JACC Vol. 28, No. 4
October 1996:964–71

Circulating Levels of Cytokines and Their Endogenous Modulators in Patients With Mild to Severe Congestive Heart Failure Due to Coronary Artery Disease or Hypertension

MARCO TESTA, MD, MICHAEL YEH, MD, PAUL LEE, MD, RAFFAELE FANELLI, MD,*
FRANCESCO LOPERFIDO, MD,* JOAN W. BERMAN, PHD, THIERRY H. LEJEMTEL, MD
Bronx, New York and San Giovanni Rotondo, Italy

Objectives. **This study sought to determine the circulating levels of cytokines and their respective endogenous modulators in patients with congestive heart failure of variable severity.**

Background. **Activation of immune elements localized in the heart or periphery, or both, may promote release of cytokines in patients with congestive heart failure. Although an increased circulating level of tumor necrosis factor-alpha (TNF-alpha) and its soluble receptor type II (sTNF-RII) is well documented, less is known about other cytokines (i.e., interleukin-1-beta [IL-1-beta], interleukin-6 [IL-6] and interleukin-2 [IL-2] and their soluble receptor/receptor antagonists).**

Methods. **Circulating levels of TNF-alpha and sTNF-RII, IL-1-beta, IL-1 receptor antagonist (IL-1-Ra), IL-6, IL-6 soluble receptor (IL-6-sR), IL-2 and IL-2 soluble receptor-alpha were measured using enzyme-linked immunosorbent assay kits (Quantikine, R&D Systems) in 80 patients with congestive heart failure due to coronary artery disease or hypertension. The severity of their symptoms, which ranged from New York Heart Association functional class I to IV, was confirmed by measurement of peak oxygen consumption.**

Results. **The percentage of patients with elevated levels of cytokines and their corresponding soluble receptor/receptor antagonists significantly increased with functional class. For TNF-alpha and IL-1-beta, the percentage of patients with elevated levels of soluble receptor/receptor antagonists was higher than that of patients with elevated levels of the cytokine itself. For IL-6, the percentage of patients with elevated levels of IL-6-sR tended to be lower than that of patients with elevated levels of IL-6. All but two patients had undetectable levels of IL-2, and all but seven had levels of IL-2-sR within a normal range.**

Conclusions. **In patients with congestive heart failure, circulating levels of cytokines increased with the severity of symptoms. In these patients, circulating levels of sTNF-RII and IL-1-Ra are more sensitive markers of immune activation than are circulating levels of TNF-alpha and IL-1-beta, respectively. Levels of IL-2 and IL-2-sR are not elevated when congestive heart failure is due to coronary artery disease or hypertension.**

(J Am Coll Cardiol 1996;28:964–71)

The circulating levels of tumor necrosis factor-alpha (TNF-alpha) and other cytokines, such as interleukin-1-beta (IL-1-beta), interleukin 6 (IL-6) and interleukin 2 (IL-2), have been reported to be increased in patients with congestive heart failure (1–9). However, cytokine levels do not appear to be increased throughout the syndrome of congestive heart failure; only the most symptomatic patients consistently have elevated levels of cytokines (1,3,9). Of interest with regard to TNF-alpha, Ferrari et al. (10) recently reported that activation of the TNF system is best assessed by measuring circulating levels of the shedded extracellular domain of its type II receptor, sTNF-RII, rather than the TNF-alpha levels. Much less is known about the levels of the respective endogenous soluble modulators of other cytokines in patients with congestive heart failure. Accordingly, the present study was undertaken to characterize the pattern of cytokine activation in patients with congestive heart failure. Circulating levels of TNF-alpha, IL-1-beta, IL-6 and IL-2 and their respective endogenous modulators, sTNF-RII, IL-1 receptor antagonist (IL-1-Ra), IL-6 soluble receptor (IL-6-sR) and IL-2 soluble receptor-alpha (IL-2-sR-alpha) were measured in ambulatory patients whose symptoms ranged from New York Heart Association functional class I to IV. The etiology of congestive heart failure was limited to coronary artery disease and systemic hypertension. We previously reported circulating levels of cytokines in patients with idiopathic dilated cardiomyopathy (7).

Methods

Study group. Eighty ambulatory patients (58 men, 22 women) with congestive heart failure due to ischemic or hypertensive cardiomyopathy were studied. All patients had stable symptoms for at least 3 months. The demographic,

From the Departments of Medicine and Pathology, Albert Einstein College of Medicine, Bronx, New York; and *Ospedale "Casa Sollievo della Sofferenza"—IRCCS, San Giovanni Rotondo, Italy.

Manuscript received January 29, 1996; revised manuscript received May 21, 1996, accepted June 3, 1996.

Address for correspondence: Dr. Thierry H. LeJemtel, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461.

0735-1097/96/$15.00
PII SI0735-1097(96)00268-9

Abbreviations and Acronyms

ELISA	= enzyme-linked immunosorbent assay
IL-1-beta	= interleukin-1-beta
IL-1-Ra	= interleukin-1 receptor antagonist
IL-2	= interleukin-2
IL-2-sR-alpha	= interleukin-2 soluble receptor-alpha
IL-6	= interleukin-6
IL-6-sR	= interleukin-6 soluble receptor
sTNF-RII	= soluble tumor necrosis factor receptor type II
TNF-alpha	= tumor necrosis factor-alpha

clinical and laboratory characteristics of the patients, as well as their medical regimens, are detailed in Table 1. The presence or absence of coronary artery disease was assessed by coronary angiography, which had been performed within 18 months of the study for diagnostic purposes. The severity of congestive heart failure ranged from functional class I to IV. Patients with significant concomitant diseases such as infections, renal failure, cancer and autoimmune disease were excluded. The presence of cardiac cachexia was also a criterion of exclusion. Cardiac cachexia was defined by a body weight at least 15% below the predicted ideal weight and minimal reduction of 30% in triceps skinfold thickness and midarm muscle circumference (11). No patients had received anti-inflammatory drugs within the preceding 2 weeks, with the exception of low dose aspirin.

The study was approved by the Ethical Review Board of the Albert Einstein College of Medicine and Montefiore Medical Center. All patients gave written informed consent.

Peak oxygen consumption. After cytokine measurements, patients and age-matched normal subjects performed two symptom-limited exercise treadmill tests using the modified Naughton protocol with an interval of 3 to 7 days. Exercise was limited by symptoms of fatigue or dyspnea, or both, in all patients. None of them experienced angina pectoris during the treadmill exercise tests. Oxygen uptake and carbon dioxide production were measured continuously during exercise by means of a breath-by-breath analysis of expired gases (CPX Metabolic Cart, Medical Graphics), which was calibrated within 1 h of testing. Peak oxygen consumption ($\dot{V}O_2$ [ml/kg body weight per min]) was determined from the maximal oxygen uptake attained during the final 30 s of exercise, when the respiratory exchange ratio was >1.0. When the two determinations of peak $\dot{V}O_2$ were within 10%, the highest value was reported. When the two determinations differed by >10%, a symptom-limited exercise test was repeated until this criterion was met and the highest value was reported.

Cytokine measurements. Sixteen milliliters of blood was withdrawn from an antecubital vein into ethylenediaminetetraacetic acid or heparinized tubes and kept on ice, and plasma was separated by centrifugation within 30 min. Aliquots were stored at −70°C.

Concentrations of cytokines and their respective soluble receptor/receptor antagonists were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Quantikine, R&D Systems) according to the manufacturer's specifications. A high sensitivity kit (Quantikine HS, R&D Systems) was used to measure TNF-alpha immunoactivity. A 1:40 dilution of plasma was used to measure soluble sTNF-RII and IL-6-sR; a 1:4 dilution was used to measure IL-2-sR-alpha. All

Table 1. Clinical, Laboratory and Therapeutic Variables in 80 Patients With Congestive Heart Failure

	NYHA Functional Class				Total No.	
	I	II	III	IV	of Pts	p Value
No. of pts	16	20	20	24	80	
Male (%)	75	85	65	67	80	0.475
Age (yr)*	60.2 ± 8.0	64.5 ± 11.3	64.0 ± 11.7	64.2 ± 6.5	72	0.490
Etiology (%)						
Ischemic	56	55	65	71	80	0.693
Hypertensive	44	45	35	29		
Measurements						
LVEF (%)*	29 ± 8	29 ± 10	30 ± 9	24 ± 7	70	0.201
Peak $\dot{V}O_2$ (ml/kg body weight per min)*	17.8 ± 2.2	15.3 ± 1.6	11.4 ± 2.9	8.8 ± 2.3	30	< 0.001
BUN (mg/dl)*	18.3 ± 5.7	19.1 ± 7.0	27.6 ± 28.8	48.9 ± 22.3	71	< 0.001
Median	16.0	17.5	17.0	41.0		
Creatinine (mg/dl)*	1.2 ± 0.2	1.2 ± 0.3	1.3 ± 0.8	1.9 ± 0.5	71	< 0.001
Median	1.1	1.3	1.1	1.8		
Therapy (%)						
ACE inhibitors	94	95	90	92	80	1.00
Cardiac glycosides	69	70	75	79	80	0.850
Loop diuretics	81	80	90	96	80	0.343
Long-acting nitrates	31	40	80	67	80	0.008
Beta-blockers	63	40	30	33	80	0.221

*Unless otherwise indicated, data are expressed as mean value ± SD. ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; LVEF = left ventricular ejection fraction (obtained by radionuclide ventriculography); NYHA = New York Heart Association; $\dot{V}O_2$ = oxygen consumption.

JACC Vol. 28, No. 4
October 1996:964–71

Table 2. Linear Range of the Assays and 95th Percentile Levels for Each Cytokine, Soluble Receptor or Receptor Antagonist for Control Subjects

	Range (pg/ml)	95th Percentile for Normal Subjects
TNF-alpha	0.5–32	3.8
sTNF-RII	7.8–500	2.8
IL-1-beta	3.9–250	8
IL-1-Ra	46.9–3,000	400
IL-6	3.13–300	10
IL-6-sR	31.2–2,000	51
IL-2	31.2–2,000	<31.2
IL-2-sR-alpha	78.1–5,000	3.2

IL-1-beta = interleukin-1-beta; IL-1-Ra = interleukin-1 receptor antagonist; IL-2 = interleukin-2; IL-2-sR-alpha = interleukin-2 soluble receptor-alpha; IL-6 = interleukin-6; IL-6-sR = interleukin-6 soluble receptor; sTNF-RII = soluble tumor necrosis factor receptor type II; TNF-alpha = tumor necrosis factor-alpha.

other measurements were carried out using undiluted plasma. All samples were run-in duplicates; the average value of the two measurements is reported. The linear range of each assay and the value used to define an elevated plasma concentration for each cytokine and its corresponding soluble receptor/receptor antagonist are shown in Table 2. Cytokines or soluble receptor/receptor antagonists were considered elevated when their levels were above the 95th percentile for control values (R&D Systems). Circulating levels of cytokines and their respective soluble modulators were measured in 20 age-matched normal subjects (13 men, 7 women) whose mean age and peak $\dot{V}O_2$ were 58.2 ± 7.3 years and 30.1 ± 7.2 ml/kg per min, respectively. All age-matched normal subjects had circulating levels of cytokines and their respective soluble receptors/receptor antagonists below the 95th percentile of control values.

Statistical analysis. Mean age, left ventricular ejection fraction and peak $\dot{V}O_2$ by functional class were compared using one-way analysis of variance. Blood urea nitrogen and creatinine by functional class were compared using the Kruskar-Wallis test. The etiology (ischemic vs. hypertensive) and pharmacologic therapy by functional class were compared using the Fisher exact test. The rates of abnormal cytokine and cytokine endogenous modulator plasma levels by functional class were analyzed using the Mantel-Haenszel test for linear trend.

Summary statistics are presented as the mean value ± 1 SD and percentages. A p value <0.05 was considered significant.

Results

Cytokines and their endogenous modulators in relation to functional class. Individual data for circulating levels of cytokines and their respective endogenous modulators are shown in Figures 1A, 2A, 3A and 4. The percentages of patients with elevated circulating levels of cytokines and their respective endogenous modulators are shown in Figures 1B, 2B and 3B. Circulating levels of TNF-alpha were within normal range in most patients in functional classes I and II, although they were elevated in 25% and 42% of patients in functional classes III and IV, respectively (Fig. 1A, B). Similarly, circulating levels of sTNF-RII were within normal range in most patients in functional classes I and II, although they were elevated in 55% and 92% of patients in functional classes III and IV, respectively (Fig. 1A, B). The percentage of patients with abnormal TNF-alpha and sTNF-RII increased with functional class ($p < 0.007$ and $p < 0.001$, respectively) (Fig. 1B).

Circulating levels of IL-1-beta were in the normal range in all but one patient in functional classes I and II, although they were elevated in 25% and 37% of patients in functional classes III and IV, respectively (Fig. 2A, B). The percentages of patients with elevated IL-1-Ra levels were 19% and 25% in functional classes I and II, respectively, and 45% and 65% in functional classes III and IV, respectively (Fig. 2A, B). As detected with TNF-alpha and sTNF-RII, the percentage of patients with abnormal IL-1-beta and IL-1-Ra increased with functional class ($p < 0.001$ and $p < 0.002$, respectively) (Fig. 2B).

Circulating levels of IL-6 were normal in the majority of patients in functional classes I, II and III and were elevated in 58% of patients in functional class IV (Fig. 3A, B). Circulating levels of IL-6-sR were normal in all patients in functional class I. They were elevated in 15% of patients in functional class II, in 25% of patients in functional class III and in 34% of patients in functional class IV (Fig. 3A, B). Overall, the percentage of patients with elevated levels of IL-6 and IL-6 sR increased with functional class ($p < 0.001$ and $p < 0.008$, respectively) (Fig. 3B).

Circulating levels of IL-2 were below the detectable levels in all but two patients with congestive heart failure. One patient was in functional class II and the other was in functional class III. Circulating levels of IL-2-sR-alpha were normal in all but seven patients with congestive heart failure. Two patients were in functional class I, one was in functional class II, two were in functional class III and the remaining two were in functional class IV (Fig. 4).

Renal function was reduced in patients in functional class IV when compared with patients in functional classes I, II and III (Table 1). Nevertheless, the percentage of patients with abnormal levels of sTNF-RII, IL-1-beta, IL-1-Ra, IL-6 and IL-6-sR was similar in patients with creatinine below and above 2 mg/dl. The percentage of patients with abnormal levels of TNF-alpha was significantly greater in patients with creatinine >2 mg/dl when compared with that of patients with creatinine <2 mg/dl (78% vs. 20%, $p < 0.02$).

Comparison of cytokines and their soluble receptor/receptor antagonists. The percentage of patients in functional class IV with elevated levels of sTNF-RII was significantly greater than that of patients with elevated TNF-alpha (92% vs. 42%) ($p < 0.001$) (Fig. 1B). This difference tended to be greater also for patients in functional class III (55% vs. 25%) ($p = 0.107$) (Fig. 1B). Similarly, the percentage of patients in functional class IV with elevated levels of IL-1-Ra tended to be

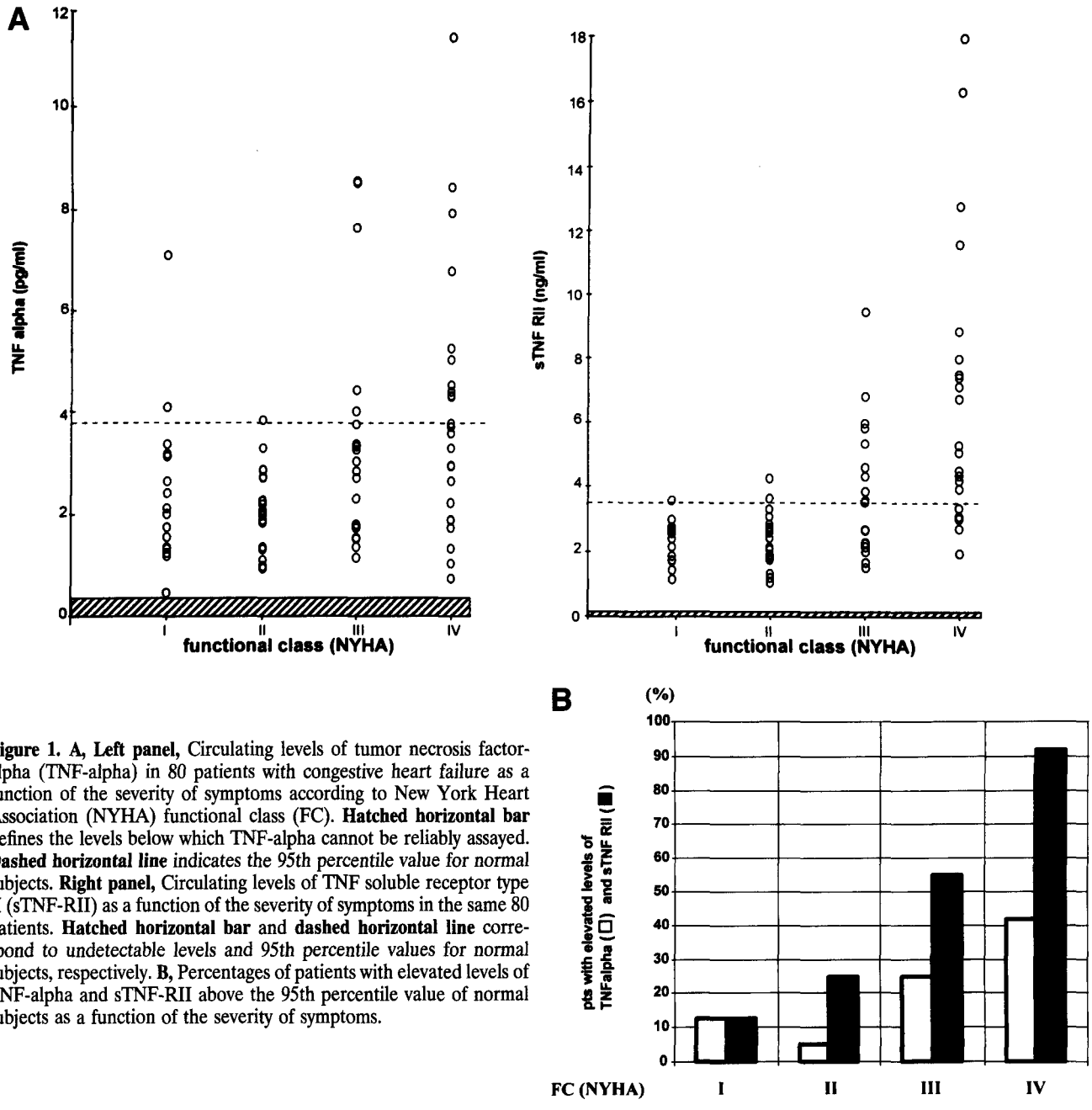


Figure 1. A, Left panel, Circulating levels of tumor necrosis factor-alpha (TNF-alpha) in 80 patients with congestive heart failure as a function of the severity of symptoms according to New York Heart Association (NYHA) functional class (FC). **Hatched horizontal bar** defines the levels below which TNF-alpha cannot be reliably assayed. **Dashed horizontal line** indicates the 95th percentile value for normal subjects. **Right panel,** Circulating levels of TNF soluble receptor type II (sTNF-RII) as a function of the severity of symptoms in the same 80 patients. **Hatched horizontal bar** and **dashed horizontal line** correspond to undetectable levels and 95th percentile values for normal subjects, respectively. **B,** Percentages of patients with elevated levels of TNF-alpha and sTNF-RII above the 95th percentile value of normal subjects as a function of the severity of symptoms.

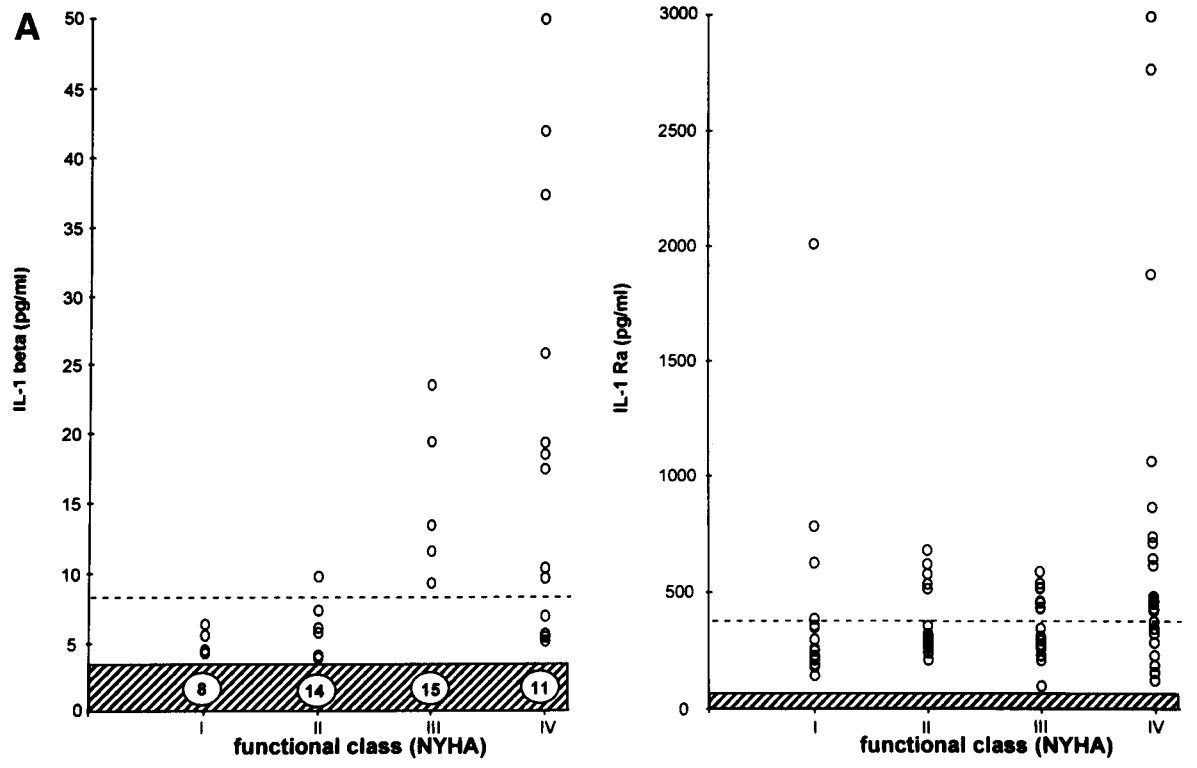
greater than that of patients with elevated levels of IL-1-beta (63% vs. 37%) ($p = 0.130$) (Fig. 2B).

In contrast, the percentage of patients in functional class IV with elevated levels of IL-6 tended to be greater than that of patients with elevated levels of IL-6-sR (58% vs. 33%) ($p = 0.147$) (Fig. 3B).

Coronary artery disease versus hypertension. The number of patients with hypertension was relatively small ($n = 30$); therefore, the comparison between patients with coronary artery disease and hypertension was performed for all cohorts rather than for each functional class. Overall, the percentage of patients with elevated levels of TNF-alpha, sTNF-RII, IL-1-beta, IL-Ra, IL-6 and IL-6-sR was not statistically different in patients with congestive heart failure due to coronary artery disease or hypertension (data not shown).

Discussion

Profile of cytokine activation. The present data demonstrate that, as previously noted with TNF-alpha in patients with congestive heart failure, circulating levels of IL-1-beta and IL-6 are only elevated in severely symptomatic patients. The present data also confirm that measurement of sTNF-RII levels, in addition to TNF-alpha levels, is essential for evalua-



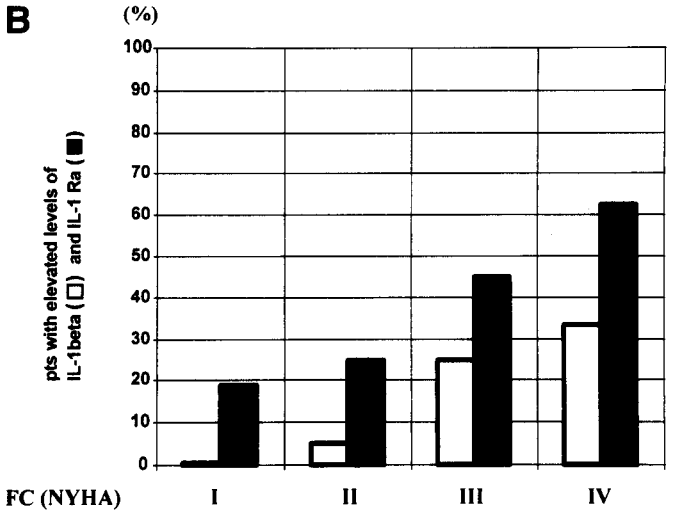


Figure 2. A, Left panel, Circulating levels of interleukin-1-beta (IL-1-beta) in 80 patients with congestive heart failure as a function of severity of symptoms according to New York Heart Association (NYHA) functional class (FC). **Hatched horizontal bar** defines the levels below which IL-1-beta cannot be reliably assayed. **Circled numbers** represent the number of patients with undetectable levels in each functional class. **Dashed horizontal line** indicates the 95th percentile values for normal subjects. **Right panel,** Circulating levels of IL-1 receptor antagonist (IL-1-Ra) as a function of the severity of symptoms in the same 80 patients. The **hatched horizontal bar** and the **dashed line** correspond to undetectable levels and 95th percentile values for normal subjects, respectively. **B,** Percentages of patients with elevated levels of IL-1-beta and IL-1-Ra above the 95th percentile value for normal subjects as a function of the severity of symptoms.

tion of this cytokine system in congestive heart failure. Moreover, our data extend this observation to IL-1, with the IL-1-sR antagonist being more elevated in a substantially greater number of patients than IL-1 itself. In contrast, this observation does not apply to IL-6, because IL-6 is more elevated in a greater number of patients than the IL-6 soluble receptor. Last, our data indicate that circulating levels of both IL-2 and IL-2-sR-alpha are normal when congestive heart failure results from ischemic or hypertensive heart disease. This last finding is at variance with the elevated IL-2 levels that we previously documented in patients with congestive heart failure due to idiopathic dilated cardiomyopathy (7) and may suggest a different mechanism for disease progression. Interleukin-2 is a product of activated T cells, and recent data demonstrate the presence of such cells in the myocardium of patients with dilated cardiomyopathy (12,13). Furthermore, elevated levels of IL-2-sR, an indicator of T-cell activation, have been reported in patients with idiopathic dilated cardiomyopathy (8). Thus, our previous data, as well as data from other laboratories, support a role for activated T cells in idiopathic dilated cardiomyopathy. The absence of these T-cell activation markers in plasma from patients with congestive heart failure due to

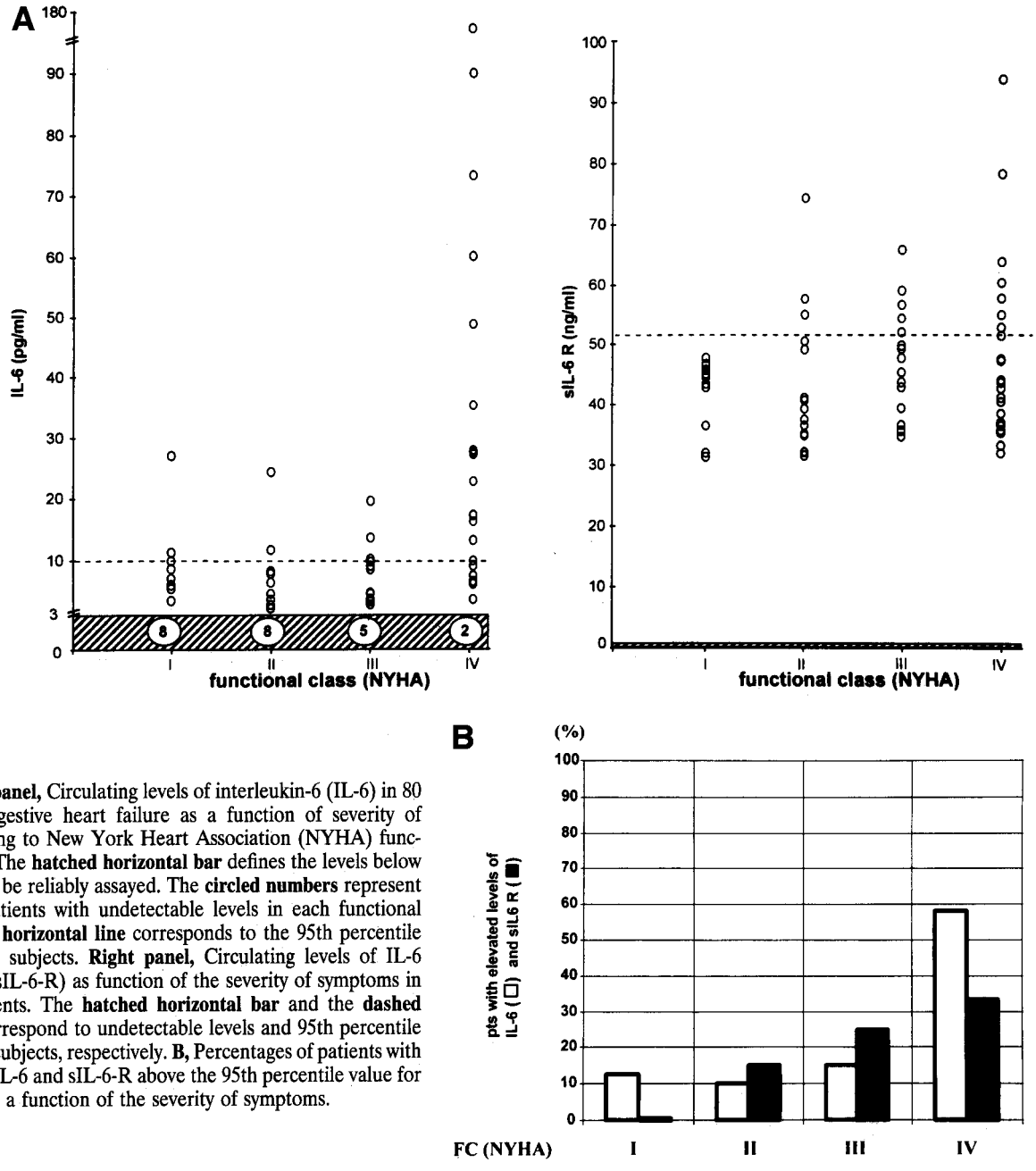


Figure 3. A, Left panel, Circulating levels of interleukin-6 (IL-6) in 80 patients with congestive heart failure as a function of severity of symptoms according to New York Heart Association (NYHA) functional class (FC). The **hatched horizontal bar** defines the levels below which IL-6 cannot be reliably assayed. The **circled numbers** represent the number of patients with undetectable levels in each functional class. The **dashed horizontal line** corresponds to the 95th percentile values for normal subjects. **Right panel,** Circulating levels of IL-6 soluble receptor (sIL-6-R) as function of the severity of symptoms in the same 80 patients. The **hatched horizontal bar** and the **dashed horizontal line** correspond to undetectable levels and 95th percentile values for normal subjects, respectively. **B,** Percentages of patients with elevated levels of IL-6 and sIL-6-R above the 95th percentile value for normal subjects as a function of the severity of symptoms.

ischemic or hypertensive heart disease suggests that activated T cells may not play a significant role when congestive heart failure occurs secondary to coronary artery disease or hypertension.

Site of cytokine production. The stimulus and site of production of TNF and other cytokines are still poorly understood in patients with congestive heart failure (5). Transforming growth factor-alpha and IL-1 are predominantly produced by activated macrophages, but what triggers such activation is still unclear in congestive heart failure. Presumably, the immune system is activated in response to foci of injury, which may develop in the heart or in the periphery, or both. Alternatively, Kapadia et al. (14) and Mann et al. (15) proposed that the heart itself may be an important producer of cytokines and especially of TNF-alpha in patients with congestive heart failure. Although the goal of the present study was not to address the site of activation of TNF-alpha and other cytokines in congestive heart failure, our data suggest that peripheral rather than cardiac foci of injury may activate the immune system and thereby elicit cytokine production. Evidence for this hypothesis is that left ventricular function was identical in patients with symptoms compatible with functional classes I, II and III, whereas circulating levels of cytokines were consistently elevated only in patients in functional class III.

JACC Vol. 28, No. 4
October 1996:964–71

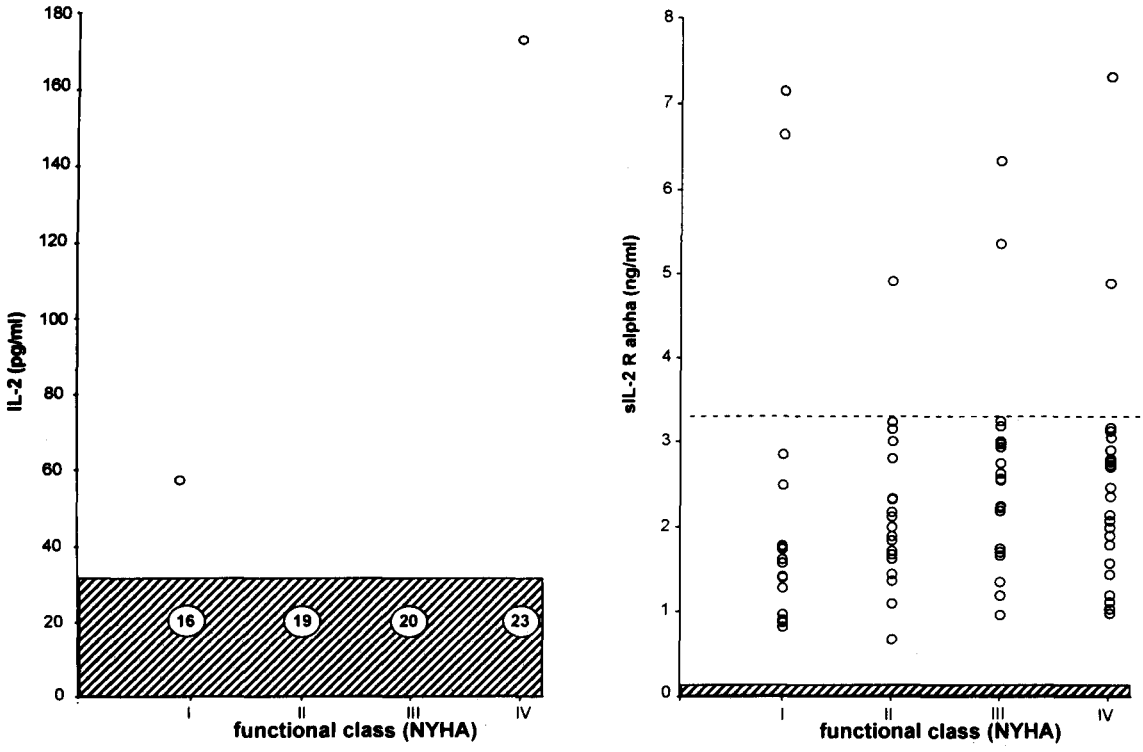


Figure 4. Left panel, Circulating levels of interleukin-2 (IL-2) in 80 patients with congestive heart failure as a function of severity of symptoms according to New York Heart Association (NYHA) functional class. The **hatched horizontal bar** defines the circulating levels below which IL-2 cannot be reliably assayed. The **circled numbers** represent the number of patients with undetectable levels in each functional class. All normal subjects have undetectable levels of IL-2. **Right panel,** Circulating levels of IL-2 soluble receptor-alpha (sIL-2-R-alpha) as function of the severity of symptoms in the same 80 patients. The **hatched horizontal bar** and the **dashed horizontal line** correspond to undetectable levels and 95th percentile values for normal subjects, respectively.

Moreover, a clear disparity was present between the slight further reduction in left ventricular ejection fraction from classes III and class IV (i.e., 29% to 24%) and the marked increase in circulating levels of cytokines in patients in functional class IV. If the elevation of circulating cytokine levels resulted predominantly from an inflammatory response within the heart, one would expect circulating levels of cytokines to be elevated in functional class I patients who have already had a substantial amount of myocardial damage, as documented by the severely depressed left ventricular ejection fraction. Moreover, because the further reduction in left ventricular ejection fraction is only modest when symptoms markedly worsen, one would not expect a steady elevation of cytokines from functional class I to IV. Thus, substantial cytokine production, which occurs at a late stage of the syndrome of congestive heart failure, suggests that peripheral abnormalities that correlate with symptoms may be an important stimulus for cytokine production. Alternatively, left ventricular diastolic dysfunction of increasing severity may be responsible for cytokine production in the late stages of the syndrome of congestive heart failure.

Cytokine activation and etiology of heart failure. Circulating levels of TNF-alpha, IL-1-beta and IL-6 did not appear to depend on the etiology of congestive heart failure in our patients. Severely symptomatic patients had similar circulating levels of cytokines whether congestive heart failure was due to ischemic heart disease or hypertensive heart disease. Increased cytokine production by mononuclear leukocytes has been reported in patients with ischemic heart disease, all of whom had either stable or unstable angina pectoris (16). None of our patients with ischemic heart disease had unstable angina and only two of these patients had occasional episodes of exertional angina. Exercise capacity was limited by symptoms of fatigue or dyspnea, or both, in all our patients with ischemic heart disease. Whether the presence of angina is a prerequisite in patients with ischemic heart disease for increased cytokine secretion by mononuclear leukocytes is presently unknown. Increased cytokine secretion due to ischemic heart disease may also be modest when compared with that induced by the congestive heart failure process, so that severely symptomatic patients have similar levels of cytokines independent of the etiology of their heart failure (i.e., ischemic or hypertensive). Cardiac release of cytokines, which has been documented in patients with acute myocardial infarction after percutaneous transluminal coronary angioplasty, is unlikely to have occurred in our patients with ischemic heart disease, who did not have any clinical or laboratory evidence of acute myocardial damage (17).

Cytokines and their modulators. It is unclear why circulating levels of cytokine receptors or antagonists are more elevated in a greater percentage of patients than the circulating levels of the cytokine itself. Soluble TNF-alpha receptors have been shown to interfere with TNF-alpha when measuring TNF-alpha with certain ELISA kits (17). However, such interference has not been reported with the assay kit that we used (R&D Systems) (18). A difference in metabolic turnover, renal clearance, rate of shedding and sensitivity of assays are likely to at least partially explain the disparity between circulating levels of the cytokine receptor/receptor antagonists (19,20). In our patients, soluble receptors for IL-6 appear to behave differently from sTNF-RII and IL-1-sR antagonists. Of note, a negative correlation between IL-6 and IL-6-sR has been reported in children with juvenile rheumatoid arthritis and in patients with sepsis (21,22). Thus, IL-6 appears to be unique among cytokines, because a negative feedback exists between IL-6 and its soluble receptor. An increased turnover of membrane-anchored IL-6-sR in the presence of high levels of IL-6 may account for the decreased levels of IL-6-sR (22).

Conclusions. This report supports and extends our previous study, as well as the investigations of others, suggesting a role for immune activation in congestive heart failure. It demonstrates a strong correlation between increased cytokine and soluble receptor/receptor antagonist levels and the severity of disease. Interestingly, it also suggests that activated T cells may not be as significant a cell type in ischemic or hypertensive cardiomyopathy as in idiopathic dilated cardiomyopathy. Additional studies assessing the contribution of monocytes/macrophages, as well as cardiac and peripheral vascular elements, are necessary to clarify the site and mechanism(s) for immune activation in this chronic disease process.

References

1. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236–41.
2. McMurray J, Abdullah I, Dargie HJ, Shapiro D. Increased concentrations of tumor necrosis in cachetic patients with severe chronic heart failure. Br Heart J 1991;66:356–8.
3. Dutka DP, Elborn JS, Delamere F, Shale DJ, Morris GK. Tumour necrosis factor α in severe congestive cardiac failure. Br Heart J 1993;70:141–3.
4. Wiedermann CJ, Beimpold H, Herold M, Knapp E, Braunsteiner H. Increased levels of serum neopterin and decreased production of neutrophil superoxide anions in chronic heart failure with elevated levels of tumor necrosis factor-alpha. J Am Coll Cardiol 1993;22:1987–90.
5. Packer M. Is tumor necrosis factor an important neurohormonal mechanism in chronic heart failure? Circulation 1995;92:1379–82.
6. Matsumori A, Yamada T, Suzuki H, Matoba Y, Sasayama S. Increased circulating cytokines in patients with myocarditis and cardiomyopathy. Br Heart J 1994;72:561–6.
7. Katz SD, Rao R, Berman JW, et al. Pathophysiological correlates of increased serum tumor necrosis factor in patients with congestive heart failure: relation to nitric oxide–dependent vasodilation in the forearm circulation. Circulation 1994;90:12–6.
8. Limas CJ, Golderberg IF, Limas C. Soluble interleukin-2 receptor levels in patients with dilated cardiomyopathy: correlation with disease severity and cardiac autoantibodies. Circulation 1995;91:631–4.
9. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 1996;27:1201–6.
10. Ferrari R, Bachetti T, Confortini R, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. Circulation 1995;92:1479–86.
11. Ansari A. Syndromes of cardiac cachexia and the cachectic heart: current perspective. Prog Cardiovasc Dis 1987;30:45–60.
12. Holzinger C, Schollhammer A, Imhof M, et al. Phenotypic patterns of mononuclear cells in dilated cardiomyopathy. Circulation 1995;92:2876–85.
13. Hwang S, Harris TJ, Wilson NW, Maisel AS. Immune function in patients with chronic stable congestive heart failure. Am Heart J 1993;125:1651–8.
14. Kapadia S, Lee J, Torre-Amione G, Birdsall HH, Ma TS, Mann DL. Tumor necrosis factor-α gene and protein expression in adult feline myocardium after endotoxin administration. J Clin Invest 1995;96:1042–52.
15. Mann DL, Lee-Jackson D, Yokoyama T. Tumor necrosis factor alpha and cardiac remodeling. Heart Failure 1995;11:166–76.
16. Vaddi K, Nicolini FA, Mehta P, Mehta JL. Increased secretion of tumor necrosis factor α and interferon γ by mononuclear leukocytes in patients with ischemic heart disease: relevance in superoxide anion generation. Circulation 1994;90:694–9.
17. Neumann FJ, Ott I, Gawaz M, et al. Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. Circulation 1995;92:748–55.
18. Kapadia S, Torre-Amione G, Mann DL. Pitfalls in measuring cytokines [letter]. Ann Intern Med 1994;121:149–500.
19. Porteu F, Hieblot C. Tumor necrosis factor induces a selective shedding of its p75 receptor from human neutrophils. J Bio Chem 1994;269:2834–40.
20. Honda M, Yamamoto S, Cheng M, et al. Human soluble IL-6 receptor: its detection and enhanced release by HIV infection. J Immunol 1992;148:2175–80.
21. DeBenedetti F, Massa M, Pignatti P, Albani S, Novick D, Martini A. Serum soluble interleukin 6 (IL-6) receptor and IL-6/soluble IL-6 receptor complex in systemic juvenile rheumatoid arthritis. J Clin Invest 1994;93:2114–9.
22. Fireling JTM, van Deuren M, Wijdenes J. Circulating interleukin-6 receptor in patients with sepsis syndrome. J Infect Dis 1995;171:469–72.