FILTRATION FRACTION: AN INDEX OF RENAL DISEASE ACTIVITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Summary

Renal plasma flow (RPF) and glomerular filtration rate (GFR) were estimated by $^{125}$I hippuran and $^{51}$Cr EDTA clearances using a single shot technique on two occasions at one-year intervals in 22 patients fulfilling the ARA criteria for systemic lupus erythematosus (SLE). All these patients had histologically proven renal disease. Filtration fraction was a better parameter than proteinuria, urinary sediment or GFR for recognising diffuse proliferative glomerulonephritis with a sensitivity of 61 per cent and a specificity of 88 per cent. After one year all the patients with an initially low filtration fraction (FF) had significantly changed their GFR, which demonstrates that this parameter indicates the presence of an active renal lesion.

Introduction

The prognosis of patients with SLE is determined by the severity of their renal involvement. In the past, information obtained by histological examination of renal tissue served both to evaluate the prognosis of the patients and to manage their disease [1]. More recently, this practice has been criticised by authors arguing on the basis of cost benefit analyses that histopathology would give patients only marginal benefit [2]. The latter opinion may not apply to patients who have severe lupus nephropathy at the onset of their SLE without abnormalities in their renal function tests, nor patients in whom a mild glomerulopathy progressed to severe disease without changes in their renal function or proteinuria.

The present work was undertaken to find an alternative to the renal biopsy to assess renal involvement in SLE patients, both at the beginning of the disease and with the passage of time by using a non-invasive technique.
Material and methods

Twenty-two patients fulfilling the ARA criteria for the diagnosis of SLE had an initial renal biopsy. Renal lesions were recorded according to the WHO classification; five patients had mesangial proliferative glomerulonephritis (class II), four focal proliferative glomerulonephritis (class III) and 13 diffuse proliferative glomerulonephritis (class IV).

Renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured simultaneously in all the patients on two occasions, separated by a one-year interval by using a single shot technique. RPF was estimated by $^{125}$I hippuran and GFR by $^{51}$Cr EDTA clearances. Both isotopes were injected simultaneously and their disappearances from the blood compartment followed with time. Clearances were calculated according to the two compartment model proposed by Sapirstein using a computer program.

Filtration fraction (FF) was calculated from the actual values obtained for GFR and RPF [3]. On the same day, microscopic examination of the urine after filtration and staining by a Papanicolaou technique was undertaken [4] and 24-hour proteinuria, anti DNA-DS antibodies, complement and circulating immune complexes (Clq fixation) [5] were measured.

Results

Table 1 shows the number of patients for each class of glomerulopathies in whom one or more abnormal laboratory data have been found.

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Total number of patients</th>
<th>Number of patients with GFR&lt;80ml/min (1)</th>
<th>Number of patients with FF&lt;18% (2)</th>
<th>Number of patients with proteinuria &gt;200mg/d</th>
<th>Number of patients with pathological urinary findings (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial proliferative GN</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Focal GN</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse proliferative GN</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>5</td>
<td>9</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

1 GFR was measured by $^{51}$Cr-EDTA clearance;
2 Filtration fraction was calculated as the ratio $^{51}$Cr-EDTA/$^{125}$I hippuran clearances times 100;
3 Urinary microscopic evaluation was performed by filtration technique and Papanicolaou staining.
Microscopic examination of the urine was very disappointing and non-specific. About half the patients in each category had microhaematuria with or without red cell casts. The percentage of patients with proteinuria increases with the severity of the renal lesion. Low GFR has been found only in those patients with diffuse proliferative glomerulonephritic lesions which bear the worst prognosis. A decrease in filtration fraction recognises this class of patients with a sensitivity of 61 per cent and a specificity of 88 per cent.

Table II confirms that patients with mesangial proliferative glomerulonephritis more often had a silent nephropathy than patients with more severe forms of renal disease. The three patients with a silent nephropathy and diffuse proliferative glomerulonephritis have been unmasked by a low filtration fraction. For these three cases, only this additional laboratory analysis provided the key information on their renal lesion.

**TABLE II. Number of patients with silent nephropathy (classical criteria, FF excluded) and with low filtration fraction as a single laboratory finding for each histological class of lupus nephropathy**

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Total number of patients</th>
<th>Number of patients with silent nephropathy</th>
<th>Number of patients with low FF (&lt;18%) as unique finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial-proliferative GN</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Focal GN</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse proliferative GN</td>
<td>13</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

NB: The three patients with silent nephropathy in the diffuse proliferative GN group were unmasked by their low FF.

Table III depicts the changes in GFR beyond the limits of reproducibility of the method at one year. All the 13 patients with a normal GFR and a normal filtration fraction at the first examination remained unchanged during the time of observation. By contrast GFR has changed in the nine patients who had a low FF from the outset.

**TABLE III. Change in the GFR one year later in two groups of patients defined by their initial filtration fraction**

<table>
<thead>
<tr>
<th>Filtration fraction at first examination</th>
<th>Number of patients who changed their GFR (&gt;7%) between the two examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: 13 patients</td>
<td>none</td>
</tr>
<tr>
<td>Low: 9 patients</td>
<td>5 increased their GFR*</td>
</tr>
<tr>
<td></td>
<td>4 increased their GFR</td>
</tr>
</tbody>
</table>

* These five patients include the one with focal GN
Discussion

To appreciate changes in renal function with time, a method with a good coefficient of reproducibility is required. Single shot clearance technique offers this possibility as its coefficient of reproducibility is seven per cent between two tests compared to 20–25 per cent for conventional methods. In addition this method has the advantage of avoiding bladder catheterisation which may be a source of urinary tract infection, especially in SLE patients. The only limitation of the method is the presence of oedema which changes the body distribution of the tracers, making the calculation of clearances impossible [3]. From Table II, it can be seen that patients with a normal GFR and normal FF are most likely to have mesangial proliferative glomerulonephritis, which has a good prognosis [6]. By contrast most of the patients with low filtration fraction, whatever the level of GFR, belong to the group with diffuse proliferative glomerulonephritis. Of note is the fact that in three such patients, low FF was the only laboratory abnormality. As shown in Table III, low FF indicates the presence of a class IV nephropathy with active renal lesions expressed by the fact that all the patients had changed their GFR one year later. Those patients at high risk of renal failure should receive treatment combining cytotoxic agents and steroids [7].

As previously reported in the literature, we confirm the absence of a correlation between circulating immune complexes, complement and antibodies to DNA-DS and the severity of the renal disease [8].

References

6 Pollak VE, Pirani CL. Mayo Clin Proc 1969; 44: 630
8 Cameron JS, Turner DR, Ogg CS et al. Quart J Med 1979; 48: 1

Open Discussion

ABORAS (Jeddah) Since there is a correlation between filtration fraction and the other parameters of activity of systemic lupus erythematosus why do you specify that this is an activity specific to systemic lupus and not to other proliferative glomerulonephritis?

FAVRE Certainly these parameters may be used for other types of glomerulonephritis. The index may change with time and as we follow the patient we may detect activity of the lesion which may be influenced by treatment. I think the data may be applicable for other types of glomerulonephritis.

RITZ (Heidelberg) I feel your concept is a breakthrough in the diagnosis of lupus nephritis but there is one point on which I am not exactly sure. You
noted some patients with normal GFR and no proteinuria who happened to have low filtration fractions and diffuse proliferative glomerulonephritis. We know from the work of Mahajan* that there may be diffuse proliferative glomerulonephritis in the absence of urinary abnormalities. Does it make any difference to treatment? Do you give them high dose steroids or what are the consequences you draw from your observations?

FAVRE Our concept based on biopsy information was to treat with prednisone and cytotoxic drugs all patients with diffuse proliferative glomerulonephritis, even those patients who had so-called silent nephropathy. Now we use the same treatment and will act in the same way on the basis of the filtration fraction. I fully agree of course that it takes a lot of discretion and it has been suggested that patients with silent nephropathy whatever the severity of the histological lesion do well without treatment. In our small study you have seen these patients and those who have changed their GFR after one year so maybe it is an indication of some need of treatment. However it is a very small study.

IAINA (Israel) Did you measure fractional excretion sodium and does it parallel with the changes in filtration fractions as an index of ischaemia?

FAVRE We did not for the good reason that our way to measure the GFR and the renal blood flow was by a single shot technique so we have no urine available.

SCHENA (Chairman) Have you found any correlation between high doses of corticosteroids or low doses of steroids?

FAVRE We have not looked at our data in terms of the effect of any kind of treatment. All the data is on computer so it is the next thing we have to do.

*Mahajan SK, Ordoneg NG, Feitelson PJ. Medicine 1977; 56: 494