect [28–30].

If the presence of aPL is accepted as a novel risk factor for cardiovascular disease in APS patients and the immunological events that take place on the endothelium are the initial step in the atherosclerotic process, then we can assess its presence in the subclinical stage of the disease by means of a non-invasive study with great reproducibility and advantages over conventional perfusion SPECT scans, and thus we could intervene at this early moment of the disease and prevent the development of subsequent ischaemic coronary events and its catastrophic consequences.

In our knowledge, this is the first study to report the presence of myocardial ischaemia in a group of asymptomatic PAPS patients by means of a non-invasive method like PET. As it was previously stated, the prevalence of perfusion defects assessed by PET is greater than that which was previously reported in the literature for SPECT.

The present study has some limitations. First, the sample of PAPS patients is small and we studied only asymptomatic patients. We infer that symptomatic patients would show more perfusion defects. We did not perform coronary angiography in

### Table 1. Clinical characteristics of PAPS patients and healthy volunteers

<table>
<thead>
<tr>
<th></th>
<th>PAPS patients</th>
<th>Healthy volunteers</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Age (yrs) ± s.d.</strong></td>
<td>41 ± 8</td>
<td>34 ± 7</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>4 (22.2)</td>
<td>11 (77.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female (%)</td>
<td>14 (77.7)</td>
<td>7 (22.2)</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>4</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Dyslipidaemia</strong></td>
<td>3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Smokers</strong></td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>BMI ± s.d.</strong></td>
<td>27 ± 4</td>
<td>26 ± 3</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not significant.
our group of asymptomatic PAPS patients and we did not take account of whether patients who showed myocardial ischaemia had an obstructive coronary lesion. The comparison of healthy volunteers and PAPS patients reveals statistical differences only in age and gender. In our PAPS population, we have older patients and a greater proportion of male subjects in the healthy volunteer group. These differences may contribute to the greater prevalence of ischaemia in our PAPS population, but the absence of significant differences in other major cardiovascular risk factors makes this situation less likely.

Conclusions

In patients with PAPS, even without manifest cardiovascular disease symptoms, it is possible to document myocardial perfusion defects in an early moment of the disease in nearly 40% of the population in comparison with none in the healthy volunteer group. 

13N-ammonia PET is an excellent non-invasive technique for the evaluation of PAPS patients long before they develop cardiovascular symptoms and it will allow us to institute preventive measures and to evaluate the treatment response repeatedly and accurately.

Rheumatology key message

- The study describes the results of 13N-ammonia PET myocardial perfusion imaging in 18 asymptomatic patients with PAPS.

Disclosure statement: The authors have declared no conflicts of interest.

References

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