Serum Levels of Carbohydrate Antigen 125 in Patients With Chronic Heart Failure

Relation to Clinical Severity, Hemodynamic and Doppler Echocardiographic Abnormalities, and Short-Term Prognosis

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OBJECTIVES	The aim of this study was to evaluate the serum levels of carbohydrate antigen 125 (CA125) in patients with congestive heart failure (CHF).
BACKGROUND	CA125 is a glycoprotein produced by serosal epithelium, found to be increased in ovarian cancer.
METHODS	Serum levels of CA125 were obtained in 286 patients (122 males and 164 females; age 69 ± 13 years) with CHF (left ventricular ejection fraction 30 ± 11%). A non-invasive evaluation was obtained by Doppler echocardiography; right heart catheterization was performed in 88 patients. An attempt to adjust medical therapy to maximally tolerated doses was done, and CA125 was repeated after 18 days (range 7 to 40) in 80 patients. The mean follow-up duration was 6 ± 3 months in 240 patients.
RESULTS	The mean value of CA125 was 68 ± 83 U/ml (range 3 to 537): 71 ± 85 in men and 56 ± 64 U/ml in women (p = NS). CA125 above the normal value (<35 U/ml) was found in 152 (53%) of 286 patients; it was higher in patients with advanced New York Heart Association (NYHA) functional class (n = 140 in class I/II: 15 ± 9 U/ml; n = 63 in class III: 57 ± 18 U/ml; n = 83 in class IV: 167 ± 94 U/ml; p < 0.005). CA125 was related to the deceleration time of early filling on transmitral Doppler (r = −0.63, p < 0.05) and to pulmonary artery wedge pressure (r = 0.66, p < 0.05) and right atrial pressure (r = 0.69, p < 0.05). During 6 ± 3 months of follow-up, a combined end point of mortality and CHF hospitalization was observed in 16 of 127 patients with CA125 <35 U/ml, compared with 70 of 113 patients with CA125 >35 U/ml (p < 0.01). After medical treatment optimization, NYHA class decreased by more than one grade in 56 of 80 patients and was unchanged or increased in 24 patients: CA125 decreased from 125 ± 98 to 53 ± 61 U/ml (p < 0.001) in the former and changed from 130 ± 81 to 153 ± 61 U/ml (p = NS) in the latter.
CONCLUSIONS	Our data suggest that CA125 is related to CHF severity and short-term prognosis. Furthermore, fluctuations of CA125 serum levels over time may reflect changes induced by therapy. Therefore, measurements of CA 125 serum levels might be proposed for the serial assessment of CHF patients. (J Am Coll Cardiol 2003;41:1805–11) © 2003 by the American College of Cardiology Foundation

The search for new prognostic markers in congestive heart failure (CHF) has intensified recently, along with interest in the use of surrogate end points, risk stratification, and clinical decision-making in these patients (1). Accordingly, several parameters have a demonstrated prognostic value in CHF patients over time: indexes of left and right ventricular function, exercise tolerance, autonomic nervous system markers, and biologic markers. Among the biologic markers, not only the neurohormones, such as plasma norepinephrine and atrial natriuretic peptides (particularly brain natriuretic peptide [BNP]), but also markers of inflammation and cytokines, such as tumor necrosis factor and interleukin-6, have shown a relationship with outcome in CHF patients (2–7).

An increase in the blood levels of carbohydrate antigen 125 (CA125), a tumoral marker initially related to ovarian cancer (8,9), has been recently reported in a group of CHF patients evaluated for heart transplantation and was shown to be related to the severity of symptoms (10). The aim of the present study was to measure the blood levels of CA125 in a large group of patients with symptomatic left ventricular dysfunction and to determine the potential relationship between this tumoral marker and the severity of CHF, the extent of underlying cardiac abnormalities, and short-term outcome.

METHODS

Study population. We prospectively evaluated 286 patients consecutively admitted with CHF to the Department of Cardiology, Spedali Civili and University of Brescia, Italy, in a period of 18 months. The diagnosis of CHF was based on clinical presentation and standard investigations; furthermore, all patients had at least one hospital admission for

Abbreviations and Acronyms

BNP	=	brain natriuretic peptide
CA125	=	carbohydrate antigen 125
CHF	=	congestive heart failure
DT	=	deceleration time of early filling
LVEDD	=	left ventricular end-diastolic diameter
LVEF	=	left ventricular ejection fraction
NYHA	=	New York Heart Association
PAWP	=	pulmonary artery wedge pressure
RAP	=	right atrial pressure
RHC	=	right heart catheterization

CHF before inclusion in the study. We excluded patients with a recent acute coronary syndrome (<3 months), those awaiting coronary artery bypass graft or valvular surgery, and those with any evidence of active infection, cancer, end-stage liver disease, or renal failure. The clinical characteristics of the study population are listed in Table 1.

Echocardiographic Examination and CA125 Measurement. All patients underwent a clinical examination, a two-dimensional Doppler echocardiographic examination, and venous blood sampling for CA125 analysis (see next paragraph) on the day of admission. Two-dimensional echocardiography was performed with commercially available equipment. Measured variables included left ventricular end-diastolic (LVEDD) and end-systolic diameter, using two-dimensionally guided M-mode echocardiography. The left ventricular ejection fraction (LVEF) was calculated using the Simpson method from the apical four-chamber view. The severity of mitral and tricuspid regurgitation was evaluated by means of color Doppler flow imaging and semiquantitatively expressed using a scale from 0 to 4+ (11). On the pulsed Doppler tracing of transmitral blood flow, recorded at the tips of the mitral leaflets from the apical four-chamber view, the following parameters were measured: peak velocity in early filling (E) and during atrial systole (A), expressed in cm/s, and their ratio (E/A), and the deceleration time of early filling (DT), expressed in ms. These parameters, particularly DT, have been shown to significantly correlate with invasively measured left atrial pressure (12).

Serum levels of CA125 were determined using a commercially available kit (Tumor Markers CA125 AxSYM System, Abbott Laboratories, Abbott Park, Illinois). The AxSYM CA125 assay is based on microparticle enzyme immunoassay; this technology uses a solution of suspended, submicron-sized latex particles to measure analytes. CA125 assay values are defined by using the OC125 monoclonal antibody. The OC125 monoclonal antibody is reactive with repeating OC125-reactive determinants, expressed by a high percentage of non-mucinous ovarian carcinomas (serous, endometrioid, clear cell, and undifferentiated histologies) and epithelial ovarian carcinoma cell lines. OC125-reactive determinants are not produced by normal cell lines and have not been found in normal or benign ovarian tissues of either fetuses or adults. However, OC125-reactive determinants have been reported to be detected in the pleura, pericardium, and peritoneum of adults. The upper normal limit of CA125 is 35 U/ml (8,13). The analytical sensitivity of the AxSyM CA125 was calculated to be 2 U/ml; the median intra-assay and inter-assay coefficients of variation are <5% and <7.5%, respectively (13).

A right heart catheterization (RHC) using a Swan-Ganz catheter was performed in 88 CHF patients within 24 to 48 h of CA125 measurement and in the absence of relevant changes in the clinical picture. Standard parameters were obtained, such as pressures in right heart chambers, pulmonary artery wedge pressure (PAWP), and cardiac output (in triplicate), using the thermodilution method.

Echocardiographic and CA125 measurements were repeated (mean interval 18 days [range 7 to 40]) in 80 patients with moderate-to-severe CHF (New York Heart Association [NYHA] functional class III and IV) after an attempt to optimize medical treatment, usually by increasing the dosage of furosemide and adding metolazone when necessary, to reduce pulmonary and systemic congestion, and by gradually increasing the daily dosage of angiotensin-converting enzyme inhibitors to maximally tolerated doses, according to the evidence derived from randomized trials. Furthermore, in some patients, oral or transdermal nitrates were added as needed.

Follow-up. Complete follow-up data were available in 240 patients with a follow-up of at least three months from the time of study inclusion. The mean follow-up duration was 6 ± 3 months (range 3 to 12). Clinical end points included total mortality, cardiovascular mortality (sudden and nonsudden death), and hospitalization for any cardiovascular cause. A combined end point, including total mortality and hospital admission for CHF, was also considered. The clinician doing the follow-up evaluation was blinded to the

Table 1. Clinical Characteristics of CHF Patients (n = 286)

Age (yrs)	69 ± 13
Men/women	122/164
Body mass index (kg/m²)	25 ± 9.3
NYHA functional class	
Mean	
I (%)	10 (3.5%)
II (%)	130 (45.5%)
III (%)	63 (22%)
IV (%)	83 (29%)
LVEF (%)	30 ± 11
Etiology (%)	
Coronary artery disease	60
Dilated cardiomyopathy	23
Hypertensive heart disease	11
Other	6
Medication use (%)	
ACE inhibitor	95
Diuretic	88
Digitalis	60
Beta-blocker	50

Data are presented as the mean value ± SD or number (%) or percentage of patients.
ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 2. Clinical, Doppler Echocardiographic and Hemodynamic Parameters, and CA125 Serum Levels in CHF Patients Classified According to NYHA Functional Class

	NYHA Class I to II (n = 140)	NYHA Class III (n = 63)	NYHA Class IV (n = 83)	p Value (global)
Men/women	42/98	31/32	49/34	
Body mass index (kg/m^2)	26 ± 12	26 ± 12	26 ± 12	NS
Serum creatinine (mg%)	1.35 ± 0.67	1.5 ± 0.8	1.43 ± 0.66	NS
CA125 (U/ml)	15 ± 9	57 ± 18*	167 ± 94†‡	< 0.005
LVEF (%)	32 ± 12	29 ± 11	27 ± 9‡	< 0.005
Mitral regurgitation score	2 ± 0.8	2.7 ± 0.8*	2.9 ± 0.7‡	< 0.005
Tricuspid regurgitation score	1.3 ± 0.8	2.25 ± 0.8*	2.6 ± 0.8‡§	< 0.005
E/A ratio	1.26 ± 0.5	1.9 ± 0.9*	2.3 ± 0.5†‡	< 0.005
DT (ms)	169 ± 45	131 ± 28*	107 ± 27†‡	< 0.005
RAP (mm Hg)	7 ± 3	13 ± 4*	16 ± 5†‡¶	< 0.005
PASP (mm Hg)	35 ± 10	51 ± 11*	55 ± 11‡¶	< 0.005
PAWP (mm Hg)	13.5 ± 5	21 ± 5*	25 ± 6‡¶	< 0.005

Analysis of variance with posthoc Scheffé correction (simple effect): *p < 0.005 between NYHA class I to II and III. †p < 0.005 between NYHA class III and IV. ‡p < 0.005 between NYHA class I to II and IV. §p < 0.01 between NYHA class III and IV. ¶p < 0.05 between NYHA class III and IV. Differences not indicated were not significant. Data are presented as the mean value ± SD.

CA125 = carbohydrate antigen 125; DT = deceleration time; E/A = ratio of early transmitral to atrial flow velocity; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; NYHA = New York Heart Association; PAWP = pulmonary artery wedge pressure; RAP = right atrial pressure.

CA125 results. The study was approved by the local ethics committee, and all patients gave written, informed consent.

Statistical analysis. Data are presented as the mean value ± SD. Logarithmic transformation was used for some variables (CA125, DT) to reduce skewness and kurtosis values toward a normal distribution. Differences between the study groups were assessed by using the Student *t* test and one-way or two-way analysis of variance for repeated measures with post hoc Scheffé correction. A p value <0.05 was considered statistically significant. Multiple correlation analysis with stepwise forward and backward methods was used to assess the factors related to CA125 levels, and final regression analysis shows only the variables confirmed by both methods. Survival curves were generated by the Kaplan-Meier method, and the log-rank test was used to evaluate the significance of differences between groups.

RESULTS

The mean serum level of CA125 in the whole population was 68 ± 83 U/ml (range 3 to 537): 71 ± 85 U/ml in men and 56 ± 64 U/ml in women (p = NS by the *t* test). Serum levels of CA125 over the normal range (≤35 U/ml) were found in 152 (53%) of 286 CHF patients; CA125 values >35 U/ml were observed in none of 10 patients in NYHA class I, in 16 (12%) of 130 patients in class II, in 53 (84%) of 63 patients in class III, and in all 83 (100%) patients in class IV. Patients in class I/II were similar in terms of demographic characteristics, etiology of CHF, LVEF, and medication use. Accordingly, they were considered together in the subsequent analysis. Mean values of CA125 were significantly higher (p < 0.001) in patients in class III/IV than in those in class I/II (Table 2, Fig. 1).

Multiple regression analysis showed that the following variables were predictive of CA125 values: LVEDD, DT, PAWP, and right atrial pressure (RAP) (final R = 0.78, p < 0.005). After the results of multiple regression analysis, we evaluated simple correlations between CA125 and sev-

eral Doppler echocardiographic and hemodynamic variables (the latter limited to 88 patients in whom RHC was performed), which are listed in Table 3. An inverse relation (statistically significant) was found between CA125 levels and DT, a reliable non-invasive index of left atrial pressure. This result was confirmed by the similar r value found between CA125 and PAWP obtained during RHC in the subgroup of 88 CHF patients. Furthermore, CA125 levels were also significantly related to the invasively determined RAP. There was no significant correlation between CA125 and LVEF or LVEDD.

Among those patients in whom an attempt to optimize medical treatment was performed and CA125 measurement repeated after a mean interval of 18 days, a clinical improvement, as expressed by a decrease in NYHA functional class of one grade or more, was observed in 56 of 80 patients, whereas no change or even a clinical worsening was observed in the remaining 24 patients. The changes observed after treatment in the relevant Doppler echocardiographic and hemodynamic variables and CA125 levels in both groups are listed in Table 4. Of interest, the serum level of CA125 decreased from 125 ± 98 to 53 ± 61 U/ml (p < 0.05) in patients showing a clinical improvement, whereas it changed from 130 ± 81 to 153 ± 61 U/ml (p = NS) in those patients with no change or even a worsening in their clinical picture (Fig. 2). Twenty of 56 patients showing a clinical improvement after therapy had a normalization (<35 U/ml) of a previously elevated CA125 level, compared with none of 24 patients without clinical improvement (p < 0.05). The behavior of CA125 in the two groups paralleled that of DT and PAWP (hemodynamic data are available in 35 patients), as reported in Table 4.

Among 240 patients followed for a mean period of 6 ± 3 months, 39 died and 47 were readmitted to the hospital at least once for worsening CHF. The cause of death was cardiovascular in all patients. The combined end point (total mortality and hospitalization for worsening CHF) was
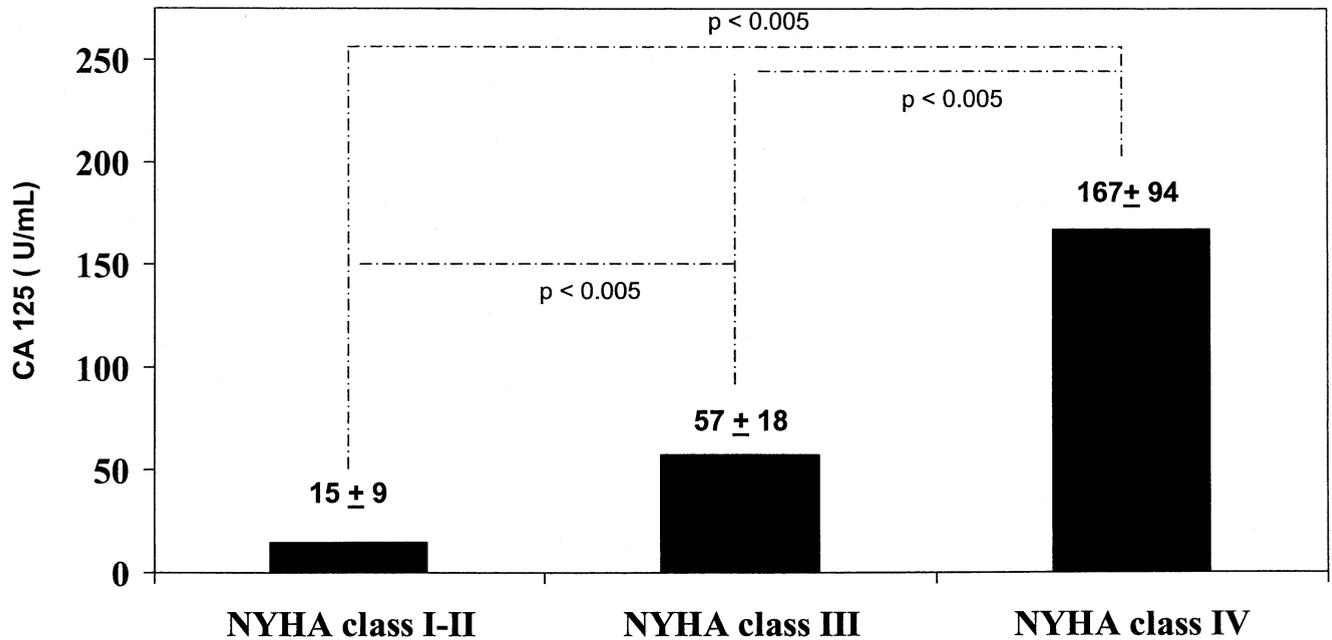
Figure 1. Serum levels of carbohydrate antigen 125 (CA125) in congestive heart failure patients classified according to the different New York Heart Association (NYHA) functional classes. Data are expressed as the mean value ± SD. Difference between groups were assessed using analysis of variance with post hoc Scheffé correction. See text for details.

observed in 70 of 113 patients with baseline CA125 values >35 U/ml, compared with 16 of 127 patients with baseline CA125 values ≤35 U/ml (p < 0.01 by the log-rank test). Kaplan-Meier cumulative survival curves separated according to CA125 levels are presented in Figure 3.

In patients with persistently high values of CA125 (on at least two separate occasions), a diagnostic work-up for cancer was negative. Furthermore, non-malignant diseases potentially responsible for CA125 elevations, such as end-stage renal failure and liver cirrhosis, were also excluded. A pleural effusion was detected on the chest X-ray film in seven patients; mild pericardial effusion on the echocardiogram was observed in two patients; and ascites was found in one patient; all of these patients were in NYHA class IV and showed an increase of CA125 levels above normal values. Pleural effusion disappeared after aggressive medical therapy

Table 3. Multiple Regression Analysis and Simple Correlation Between CA125 and Serum Sodium and Doppler Echocardiographic and Hemodynamic Parameters

	r	p Value
Multiple regression analysis (R)	0.78	0.005
LVEF*	−0.15	NS
LVEDD*	0.11	NS
DT*	−0.63	0.05
E/A ratio	0.60	0.05
RAP*	0.69	0.05
PASP	0.58	0.05
PAWP*	0.66	0.05
Serum sodium	0.18	NS

*Variables entered in multiple regression analysis forward and backward. See text for details. All values, except for multiple regression analysis, are expressed as r.
   LVEDD = left ventricular end-diastolic diameter; other abbreviations as in Table 2.

of CHF, and a concomitant reduction of CA125 was found in four patients in whom this measurement was repeated. The patient with ascites underwent paracentesis, and the peritoneal fluid was negative for neoplastic cells. The patient died 12 days later due to refractory heart failure.

DISCUSSION

The principal results of this study of patients with CHF is that serum levels of CA125 correlated with clinical status, as demonstrated by significantly higher values in NYHA class III/IV, compared with those in class I/II. Moreover, CA125 levels also correlated with invasive and non-invasive hemodynamic abnormalities, particularly the level of RAP and PAWP. In patients with moderate-to-severe CHF, abnormally elevated values of CA125 were significantly reduced by aggressive medical treatment, in parallel with improvements of the clinical picture and indexes of hemodynamic impairment. Finally, elevated serum levels of CA125 were predictive of a worse prognosis in short-term follow-up.

An increase of serum levels of CA125 has been initially described in women affected by ovarian carcinoma, especially with peritoneum involvement (8,9). Accordingly, serial measurements of this tumoral marker are currently used in the follow-up of these patients and to evaluate the response to therapy (14). High CA125 values have also been observed in patients with lung, breast, uterine, or gastrointestinal tract cancer (15). Furthermore, it has been reported that some non-malignant diseases such as nephrotic syndrome and hepatic cirrhosis, along with their concomitant serosal effusions (i.e., fluid accumulation in the pleural, peritoneal, or pericardial space), may be associated with

Table 4. Characteristics of 80 Patients Before and After Medical Therapy Optimization, Classified According to Clinical Improvement or No Change/Worsening

|	NYHA Class Reduced (n = 56)			NYHA Class Unchanged or Increased (n = 24)		
	Before MTO	After MTO	p Value	Before MTO	After MTO	p Value
NYHA class*	3 ± 0.8	1.5 ± 0.5	0.005	3.6 ± 0.5	3.5 ± 0.5	NS
LVEF (%)*	28 ± 10	32 ± 11	NS	25.5 ± 8.5	25.5 ± 8.4	NS
E/A ratio*	1.8 ± 0.5	1.3 ± 0.5	0.001	2.4 ± 0.6	2.3 ± 0.7	NS
DT (ms)*	123 ± 32	167 ± 47	0.001	109 ± 20	111 ± 23	NS
PAWP (mm Hg)*†	23 ± 6	13 ± 3	0.001	23 ± 5	24 ± 6	NS
CA125 (U/ml)	125 ± 98	53 ± 61	0.001	130 ± 81	153 ± 61	NS

*Analysis of variance interaction has been verified for all comparisons: all parameters obtained before optimization were similar between the two groups, whereas differences between groups observed after optimization were statistically significant (p < 0.001 for all variables). †Data available for 35 patients. Data are presented as the mean value ± SD.

MTO = medical therapy optimization; other abbreviations as in Table 2.

elevated serum levels of CA125, and even higher CA125 values in the serosal fluids. In contrast, CA125 levels were normal in those patients without serosal effusions (16,17). Subsequent studies have demonstrated that mesothelial cells from the pleura and peritoneum are able to produce CA125 (18). Of interest, blood levels of CA125 above normal were also found in 65% of 57 patients with pericardial effusion of different etiologies, including 25 with some degree of heart failure; significantly higher values of CA125 were found in subjects with a larger effusion, as documented by echocardiography, and were reported to decrease or even normalize along with a reduction or disappearance of effusion (19). Furthermore, in 17 patients, the pericardial tissue obtained at autopsy was stained with anti-CA125 antibodies: serum and pericardium CA125 levels were significantly higher in subjects with CA125-positive-stained pericardium, com-pared with those in whom the pericardium was negative for CA125, confirming a pericardial production of this marker (19). Thus, in chronic non-malignant diseases, high plasma levels of CA125 have been attributed to its production by serosal mesothelium, as a consequence of inflammation, stasis, or other stimulatory mechanisms.

Nagele et al. (10) measured CA125 serum levels in CHF patients evaluated for heart transplantation; although the prevalence of pleural or pericardial effusion was not reported, the authors found an increase in CA125 levels above normal not only in patients with advanced CHF (NYHA class III/IV), in whom some degree of fluid accumulation may be expected, but also in those with mild or no symptoms (NYHA I/II), in whom serosal effusion is unlikely. In our study population, CA125 was elevated both in the few patients with pleural, pericardial, or peritoneal

Patients (n=56) with a clinical improvement

Patients (n=24) with no clinical change or worsening
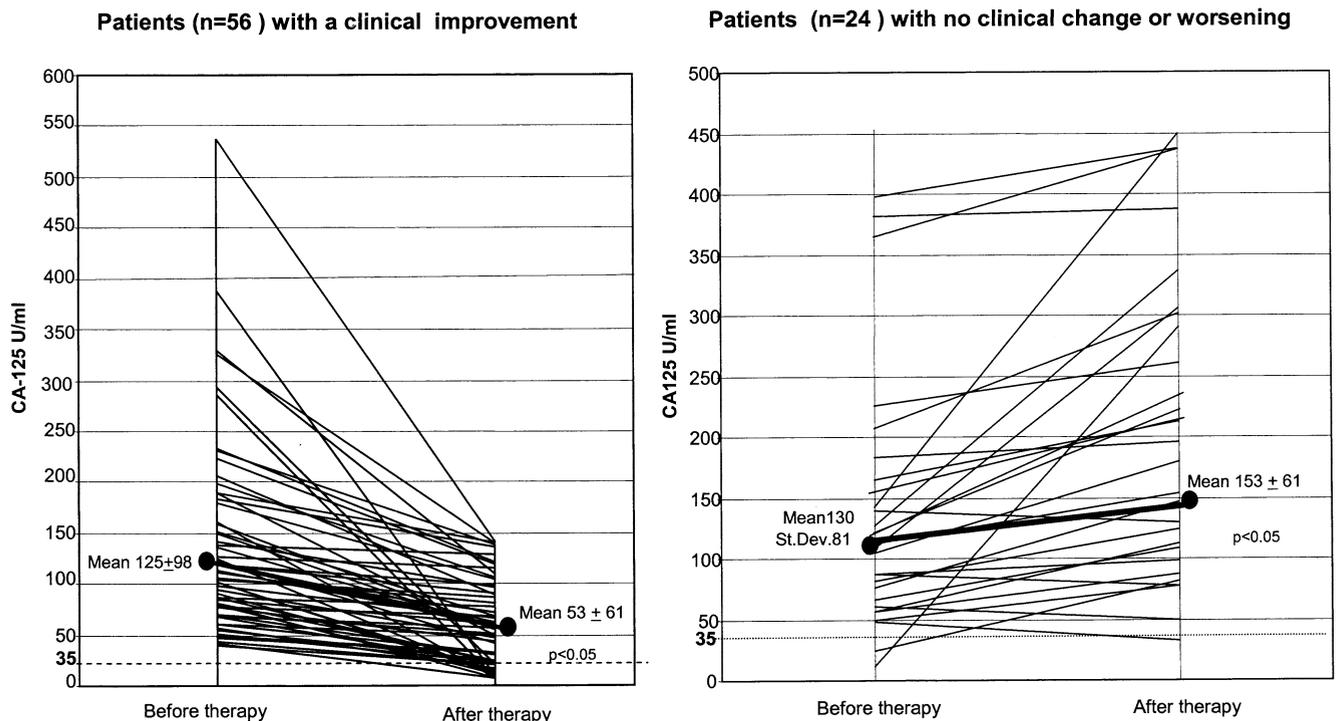
Figure 2. Changes in serum levels of carbohydrate antigen 125 (CA125) after optimization of medical therapy for congestive heart failure. The **left panel** presents data from the patients in whom a clinical improvement after therapy was observed. The **right panel** presents data from the patients in whom no clinical improvement, or even a worsening, was observed despite intensive medical treatment. See text for details.
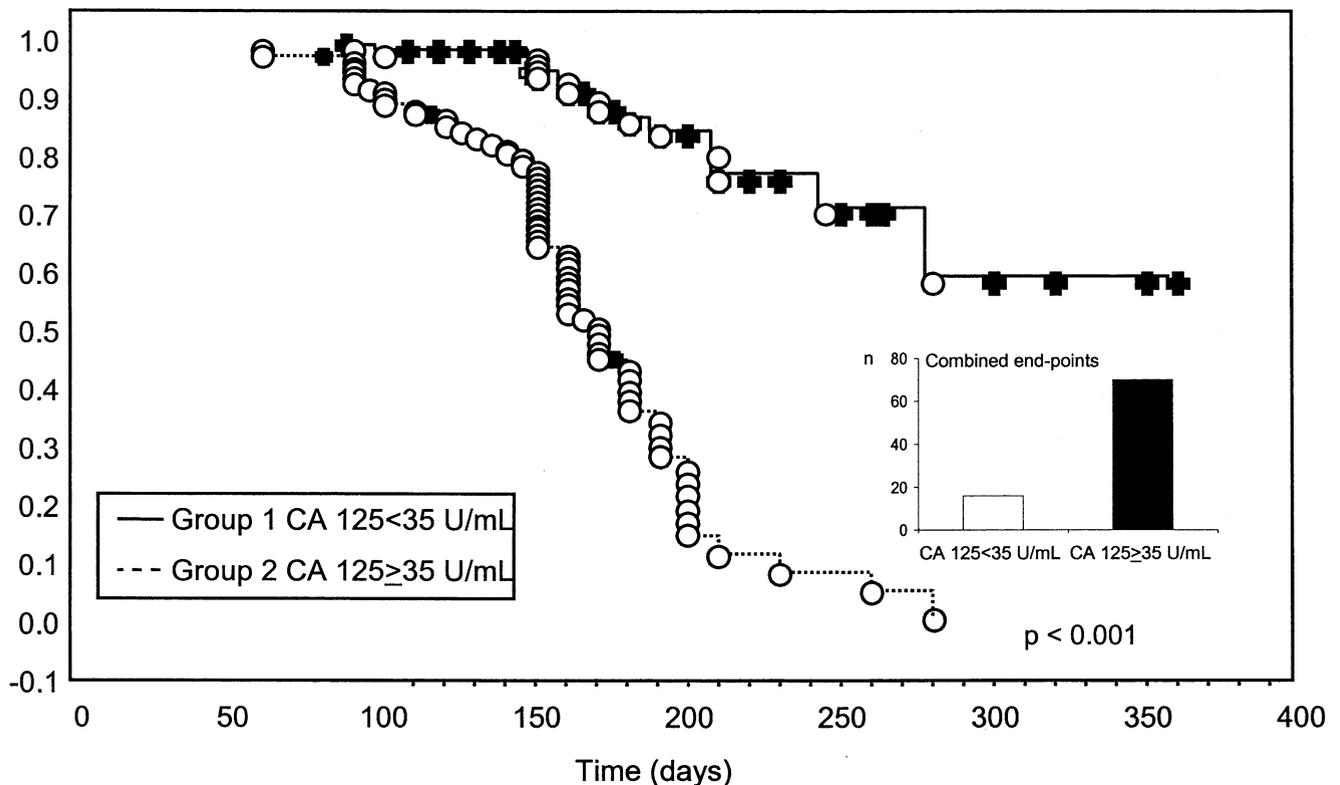
Figure 3. Kaplan-Meier curves for congestive heart failure patients classified according to baseline serum levels of carbohydrate antigen 125 (CA125). See text for details. Cumulative proportion surviving: **open circles** = complete; **solid plus signs** = censored.

effusion and in the large majority of patients with moderate-to-severe CHF and no effusion. It could be hypothesized that CA125 might be produced from mesothelial cells, even in the absence of classic stimuli (such as fluid accumulation), and/or that it might also be secreted by other cell lines. Of interest, it has been reported that CA125 is produced and released from ovarian cancer cells and lymphoma cells when stimulated by cytokines (20–22), such as tumor necrosis factor and interleukin-6, which are also elevated in heart failure (4–7). However, the potential pathogenetic link between cytokine activation and production of CA125 in CHF patients, as well as its clinical relevance, needs further study.

To our knowledge, there is only one published study that has evaluated the behavior of CA125 in patients with chronic CHF (10). In contrast to our results, Nagele et al. (10) found that mean values of CA125 serum levels were higher than normal not only in patients with moderate-to-severe CHF (NYHA class III/IV) but also in patients with mild symptoms (class II) and even in those with asymptomatic left ventricular dysfunction (class I). Furthermore, they reported higher mean values of CA125 in each functional class than those we observed in our study population; this may reflect both the different analytical method used for measuring CA125 levels, compared with that used in our study, and, possibly, differences in the study populations, as

all individuals were evaluated for heart transplantation (10). Consistent with our findings was a significant correlation between CA125 and filling pressures, as well as a reduction of CA125 serum levels in a subgroup of patients after improvement in clinical status. No data on the prognostic role of CA125 were reported in the study (10).

Study limitations. Several points regarding the meaning of CA125 elevations in CHF patients still need to be addressed, such as its regulatory mechanisms and sites of production. Little is known about the biologic role of this substance: whether it simply reflects the increased activation of the cytokine pathway (or other pathophysiologic pathways), or whether CA125 is an active substance truly responsible for myocardial and/or peripheral dysfunction. The relationship between CA125 and indexes of functional capacity that are more objective than NYHA classification, such as exercise tolerance and long-term outcome, should be investigated. In many regards, CA125 at this early stage appears to resemble some aspects of BNP. Preliminary data show a good correlation between simultaneous CA125 and BNP levels in 54 CHF patients (r = 0.74, p < 0.05) (unpublished observation). Further work will need to clarify the relative value of CA125 compared with BNP in the diagnosis and subsequent treatment of CHF.

Nevertheless, based on the results reported herein, the serum level of CA125 seems to represent an easily obtain-

able and repeatable, relatively inexpensive (less than $4 per patient in Italy), and reliable marker of moderate-to-severe CHF, which appears to be related to hemodynamic abnormalities and might reflect both the effects of treatment and short-term prognosis. Similar to more sophisticated hormonal and immunologic markers, it might therefore be proposed for the serial assessment of patients with CHF.

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