Prognostic Value of Cytokines and Neurohormones in Severe Heart Failure

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Background and objectives. The screening of candidates for heart transplantation continues to present difficulties. High plasma levels of cytokines and neurohormones have been associated with a poor prognosis in heart failure but their usefulness for identifying candidates for heart transplantation is still not established.

Methods. In 83 patients (59 ± 11 years old), with systolic left ventricular dysfunction and New York Heart Association functional class III-IV, we assessed levels of aldosterone, atrial natriuretic peptide, plasma renin activity, angiotensin II, norepinephrine, endothelin, interleukin-6 and tumor necrosis factor-α.

Results. Over the following year, 13 patients died and 26 received heart transplantation. Mean ejection fraction was 23 ± 6%, end-diastolic and end-systolic diameters were 73 ± 10 and 60 ± 10 mm, respectively. Univariate analysis identified the following variables to be associated with poor prognosis: angiotensin II (p = 0.001), norepinephrine (p = 0.003), plasma renin activity (p = 0.02), systolic blood pressure (p = 0.006), end-diastolic diameter (p = 0.02) and end-systolic diameter (p = 0.04). Multivariate regression analysis identified the following variables to be independent predictors of death or need for heart transplantation: a low cardiac index (p = 0.007), plasma angiotensin II (p = 0.001) and pulmonary capillary wedge pressure (p = 0.04) The sensitivity and specificity of angiotensin II for predicting poor outcome was only moderate according to interpretation of the receiver operating curves.

Conclusions. Although plasma angiotensin II was the best neurohormone for identifying patients with severe heart failure and the worst prognosis, its sensitivity and specificity for predicting death or the need for heart transplantation was limited. The decision to transplant should continue to be based on clinical and hemodynamic parameters.

Key words: Severe heart failure. Angiotensin II. Cytokines. Heart transplantation.
Methods

From January 1996 to December 2000, 220 patients with heart failure secondary to left ventricular dysfunction, diagnosed by an ejection fraction of less than 40% in conventional echocardiography, were seen in the heart failure unit of the Institut de Malalties Cardiovasculars of the Hospital Clinic de Barcelona. Of this population, 94 patients had advanced heart failure and were NYHA functional class III-IV. The cause of heart failure was secondary to ischemic heart disease in 40 patients (48%), to idiopathic dilated myocardiopathy in 40 (48%), and to valvular heart disease in the remaining 3 patients, who had a normofunctional mechanical mitral prosthesis. The treatments given are listed in Table 1. The mean dose of enalapril was 18±9 mg/day; captopril 94±68 mg/day, and furosemide 90±41 mg/day.

Patients with concomitant diseases like infection, chronic renal insufficiency, autoimmune disease, or cancer, as well as patients with acute myocardial infarction within the last 6 months were excluded. Eleven patients who received antagonists of the AT1 receptors of angiotensin II (Ag-II) were excluded from the study. The remaining 83 patients constituted the study population.

Echocardiography

A bidimensional M-mode echocardiogram with pulsed Doppler was performed with the Hewlett Packard Ultrasound System (Sonos 2000) using a 2.5-MHz electronic transductor. Ventricular function was analyzed following the recommendations of the American Society of Echocardiography.

Neurohormone and cytokine determinations

Plasma determinations of neurohormones and cytokines were performed in all the patients at the start of the study. Neurohormones were measured by radioimmunoassay and cytokines by enzyme-linked immunosorbent assay. The clinical characteristics of the population are summarized in Table 1.
citocequinas fueron medidos en muestras de sangre obtenidas en pacientes con el antebrazo, durante 45 min de descanso. Los valores plasmáticos de aldosterona (AL), N, Ag-II, plasminación de renina (PRA), ANF, EN, TNF-α y IL-6 fueron determinados. Los valores normales son <5 pg/mL (Medgenix Diagnostics, Fleurus, Belgium) and IL-6 (commercial assays). Las determinaciones plasmáticas se realizaron mediante enzim-linked immunoabsorbent assays, y la terapia inmunológica fue efectuada en 3 pacientes como una medida de emergencia.

**TABLA 2. Valores de mediana y rango de valores del neurohormonas y citocequinas estudiados**

<table>
<thead>
<tr>
<th>Neurohormona</th>
<th>Mediana</th>
<th>Rango</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARA, ng/mL/h</td>
<td>3.3</td>
<td>(0.07-44)</td>
</tr>
<tr>
<td>AL, ng/mL</td>
<td>17</td>
<td>(4-70)</td>
</tr>
<tr>
<td>Ag-II, pg/mL</td>
<td>33</td>
<td>(8-480)</td>
</tr>
<tr>
<td>N, pg/mL</td>
<td>285</td>
<td>(81-1886)</td>
</tr>
<tr>
<td>ANF, fmol/mL</td>
<td>95</td>
<td>(7-296)</td>
</tr>
<tr>
<td>EN, pg/mL</td>
<td>9.3</td>
<td>(1.3-25)</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>42</td>
<td>(7-99)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>20</td>
<td>(1-107)</td>
</tr>
</tbody>
</table>

*Ag-II indica angiotensina II; AL, aldosterona; PARA, plasma renina actividad; EN, endotelina; ANF, atrial natriurético factor; IL-6, interleukin 6; N, norepinefrina; TNF-α, tumor necrosis factor alfa.*

**RESULTAS**

Los datos clínicos de los 83 pacientes en NYHA funcional clase III-IV estudiados se describen en Tabla 1. Los valores de las citocequinas y neurohormonas analizados, expresados como mediana y rango de valores, se muestran en Tabla 2.

Durante el primer año de seguimiento, 13 pacientes murieron y 26 recibieron un trasplante cardíaco. Uno de los 13 pacientes que murió se encontraba en la lista de espera para el trasplante cardíaco, y el trasplante cardíaco fue realizado en 3 pacientes como una medida de emergencia. Veinticuatro pacientes requirieron tratamiento inotrópico intravenoso durante el seguimiento debido a una exacerbación de los síntomas; 11 se encontraban en la lista de espera para un trasplante cardíaco.

**Predicadores de muerte o la necesidad de trasplante cardíaco**

Ag-II, N, y PRA fueron los neurohormonas asociados significativamente con la mortalidad o la necesidad de trasplante cardíaco durante el seguimiento, junto con el bajo presión arterial sistémica, mayor presión arterial pulmonar, dilatación ventricular, presión arterial pulmonar media, y bajo índice de corazón, en análisis univariado (Tabla 3). La elevación de TNF-α o IL-6 no estuvo asociada con un peor pronóstico en estos pacientes.

Multivariado análisis de todas las neurohormonas y citocequinas identificó Ag-II (<0.0002; 95% CI, 1.3-2.3) como el predictor más independiente de la predicción de la muerte o la necesidad para un trasplante cardíaco en el primer año de seguimiento. Cuando hubo una presión endocavitaria, índice de corazón, presión arterial pulmonar, y ecardiográfica...
ventricular diameter were added to the previous analysis, multivariate analysis identified cardiac index, followed by Ag-II and pulmonary capillary pressure, as the variables with the greatest independent predictive power for predicting death or the need for heart transplantation (Table 4).

Comparison of the sensitivity and specificity curve (ROC curves) of Ag-II with those of other neurohormones and cytokines studied showed that all the curves were similar, and the sensitivity and specificity of Ag-II in predicting death or transplantation was moderate (Figure 1). Comparison of the curve of Ag-II with the curves of cardiac index and pulmonary capillary pressure revealed that cardiac index was the most sensitive and specific parameter for predicting death or the need for heart transplantation (Figure 2).

**DISCUSSION**

In this study, the usefulness of cytokine and neurohormone titers was analyzed to assess the prognosis of patients with severe heart failure and to determine if these titers were useful in selecting patients who were candidates for heart transplantation. Ag-II was identified as the most powerful independent predictor of death or the need for heart transplantation. However, its sensitivity and specificity analyzed by means of ROC curves were only moderate and not significantly superior to those of the other neurohormones and cytokines studied, in such a way that improvements in sensitivity were always at the expense of a reduction in specificity, and vice versa. The best sensitivity and specificity values for predicting death or the need for heart transplant ranged from 50% to 60%; therefore, this study confirmed that neurohormone and cytokine determinations have limited value in clinical practice to identify candidates for heart transplantation.

Increased TNF-α or IL-6 were not associated with a worse prognosis in this study, in contrast with the findings of earlier studies.13,16 This can be attributed to differences in the study population; in the present study, all the patients were NYHA functional class III-

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**TABLA 3. Predictors of death or the need for heart transplantation during follow-up. Univariate analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
<th>95% CI HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag-II</td>
<td>0.001</td>
<td>1.2-2.1</td>
</tr>
<tr>
<td>PRA</td>
<td>0.01</td>
<td>1.04-1.7</td>
</tr>
<tr>
<td>N</td>
<td>0.04</td>
<td>1.006-3.1</td>
</tr>
<tr>
<td>ANF</td>
<td>0.06</td>
<td>0.96-2.6</td>
</tr>
<tr>
<td>AoSP</td>
<td>0.006</td>
<td>0.95-0.99</td>
</tr>
<tr>
<td>ESD</td>
<td>0.02</td>
<td>1-1.06</td>
</tr>
<tr>
<td>EDD</td>
<td>0.04</td>
<td>1-1.06</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.003</td>
<td>0.12-0.65</td>
</tr>
<tr>
<td>mPAP</td>
<td>0.04</td>
<td>1-1.07</td>
</tr>
</tbody>
</table>

Ag-II indicates angiotensin II; PRA, plasma renin activity; EDD, end-diastolic diameter; ESD, end-systolic diameter; ANF, atrial natriuretic factor; HR, hazard ratio (risk rate); CI, confidence interval; N, norepinephrine; mPAP, mean pulmonary artery pressure; AoSP, aortic systolic pressure.

**TABLA 4. Predictors of death or the need for heart transplantation during follow-up. Multivariate analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
<th>95% CI HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index</td>
<td>0.007</td>
<td>0.14-0.73</td>
</tr>
<tr>
<td>Ag II</td>
<td>0.01</td>
<td>1.09-2.06</td>
</tr>
<tr>
<td>PCP</td>
<td>0.04</td>
<td>1-1.08</td>
</tr>
</tbody>
</table>

Ag-II indicates angiotensin-II; HR, hazard ratio (risk rate); CI, confidence interval; PCP, pulmonary capillary pressure.

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**Fig. 1.** Comparison of the areas under the curves obtained with the sensitivity and specificity of the plasma levels of angiotensin II (Ag-II), norepinephrine (N), atrial natriuretic factor (ANF), and tumor necrosis factor alpha (TNF-α) to predict death or the need for heart transplant. No differences were observed between them.

**Fig. 2.** Comparison of the areas under the curves obtained with the sensitivity and specificity of plasma levels of angiotensin II (Ag-II) and the cardiac index (CI) to predict death or the need for heart transplant.
IV, so it is possible that mediators of inflammation were not the only determinants of short-term prognosis in this population of patients with advanced heart failure. Recently it has been demonstrated that soluble TNF receptors have more prognostic value than TNF itself, consequently, soluble TNF receptor I (sTNF-r1) has been associated with a greater mortality in functional class II-III patients. In addition, it is possible that elevated cytokine or neurohormone titers are more effective in predicting mortality than the need for heart transplantation, giving the subjectivity of this indication.

The decision to include a patient on a waiting list for transplantation continues to be difficult, considering the probable time that the patient will remain on the list before transplantation and the natural evolution of the disease. Various studies have identified clinical data like the ischemic origin of ventricular dysfunction, degree of ventricular dilation, arterial hypotension, need for intravenous inotropic treatment, reduction of peak oxygen consumption in the effort stress test, high endocavitary pressures, and low cardiac index as factors associated with a greater short-term mortality and thus useful in identifying the patients with a less favorable prognosis who are therefore candidates for heart transplantation. Nonetheless, no single parameter allows us to reliably identify the patients and moments in which the option of heart transplantation must be considered. Although high plasma N values have also been associated with an increase in mortality in diverse studies, their usefulness in selecting candidates for transplantation is limited, mainly because values can vary widely in time due to the influence of external circumstances, such as the use of diuretics or a low-salt diet. Although analysis of the benefit of inhibitors of angiotensin-converting enzyme (ACEI) in heart failure revealed an association between high mortality and high plasma values of N, Ag-II and ANF in patients in the placebo group, this relation disappeared in the group that received ACE inhibitors. Currently, 95% of patients with severe heart failure are treated with ACEI, and an increasing percentage with beta-blockers, because both drugs modulate the effects of neurohormonal activation and can modify its prognostic value.

As found in previous studies, Ag-II was the most powerful variable for identifying patients with a poor prognosis. Nonetheless, a more complete blockade of the renin-angiotensin system by the administration of very high doses (60 mg/day) of enalapril or the addition of antagonists of the Ag-II receptor to ACEI has not been accompanied by the expected reduction in mortality. This suggests that investigation in this field must continue, since other, still unknown, factors can influence the prognosis of heart failure. It is possible that some activation of Ag-II is necessary to maintain blood pressure and hemodynamic stability in terminal phases of the disease when ventricular function is severely depressed. In recent decades, mediators activated in the endothelium in heart failure have been identified, such as EN, whose increase in serum is associated with a worse prognosis in several studies. Although EN probably has an important role in the evolution of heart failure, because it increases as heart failure worsens, its tissue activation may have a determinant role in the evolution of the disease.

Limitations of the study

The decision to refer a patient for heart transplantation is a questionable endpoint due to its subjectivity. However, the time on the waiting list in our hospital is short. Only very symptomatic patients are added to the waiting list for heart transplantation and such patients have a very high expected short-term mortality.

The peripheral activation of cytokines and neurohormones probably does not adequately reflect their tissue activation, since the activation of mediators favoring ventricular remodeling and, definitively, the evolution of the disease takes place at this level.

CONCLUSION

The results of this study assign limited value to high cytokine and neurohormone levels in terminal heart failure for the selection of patients for heart transplantation. According to these results, the decision to refer a patient for heart transplantation must continue to be based on a combination of clinical and hemodynamic data.

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REFERENCES


