

Are there differences in acute phase inflammation markers regarding the type of heart failure?

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Abstract

This study aimed to determine if there are differences in inflammatory markers in the acute phase between systolic heart failure and heart failure with preserved systolic function. One hundred and thirty-one patients with acute heart failure were recruited consecutively. At admission, plasma fibrinogen, C-reactive protein, sialic acid, von Willebrand factor, vascular endothelial growth factor, interleukin-6 and NTproBNP were all evaluated. If the ejection fraction was 45% or over

patients were included in the HF-PSF group; the remaining patients were included in the SHF group. The HF-PSF patients were older (72 ± 10 vs 63 ± 12 years, $P < 0.001$), presented a higher rate of atrial fibrillation (56.1 vs 21.3% , $P < 0.001$), and had a lower rate of hemoglobin (12.2 ± 2 vs 13.3 ± 2.1 g/dL, $P < 0.01$). No significant differences were observed in the inflammation markers analyzed among SHF and HF-PSF groups. In the acute phase of heart failure there is a marked elevation of inflammatory markers but there are no differences in the inflammatory markers analyzed between the two different types of heart failure.

the persistence of the disease. Certain inflammatory markers (IM) of a prognostic value have been identified. Some of them have even been shown to have a clinical use,^{6,7} like brain natriuretic peptide (BNP) and its non-active aminoterminal fragment NTproBNP. On the other hand, there have been very few studies of inflammatory status in HF-PSF patients.⁸

HF studies generally tend to cover only one type of HF; very few have covered both. As a result, only a few studies have compared SHF with HF-PSF, and even fewer studies have been concerned with research into inflammation. To date, there has been only one article comparing several IM in stable patients in terms of HF type.⁸

The objective of this study was to assess the levels of specific IM in patients who had been diagnosed with acute HF while hospitalized according to the type of HF presented (SHF vs HF-PSF).

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Key words: heart failure, inflammation

Funding: this work was supported in part by grants from Conselleria Sanitat GVA: AP037/07, research grants from Ministerio de Ciencia, Tecnología e Innovación, Instituto de Salud Carlos III: FIS PI08124, and Fundación Mutua Madrileña.

Conflict of interest: the authors report no conflicts of interest.

This article is part of the doctoral thesis of Ignacio J. Sánchez Lázaro in the Medicine Department of the Universitat Autònoma de Barcelona, Spain.

Received for publication: 7 May 2011.
Revision received: 25 August 2011.
Accepted for publication: 7 October 2011

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Licensee PAGEPress, Italy
Heart International 2011; 6:e17
doi:10.4081/hi.2011.e17

Introduction

Heart failure (HF) is currently one of the most prevalent diseases and it inflicts a considerable economic burden on the health care system.¹ Until a few years ago, attention was only paid to HF with depressed systolic function (SHF). It was not until quite recently that an interest in HF with preserved systolic function (HF-PSF) has been shown.²

Despite the fact that HF-PSF represents 50% of the population with HF,^{3,4} few specific studies have been conducted in clinical, prognostic, and treatment terms. This implies assuming that what we know about SHF applies to HF-PSF. Nonetheless, there are some studies which prove that the two types of HF differ. Thanks to a number of studies, an improved prognosis in SHF has been observed in recent years, while there has been no such improvement in the field of HF-PSF given the lack of specific studies. Inflammation has generally been shown to play a key role in HF, particularly in SHF.⁵ In these patients, an increased inflammation status occurs in the stable phase of the disease. This increases in the decompensation periods. This inflammation contributes not only to the central and peripheral manifestations of the disease, but also to

Materials and Methods

Study population

From September 2006 to November 2007, 155 patients diagnosed with acute HF and admitted to the Cardiology Unit were consecutively enrolled. HF diagnosis was made according to the patients' signs and symptoms and to the Framingham criteria.⁹ All the patients had a functional NYHA class of III or over. HF etiology was based on medical records and on the results of complementary tests. Patients who had been previously hospitalized, had undergone coronary/heart surgery three months prior to being admitted to the Cardiology Unit, or had not signed the informed consent, were excluded from the study. A total number of 131 patients went forward for analysis (SHF n=62, HFPSF n=69).

This study was carried out in accordance with the Declaration of Helsinki. It was also approved by the Biomedical Research Ethics

Committee at the University La Fe Hospital. All the patients gave their written informed consent to participate in this study.

Variables and complementary tests

High blood pressure, dyslipidemia and diabetes were considered when patients were prescribed drugs to control these risk factors.

An electrocardiogram was performed for all patients upon arrival. An echocardiography was performed within 48 h of hospital admission to rule out transient systolic dysfunction. The equipment used was an HP Sonos 5500[®] with a 2.5 MHz probe (Philips, Eindhoven, The Netherlands). All the readings, including the ejection fraction (EF), were taken according to the recommendations of the American Society of Echocardiography.¹⁰ If the EF was below 45%, the patient was included in the SHF group, while the remaining patients were included in the HF-PSF group. Coronary catheterization was performed in those patients who had not previously undergone the procedure, or who had had this performed more than one year before.

Markers and biochemical determinations

In an attempt to minimize the influence of the treatment, blood samples were obtained from all patients within 24 h of hospital admission. IM included were: plasma fibrinogen (PF), C-reactive protein (CRP), sialic acid (SA), von Willebrand factor (vWF), vascular endothelial growth factor VEGF, interleukin-6 (IL-6), and NTproBNP. PF levels were obtained by measuring the plasma fibrin formation rate by a turbidity assay. The coefficient of variation was 8%. CRP plasma levels were measured by nephelometry using a commercial high sensitivity assay (Dade-Behring, Germany). The coefficient of variation was 4.3%. Total SA plasma levels were measured using a commercial enzymatic-colorimetric method (Sialic acid Farbtest, Boehringer Mannheim, Germany). The coefficient of variation was 3.6%. As an endothelial dysfunction marker, vWF antigen levels were measured in an ACL-TOP (3G) (Instrumentation Laboratory) using latex particles coated with a polyclonal antibody directed against vWF. The coefficient of variation was 7.5%. As well as the angiogenesis markers, total serum levels of VEGF were determined by ELISA according to the manufacturer's instructions (VEGF Biosource International). The coefficient of variation was 4.9%. IL-6 serum levels were determined by ELISA method (High Sensitivity Human IL-6 ELISA kit, Diaclone). The coefficient of variation was 3.6%. NT-proBNP was measured by electrochemiluminescence immunoassays in an Elecsys[®] 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

The continuous variables were expressed as mean \pm standard deviation. Student's t-test was used to analyze the quantitative variables, while the χ^2 test was performed to analyze the qualitative variables. Pearson's correlation was performed for correlations. The normality of IM was verified by the Kolmogorov-Smirnov test and the Mann-Whitney U-test. The statistical package used was SPSS[®], v. 15.0 (SPSS Inc. Chicago, Ill, USA).

Results

Baseline characteristics

Patients' baseline characteristics and treatments are shown in Tables 1 and 2, respectively. SHF patients were significantly older (72 \pm 10 vs 63 \pm 12 years, $P<0.001$). The HF-PSF group included more non-smokers (73.9 vs 38.7%, $P<0.001$), and patients presented a higher rate of atrial fibrillation (56.1 vs 21.3%, $P<0.001$). Among the etiologies, valvular (46.4 vs 11.5%, $P<0.001$) and hypertensive etiologies (20.3 vs 8.2%, $P<0.001$) were more frequent in

HF-PSF patients, while ischemic (39.2 vs 20.3%, $P<0.001$) and idiopathic dilated cardiomyopathy etiologies (26.2 vs 1.4%, $P<0.001$) were more frequent in SHF patients. EF was lower in the SHF group (28 \pm 9 vs 57 \pm 4%, $P<0.001$) and the end diastolic diameter was higher (63 \pm 9 vs 49 \pm 7 mm, $P<0.001$). Differences in patients' basal treatment were related to their basic pathologies; nonetheless, acetylsalicylic acid was the most frequent treatment in the SHF group (46.6 vs 28.4; $P<0.05$), and anticoagulants (24.1 vs 44.8%; $P<0.05$) and calcium antagonists (15.5 vs 34.3%; $P<0.05$) were the most frequent treatment in the HF-PSF group.

Of the general analytical data (Table 1), only hemoglobin was significantly lower in the HF-PSF patient group (12.2 \pm 2 vs 13.3 \pm 2.1 g/dL, $P<0.01$). No differences were found in the remaining ordinary analytical values, including the Quick Index or creatinine.

Inflammatory markers

No significant inter-group differences were found in the IM analyzed (Table 3); only a high VEGF tendency was found among the SHF patients (424 \pm 323 vs 337 \pm 263 pg/mL, $P<0.1$). We performed an analysis between the

Table 1. Basal characteristics.

Total HF (n=131)	SHF (n=62)	HF-PSF (n=69)	
Sex male (%)*	59	77	42
Age (years)*	68 \pm 11	63 \pm 12	72 \pm 10
AHT (%)	72.5	72.6	72.5
Dyslipidemia (%)*	48.9	58.1	40.6
Diabetes (%)	37.4	40.3	34.8
Smoking (%)*			
Yes	6.8	9.7	4.3
No	56.8	38.7	73.9
Ex	36.4	51.6	21.7
Permanent AF (%)**	40	21.3	56.5
Etiology (%)*			
Ischemic	29.2	39.3	-20.3
IDCM	13.1	26.2	-1.4
Valvular	30.0	11.5	-46.4
AHT	14.6	8.2	-20.3
Other	13.1	14.9	-1.6
EF (%)**	43 \pm 16	28 \pm 9	57 \pm 4
EDD (mm)**	56 \pm 10	63 \pm 9	49 \pm 7
PsAP (mmHg)	44 \pm 18	44 \pm 16	45 \pm 19
Glucose (mg/dL)	114 \pm 41	112 \pm 47	115 \pm 36
Creatinine (mg/dL)	1.34 \pm 0.51	1.38 \pm 0.55	1.31 \pm 0.48
Total cholesterol (mg/dL)	169 \pm 44	168 \pm 43	170 \pm 45
Total proteins (mg/dL)	6.7 \pm 0.8	6.7 \pm 0.9	6.7 \pm 0.6
Sodium (mEq/L)	138 \pm 4	138 \pm 4	138 \pm 3
Hemoglobin (g/dL)*	12.7 \pm 2.1	13.3 \pm 2.1	12.2 \pm 2.0
Quick index (%)	67 \pm 28	68 \pm 25	67 \pm 30

HF, heart failure; SHF, systolic heart failure; HF-PSF, heart failure with preserved systolic function; AHT, arterial hypertension; FA, atrial fibrillation; IDCM, idiopathic dilated cardiomyopathy; EF, ejection fraction; sPAP, systolic pulmonary artery pressure; EDD, end-diastolic diameter; RV, right ventricle; differences SHF vs. HF-PSF. * $P<0.05$. ** $P<0.001$.

patients in functional class III (20 patients) or IV/IV (111 patients) but no significant differences were found.

Correlations

SA related inversely and significantly with the end-diastolic diameter in the HF-PSF group ($r = -0.375$, $P < 0.05$) (Table 4). The same occurred in the SH group with hemoglobin ($r = -0.330$, $P < 0.05$). We found a positive relationship between NTproBNP and creatinine in both groups, particularly in the SHF group ($r = 0.471$, $P < 0.05$). Similarly, creatinine associated inversely with hemoglobin in both the SHF ($r = -0.384$, $P < 0.05$) and the HF-PSF ($r = 0.278$, $P < 0.05$) groups.

Discussion

Our results show that there are no significant differences in the elevation of certain IM regarding the type of HF in the acute phase of HF. HF can be classified into two groups according to the EF: SHF and HF-PSF. Both groups share many characteristics, but there are others that clearly differentiate them. Most of the studies in the field of HF were performed in patients with SHF. Consequently, while the prognosis of SHF has improved in the last decade, HF-PSF prognosis has seen no such improvement.

Inflammation plays a key role in the pathophysiology of HF and many studies have been conducted in this area; however, these studies were mainly on patients in stable phase. These studies have proven that the elevation of IM is related to severity.

The pathophysiology of inflammation within HF is complex, as many elements contribute to

it through the secretion of IM. Thus, in some studies, rather than focusing on identifying isolated IM as prognostic factors, a combination of IM has been investigated.¹¹ Therefore, a wide and varied range of IM have been determined in the present study with the aim of covering as many aspects involved in inflammation as possible.

The first conclusion of this study can be drawn from patients' basal characteristics. As shown in Tables 1 and 2, differences were concordant with other studies¹² and were also logical from a pathophysiological point of view.

Regarding prognosis, that of SHF is worse than that for HF-PSF in the stable phase, but prognosis is the same for the two types when HF-PSF patients are hospitalized.¹³ Therefore, prognosis does not only depend on the EF. On the other hand, and as already proven by our group,¹⁴ inflammation is more related to functional status than to EF.

As shown in Table 3, IM elevation was significant in both groups, and 3-4 times higher than the values from other studies performed in patients with stable HF.¹⁵

Fibrinogen is a marker which allows exploration of both the general inflammatory status and the hypercoagulable state. Multiple studies have associated this to ischemic heart disease, although it also increases in other heart pathologies^{16,17} and in stable phase regardless of the anticoagulant therapy.¹⁸ There were no differences in the PF, which proves that in this phase the hypercoagulable state is similar in both groups.

SA is particularly high in patients with ischemic heart disease.¹⁹ Our group proved that SA is also increased in patients with stable HF of other etiologies,¹⁴ as it also occurs in

this study in the acute phase of HF.

The most sensitive and less specific IM is the CRP. Some groups consider it to be the IM paradigm.²⁰ Its chronic and sustained elevation (>3 mg/dL) has been proven to have negative prognostic values in multiple diseases, including HF. CRP is strongly associated with atherosclerosis and, therefore, to the ischemic etiology.²¹ Some studies have shown that there are no differences in the increase in CRP between SHF and HF-PSF in stable phases.²² We have found no differences in the acute phase either. This proves, on the one hand, the non-specificity of CRP, and on the other that an increase in CRP seems to be more related to the function status than to the etiology or the type of HF.

HF is associated with a marked endothelial dysfunction and coagulation alterations.²³ vWF is a marker of endothelial dysfunction and coagulation status. Some studies have demonstrated a marked elevation of vWF in HF patients,²⁴ but to date no comparison has been made between patients with SHF and HF-PSF. Nevertheless, we have proved that vWF levels are remarkably high in our sample and, in addition, that there is no relationship between the EF and the type of HF. Both groups presented a similar Quick index, implying that coagulation therapy does not seem to have influenced these results. IL-6 is a cytokine that has been related to the severity of HF and has prognostic value.^{25,26} IL-6 levels increase with the functional status of HF patients; therefore, the levels presented herein were considerably higher than those published by other authors involving patients with stable HF, and were very similar to the subgroups with worse prognosis.²⁷ The association between IL-6 and the

Table 2. Treatment upon hospital admission in both groups.

	SHF (n=62)	HF-PSF (n=69)
IECA/ARA-II	53.4	41.8
Beta-blockers	29.3	22.4
Antialdosteronics	29.3	22.4
ASA*	46.6	28.4
Anticoagulants*	24.1	44.8
Nitrates	27.6	17.9
Calcium antagonists*	15.5	34.3
Digoxin*	15.5	35.8
Furosemide	56.9	53.7
Insulin	10.3	16.4
Statins [‡]	36.2	20.9
Allopurinol	8.6	3

SHF, systolic heart failure; HF-PSF, heart failure with preserved systolic function. All the values are expressed as percentages. [‡] $P < 0.1$. * $P < 0.05$.

Table 3. Comparison of inflammatory markers between both groups.

	Total HF (n=131)	SHF (n=62)	HF-PSF (n=69)
PF (mg/dL)	349±79	348±86	352±71
CRP (mg/L)	37.2±47.5	36.0±46.4	38.8±48.9
SA (mg/dL)	71.8±16.8	71.6±18.2	72.3±15.7
vWF (%)	331±127	318±128	347±124
VEFG (pg/mL)*	378±295	424±323	337±263
IL-6 (pg/mL)	15.5±20.4	16.6±24.8	14.9±15.9
NTproBNP (pg/mL)	6929±7014	8121±8526	5453±4262

HF, heart failure; SHF, systolic heart failure; HF-PSF, heart failure with preserved systolic function; PF, plasma fibrinogen; SA, sialic acid; CRP, C-reactive protein; vWF, von Willebrand factor; VEGF, vascular endothelial growth factor. No significant differences were observed in any of the comparisons. Differences SHF vs HF-PSF, * $P < 0.1$.

Table 4. Correlations upon hospital admission.

	Total HF (n=131)	SHF (n=62)	HF-PSF (n=69)
SA-EDD	-0.219*	0.220#	-0.375*
SA-HB	-0.210*	-0.330*	-0.078 [‡]
NTproBNP-creatinine	0.408*	0.471*	0.441 [‡]
Creatinine-HB	-0.311**	-0.384*	-0.278*

HF, heart failure; SHF, systolic heart failure; HF-PSF, heart failure with preserved systolic function; SA, sialic acid; EDD, end diastolic diameter; HB, hemoglobin; sPAP, systolic pulmonary artery pressure. Differences SHF vs HF-PSF, [‡] $P < 0.1$. * $P < 0.05$. ** $P < 0.001$.

EF has not been clearly determined, as there are many studies providing contradictory data.^{28,29} In our case, no relationship was observed in IL-6 whether the EF was higher or lower than 45%.

In HF, oxygen supply to tissue is reduced. This stimulates new vessel formation at the tissue level. VEGF is an angiogenesis marker believed to be involved in the pathophysiology of HF; it also has prognostic value. VEGF levels are increased in stable HF patients in comparison with controls.¹⁵ From all the markers analyzed, this is the only one in which a significant tendency was found. Thus, patients with SHF have slightly greater values, which may indicate that these patients present more tissue hypoxia and more angiogenic proliferation. BNP and its precursor NTproBNP are the most commonly used markers in HF. We analyzed NTproBNP as its determination was easier to obtain than the brain natriuretic peptide. Both markers have a significant diagnostic and prognostic value.^{30,31} In stable HF patients, those with depressed EF present higher values of these peptides than patients with preserved EF.⁸ Iwanaga *et al.*³² found that in patients with symptomatic HF, BNP was higher in those with an EF below 50%. However, the functional status of 68% of these patients was below II. In our study, all the patients presented a clear deterioration of the functional status (functional class \geq III), and in that context, no differences were observed in the BNP and NTproBNP values regarding the type of HF.

In patients with stable HF, multiple correlations between the different IM and echocardiographic and clinical parameters were established. SA negatively correlated with the end-diastolic diameter in patients with HF-PSF, and with hemoglobin in patients with SHF. As no explanation has been found for this, it is thought to be a casual correlation. It is logical indeed that NTproBNP was found to be higher as creatinine increased and as hemoglobin decreased. Renal elimination of NTproBNP causes patients with renal failure to present an increase in its values. In addition, it has been proven that anemia acts as an aggravating factor; therefore, it is normal that NTproBNP concentrations in patients with anemia are higher. This study has several limitations. Recruiting patients only admitted to the Cardiology Unit could have biased the sample. Our hospital has other units with HF patients, but these are only those less symptomatic. Perhaps in our sample there is a profile of patients with advanced HF. Moreover, a control group has not been established, but we believe that there are many studies in the literature in which the normal range of the analyzed IM has been established. Therefore, these limitations do not invalidate the study results.

Conclusions

The main conclusion of this work is that, in the acute phase of HF, no differences are observed in the analyzed IM regarding the type of HF (SHF *vs* HF-PSF). Further long-term studies are needed in order to determine when differences in patients with stable HF appear, and what prognostic value these differences may have.

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