Uric acid: a prognostic marker not only before but also after heart transplantation

Natália António, David Prieto, Manuel J. Antunes*

Department of Cardiothoracic Surgery, University Hospital, Coimbra, Portugal

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Abstract

Objectives: Early diagnosis of rejection after heart transplantation is mandatory, since even mild rejection can rapidly progress to more severe rejection. However, the identification of patients at high risk of acute cellular rejection and their non-invasive diagnosis remains a challenge. To identify patients with a high risk of acute cellular rejection during the first post-transplantation year. Methods: A retrospective study of 114 consecutive patients submitted to first heart transplantation (between November 2003 and January 2008). The International Society for Heart and Lung Transplantation (ISHLT) grading system was used for the classification of endomyocardial biopsies. Patients were divided into two groups: group A (non-rejecting) – 90 patients who had no significant rejection episodes (ISHLT grade <2R); and group B (rejecting) – included 24 patients with moderate or severe rejection episodes (grade ≥2R) during a 1-year post-transplantation follow-up. The Kaplan–Meier method was used for cumulative survival analysis with the Breslow test for assessing statistical differences between curves. Results: The group B patients tended to have more ischaemic aetiology (42% vs 26%, p = 0.13) and lower baseline triglycerides (99.1 ± 34.2 vs 117.9 ± 63.6 mg dl⁻¹, p = 0.17), tended to receive less cardiac allografts from donors of the same ABO blood type (83% vs 92%, p = 0.25) and to have longer cardiopulmonary bypass times (108 ± 64 min vs 94 ± 26 min, p = 0.12). Significantly, they had more hyperuricaemia (71% vs 43%, p = 0.02) and longer mechanical ventilation times (19.2 ± 17.9 h vs 14.3 ± 5.3 h, p = 0.031). During follow-up, the group B patients tended to have more severe infections (46% vs 31%, p = 0.16), to be more frequently Quilty-positive (50% vs 30%, p = 0.073) and to have a higher 1-year mortality (8% vs 2%, p = 0.18). Uric acid levels higher than 7.2 mg dl⁻¹ were identified as the optimal cut-off value to predict acute rejection after heart transplantation (with a sensitivity of 71%, a specificity of 62% and an area under the curve of 0.64). Conclusions: Our work suggests that hyperuricaemia may be a marker of acute cellular rejection that could be another tool helping to identify acute rejection during the follow-up of cardiac-transplanted patients.

Keywords: Heart transplantation; Rejection; Predictors; Uric acid

1. Introduction

Heart transplantation is an accepted treatment modality for end-stage heart failure [1]. However, despite the improvement in immunosuppressive therapy, the immunogenic conflict between the recipient host and the donor heart organ remains a problem [2]. In fact, acute cellular rejection still constitutes a significant problem, especially during the first year after heart transplantation, and rejection episodes seem to predispose to the development of chronic allograft vasculopathy [3,4].

An early diagnosis of heart transplant rejection is, thus, mandatory; however, the identification of patients at high risk of transplant rejection and their diagnosis remain a challenge. Frequent surveillance with endomyocardial biopsy remains the gold standard for rejection diagnosis, although it is an invasive procedure and carries a certain risk [2]. Therefore, non-invasive biomarkers that are able to stratify the risk of acute rejection could be a further helpful tool in patient management, at least to reduce the number of endomyocardial biopsies in patients with a low risk of acute rejection.

Chronic heart failure is associated with hyperuricaemia and elevation of circulating markers of inflammation. Moreover, it is well known that elevated levels of uric acid are a strong, independent marker of impaired prognosis in patients with chronic heart failure [5,6]. It has been shown that serum uric acid levels are strongly related to circulating markers of chronic inflammation, suggesting that xanthine oxidase (XO) activity may be important in the chronic inflammation that characterises chronic heart failure [7].

Acute cellular rejection seems to be associated with a pro-inflammatory state. However, very few attempts have been made to analyse the utility of inflammatory markers, to
predict rejection in heart transplant patients [8,9]. In addition, there are no studies in the literature that addressed the value of uric acid levels, prior to the heart transplantation, as a predictor of acute rejection.

The aim of the present study was to identify predictors of acute rejection trying to investigate the value of baseline uric acid serum levels as a marker of acute rejection during the first year after heart transplantation.

2. Materials and methods

2.1. Study design and patient population

This is a retrospective study of 114 consecutive patients, submitted to first heart transplantation, between November 2003 and January 2008, for a 1-year complete follow-up. All patients were under diuretics prior to transplantation. The procedure was performed using the bicaval anastomosis technique.

All patients received the anti-interleukin (IL)-2 receptor antibody (basiliximab) for immunosuppressive induction therapy. During the first year post-transplantation, maintenance therapy generally consisted of a low dose of prednisone (5 mg), a calcineurin inhibitor with either cyclosporine (target levels, 300–350 ng ml⁻¹) or tacrolimus (target levels, 10–15 ng ml⁻¹) and mycophenolate mofetil (1 g twice daily). All patients were submitted to close monitoring of immunosuppressive blood levels and dosage adjustment. In 102 patients (90%), a statin was prescribed.

Routine endomyocardial biopsies were performed weekly during the first month, every other week during the second month, every 3 weeks during the third month, monthly until the sixth month and every 2 months until the end of the first year. Right and left heart catheterisation with ventriculography and biopsy was performed at 1 year. The International Society for Heart and Lung Transplantation (ISHLT) grading system was used for histological classification of the biopsy tissue [2]. Cardiac rejection was defined as ISHLT grade ≥2R.

Therefore, based on the maximal severity of rejection at any biopsy within this 1-year follow-up period, patients were divided into two groups: group A (non-rejection group) — 90 patients with ISHLT grade <2R and group B (rejection group) — 24 patients with moderate or severe rejection episodes (ISHLT grade ≥2R) post-transplantation.

Patients with moderate-to-severe acute rejection were aggressively treated with increased immunosuppressive therapy, including pulse therapy with steroids (prednisolone 500 mg day⁻¹ for 3 days), and had a repeat biopsy 7–10 days later. In three patients with repeated episodes of rejection, cyclosporine was changed to tacrolimus.

Serum uric acid levels, lipid profile, fasting glycaemia, creatinine clearance (CrCl), C-reactive protein (CRP) and haemoglobin were analysed before heart transplantation in all patients. Clinical and demographic characteristics, aetiology of heart failure, laboratorial data and complications during and after hospitalisation (including mortality, severe infection and renal failure) were recorded.

CrCl was calculated with the Cockcroft–Gault formula and renal dysfunction was defined as a CrCl <60 ml min⁻¹.

Hyperuricaemia was defined as a serum uric acid level >7.0 mg dl⁻¹ in men or >6.0 mg dl⁻¹ in women. Severe infection was defined as the need for hospitalisation as a result of infection.

The protocol was approved by our institutional Research Ethics Committee and all patients gave informed consent.

2.2. Statistical analysis

Statistical analyses were performed using SPSS software version 15. Results are expressed as mean ± standard deviation for continuous variables and as counts and percentages for categorical variables. Discrete variables were compared by the chi-square test or by Fisher's exact test, whichever was appropriate. Continuous variables were compared using unpaired Student’s t-test or Mann–Whitney U-test, as appropriate.

The Kaplan–Meier method was used for cumulative survival analysis with the Breslow test for assessing statistical differences between curves.

A p value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of recipients and donors

The mean age of recipients was 53.1 ± 11.7 years. The male:female ratio was 3:1. The indications for heart transplantation consisted of ischaemic heart disease in 35 patients (31%), idiopathic dilated cardiomyopathy in 56 patients (49%), uncorrectable congenital heart disease in one case (1%), valvular cardiomyopathy in 11 patients (10%) and other heart conditions in another 11 patients (10%).

There were 4% of recipients transplanted as the United Network for Organ Sharing (UNOS) status IA (n = 4), 21% as status IB (n = 24) and 75% as status II (n = 86).

Regarding donor characteristics, most were male (77%), the mean age was 31.3 ± 10.9 years and the average graft ischaemic time was 90.0 ± 32.9 min. The cause of brain death was traumatic in 66% of cases.

3.2. Post-transplantation acute rejection

During the follow-up period, 1459 biopsies from 90 patients were graded <2R (1319 grade 0R and 140 grade 1R; group A) and 27 biopsies from 24 patients were graded ≥2R (24 grade 2R and three grade 3R; group B). The characteristics of the two patient groups are summarised in Table 1.

There were no significant differences between the groups for donor or recipient age and gender, donor cause of brain death or recipient UNOS status prior to heart transplantation. Group B patients tended to have more ischaemic aetiology and to show more ABO mismatch. However, these differences were not statistically significant. Regarding baseline laboratorial parameters, the only significant difference was in uric acid levels that were higher in the rejection group (43% of patients with hyperuricaemia in group A vs 73% in group B, p = 0.017). CrCl was similar in both groups, with renal failure in 58% of patients in group A and 50% in group B (p = 0.49).
were no significant differences in the proportion of patients in Group A vs Group B (25% vs 12% in group A, p = 0.11).

The uric acid levels at 1-year follow-up were similar to the baseline levels (6.9 ± 2.1 vs 7.1 ± 2.7, p = 0.85). In addition, group B patients still showed higher uric acid levels at 1 year after the heart transplantation; however, the difference was not statistically significant (7.2 ± 1.9 vs 6.9 ± 2.1, p = 0.58).

Within the first year of heart transplantation, group B patients tended to have more severe infections (46% vs 31% in group A, p = 0.16). However, cytomegalovirus seroconversion was observed in only three patients and none of them had acute cellular rejection.

Group B patients tended to have a higher 1-year mortality rate (8% vs 2%, p = 0.18). However, in our population, acute cellular rejection was not a cause of death during the first year after heart transplantation.

The Kaplan–Meier analysis showed no significant differences in survival between patients with and without acute rejection within 1 year of heart transplantation (Fig. 1).

4. Discussion

The documentation of high serum uric acid levels as a marker of acute rejection in heart transplantation patients represents the major finding of this study.

4.1. Prediction of acute cellular rejection

Although acute rejection seems to be less common with current immunosuppressive strategies, it remains a major cause of morbidity and mortality during the first year following heart transplantation [10]. Therefore, early detection of acute rejection remains an important feature of transplant management, especially in the early phase.

According to the data from ISHLT, the incidence of acute cellular rejection during the first 6 months of heart transplantation was reduced from 70–85% to 40% between 1982 and 2004 [11]. In our population, the incidence of acute cellular rejection within 1 year of heart transplantation was 21%, which is lower than that reported in some previous studies.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of baseline parameters between patients with and without significant acute cellular rejection.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (n = 90)</td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>53.2 ± 11.2</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>31.5 ± 10.9</td>
</tr>
<tr>
<td>Male recipients (%)</td>
<td>73</td>
</tr>
<tr>
<td>Male donors (%)</td>
<td>79</td>
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<tr>
<td>Ischaemic aetiology of HF (%)</td>
<td>26</td>
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<tr>
<td>Previous cardiac surgery (%)</td>
<td>22</td>
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<tr>
<td>Donor–recipient ABO agreement (%)</td>
<td>92</td>
</tr>
<tr>
<td>Donor traumatic brain death (%)</td>
<td>65</td>
</tr>
<tr>
<td>Graft ischaemic time [1]</td>
<td>94.0</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time [1]</td>
<td>108.0 ± 63.7</td>
</tr>
<tr>
<td>Mechanical ventilation time (h)</td>
<td>14.3 ± 5.3</td>
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<tr>
<td>Recipient UNOS status (%)</td>
<td></td>
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<tr>
<td>IA</td>
<td>2</td>
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<tr>
<td>IB</td>
<td>26</td>
</tr>
<tr>
<td>II</td>
<td>72</td>
</tr>
<tr>
<td>Laboratory data prior to the heart transplantation</td>
<td></td>
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<tr>
<td>Haemoglobin (g dl⁻¹)</td>
<td>13.2 ± 1.7</td>
</tr>
<tr>
<td>CrCl (ml min⁻¹)</td>
<td>59.8 ± 21.4</td>
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<tr>
<td>Triglycerides (mg dl⁻¹)</td>
<td>117.9 ± 63.6</td>
</tr>
<tr>
<td>Total cholesterol (mg dl⁻¹)</td>
<td>172.6 ± 44.0</td>
</tr>
<tr>
<td>LDL cholesterol (mg dl⁻¹)</td>
<td>108.4 ± 35.7</td>
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<tr>
<td>HDL cholesterol (mg dl⁻¹)</td>
<td>42.4 ± 12.9</td>
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<tr>
<td>Fasting glycaemia (mg dl⁻¹)</td>
<td>126.7 ± 55.6</td>
</tr>
<tr>
<td>Triglycerides (mg dl⁻¹)</td>
<td>6.7 ± 2.4</td>
</tr>
<tr>
<td>e- Reactive protein (mg dl⁻¹)</td>
<td>1.3 ± 2.0</td>
</tr>
<tr>
<td>Haemodynamic data of heart recipients prior to the transplantation</td>
<td></td>
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<tr>
<td>LV EF (%)</td>
<td>21.3 ± 9.0</td>
</tr>
<tr>
<td>SPAP (mmHg)</td>
<td>45.8 ± 14.8</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>Peak VO₂ (ml min⁻¹ kg⁻¹)</td>
<td>13.1 ± 2.7</td>
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<tr>
<td>Transpulmonary gradient (mmHg)</td>
<td>7.8 ± 4.1</td>
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</tbody>
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CrCl, clearance of creatinine; LV EF, left ventricular ejection fraction; SPAP, systolic pulmonary artery pressure; PVR, pulmonary vascular resistance; VO₂, oxygen consumption.

The group B patients tended to receive hearts with longer ischaemic times and have more prolonged cardiopulmonary bypass times. In addition, these patients had significantly longer mechanical ventilation times. Regarding haemodynamic parameters, group B tended to have higher transpulmonary gradients before the transplantation (Table 1).

The Quilty effect was described in 61 biopsies (34% of patients) and group B tended to be more frequently Quilty-positive (50% vs 30%, p = 0.073). Nevertheless, there was no correlation between graft rejection according to ISHLT classification and Quilty lesions in the previous biopsy.

Receiver operating characteristic (ROC) analysis identified uric acid levels higher than 7.2 mg dl⁻¹ as the optimal cut-off value to predict acute rejection after heart transplantation (with a sensitivity of 71%, a specificity of 62% and an area under the curve ROC of 0.64).

3.3. Clinical evolution during follow-up

After heart transplantation, a triple-immunosuppressive maintenance regimen was initiated in all patients. There were no significant differences in the proportion of patients who started with cyclosporine instead of tacrolimus (92% of patients under cyclosporine in group A vs 91% in group B, p = 0.92). However, 1 year after the transplantation, there was a trend to have more patients under tacrolimus in group B (25% vs 12% in group A, p = 0.11).

Although acute rejection seems to be less common with current immunosuppressive strategies, it remains a major cause of morbidity and mortality during the first year following heart transplantation [10]. Therefore, early detection of acute rejection remains an important feature of transplant management, especially in the early phase.

According to the data from ISHLT, the incidence of acute cellular rejection during the first 6 months of heart transplantation was reduced from 70–85% to 40% between 1995 and 2004 [11]. In our population, the incidence of acute cellular rejection within 1 year of heart transplantation was 21%, which is lower than that reported in some previous studies.

Fig. 1. Effect of acute cellular rejection on survival in transplanted patients.
hyperuricaemia and acute cellular rejection [5]. It should be noted that our first heart transplantation was performed in November 2003, at a time when acute cellular rejection had become less frequent and more easily treated.

Currently, the most reliable technique to evaluate allograft rejection is endomyocardial biopsy [17]. However, the invasive nature of the procedure limits its use for frequent monitoring of cardiac status after transplantation. Evidently, reliable non-invasive sensitive markers to identify patients at high risk of acute rejection would be of great value.

Inflammation and rejection phenomena partially develop over common pathways and several studies have analysed the predictive value of inflammation markers for detecting acute cellular rejection after heart transplantation, including serum CXCL9 and CXCL10 [18], interleukin (IL)-6 [19], dendritic cells [20], sialic acid [16] and CRP [16].

In chronic heart failure, hyperuricaemia is a recognised marker of inflammation [5,7]. Moreover, high serum uric acid levels are a strong, independent marker of impaired prognosis in this disease and are also independently associated to all-cause cardiovascular mortality in the general population [5]. It has been suggested that hyperuricaemia reflects increased XO activity in chronic heart failure [5]. The XO enzyme system is an important source of oxygen free radicals, which could explain several pathological processes associated with hyperuricaemia (including increased cytokine production, cell apoptosis and endothelial dysfunction) and could explain the link between hyperuricaemia and acute cellular rejection [5].

Recently, in a study of 405 stable renal transplant recipients, Bandukwala et al. demonstrated that hyperuricaemia is associated with a decrease in renal allograft function [21]. In the context of heart transplantation, this is, to the best of our knowledge, the first study that analysed the value of uric acid as a marker of 1-year acute cellular rejection. In our population, hyperuricaemia was associated with higher rates of acute rejection.

Thiazide and loop diuretics cause a dose-dependent elevation of serum uric acid by increasing its tubular reabsorption in the context of volume depletion [22]. In our populations, all patients were under diuretics before the heart transplantation; however, we could not adjust uric acid levels for diuretic dose, as this information was not available.

Intercurrent infection is a well-known predictor of acute cellular rejection [10]; however, in our population there was only a trend to increased occurrence of acute cellular rejection in patients with severe infections, perhaps due to insufficient sample size. Regarding cymotegamolavirus seroconversion, our work is in accordance with a recent study of Brunner-La Rocca et al., showing that it did not independently influence the risk of acute graft rejection [23].

In our population, Quilty lesions were not associated with higher risk of further acute cellular rejection. Although the pathogenesis and significance of Quilty lesions remain unclear, some investigators have suggested that Quilty lesions may predict or represent graft rejection [23], whereas others [24] have suggested that they are of little clinical significance and require neither increased immunosuppression nor short-term follow-up.

4.2. Impact of acute rejection on outcome

Although this was not the main purpose of this investigation, it is interesting to note that graft rejection was not associated with increased overall mortality after heart transplantation even in the extended survival analysis. This result is in contrast with some studies that indicated acute rejection as a major cause of death [25]. One possible explanation for this result is the prompt and aggressive rescue protocol of immunosuppression used and the frequent change from cyclosporine to tacrolimus after acute cellular rejection. In fact, in a recent large European trial, it has been demonstrated that tacrolimus is superior to cyclosporine in prevention of acute cellular rejection after heart transplantation [26].

4.3. Clinical implications

Our work analysed, for the first time, the prognostic value of uric acid in acute cellular rejection after heart transplantation and indicates a potential relationship between hyperuricaemia and acute rejection, which should be explored further.

4.4. Study limitations

This is a single-centre, observational cohort study. We acknowledge that the most important limitations of this study are the small number of patients included and the relatively short period of follow-up. Another limitation is that uric acid levels were not adjusted for diuretic dose.

References


