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ORIGINAL ARTICLE

Anemia in chronic heart failure patients: comparison between invasive and non-invasive prognostic markers

Anemia nello scompenso cardiaco cronico: confronto tra indicatori prognostici invasivi e non invasivi

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ABSTRACT: ***Anemia in chronic heart failure patients: comparison between invasive and non-invasive prognostic markers. M. Ceresa, S. Capomolla, G.D. Pinna, E. Aiolfi, M.T. La Rovere, O. Febo, V. Paganini, A. Rossi, G. Guazzotti, A. Caporotondi, R. Maestri, F. Cobelli.***

Background: **The prognosis of chronic heart failure (CHF) remains poor despite advances in medical management. Several different variables determine prognosis. Recently anemia has emerged as an independent prognostic variable in the evaluation of CHF. It is therefore important to analyze the role of anemia in patients with mild to severe CHF already well characterized by hemodynamic, echo-Doppler, and cardiopulmonary exercise testing.**

Objective: **We performed this study to evaluate, in a large general cohort of CHF patients, the frequency of anemia and its correlation with their clinical profile. We assessed the prognostic value of anemia in relation to other known prognostic variables.**

Methods: **Two-dimensional echocardiography, right heart catheterization, cardiopulmonary tests and laboratory examinations were performed in a population of 980 consecutive patients with CHF (53±9.4 years, 85% male, LVEF 25±8%; 45% with NYHA class III-IV). A hemoglobin (Hb) concentration less than 12 g/dl was used to define anemic patients. The primary end point was cardiac death or urgent heart transplantation.**

Results: **Nineteen percent of patients were anemic. These patients had a lower body mass index (24±3 vs. 25±4 Kg/m^2 p <0.0004), a worse functional class (64% were in NYHA class III-IV vs 41% in the non-anemic group, p <0.0001), poorer exercise capacity (12.4 vs. 14.8 ml/kg/min peak VO_2, p <0.0001) and increased right (7±5 vs. 5±4 mmHg, p <.0004) and left (21±9 vs. 19±10 p <0.007) ventricular filling pressures. During a 3-year follow-up cardiac deaths occurred in 236 (24%) and 52 (5%) of patients received an urgent heart transplant. On univariate regression analysis anemia was significantly correlated with these "hard" cardiac events (39% of anemic patients vs 27% of non-anemic patients). By multivariate logistic regression analysis different prognostic models were identified using non-invasive, with or without peak VO_2, or invasive parameters. The prognostic model including anemia (AUC_{ROC}: 0.720) showed similar accuracy in predicting cardiac events to other prognostic models with peak VO_2 (AUC_{ROC}: 0.719) or invasive variables (AUC_{ROC}: 0.719).**

Conclusions: **The present study demonstrates that anemia in CHF patients is associated with prognosis, worse NYHA functional class, exercise capacity and hemodynamic profiles. The relationship between anemia and mortality is independent of other simple non-invasive prognostic factors. Prognostic models with more complex or invasive independent predictors did not increase the accuracy to predict cardiac mortality or the need for urgent transplantation.**

Keywords: anemia, chronic heart failure, prognosis.

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The prognosis of chronic heart failure (CHF) remains poor despite advances in medical management, and mortality has been rising despite the improvements in medical and surgical therapy.[1]

Many factors are reported in the literature to predict prognosis, but their wide variety emphasises the fact that the prognostic accuracy of these factors still lacks consistency. Moreover, the clinical application of proposed prognostic models is limited because the characteristics of the derivation and application to patient-populations are different, or because the prognostic power of the variables has not been compared with those of consolidated variables.[2] In recent years anemia has emerged as another prognostic variable for CHF.[3-5] We therefore performed this study to evaluate, in a large general population of patients with CHF, the frequency of anemia and its correlation with the clinical profile. Furthermore, we assessed the prognostic value of anemia in conjunction with other established non-invasive and invasive prognostic variables.

Methods

Study population

We evaluated 980 consecutive patients with CHF caused by ischemia, idiopathic dilated cardiomyopathy, or other disease (i.e. hypertension, valvular disease) admitted to the Heart Failure Unit of Montescano Medical Center for evaluation and treatment of advanced heart failure. All patients, in stable condition and receiving optimized therapy, had a functional evaluation by two-dimensional echocardiography, right heart catheterization, cardiopulmonary tests and laboratory examinations.

Clinical evaluation

We evaluated symptomatic severity by New York Heart Association (NYHA) classification. The clinical examination included assessment of body weight, body mass index (BMI), heart rate, third heart sound, and presence of peripheral or pulmonary edema (rales and/or orthopnea and turgor and/or hepato-jugular reflux).

The presence of other risk factors for CHF, such as increased age, male gender, family history of coronary artery disease, hypertension, smoking and diabetes mellitus were entered into the regression models.

Laboratory testing

Biochemical (serum concentrations of sodium, potassium, urea, creatinine, aspartate transaminase, glutamate transaminase, and bilirubin) and hematologic parameters (hemoglobin concentration, white cell and platelet counts) were measured. A hemoglobin concentration lower than 12 g/dl was used to identify anemic patients.

Cardiac catheterization

Right heart catheterization was performed using a 7 F Swan-Ganz balloon-tipped catheter inserted into the right internal jugular vein and advanced to the pulmonary artery. Measurements were obtained with the patients in a supine position, using a HP transducer connected to a 7005 Marquette polygraph.

Pressure tracings were recorded at a speed of 50 cm/sec on a scale calibrated from 0 to 60 mmHg.

Cardiac output was determined by averaging three consecutive thermodilution curves obtained by injecting 10 ml of saline solution at 0° C into the right atrium.

Right atrial pressure, pulmonary artery pressures and mean pulmonary wedge pressure were recorded. The pulmonary capillary wedge position was confirmed by the appearance of a typical wedge pressure tracing during fluoroscopic observation of the catheter tip during balloon inflation.

Arterial systolic and diastolic blood pressures were measured with a non-invasive method by a calibrated v-lok-cuff connected to a 7005 Marquette system.

Heart rate was monitored continuously from a standard ECG.

Echocardiography

Echocardiographic studies were performed using an HP Sonos 1000 ultrasound system with 2.5 and 3.5 MHz transducers.

We evaluated the diastolic and systolic left ventricular diameters from a parasternal long axis view and calculated left ventricular ejection fraction using a B-mode four-chamber view.[6] The mitral regurgitation jet was evaluated as the ratio between jet area and left atrial area; regurgitation was ranked as mild, moderate or severe.[7] In our analysis we considered moderate or severe mitral regurgitation in contrast to mild or no mitral regurgitation.

Cardiopulmonary test

Cardiopulmonary testing was performed in the upright position on an electronic bicycle. The cardiopulmonary parameters were measured breath by breath with an Oxycon Delta (Seager™ Medical technology) which was calibrated before each test. The following parameters were calculated: basal and peak VO_2 in ml/min/kg of body weight.

End points

In this study the outcome event was cardiac death or urgent heart transplant. Cardiac deaths were those due to heart failure or sudden death; transplants were included in the outcome because we assumed that these patients would have died without transplant.

Non-urgent transplants were not considered in the primary end point analysis.

We considered a death sudden if it occurred within 1 hour of the onset of unexpected symptoms or during sleep in patients who were symptomatically stable during the 24 hours preceding death, or was unwitnessed death and occurred within 1 hour of the patient last being seen alive. Death from heart failure was considered to have occurred in conjunction with a worsening of congestive symptoms.

Statistical analysis

Comparisons between groups for continuous variables were performed by the ANOVA or Mann-Whitney test when appropriate. Categorical variables were compared by the Chi-square test. The association between prognostic variables and the outcome (cardiac death or urgent heart transplantation) was analysed by univariate and multivariate logistic regression. For each significant prognostic variable, the corresponding odds ratio (OR) and 95% confidence interval (CI) were computed. In building multivariate models, two different sets of candidate variables were considered. The first set included only non-invasively measured parameters, while the second set included both non-invasively and invasively measured parameters. Accordingly, the two models have been referred to as respectively non-invasive and invasive model.

To assess the overall predictive discrimination of each logistic model, we computed the area under the receiver operator characteristic (ROC) curve ob-

tained from the model.[8] This area measures the ability of the model to separate patients with poor outcome from those who did not have a poor outcome. A ROC curve area of 0.5 indicates no discrimination power, whereas an area of 1 indicates perfect discrimination. Selection of variables to be included in the multivariate models was performed using the stepwise method. In all hypothesis tests a p value <0.05 was considered statistically significant.

Results

Patients' characteristics

The clinical characteristics of the 980 patients enrolled in the study are shown in table 1. The mean age of the patients was 53±9 years (range 15 to 77 years) and 85% of them were male. The etiology of heart failure was coronary artery disease in 44% (428 patients), a primary dilated cardiomyopathy in 39% (384 patients), and other cardiac disease (hypertension, valvular disease) in 17% (168 patients). Forty-six percent were categorized as having NYHA functional class III-IV disease and the remaining 54% were in NYHA class I-II. The mean echocardiographic left ventricular ejection fraction was 25±8%. Thus the patients presented a compromised hemodynamic profile and decreased exercise capacity.

Relationship between anemia and clinical findings

Of the total study population, 19% of patients were anemic. Anemia was more frequent in females and in older patients. No differences were found between patients with and without anemia in LVEF, LVEDD, LVESD, deceleration time, cardiac index, history of hypertension, family predisposition, smoking habits, serum sodium and potassium concentrations, and etiology of CHF. However, anemic patients had a lower body mass index (24±3 vs. 25±4 Kg/m^2 p <0.001), a worse functional class (NYHA functional class III-IV 64% vs 41% p <0.001), poorer exercise capacity (12.4 vs. 14.8 ml/kg/min peak VO_2, p <0.001) and higher right (7±5 vs 5±4 mmHg, p <0.001) and left ventricular filling (21±9 vs. 19±10 p <0. 001) pressures (table 1).

Outcome events

Over a three-year follow-up there were 288 (29%) outcome events. Cardiac death occurred in 236 (24%) patients; progressive CHF accounted for 141 (60%) of these deaths, while 95 (40%) were sudden. Fifty-two (5%) patients received a heart transplant in Status I. The percentage of patients who therefore had suffered a hard cardiac event was higher among anemic than among non-anemic patients (39% vs. 27% p <001) (figure 1).

Table 1. - Baseline clinical, Doppler echocardiographic and hemodynamic characteristics in all patients and in the patients with and without anemia

	All	Anemic	Non-anemic	p
N	**980**	**187**	**793**	
Age (*years*)	**53±9**	**55±9**	**52±9**	**<0.001**
Sex (*Male/Female*)	**834/146**	**134/53**	**700/93**	**<0.001**
Etiology (*ischemic/idiopathic/other*)	**428/384/168**	**81/59/47**	**347/325/121**	**<0.001**
NYHA I-II/III-IV	**533/447**	**67/120**	**466/327**	**<0.001**
Heart rate (*beats/min*)	**80±18**	**81±18**	**80±18**	**Ns**
Systolic pressure (*mmHg*)	**112±16**	**108±15**	**111±16**	**0.004**
Peak VO_2 (*ml/min/Kg*)	**14.4±4**	**12.4±3**	**14.8±5**	**<0.001**
LVEDD (*mm*)	**71±10**	**71±11**	**71±10**	**Ns**
LVESD (*mm*)	**60±11**	**60±12**	**60±11**	**Ns**
LVEF (*%*)	**25±8**	**25±8**	**25±8**	**Ns**
E/A	**2.1±1.5**	**2.3±1.6**	**2.1±1.5**	**Ns**
Deceleration time E (*msec*)	**138±54**	**138±48**	**139±55**	**Ns**
Mitral regurgitation grade 2-3 (*N (%)*)	**379(39)**	**82(44)**	**297 (37)**	**Ns**
Cardiac index (*l/min/m^2*)	**2.1±0.5**	**2.1±0.5**	**2.1±0.6**	**Ns**
Pulmonary wedge pressure (*mmHg*)	**19±6**	**21±9**	**19±10**	**0.007**
Right atrial pressure (*mmHg*)	**6±5**	**7±5**	**5±4**	**<0.001**
BMI (*Kg/m^2*)	**25±4**	**24±3**	**25±4**	**<0.001**
THERAPY				
Diuretics (*N (%)*)	**921 (94)**	**183 (98)**	**738 (93)**	**0.01**
Digitalis (*N (%)*)	**578 (59)**	**142 (76)**	**436 (55)**	**<.0001**
ACE-inhibitors (*N (%)*)	**829 (85)**	**146 (78)**	**683 (86)**	**0.01**
Beta-blockers (*N (%)*)	**155 (16)**	**29 (15)**	**126 (16)**	**Ns**

Legend: BMI: body mass index; E/A: early to late diastolic peak velocity ratio; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association class. Continuous variables are described as mean ±SD.

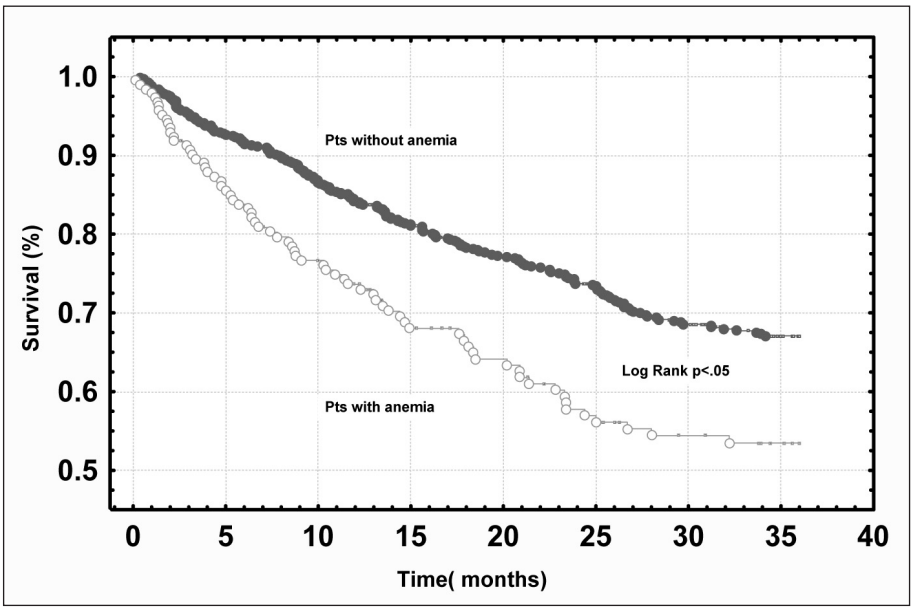

Figure 1. - Survival curves among heart failure patients with and without anemia.

Univariate analysis

Univariate logistic regression analysis identified many variables that were predictive of cardiac mortality or urgent cardiac transplantation in the three-year follow-up (table 2).

We also analyzed the relation between chronic renal failure (CRF) and anemia and found that anemia was more frequent in patients with CRF than in patients with normal renal function (38% vs. 18%; p =0.001), anemia, however, maintained its univariate prognostic value both in CRF patients (p =0.015) and in those without renal failure (p =0.03).

Multivariate logistic analysis

Among all clinical and Biochemical and hematologic non-invasively measured parameters which significantly predicted primary outcome in the univariate analyses, the following set of variables in the multivariate predictive model were predictive (table 4): NYHA functional class, mitral regurgitation, anemia, LVEF and serum sodium. When we repeated the multivariate analysis including all non-invasive parameters and peak VO_2, the final model predicting the primary outcome included: NYHA functional class, mitral regurgitation, LVEF, serum sodium and peak VO_2, but not anemia. In the multivariate model incorporating non-invasive and invasive parameters, the following variables were independent predictors (table 3): NYHA functional class, mitral regurgitation, LVEF, serum sodium and right atrial pressure. To appraise differences in prognostic accuracy between the various prognostic models (with peak VO_2 or anemia, or RAP), we compared them using ROC curves. The areas under the ROC curves of the three models were not significantly different (figure 2, table 3).

Table 2. - Univariate analysis: Univariate predictors of cardiac death or urgent cardiac transplantation

	OR	*CI*	*p*
Sex	**0.85**	**0.57-1.27**	**Ns**
Age	**1.00**	**0.99-1.02**	**Ns**
Etiology	**0.99**	**0.82-1.20**	**Ns**
NYHA	**2.54**	**1.92-3.38**	**<0.001**
Heart rate	**1.02**	**1.00-1.03**	**0.007**
Systolic pressure	**0.96**	**0.95-0.97**	**<0.001**
Peak VO_2	**0.89**	**0.86-0.93**	**<0.001**
LVEDD	**1.02**	**1.01-1.04**	**0.002**
LVESD	**1.03**	**1.02-1.04**	**0.001**
LVEF	**0.93**	**0.91-0.95**	**<0.001**
Mitral regurgitation	**1.94**	**1.47-2.57**	**<0.001**
Cardiac index	**0.48**	**0.36-0.64**	**<0.001**
Pulmonary wedge pressure	**1.05**	**1.03-1.06**	**<0.001**
Right atrial pressure	**1.12**	**1.08-1.15**	**<0.001**
Anemia	**1.67**	**1.20-2.33**	**0.002**
BUN	**1.01**	**1.01-1.02**	**0.001**
Creatinine	**1.66**	**1.19-2.33**	**0.003**
Serum Sodium	**0.86**	**0.82-0.89**	**<0.001**
Bilirubin	**1.67**	**1.36-2.04**	**<0.001**

Legend: BUN: blood urea nitrogen. OR: Odds ratio: CI:95% confidence interval

Table 3. - Multivariate logistic regression models with non-invasively and invasively measured variables

	Wald χ^2	p	OR(CI)	AUC
Multivariate non-invasive				
Serum sodium	**37.55**	**<.0001**	0.88(0.84-0.91)	
LVEF	**19.13**	**<.0001**	0.95 (0.93-0.97)	
NYHA Class III-IV vs. NYHA Class I-II	**14.16**	**0.0002**	1.79 (1.32-2.44)	**0.720**
Mitral regurgitation 2-3 vs. 0-1	**8.32**	**0.0039**	1.55 (1.15-2.09)	
Anemia	**3.91**	**0.04**	1.44 (1.00-2.06)	
Multivariate non-invasive model including peak VO_2				
Serum sodium	**30.4487**	**<.0001**	0.88(0.84-0.92)	
LVEF	**12.759**	**0.0004**	0.95 (0.93-0.98)	
NYHA class III-IV vs. I-II	**8.729**	**0.0031**	1.64 (1.18 -2.82)	**0.719**
VO_2 peak	**7.862**	**0.005**	0.94 (0.90-0.98)	
Mitral regurgitation 2-3 vs. 0-1	**6.519**	**0.0107**	1.51 (1.10-2.08)	
Multivariate invasive model				
RAP	**22.098**	**<.0001**	1.086 (1.04-1.12	
Serum sodium	**20.665**	**<.0001**	0.90 (0.86-0.94)	
LVEF	**15.629**	**<.0001**	0.95 (0.93-0.97)	**0.719**
Mitral regurgitation 2-3 vs. 0-1	**5.891**	**0.0152**	1.48 (1.08-2.05)	
NYHA class III-IV vs. I-II	**5.481**	**0.019**	1.49 (1.06-2.07)	

Legend: AUC: area under the receiver operator characteristic (ROC) curve.

Table 4. - Laboratory findings characteristics in all patients and in the patients with and without anemia

	All	Anemic	Non-anemic	p
Hemoglobin (g/dl)	**13.5±1.8**	**10.8±1.1**	**14.2±1.3**	**<0.001**
Red cell count (x 10^{12}/l)	**4.6±.6**	**4.0±.6**	**4.7±.5**	**<0.001**
White cell count (x 10^9/l)	**7.3±1.9**	**7.0±2.0**	**7.3±1.9**	**Ns**
Platelet count (x 10^9/l)	**222±71**	**233±84**	**219±67**	**Ns**
Potassium (meq/l)	**4.3±0.4**	**4.3±0.4**	**4.3±.4**	**Ns**
BUN (mg/dl)	**55±26**	**64±32**	**53±23**	**<0.001**
Creatinine(mg/dl)	**1.24±0.45**	**1.33±0.45**	**1.22±0.45**	**<0.001**
Serum sodium (meq/l)	**139±4**	**138±4**	**139±4**	**<0.03**
Albumin (g/dl)	**4.37 ±.83**	**4.1±.51**	**4.6±.50**	**<0.001**
Cholinesterases	**8730±2762**	**7489±2671**	**9033±2701**	**0.003**
Cholesterol (mg/dl)	**197±49**	**179±54**	**202±46**	**<0.001**
Bilirubin (mg/dl)	**1.15±0.67**	**1.17±.65**	**1.17±.67**	**Ns**

Legend: BUN: blood urea nitrogen.

Discussion

The present study, conducted in a large cohort of patients with CHF of different etiologies and with various degrees of cardiac dysfunction, demonstrates that anemia is associated with prognosis in CHF. Our study confirms and extends previous evidence.[3-5,9-20] In agreement with previous studies, anemia was associated with a worse NYHA functional class, exercise capacity and hemodynamic profile (table 5). However this study is the first that analyzed the independent prognostic power of anemia among other considered non-invasive and invasive prognostic indices which are validated in routine clinical practice. In agreement with previous studies it identifies the relationship between anemia and a "hard" cardiac event but highlights the fact that the use of complex non-invasive and invasive prognostic models obtained in different settings provides similar prognostic power to that with the simpler measurement of anemia.

This result can be explained by the close physiopathologic relationship that exists between anemia and the different prognostic determinants.[21]

Anemia in chronic heart failure

Several different factors may work together in CHF to cause anemia. Impaired renal function and

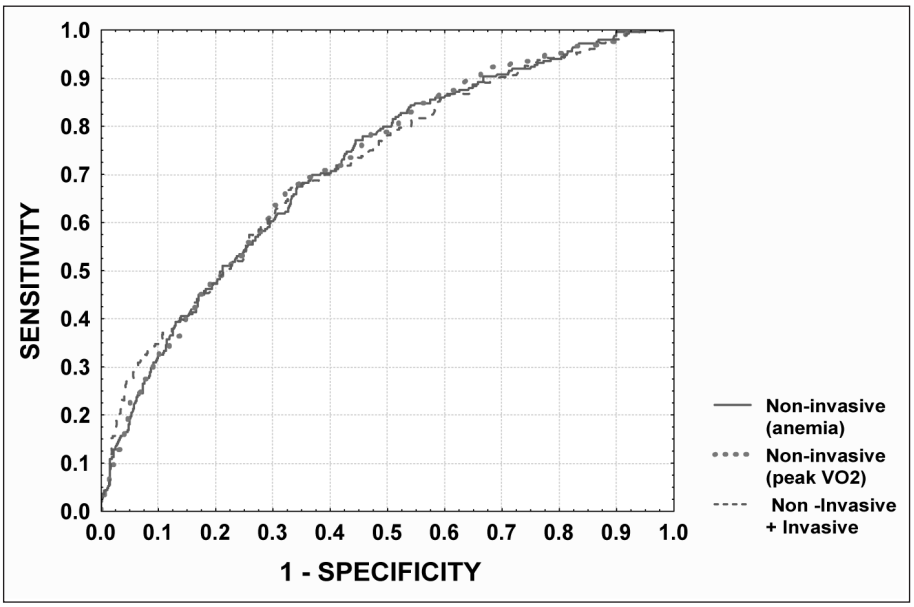

Figure 2. - ROC curves for the combined end-point of cardiac mortality or urgent heart transplantation using non-invasive and invasive models.

disturbance of erythropoietin metabolism can be associated with anemia; on the other hand, lower Hb can be associated with higher creatinine. Recent data show how the use of erythropoietin can modify prognosis in CHF patients.[4] We analyzed our patients in two groups according to whether they did or did not have renal failure and found that the association between low Hb and increased cardiac mortality was present in both subsets of patients; likewise, in the SOLVD study, anemia was related to an increased risk of mortality after adjustment for renal dysfunction.[11] These apparent discrepancies can be explained by the different etiologies of the anemia in the various CHF populations evaluated.

Anemia in CHF is at least partially due to excessive production of cytokines (such as tumor necrosis factor alpha (TNFα)) and leukotrienes that interfere both with the effect of erythropoietin on bone marrow (they inhibit its effect) and the release of stored iron in the reticuloendothelial system.[22] Recent data show that TNFα may suppress both early and late stages of hematopoiesis and can induce programmed cell death with consequent decrease of hematopoiesis.[23]

Only the red cell count was decreased in our anemic patients; platelets and white cell counts were similar to those in the non-anemic patients (table 4). This observation allows us to draw two important implication: first, TNF could play an important role in the genesis of anemia in these patients; second, the anemia cannot be considered simply as the result of hemodilution, or of general illness, because otherwise all the cell lineages would be affected.

Cardiac cachexia due to malnutrition, a catabolic state, malabsorption, and atrophic gastritis can induce anemia in CHF.[24] We analyzed the nutritional state of our population and found that the BMI was lower in anemic patients than in non-anemic ones. Compromised liver function is often associated with chronic heart failure. A conjunction of different causes (hypoxia, chronic congestion, malnutrition) can decrease the biosynthetic capacity of the liver with decreased synthesis of glycine and succinyl-CoA. These alterations could limit the synthesis of the heme group precursor of Δ-aminolevulinate acid and, finally, of hemoglobin.[25,26] In this scenario the final result is the development of mild normocytic anemia. In our cohort of patients, the anemic ones had poorer liver synthesis function (table 4).

Different studies underline the role of anemia in modifying the natural outcome of CHF.[27-31] In this context its prospective prognostic informative content is transferred to already consolidated markers (i.e. NYHA class, mitral regurgitation, volemia, peak VO_2).Thus anemia should also be considered as one of chronic conditions that determine a poor prognosis.

Prognostic models

Various sets of prognostic variables for patients with CHF have been proposed in the literature. In a scenario in which it is essential to consider scarce resources,[32] it is important to identify simpler prognostic models that are practical in different settings. In primary care, a simple model containing anemia and other established non-invasive markers can stratify risk and identify patients who should be referred to specialist intensive care. In this simple model the parameters of peak VO_2 and anemia compete. Peak VO_2 showed a greater prognostic power because it combines both oxygen transport capacity (i.e. hemoglobin) but also it's central and peripheral determinants. The multivariate model selects this variable instead of anemia. But cardiopulmonary exercise test (VO_2) are rarely performed in the context of community care and their prognostic power is weakened by the wide range of values.[33] In contrast when anemia is considered in the model, prognostic accuracy remains substantially unchanged. Analogous considerations could also be made for invasive variables.

Open clinical questions

Although our results once again underline the strong link between anemia, CHF and mortality, there are many unclear areas in this relationship that deserve further investigation. Currently there are no data about the type of anemia in patients with chronic heart failure. Silverberg analyzed the correlation between chronic diseases (such as chronic renal failure, chronic heart failure, chronic inflammatory bowel disease and rheumatoid arthritis) and anemia.[4] Differences between anemia Classifica-

Table 5. - Summary of published reports on prognosis of anemia in patients with chronic heart failure

Authors	Year	N. pts	Age	NYHA I-II/III-IV	LVEF	Anemia (%)	Type of study	FU months	Covariates adjustments	Therapy optimization	NC	Ref
Alexander	1999	90316	73.2	NA	NA	NA	R	12	Age, secondary diagnoses	NA	NA	9
Silveberg	2000	142	71±8	26/74	32±11	<12 (55.6)	P	-	-	-	Yes	4
Felker	2001	949	66±14	6.7/92.3	24±8	Hb<13(F) Hb<12(M) (49)	R	2	**DEATH** Age, NYHA, Systolic blood pressure, BUN Sodium **DEATH+ REOSPITALIZATION** HF, duration HF hospitalization creatinine Hemoglobin	Age, ACEI: 70% ARB: 1212.5% Beta-blockers: 22.3% Diuretics: 90.2% Digoxin: 72.9% Calcium channel blockers 13.2 Amiodarone: 15.4%	Yes	10
Al-Ahmad	2001	6635	60±10	88/12	27±6	Htc≤39% (22) Htc<35% (4.3)	R	33.4	Gender, treatment assignement Trial assignement, NYHA functional class, LVEF, Hypertension, etiology of left ventricular dysfunction, diabetes, beta-blockers, digoxin and diuretics use, GFR	Beta-blockers 18% Diuretics 42% Digoxin 33%	Yes	11
Polanczyk	2001	205	72±12	NA	41±19	NA	P	3	3 admission for CHF, low diastolic pressure, high BUN Low Hematocrit (univariate analysis)			12
Horwich	2002	1061	52±13	-/100	22±7	≤13 (30)	P	12	Age, gender, BMI, LVEDD, (Hypertension, diabetes, smoking) History, Serum sodium, albumin, creatinine HF etiology	ACEI use Hb≥12.3: 73% Hb< 12.3 64.6% Other drugs non available	Yes	3
McClellan	2002	665	76±11	74/26	38±17 NA in 40%	Htc≤30% (13.6) 30-35% (33.2) 36-39% (22.9) >40 (30.3)	R	12	Age, gender, race LVEF Comorbidity history Hypertension NYHA	NA	Yes	13
Tanner	2002	193	54±10	43/57	29±13	Hb<12 (15)	R	17	No differences in mortality between anemic and non anemic patients	ACEI 85% Beta blockers 38% Diuretics 92% Spironolactone 58%	Yes	14

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(segue) Table 5. - Summary of published reports on prognosis of anemia in patients with chronic heart failure

Authors	Year	N. pts	Age	NYHA I-II/III-IV	LVEF	Anemia (%)	Type of study	FU months	Covariates adjustments	Therapy optimization	NC	Ref
Maggioni In-CHF	2002	2411		NA	NA	Hb<12 F Hb<11 M (15.5)	R	12	NA	NA	NA	15
Maggioni Val- HeFT	2002	5010	NA	NA	NA	Hb<12 F Hb<11 M (9.9)	R	12	NA	NA	NA	15
Androne	2003	196	52±11	NA	M(23±9) F(29±11)	Htc<41% M(64) Htc<38% F(52)	P	12	NA	NA	NA	16
Szachniewicz	2003	176	62±12	55/45	42±11	≤12 (10)	P	18	NYHA LVEF	Beta-Blockers 37% ACEI 52% Diuretics 40%	Yes	17
Ezekowitz	2003	12065	78±12	NA	NA	NA	R	12 60	Age, gender, BMI, (Hypertension, diabetes, COPD) History, Hyperlipidemia CAD, cerobrovascular disease, Atrial fibrillation, chronic renal insufficiency, malignancy	NA	NA	18
Kosiborod	2003	2281	79±8	NA	≤20(11%) ≤40(14%) >40(38%) NA(27%)	Htc≤37% (48)	R	12	Age, gender, LVEF, CCI creatinine, Sodium Systolic blood pressure terminal illness	ACEI 37% Beta-blockers 21% Diuretics 69% Ca++channel blockers 40% Digoxin 41%	Yes	5
Sharma	2004	3044	71.5±6.8	2.5±0.6	31±7	Hb≤12.5 (16) 12.5-3.9 (30) 14-15 (30) >15 (24)	R	24	Age, gender, LVEF, NYHA class Serum creatinine, COPD	NA	NA	19
Anand	2004	912	62±12	23/77	22±6	Hb<12 (12) Hb<12.5 (20)	R	12.7	Use Beta-Blockers Antiarrhythmic NYHA DBP Serum creatinine	ACEI 78% ARB 19% Beta-blockers 59% Diuretics 98% K+ sparing diuretic 34% Digoxin 4182	Yes	20

ACEI: ACE-inhibitors; ARB: angiotensin recepetor blockers; BUN: blood urea nitrogen; CCI: Charlson Comorbidity Index; F: female; FU: follow-up; GFR: Glomerular filtration rate; HF: heart failure; K+: potassium; LVEF: left ventricular ejection fraction; M: months; M: men; NA: non available; NC: Negative correlation between anemia and NHYA; NHYA: New York Heart Association; P: prospective study; R: retrospective study; Ref: references.

tion, population characteristics, study design, therapeutic optimization limits the comparison between several studies. The prognostic power of anemia in many reports was not adjusted for all established non-invasive and invasive prognostic variables (table 5). Gender and diastolic heart failure have not been evaluated in the different studies. Silverberg showed favorable clinical results after the use of erythropoietin and iron, but in a randomized clinical trial in anemic patients with end-stage renal and heart failure, normalization of hematocrit produced by erythropoietin and iron infusion was associated with increased myocardial infarction.[34] Currently there are few data about the relationship between hemoglobin changes and long term prognosis in CHF patients.[20]

Study limitations

This study has limitations. First, we examined selected patients who were entering a heart transplantation program. Second, elderly patients, those with diastolic heart failure, and women were underrepresented. Third, the etiology of the anemia was not studied. Finally, several iatrogenic causes of anemia and possible therapeutic treatments undertaken, which could have conditioned the clinical outcome, were not considered.

Conclusions

The present study was conducted in a large cohort of patients with CHF of different etiology and degree of cardiac dysfunction. The study demonstrates that anemia was associated with a worse NYHA functional class, exercise capacity and hemodynamic profile. We found that the relationship between anemia and mortality is independent of non-invasive established prognostic factors. In a selected prognostic model using simple non-invasive predictors which include anemia, the addition of complex independent predictors did not increase the accuracy of the model in predicting cardiac mortality. Supplementary studies are needed to understand the etiology and pathology of anemia in CHF patients in order to verify whether treatment of anemia will indeed improve survival.

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LIST OF ABBREVIATIONS

CHF: chronic heart failure
Hb: hemoglobin
LVEF: Left ventricular ejection fraction
Pts: patients
AUC_{ROC}: Area Under Curve Receiver Operator Curve
ROC: Receiver Operator Curve

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