Prognostic Value of Cytokines and Neurohormones in Severe Heart Failure

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Background and objetives. 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.*

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Valor pronóstico de los niveles de citocinas y neurohormonas en la insuficiencia cardíaca severa

Introducción y objetivos. La selección de pacientes candidatos a trasplante cardíaco sigue siendo un problema difícil. Los valores elevados de citocinas y neurohormonas se han asociado a peor pronóstico en la insuficiencia cardíaca, pero su utilidad para seleccionar pacientes candidatos a trasplante cardíaco es todavía incierta.

Métodos. Se analizaron los valores plasmáticos de aldosterona, factor natriurético auricular, actividad de la renina plasmática, angiotensina II, noradrenalina, endotelina, interleucina 6 y factor de necrosis tumoral alfa, en 83 pacientes con insuficiencia cardíaca severa en clase funcional III-IV de la NYHA.

Resultados. Durante el seguimiento, 13 pacientes fallecieron y 26 precisaron un trasplante cardíaco. La fracción de eyección fue del 23 ± 6% y los diámetros telediastólico y telesistólico de 73 ± 10 y de 60 ± 10 mm, respectivamente. El análisis univariado identificó los valores de angiotensina II (p = 0,001), noradrenalina (p = 0,003), actividad de la renina plasmática (p = 0,02), presión arterial sistólica (p = 0,006) y los diámetros telediastólico (p = 0,02) y telesistólico (p = 0,04) como factores asociados a un peor pronóstico. El análisis de regresión multivariado identificó el índice cardíaco (p = 0,007), los títulos de angiotensina II (p = 0,001) y la presión capilar pulmonar (p = 0,04) como predictores independientes de muerte o necesidad de trasplante cardíaco.

La sensibilidad y especificidad de la angiotensina II, representadas mediante las curvas ROC, para identificar a los pacientes con peor pronóstico fueron sólo moderadas.

Conclusiones. La angiotensina II fue la neurohormona más eficaz para identificar a los pacientes con insuficiencia cardíaca severa y peor pronóstico. No obstante, la sensibilidad y la especificidad para detectar mayor mortalidad o necesidad de trasplante cardíaco fueron sólo moderadas. La decisión de indicar trasplante cardíaco debe seguir basándose en datos clínicos y hemodinámicos.

Palabras clave: *Insuficiencia cardíaca. Angiotensina II. Citocinas. Trasplante.*

INTRODUCTION

The prognosis of heart failure has improved in recent years, thanks mainly to new advances in therapy. However, an appreciable number of patients

ABBREVIATIONS

PRA: plasma renin activity
Ag-II: angiotensin II
AL: aldosterone
ACEI: angiotensin-converting enzyme inhibitors
EN: endothelin
ANF: atrial natriuretic factor
IL-6: interleukin 6
N: norepinephrine
TNF-α: tumor necrosis factor alpha

continue to progress to severe heart failure and have a very high short-term mortality.[1,2] In these patients, heart transplantation continues to be the only treatment that improves the prognosis and quality of life. Although the reduction of functional capacity is the most important clinical parameter in the decision to order heart transplantation, selection of the optimal moment for accepting a patient for transplantation continues to be an unsolved problem.[3] In several studies, different parameters, both clinical and hemodynamic, have been identified that are associated with worse prognosis and are useful in the selection of patients who will benefit from heart transplantation.[4-9] High plasma concentrations of certain neurohormones, like norepinephrine (N) and atrial natriuretic factor (ANF), have been associated with a worse prognosis, although their real clinical utility is very limited.[10,11] Most of the previous studies have been very heterogeneous, with only a few patients of advanced functional class, and analyze the prognostic value of one or several neurohormones, as opposed to all of them as a whole, which is why it is difficult to deduce which of them may be most useful in these patients.

More recently, other mediators activated in the endothelium, such as endothelin (EN)[12] and cytokines like tumor necrosis factor (TNF) and interleukin 6 (IL-6), have also been associated with a greater mortality in patients with heart failure.[13] It remains to be seen if high titers of these mediators are useful for establishing the prognosis of these patients.

The objectives of this study are: *a)* to analyze the prognostic value of high serum values of TNF and IL-6 in patients with severe heart failure, functional class III-IV of the New York Heart Association (NYHA), and *b)* to analyze together all the neurohormones and cytokines to determine their usefulness in the selection of patients for 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 Clínic 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.

TABLA 1. **Clinical characteristic of the population**

Clinical characteristics	Mean±SD
Age, years	59±11
Ejection fraction, %	23±6
EDD, mm	73±10
ESD, mm	60±10
Duration, months	43±55
Previous CI	60 (72%)
LBBB	55 (66%)
ACEI	83 (100%)
BB	21 (25%)
Digoxin	67 (81%)
IAD	13 (16%)
Amiodarone	33 (40%)
Dobutamine i.v.	24 (29%)

BB indicates beta-adrenergic blockers; LBBB, left bundle-branch block; IAD, implantable automatic defibrillator; SD, standard deviation; EDD, end-diastolic diameter; ESD, end-systolic diameter; i.v., intravenous; HF, heart failure ACEI, angiotensin-converting enzyme inhibitor.

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 made in blood samples obtained in fasting patients, through the antecubital vein, after 45 min of rest. Plasma values of aldosterone (AL), N, Ag-II, plasma renin activity (PRA), ANF, EN, TNF-α, and IL-6 were determined. Samples were kept on ice at 4°C and centrifuged promptly, then the plasma was frozen at 30°C until use.[14] The values for normality in our laboratory are: PRA, 1.4±0.9 ng/ml/h; AL<30 ng/mL; N, 253±114 pg/mL; ANF, 19±5 fmol/ml, and Ag-II, 15±8 pg/ml. Radioimmunoassay was used to measure serum TNF-α values (<20 pg/mL) (Medgenix Diagnostics, Fleurus, Belgium) and IL-6 (commercial enzyme-linked immunoabsorbent assays; Medgenix Diagnostics), the normal values being <5 pg/mL.

TABLA 2. **Values of the median and range of values of the neurohormones and cytokines studied**

Neurohormone	Median	Range
PARA, ng/mL/h	3.3	(0.07-44)
AL, ng/mL	17	(4-70)
Ag-II, pg/mL	33	(8-480)
N, pg/mL	285	(81-1886)
ANF, fmol/mL	95	(7-296)
EN, pg/mL	9.3	(1.3-25)
TNF-α, pg/mL	42	(7-99)
IL-6, pg/mL	20	(1-107)

Ag-II indicates angiotensin II; AL, aldosterone; PARA, plasma renin activity; EN, endothelin; ANF, atrial natriuretic factor; IL-6, interleukin 6; N, norepinephrine; TNF-α: tumor necrosis factor alpha.

Statistical analysis

Data are expressed as the mean and standard deviation. The plasma determinations of neurohormones and cytokines were expressed as the median and range of values. The statistical analysis was carried out using the Statistical Program for the Social Sciences (SPSS), version 10.0. The Kolmogorov test was used to determine if the variables studied in each group had a normal distribution. The variables that did not have a normal distribution were transformed logarithmically to homogenize the sample before analysis. Differences between groups were analyzed by means of the Student *t* test for independent samples, or the Chi-square test when indicated. The following variables were analyzed: ejection fraction, end-diastolic and end-systolic diameters, duration of heart failure, systolic blood pressure, etiology, history of previous cardiac insufficiency, and the neurohormones PRA, AL, ANF, N and EN, and the cytokines TNF-α and IL-6. In 56 patients, pulmonary artery and pulmonary capillary pressures and the cardiac index were analyzed. Cox univariate regression models were used to identify the predictors of death or the need for heart transplantation within a year. Two Cox multiple regression analyses were performed to identify independent predictors of death or the need for heart transplantation during follow-up; in the first analysis, all the neurohormones and cytokines mentioned above were analyzed, and in the second analysis, the rest of the variables were added. The 95% confidence interval (CI) of the hazard ratio (risk rate) was determined. In order to graphically compare the sensitivity and specificity of cytokines and neurohormones in predicting death or the need for heart transplantation, ROC (receiver-operating characteristic) curves were plotted. The ROC curves were plotted to analyze the sensitivity and specificity of each value in the sample. These curves allow the graphic representation of 100% sensitivity and specificity. The superimposition of the curves corresponding to different regression equations allowed the plot of the most sensitive and specific equation to be identified. A valor of $P<.05$ was considered statistically significant.

RESULTS

The clinical characteristics of the 83 patients in NYHA functional class III-IV studied are described in Table 1. The values of the cytokines and neurohormones analyzed, expressed as the median and range of values, are shown in Table 2.

During the first year of follow-up, 13 patients died and 26 received a heart transplant. One of the 13 patients who died was on the waiting list for heart transplantation, and heart transplantation was performed in 3 patients as an emergency procedure. Twenty-four patients required intravenous inotropic treatment during follow-up due to severe exacerbation of symptoms; 11 were on the waiting list for a heart transplant.

Predictors of death or the need for heart transplantation

Ag-II, N, and PRA were the neurohormones associated significantly with mortality or the need for heart transplantation during follow-up, together with low systolic blood pressure, greater ventricular dilation, high mean pulmonary artery pressure, and low cardiac index, in univariate analysis (Table 3). The elevation of TNF-α or IL-6 was not associated with a worse prognosis in these patients.

Multivariate analysis of all the neurohormones and cytokines together identified Ag-II ($P=.0002$; 95% CI, 1.3-2.3) as the variable with the greatest independent predictive power for predicting death or the need for heart transplantation in the first year of follow-up. When right endocavitary pressure, cardiac index, systolic blood pressure, and echocardiographic

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

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

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**

Variable	Significance	95% CI HR
Cardiac index	0.007	0.14-0.73
Ag II	0.01	1.09-2.06
PCP	0.04	1-1.08

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

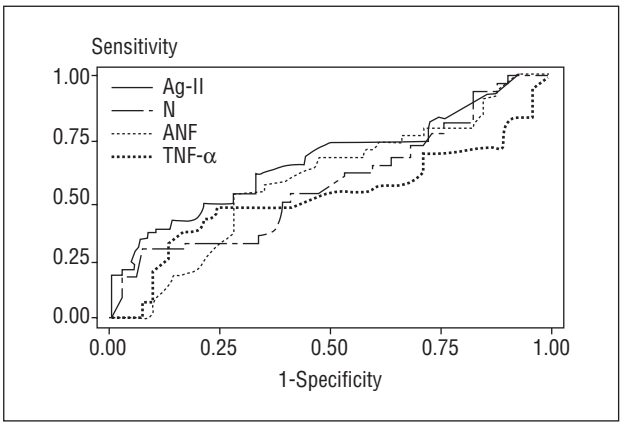

Fig. 1. Comparison of the areas under the curves obtained with the sensitivity and specificity of the plasma levels of angiotensin II (Ag-II), norepinephrine (N), atrial natriuretic factor (ANF), and tumor necrosis factor alpha (TNF-α) to predict death or the need for heart transplant. No differences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

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).

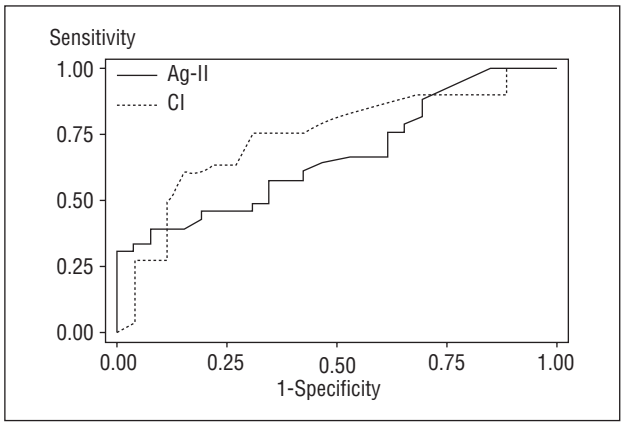

Fig. 2. Comparison of the areas under the curves obtained with the sensitivity and specificity of the plasma levels of angiotensin II (Ag-II) and the cardiac index (CI) to predict death or the need for heart transplant.

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-

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;[17] consequently, soluble TNF receptor I (sTNF-r1) has been associated with a greater mortality in functional class II-III patients.[18] In addition, it is possible that elevated cytokine or neurohormone titers are more effective in predicting mortality than the need for heart transplantation, given 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.[19] 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.[5,6,20] 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,[10,21,22] 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.[23] 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 neurohumoral 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.[24,25] Nonetheless, a more complete blockade of the renin-angiotensin system by the administration of very high doses (60 mg/day) of enalapril[26] or the addition of antagonists of the Ag-II receptor to ACEI has not been accompanied by the expected reduction in mortality.[27] 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.[28] 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.[29]

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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