

Prognostic Value of Serum Levels of Tumor Necrosis Factor-Alpha in Patients with Heart Failure

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Introduction and objective. Tumor necrosis factor-alpha is an inflammatory cytokine which rises in heart failure and has prognostic value in severe cases. Its value is less established in moderate cases. Our aim was to determine its prognostic value in cases from a community hospital.

Patients. We studied 50 patients, average age 59.5 ± 12.3 years, with dilated cardiomyopathy (72% non-ischemic) and moderate heart failure (59% functional class II).

Methods. Patients were evaluated with an echocardiogram and cardiopulmonary treadmill stress test (Naughton), muscular strength measurements (hand dynamometer), blood tumor necrosis factor levels, and an average follow-up of 17.5 ± 9 months (range, 1-29 months). All causes of mortality, cardiac transplantation, and readmissions for heart failure were recorded.

Results. Twenty-three patients experienced events. These patients were older (63 ± 12.7 vs 55.7 ± 11.4 years; $p = 0.042$), had a lower peak VO_2 (13.7 ± 3.9 vs 16 ± 3.3 ml/kg/min; $p = 0.035$), and higher peak VE/VCO_2 and factor levels [41.9 ± 10.6 vs 33.2 ± 5.7 ; $p = 0.001$ and 4.3 ($3.1-7.9$) vs 3.3 ($2.4-4.3$) pg/ml; $p = 0.021$, respectively]. In the Cox model, the only variable with independent prognostic value was peak VE/VCO_2 [HR 1.13 (1.07-1.19); $p < 0.001$]. The best cutoff point was 34.5 (sensitivity, 86.4%; specificity, 58.3%; $p = 0.0007$). The cytokine had no independent prognostic value.

Conclusions. Our patients with events were older, had a lower peak VO_2 , and higher peak VE/VCO_2 and serum tumor necrosis factor levels. However, only peak VE/VCO_2 had independent prognostic value.

Key words: Heart failure. Cytokines. Prognosis.

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Valor pronóstico de los niveles séricos del factor de necrosis tumoral alfa en pacientes con insuficiencia cardíaca

Introducción y objetivos. El factor de necrosis tumoral alfa es una citocina inflamatoria que se eleva en la insuficiencia cardíaca, con valor pronóstico en casos graves, aunque menos establecido en casos moderados. Pretendemos conocer su valor pronóstico en los casos de un hospital secundario.

Pacientes. Se estudian 50 pacientes de $59,5 \pm 12,3$ años, con miocardiopatía dilatada (72% no isquémica), con insuficiencia cardíaca moderada (clase funcional II, 59%).

Métodos. Se realizó un ecocardiograma y una ergoespirometría (Naughton), y se determinaron la fuerza muscular (dinamómetro de mano) y los valores plasmáticos del factor de necrosis tumoral; se efectuó un seguimiento de $17,5 \pm 9$ meses (intervalo, 1-29), en el que se recogieron la mortalidad total, el trasplante cardíaco y el reingreso por insuficiencia cardíaca.

Resultados. Tuvieron episodios 23 pacientes, que tenían mayor edad ($63 \pm 12,7$ frente a $55,7 \pm 11,4$ años; $p = 0,042$), un VO_2 pico (pVO_2) más bajo ($13,7 \pm 3,9$ frente a $16 \pm 3,3$ ml/kg/min; $p = 0,035$), y una relación pVE/VCO_2 y valores del factor más elevados ($41,9 \pm 10,6$ frente a $33,2 \pm 5,7$; $p = 0,001$ y $4,3$ [$3,1-7,9$] frente a $3,3$ [$2,4-4,3$] pg/ml; $p = 0,021$, respectivamente). En el análisis de Cox, la única variable con valor pronóstico independiente fue la relación pVE/VCO_2 (RR = 1,13 [$1,07-1,19$]; $p < 0,001$), con un mejor punto de corte de 34,5 (sensibilidad, 86,4%; especificidad, 58,3%; $p = 0,0007$). La citocina no tuvo valor pronóstico independiente.

Conclusiones. Nuestros pacientes con episodios tienen mayor edad, un pVO_2 menor y la relación pVE/VCO_2 y los valores séricos del factor de necrosis tumoral más elevados, aunque sólo el pVE/VCO_2 tiene valor pronóstico independiente.

Palabras clave: Insuficiencia cardíaca. Citocinas. Pronóstico.

INTRODUCTION

Tumor necrosis factor alpha (TNF- α) is an inflammatory cytokine that is elevated in patients with congestive heart failure (CHF),¹ and that has been found to be associated with the genesis of cardiac cachexia.²

ABBREVIATIONS

TNF- α : tumor necrosis factor alpha.
 CHF: congestive heart failure.
 pVO₂: peak oxygen consumption.
 pVE/VCO₂: peak carbon dioxide ventilation equivalent.
 BMI: body mass index.

TNF- α is associated with, on one hand, musculoskeletal atrophy,^{3,4} and on the other hand it produces a negative inotropic effect.⁵⁻⁸ Nevertheless, it does not appear to be related to neurohumoral activation in CHF.^{9,10} In a study by Rauchhaus et al,¹¹ performed on patients with CHF caused by systolic dysfunction in (predominantly) functional class III and IV, it was reported that the plasma values of TNF- α receptor 1 had an independent prognostic value, adjusted for the ejection fraction (EF) and peak oxygen consumption (pVO₂). Similarly, in the placebo group of the VEST study,¹² which included patients with CHF caused by systolic dysfunction in functional classes III and IV, TNF- α plasma values and the TNF- α circulating receptors 1 and 2 were independent predictors of death, after adjusting for EF and functional class. Nevertheless, in patients in the SOLVD study¹⁰ (NYHA functional class I to II), the plasma values of TNF- α had a tendency to be independent predictors of survival ($P < .07$).

The goals of our study were:

1. To determine the relationship between TNF- α blood levels and: *a*) the severity of CHF as evaluated by pVO₂; *b*) ventricular function as evaluated by the EF; *c*) the patients' nutritional level as evaluated by body mass index (BMI), and *d*) muscular strength as evaluated by a hand-held dynamometer.

2. To find out the prognostic value of serum TNF- α values in patients with CHF and controlled left ventricular systolic dysfunction in secondary hospitals (Hospitales de Elche and Alicante), corrected for variables of known prognostic value (EF, pVO₂,¹³⁻¹⁵ and peak carbon dioxide ventilation equivalent [VE/VCO₂]).¹⁶

Our hypothesis was, primarily, that TNF- α has a negative correlation with pVO₂, contractility (measured as EF), nutrition level (measured as BMI), and muscle strength. Secondly, we theorized that in patients with CHF, TNF- α has an independent prognostic value.

The Hospital de Elche treats a population of approximately 250 000 inhabitants and has noninvasive cardiology techniques available. The Hospital de Alicante tre-

ats a slightly smaller population (approximately 230 000) and offers invasive techniques (hemodynamic and electrophysiological). Neither center is a referral center for cardiac transplants.

PATIENTS AND METHODS

Inclusion criteria

Patients with clinical CHF and left ventricular systolic dysfunction (EF < 0.50), in other words, with dilated cardiomyopathy of any etiology, were included. At the time of the study, the patients were stable, without pleural effusion, ascitis, or edema.² Patients also had to be free of anti-inflammatory drugs and steroids during the previous 2 weeks.¹⁷

Exclusion criteria

- Significant aortic stenosis. Hyperdynamic cardiac insufficiency.
- Orthopedic or rheumatic problems that prevented ambulation
- Documented chronic air flow obstruction. (In questionable cases, spirometry was performed.)
- Occurrence of an acute myocardial infarction during the previous 3 months. Clinical occurrence of chest pain (stress or unstable).^{2,18} In the presence of ischemic cardiopathy, existence of a complete left bundle branch block.

Signs of acute infection, diagnosis of neoplasia, thyroid disease, chronic liver disease, neuromuscular disease, advanced renal insufficiency, and collagenosis.^{2,17}

Patients were selected consecutively from the database of the hospital's Servicio de Documentación Clínica (clinical documentation service) (patients diagnosed upon hospital discharge with heart failure and dilated cardiomyopathy of any etiology). After reviewing the clinical history, we selected the patients who met the inclusion criteria and did not meet any of the exclusion criteria. We included all patients who met all required criteria after testing was completed.

We used the following methods:

- M-mode, 2D, and Doppler echocardiogram (Toshiba SSH-140; 2.5 MHz transducer). We recorded: *a*) the EF by the Teicholz method or ellipsoid single-plane algorithm (4-chamber apical) in cases of ventricular asynergy, and *b*) the left ventricular diameter in diastole (LVDD). The values are the average of 3 heartbeats.
- Cardiopulmonary stress test as usually performed (Marquette MAX 1 treadmill), following the Naughton protocol. The test was stopped at the point of exhaustion, and required reaching a respiratory exchange ratio ≥ 1 . We measured the pVO₂, anaerobic thresh-

hold with the V slope method, the exertion time, and the peak VE/VCO₂¹⁹ (CPX Express. Medgraphics. Cardiorespiratory Diagnostic Systems), and calculated the product of cardiac frequency multiplied by arterial pressure.

- Determination of TNF-α plasma values using the ELISA technique (Quantikine, R&D Systems).

- Measurement of muscle strength (average of 3 measurements) with hand-held dynamometer. Measurement was performed on the dominant hand, with the patient standing and the forearm extended,²⁰ contracting the hand progressively until reaching maximum strength.

Statistical analysis

The normal distribution continuous variables were described as mean±standard deviation (SD), and those that did not follow normal distribution were described as median (25th to 75th percentiles).

The comparisons of the groups (patients with and without episodes) for continuous variables were performed with the Student *t* test for independent samples (normal values) or the Mann-Whitney *U* test (variables without normal distribution). The comparison of discrete variables was done via the χ^2 test or the Fisher test (with expected frequencies <5).

The relationship between TNF-α and the remaining continuous variables was studied using the Pearson correlation test; we used the Spearman rank correlation test when any of the variables did not follow a normal distribution. During followup of the cardiovascular events (which was performed by reviewing the clinical history and by telephone interview) we documented death due to any cause, readmission due to CHF, and cardiac transplant. We performed stepwise Cox proportional hazard model analysis, considering the endpoint to be the presence of any event and introducing as explanatory variables age, sex, BMI, cause of the CHF (ischemic or non-ischemic dilated cardiomyopathy), cardiac rhythm (sinus or non-sinus), EF, pVO₂, pVE/VCO₂, TNF-α, and muscle strength. We analyzed survival that was event-free using the Kaplan-Meier method. We obtained Receiver Operating Characteristics (ROC) curves from the variables with independent prognostic value and from TNF-α values in order to obtain the best cut points for these variables which allowed us to separate the groups of patients with different prognoses. The comparison of survival rates obtained from the various groups was done by the log-rank test. We chose as the cut-off point the value that corresponded to the highest product of the sensitivity multiplied by specificity, always when the log-rank test was significant. The statistical analysis was performed with the SPSS 10.0 statistical package.

RESULTS

Fifty patients were included in the study. Their baseline clinical characteristics are shown in Table 1. The patients were categorized into New York Heart Association (NYHA) class I-III (only 1 patient was class IV), with most patients categorized as class II (59%). There were no cachexic patients: 48 of the 50 patients had a BMI>20 kg/m². Twenty-six percent of patients had atrial fibrillation. In our series, only 28% of patients had ischemic dilated cardiomyopathy. In our hospitals coronary angiography is not routinely performed on all patients with systolic dysfunction and CHF, unless clinical, electrocardiographic, or echocardiographic data (ventricular asynergy) point to suspected ischemic cardiopathy. Therefore, it is possible that the prevalence of ischemic dilated cardiomyopathy may be somewhat high in our study. The patients were treated with digitalis (64%), diuretics (85%), spironolactone (48%), angiotensin-converting enzyme inhibitors I (64%), angiotensin II receptor inhibitors (30%), nitrites (15%), and beta-blockers (6%).

The functional capacity (pVO₂) had a negative correlation with the TNF-α (variable that was not adju-

TABLE 1. Clinical characteristics

N	50
Age, years	59.5±12.3
Sex, M, n (%)	36 (72%)
BMI, kg/m ²	28.2±4.9
Cause, n (%)	I DCM 22 (44) ISQ DCM 14 (28) AHT DCM 10 (20) ALC DCM 3 (6) MR DCM 1 (2)
NYHA, n (%)	I: 6 (12.2) II: 29 (59.2) III: 13 (26.5) IV: 1 (2)
Rhythm, n (%)	SR: 34 (69.4) AF: 13 (26.5) Others: 2 (4.1)
EF	0.33±0.08
LVDD, mm	64.3±8.4
pVO ₂ , mL/kg/min	14.9±3.8
Exercise time, min	8.8±3.6
DP	21 013±6090
Strength, kg	46.9±37.1
TNF-α, pg/mL	3.9 (2.9-5.3)
pVE/VCO ₂	37.7±9.5

Data about rhythm was known in 49 patients. There was no data on the NYHA class of 1 patient (but their pVO₂ was available). ALC indicates alcoholic; LVDD, left ventricle diastolic diameter; DP, double product; AF, atrial fibrillation; EF, ejection fraction; AHT, arterial hypertension; I, idiopathic; MR, mitral regurgitation; BMI, body mass index; ISQ, ischemic; DCM, dilated cardiomyopathy; SR, sinus rhythm; TNF-α, tumor necrosis factor alpha; M, men; pVE/VCO₂, peak carbon dioxide ventilation equivalent at peak exercise; pVO₂, peak oxygen consumption.

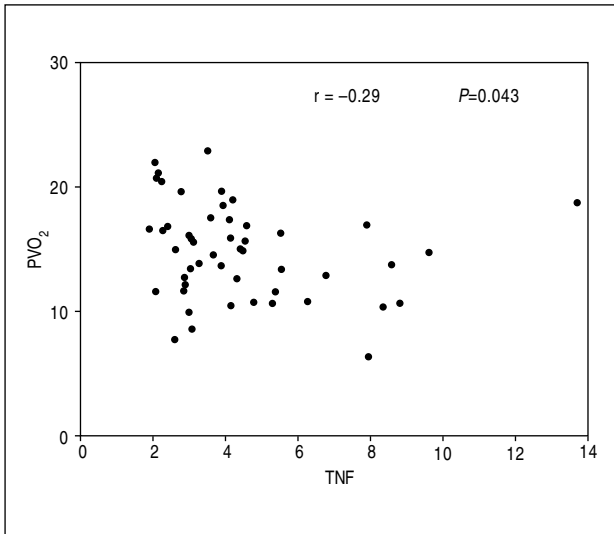


Fig. 1. Spearman correlation between TNF- α and pVO₂ values (the TNF- α does not have normal distribution). pVO₂ indicates peak oxygen consumption; TNF- α , tumor necrosis factor alpha.

ted to normal; Spearman $r = -0.29$; $P = .043$; Figure 1). The rest of the variables we studied did not have a significant correlation with the TNF- α (EF: $r = -0.15$; $P = .30$. BMI: $r = -0.02$; $P = .90$. Strength: $r = -0.19$; $P = .20$).

The patients were followed for 17.5 months \pm 9 months (range 1 to 29). We were unable to obtain complete information from 2 patients: 1 whose where-

abouts were unknown and the other whose survival was only known anecdotally, but there is no data on the other 2 events during the study, and they were excluded from the analysis of the group of patient who survived without events (analysis of 48 patients total). Ten patients died (20.4%), 19 were readmitted due to CHF (39.6%), and 2 (4.2%) underwent cardiac transplant. Overall, 23 patients (47.9%) had some type of event.

The patients who had events did not differ from those who did not by sex, BMI, left ventricle diastolic diameter, EF, or muscle strength (Table 2). The patients who had events were found to be in sinus rhythm less frequently than those who did not (59.1% vs 84%; $P = .056$), and showed a tendency to have a higher occurrence of ischemic dilated cardiomyopathy than those who had no cardiovascular events (39.1% vs 16%; $P = .071$). The group with cardiovascular events were older (63 years versus 56 years; $P = .042$) and had a lower pVO₂ (13.7 mL/kg/min vs 16 mL/kg/min; $P = .035$) and a higher pVE/VCO₂ (41.9 vs 33.2; $P = .001$), and a higher TNF- α (4.3 pg/mL vs 3.3 pg/mL; $P = .021$).

A stepwise Cox proportional hazards model analysis as performed, introducing the 10 preselected clinical and analytical variables. The only variable that showed an independent predictive value for a cardiovascular episode was the pVE/VCO₂ ($\chi^2 = 34.68$; $P < .001$; hazard ratio [RR], 1.13 [1.07-1.19]). The TNF- α values did not have an independent prognostic value ($P = .087$).

TABLE 2. Comparison of patients according to the presence of events

	Events	Without events	P
N	23	25	
Age, years	63 \pm 12.7	55.7 \pm 11.4	.042
Sex, M, n (%)	18 (78.3)	16 (64)	.277
BMI, kg/m ²	28.2 \pm 4.6	28.3 \pm 5.4	.941
Cause, n (%)	ISQ DCM: 9 (39.1) NON ISQ DCM: 14 (60.9)	4 (16) 21 (84)	.071
NYHA, n (%)	I: 1 (4.3) II: 16 (69.6) III: 6 (26.1) IV 1 (4.2)	5 (20.8) 12 (50) 6 (25)	.238
Rhythm, n (%)	SR: 13 (59.1) Non SR: 9 (40.9)	21 (84) 4 (16)	.056
LVDD, mm	66.4 \pm 8.8	62.93 \pm 7.7	.143
EF	0.33 \pm 0.07	0.33 \pm 0.08	.967
DP	19 489 \pm 4737	21 900 \pm 6945	.170
Strength, kg	51.6 \pm 40.8	44.9 \pm 34.1	.547
TNF- α , pg/mL	4.3 (3.1-7.9)	3.3 (2.4-4.3)	.021
Effort time, min	7.1 \pm 2.8	10.8 \pm 3.4	<.001
pVO ₂ , mL/kg/min	13.7 \pm 4	16 \pm 3.3	.035
pVE/VCO ₂	41.9 \pm 10.6	33.2 \pm 5.7	.001

Followup of 2 patients was not possible. Data on rhythm was unknown in 1 patient. There was no data on the NYHA class of 1 patient (but the VO₂ was known). LVDD indicates left ventricle diastolic diameter; DP, double product; BMI, body mass index; ISQ, ischemic; DCM, dilated cardiomyopathy; SR, sinus rhythm; TNF- α , tumor necrosis factor alpha; M, men; pVE/VCO₂, pVE/VCO₂, peak carbon dioxide ventilation equivalent at peak exercise; pVO₂, peak oxygen consumption.

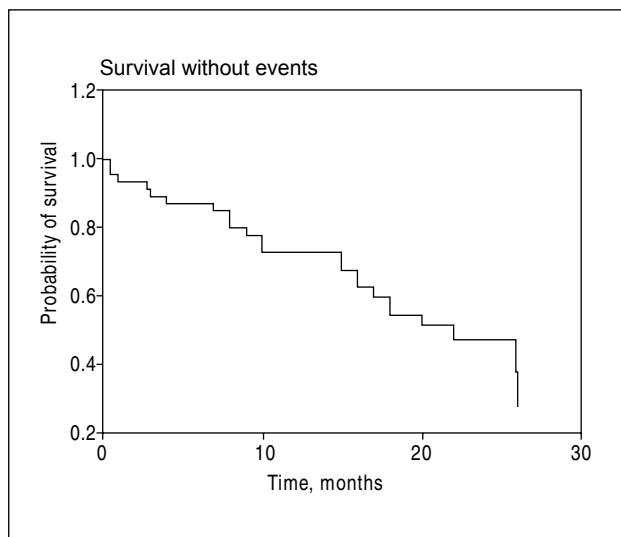


Fig. 2. Graphic representation of survival free of events (Kaplan-Meier method). P indicates probability; time, followup time.

The probability of survival free of events at 7 months was 85% (80% to 90%), at 15 months was 68% (61% to 75%), and at 26 months was 28% (25% to 31%), with all the events having taken place (Figure 2).

Using the ROC curves, we obtained the best pVE/VCO₂ value that significantly separated 2 groups of patients with different prognoses. This value was 34.5 (sensitivity, 86.4%; specificity, 58.3%; RR, 2.53 [1.37 to 4.70]; *P*=.0007; Figure 3). Although it did not have an independent prognostic value, we used the same analysis for TNF- α blood values, and we obtained the number 2.92 pg/mL (sensitivity, 87%; specificity, 40%; RR, 1.851 [1.003 to 3.415]; *p*=.035; Figure 4).

DISCUSSION

We studied a group of patients who basically had idiopathic and ischemic dilated cardiomyopathy with moderate CHF (predominantly NYHA functional class II) without cachexia. The serum TNF- α values were found to be similar to those reported in the analyses of serum in the SOLVD study.¹⁰ Milani et al²¹ and Testa et al²² also reported similar values in their patients. There are studies that report no elevation of TNF- α in patients with slight to moderate CHF.^{18,23}

Muscle changes have been described in patients with CHF. Massie et al²⁴ found a lower muscle fatigue index in the quadriceps (greater decrease in strength after 15 successive contractions) in patients compared with controls. In addition, the patients had less type I and more type II a and b fibers, and less succinate dehydrogenase enzyme activity. In short, the activity of this enzyme had a positive correlation with the

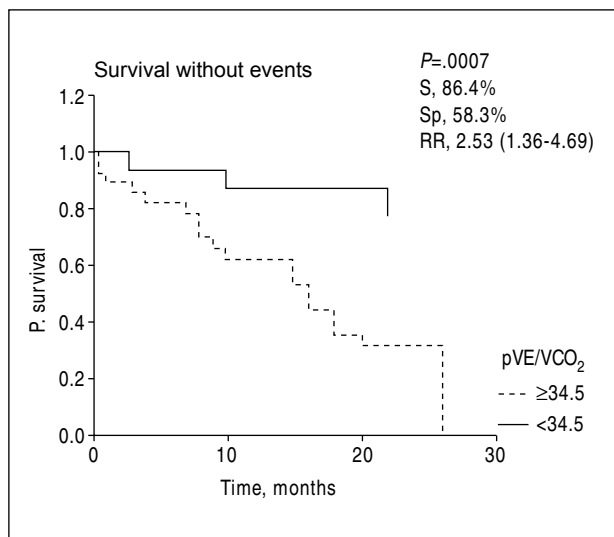


Fig. 3. Graph patient survival groups according to their pVE/VCO₂ value taking into account the best cut-off value of this variable. Comparison of curves was achieved according to the log-rank method. P indicates probability; time, followup time; S, sensitivity; Sp, specificity; RR, relative risk.

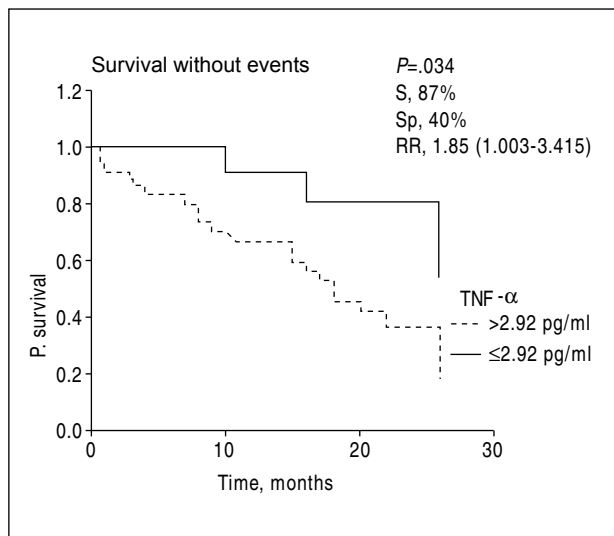


Fig. 4. Graph of the probability of survival of patient groups according to their TNF- α taking into account the best cut-off value of this variable. Comparison of the curves was done using the log-rank method. P indicates probability; time, followup time; S, sensitivity; Sp, specificity; RR, relative risk.

pVO₂. Volterrani et al²⁵ found a clear positive correlation between quadriceps strength and pVO₂.²⁵ In our study, however, we did not find a relationship between muscle strength and functional capacity among our patients (pVO₂; Pearson *r*, 0.23; *P*=.112).

We have found that a significant negative correlation exists between TNF- α values and pVO₂ (*r*, -0.29; *P*=.043). Other studies have found that as functional class worsens, the TNF- α values increase;^{10,22} our results are in accordance with previous data. We did not

observe, however, a relationship between TNF- α and BMI or with muscle strength, perhaps because patients with moderate CHF were included. However, in experimental studies in rats with CHF²⁶ it has been shown that when TNF- α values are lowered with irbesartan, an angiotensin II AT₁ receptor antagonist, the animals have reduced atrophy of the skeletal muscle. It is possible that patients categorized as functional class IV may confirm this relationship. In fact, in a study by the London National Heart and Lung Institute,²⁷ patients with CHF and slightly elevated TNF- α values (0.98 to 4.90 pg/mL), similar values to the patients in our series, also did not have a decrease in muscle strength of the quadriceps. This only occurred in those patients with elevated cytokine values (9.8-32 pg/mL), who were also the group of patients who showed greater functional deterioration (pVO₂, 13.1 mL/kg/min \pm 4.1 mL/kg/min; in our study the pVO₂ was 14.9 mL/kg/min \pm 3.8 mL/kg/min).

We know that patients with CHF have a volume per minute ventilation for each PCO₂ value greater than the normal individuals. Therefore, in order to study ventilation in CHF, the VE/VCO₂ at peak of exercise is used, or the gradient of the ratio of these parameters during exercise is used.¹⁹ Many reasons have been put forth to explain this hyperventilation, eg, an increase in the physiological dead space due to pulmonary hypoperfusion, dependent receptor mechanisms (metabolic receptors?) in skeletal muscle,¹⁹ and decrease in inspiratory muscle strength.²⁸

Our patients had a somewhat high mortality rate (20%), with a 28% probability of being free of episodes at the end of the followup period. The only factor with independent prognostic value was the pVE/VCO₂, more than the pVO₂ and the TNF- α . Although the prognostic value of pVO₂ is generally accepted,^{13,14} some studies have reported that pVE/VCO₂ has an independent prognostic value. Similarly, in a series of patients with CHF, serious systolic dysfunction, and good exercise capacity (pVO₂>18 mL/kg/min),¹⁶ pVE/VCO₂ (and not VO₂) influenced the mortality rate. Patients with an elevated pVE/VCO₂ (>34, the number obtained after a study of the normal population) had an elevated central and peripheral chemosensitivity and a decreased baroreflexive sensitivity; this value differentiated 2 groups of patients with different survival rates and is very similar to the higher prognostic cut-off value that we obtained (>34.5).

Rauchhaus et al¹¹ published a study of patients with CHF and systolic dysfunction, 29% of whom were cachexic. In that series, the type 1 circulating receptors of TNF- α had an independent prognostic value, along with pVO₂ and EF values. Similarly, in the placebo group of the VEST study (patients with CHF and NYHA functional class III and IV),¹² both the circulating values of TNF- α and the type 1 and 2 circulating

receptor values of the cytokine influenced the survival rate independently, along with the NYHA functional class and the EF, although the type 2 circulating receptors had the greatest predictive value. Nevertheless, in a recent study from the Hospital Clínic de Barcelona of patients with CHF and classified as NYHA class III-IV who had systolic dysfunction,²⁹ only the angiotensin II values, along with the cardiac index and pulmonary capillary pressure, had an independent predictive value for death or cardiac transplant. In that study, the authors analyzed, among other variables, the TNF- α and interleukin⁶ values. In our study, only the pVE/VCO₂ ventilation index could independently predict survival.

The differences between the aforementioned studies and our study should be pointed out. In the Rauchhaus study, 57% of the patients were in NYHA functional classes III-IV. In the VEST study, all the patients were in the same functional classes, as were the patients in the study from the Universidad de Barcelona. In our series, only 28% of the patients were in this functional class, with 59% of patients being in NYHA functional class II. Our patients were not cachexic (although the numbers for TNF- α receptor 1 in plasma maintained their prognostic value in the subgroup of patients without cachexia in the Rauchhaus study). It is possible that 26% of the patients who had an EF between 0.40 and 0.50 in our series could improve the overall prognosis; nevertheless, in the study from the University of Berlin,¹¹ the cytokines had prognostic value in spite the fact that 20% of patients had this EF. In addition, the EF in our study overlapped in the groups with and without events. The overall mortality rate of the 4 series is different: a rate of 41% at an average followup of one year (maximum followup period, 6 years) in the Rauchhaus study, 17% at 1-year mean followup (maximum followup period of 19 months) in the VEST study, and 16% (47% death or cardiac transplant) per year in the study from the Hospital Clínic de Barcelona,²⁹ vs a rate of 20% at a mean 18-month followup (maximum followup period 29 months) in our series. One factor that may have influenced the patient course is treatment with beta-blockers: these were prescribed in 12% of patients in the Rauchhaus series, 25% of patients in the Barcelona study, and 6% of our patients (this was not a factor in the VEST study). The scant use of these drugs in our series may explain the relatively high mortality rate. Another difference between the studies that may explain differences in the prognostic value of TNF- α is the final followup point: death due to any cause in the Rauchhaus and VEST studies, death due to any cause or cardiac transplant in Hospital Clínic de Barcelona study, and death due to any cause, cardiac transplant, or readmission due to CHF in our study.

Nevertheless, in the study by Torre-Amione,¹⁰ which was performed on patients from the SOLVD

study in NYHA functional classes I to III, the blood values of TNF- α alone tended to be of independent prognostic value ($P=.07$), which is a result that is compatible with ours from patients in similar functional classes (90% in NYHA functional classes II-III; 86% in our series).

Study limitations

Our study was performed in a small sample size, which could have had an effect on the results of the multivariate analysis. In our series, 26% of patients had an EF between 0.4 and 0.5; this may have influenced the prognosis, making it more favorable, although in the other series mentioned such as the Rauchhaus series,¹¹ with a similar rate (20%), the mortality rate was double. The small number of patients treated with beta-blockers could have influenced the prognosis, making it more unfavorable. In our study we only determined the values of circulating TNF- α , and did not analyze the values of the TNF- α circulating receptors. Nevertheless, although there are studies in which only the circulating receptor values have independent prognostic value,¹¹ in other studies¹² TNF- α also has prognostic value, although it is less than that of circulating receptors. Since this is a non-invasive clinical study, we do not know the myocardial TNF- α values. It has been reported that although almost all patients with elevated myocardial TNF- α also have elevated circulating TNF- α , only approximately 50% of patients with increased circulating TNF- α have increased myocardial TNF- α ;³⁰ nevertheless, we know of no study that has analyzed whether myocardial TNF- α has a greater prognostic value than its circulating values. Our followup endpoint was a combination of episodes, not only death, so that our results are not comparable to other series in the literature.

CONCLUSIONS

1. In patients with moderate CHF due to left systolic ventricular dysfunction without cachexia, we did not find a relationship between serum TNF- α values and EF, the nutrition level, or muscle strength.

2. Circulating TNF- α has a negative correlation with functional capacity, measured as pVO₂.

3. The group of patients with the cardiac events are older, have a smaller pVO₂, have a higher pVE/VCO₂ (with independent prognostic value), and have higher TNF- α values, although they do not add prognostic value.

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