Temporal variations in hematocrit values in patients with left ventricular dysfunction: Relationship with cause-specific mortality and morbidity and optimal monitoring – further insights from SOLVD

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S de Denus, J-C Tardif, M White, et al. Temporal variations in hematocrit values in patients with left ventricular dysfunction: Relationship with cause-specific mortality and morbidity and optimal monitoring – further insights from SOLVD. *Can J Cardiol* 2008;24(1):45-48.

BACKGROUND: Anemia is associated with an increased risk of death in heart failure (HF) patients. Currently, the relationship between temporal variations in hematocrit and specific causes of mortality and morbidity, as well as the most appropriate way to monitor changes in hematocrit, is unknown.

OBJECTIVE: To evaluate the prognostic value of changes in hematocrit during follow-up on specific causes of mortality and morbidity in the Studies Of Left Ventricular Dysfunction (SOLVD).

METHODS: A retrospective analysis of the SOLVD trials was conducted. Changes in hematocrit were evaluated in two ways: hematocrit as an absolute value at baseline and at each visit, and relative hematocrit variations compared with baseline.

RESULTS: Low absolute hematocrit values during follow-up were associated with cardiovascular (CV), non-CV and HF mortality, HF and non-CV hospitalizations, and cardiac ischemic events ($P < 0.05$ for all end points). Decreases in hematocrit during follow-up compared with baseline were associated with HF hospitalizations ($P < 0.05$) and non-CV death in patients receiving placebo ($P = 0.01$ for interaction).

CONCLUSIONS: Hematocrit values during follow-up provide independent prognostic information in patients with HF for both CV and non-CV events. Absolute values of hematocrit are more closely related with outcomes and are therefore more clinically relevant to monitor than relative variations.

Key Words: Anemia; Congestive heart failure; Morbidity; Mortality

Anemia is a common comorbidity in patients with heart failure (HF), being present in 12% to 61% of patients (1-4). It is independently associated with increased mortality, regardless of HF severity (1-3,5-7). Nonetheless, controversy persists as to whether the presence of anemia reflects comorbidity, relates to the severity of the cardiac dysfunction, or truly independently relates to prognosis.

Recent data from the Candesartan in Heart Failure: Assessment of Reduction in mortality and Morbidity (CHARM) program (8) have suggested that anemia at baseline is not only associated with all-cause and HF mortality, but also with sudden death, fatal myocardial infarction and noncardiovascular (CV) death. In addition, data from the

Des variations temporelles des valeurs d'hématocrite chez des patients atteints d'une dysfonction ventriculaire gauche : La relation avec la mortalité et la morbidité par cause et la surveillance optimale – d'autres points de vue des SOLVD

HISTORIQUE : L'anémie s'associe à une augmentation du risque de décès chez les patients atteints d'insuffisance cardiaque (IC). On ne connaît ni le lien entre les variations temporelles d'hématocrite et les causes précises de mortalité et de morbidité, ni le moyen le plus pertinent de surveiller les changements d'hématocrite.

OBJECTIF : Évaluer la valeur pronostique des changements d'hématocrite pendant le suivi sur les causes exactes de mortalité et de morbidité des études SOLVD sur la dysfonction ventriculaire gauche.

MÉTHODOLOGIE : Les auteurs ont procédé à une analyse rétrospective des études SOLVD. Ils ont évalué les changements d'hématocrite de deux façons : l'hématocrite comme valeur absolue à la première consultation et à chaque consultation suivante, et les variations relatives d'hématocrite par rapport à la valeur de départ.

RÉSULTATS : De faibles valeurs d'hématocrite absolues au suivi s'associaient à une mortalité cardiovasculaire (CV), non CV et imputable à l'IC, à des hospitalisations attribuables à l'IC et à des raisons non CV ainsi qu'à des cardiopathies ischémiques ($P < 0,05$ pour tous les paramètres ultimes). Des diminutions d'hématocrite au suivi par rapport aux valeurs de base s'associaient à des hospitalisations imputables à l'IC ($P < 0,05$) et à des décès non CV chez les patients qui prenaient un placebo ($P = 0,01$ pour l'interaction).

CONCLUSIONS : Les valeurs d'hématocrite pendant le suivi fournissent de l'information pronostique indépendante chez les personnes atteintes d'IC pour ce qui est des événements CV et non CV. Les valeurs absolues d'hématocrite sont plus étroitement liées aux issues et sont donc plus pertinentes à surveiller d'un point de vue clinique que les variations relatives.

Studies Of Left Ventricular Dysfunction (SOLVD) (9) and the Valsartan Heart Failure Trial (Val-HeFT) (10) have suggested that temporal changes in hematocrit also provide prognostic information. It remains unknown whether absolute values or relative variations are more closely related to outcomes in patients with HF, and whether these variations are related to specific causes of CV and non-CV death.

The objectives of the present study were to assess the relationship between hematocrit changes, as time-dependent variables, and the specific causes of mortality and morbidity in patients randomly assigned in the SOLVD trials, and to determine the best way to monitor

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Received for publication May 26, 2006. Accepted November 19, 2006

TABLE 1
Baseline characteristics (n=6538)

Characteristic	
Male sex, %	85.8
Age, years (mean $\pm$ SD)	59.9 $\pm$ 10.2
Ethnicity, %	
Caucasian	84.5
African American	11.5
Other	4.1
Etiology, %	
Ischemic	79.0
Baseline left ventricular ejection fraction, % (mean $\pm$ SD)	27.0 $\pm$ 6.3
New York Heart Association class, %	
I	46.0
II	42.1
III or IV	12.0
History of hypertension, %	38.8
History of angina, %	57.3
History of myocardial infarction, %	75.0
History of cerebrovascular accident, %	6.6
History of atrial fibrillation, %	6.4
History of diabetes, %	19.0
Current smoker, %	22.9
Baseline systolic blood pressure, mmHg (mean $\pm$ SD)	125 $\pm$ 17
Baseline diastolic blood pressure, mmHg (mean $\pm$ SD)	78 $\pm$ 10
Baseline sodium, mmol/L (mean $\pm$ SD)	140.0 $\pm$ 3.0
Baseline creatinine, μ mol/L (mean $\pm$ SD)	106 $\pm$ 27
Baseline estimated GFR*, mL/min/1.73 m ² (mean $\pm$ SD)	70.3 $\pm$ 19.3
Hematocrit (mean $\pm$ SD)	42.7 $\pm$ 4.5

*According to the abbreviated Modification of Diet in Renal Disease (13) equation. GFR Glomerular filtration rate

hematocrit changes. The use of time-dependent variables permits evaluation of the relationship between variables as they change over time with the end point of interest. We hypothesized that low or decreasing hematocrit levels are associated with increased mortality and morbidity.

PATIENTS AND METHODS

Patients

A retrospective analysis of the SOLVD trials was conducted. The methods of the SOLVD trials have been reported elsewhere (11,12). In brief, the SOLVD trials were multicentre, randomized, double-blinded, placebo-controlled studies evaluating the benefits of enalapril in patients with left ventricular dysfunction (ejection fraction 35% or lower). Patients enrolled in the SOLVD prevention trial (11) had depressed left ventricular function not requiring pharmacological treatment, while patients included in the SOLVD treatment trial (12) had overt HF requiring treatment. Major exclusion criteria included a baseline serum creatinine higher than 221 μ mol/L. For the purpose of the present analysis, only patients who had a documented hematocrit at baseline and at least one hematocrit measurement available during follow-up were included.

End points

The authors assessed the relationship between changes in hematocrit during follow-up and specific causes of mortality (CV mortality, death from HF, death from arrhythmias without worsening HF and non-CV mortality), non-CV and HF hospitalizations, and cardiac ischemic events (fatal and nonfatal myocardial infarction, and hospitalizations for new or worsening angina).

Statistical analysis

Continuous data are presented as mean $\pm$ SD and categorical variables are presented in percentages. The predictive value of changes in hematocrit over time was evaluated in two ways: the absolute values at baseline and during follow-up and the relative variations in relation to

baseline. To assess the independent value of hematocrit on a specific outcome, a univariate analysis was performed with the following baseline variables for each outcome: age, sex, ethnicity, history of atrial fibrillation, angina pectoris, myocardial infarction, hypertension, diabetes, cerebrovascular events, current smoking habit, primary ischemic cause of left ventricular dysfunction, baseline left ventricular ejection fraction, functional capacity (New York Heart Association classification), random assignment to enalapril, use of medications (antiplatelets, anticoagulants, beta-blockers, potassium-sparing diuretics, loop diuretics, thiazide diuretics, metolazone and digitalis), systolic and diastolic blood pressure, serum sodium concentration and renal function. Renal function was evaluated by estimating the glomerular filtration rate (GFR) using the abbreviated Modification of Diet in Renal Disease equation (13). To be consistent with the evaluation of hematocrit changes over time, renal function was included as a time-dependent variable in the respective models as follows: the absolute values at baseline and during follow-up, and the relative variations compared to baseline. All variables with $P \leq 0.25$ by univariate analysis were entered into a multivariate Cox regression model. Data analysis was performed using SAS version 8.2 (SAS Institute, USA).

RESULTS

A total of 6538 patients were included. Baseline characteristics are presented in Table 1. The mean follow-up was 2.7 $\pm$ 1.2 years, with an average of 5.0 $\pm$ 2.8 hematocrit samples per patient available during follow-up.

A total of 1509 patients (23.1%) died during follow-up. Of these, 1335 (20.4%) died of CV causes (624 [9.5%] died of pump failure, 398 [6.1%] died of arrhythmia and 313 [4.8%] died of other CV causes) and 174 (2.7%) died of non-CV causes. In addition, 1199 patients (18.3%) were hospitalized for HF, while 1312 patients (20.1%) experienced a cardiac ischemic event. Finally, 1977 patients (30.2%) experienced a non-CV hospitalization.

CV events

After adjusting for possible confounders, including renal function, low absolute hematocrit values during follow-up were associated with the risk of CV mortality, HF death, HF hospitalization and cardiac ischemic events (Tables 2 and 3). Relative hematocrit variations were only modestly related to the risk of HF hospitalization. No association between arrhythmic death and hematocrit was observed.

Non-CV events

Absolute values of hematocrit over time were the strongest predictor of non-CV mortality and the second strongest predictor of non-CV hospitalization after age (data not shown for age) (Tables 2 and 3). Decreases in hematocrit during follow-up were associated with non-CV death in patients receiving placebo ($P=0.01$ for interaction).

Renal function

Absolute GFR during follow-up was a powerful predictor of all end points except cardiac ischemic events, while the predicting value of GFR variations during follow-up was more limited (Tables 2 and 3).

DISCUSSION

Previous studies (1,6,7,14,15) established that single baseline hematocrit and hemoglobin values provide prognostic information in patients with HF. More recent data (9,10) suggested that temporal changes in these markers also offer additional prognostic information. Our results demonstrate that absolute values are more closely associated to specific causes of mortality and morbidity than relative variations, making them more clinically relevant to monitor.

Our results provide other important findings, with the first detailed information regarding the specific causes of mortality and morbidity in HF patients related to temporal variations in hematocrit. Our analysis suggests that low hematocrit levels are closely related to HF death and hospitalization, but have no relationship with arrhythmic

TABLE 2
Predictive value of time-dependent hematocrit for mortality end points*

Variable	Cardiovascular mortality			Death from pump failure			Arrhythmic death			Noncardiovascular mortality		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Model 1												
Baseline hematocrit value†	1.02	0.95–1.10	0.57	1.04	0.93–1.15	0.53	1.02	0.88–1.17	0.83	0.96	0.80–1.16	0.68
Absolute hematocrit value during follow-up†	1.17	1.08–1.26	<0.0001	1.16	1.04–1.29	0.007	1.10	0.95–1.26	0.21	1.77	1.54–2.04	<0.0001
Baseline GFR‡	0.99	0.95–1.03	0.69	0.99	0.94–1.05	0.74	1.03	0.96–1.11	0.43	1.14	1.01–1.28	0.03
Absolute GFR during follow-up‡	1.12	1.08–1.17	<0.0001	1.13	1.07–1.20	<0.0001	1.09	1.01–1.18	0.03	0.89	0.81–0.99	0.03
Model 2												
Hematocrit variations§	1.05	0.99–1.11	0.08	1.03	0.96–1.12	0.40	1.04	0.93–1.15	0.51	Enalapril: 1.14 Placebo: 1.59	0.93–1.40 1.36–1.87	0.21** <0.0001
GFR variations¶	1.06	1.04–1.09	<0.0001	1.07	1.03–1.11	0.0006	1.04	0.99–1.09	0.13	0.94	0.88–1.00	0.06

The relative variations of hematocrit were calculated as follows: (follow-up_i count – baseline count)/baseline count, where *i* = samples at follow-up visits. *After adjusting for demographics, past medical history, baseline evaluation and medication use; †For each 5% in hematocrit decrement; ‡For a 10 mL/min/1.73 m² decrement in glomerular filtration rate (GFR); §For each 10% diminution in hematocrit during follow-up; ¶For each 10% diminution in estimated GFR during follow-up; **Significant treatment interaction (*P*=0.01)

TABLE 3
Predictive value of time-dependent hematocrit for hospitalization and cardiac ischemic events*

Variable	Heart failure hospitalization			Cardiac ischemic events			Noncardiovascular hospitalization		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Model 1									
Baseline hematocrit value†	1.01	0.93–1.09	0.91	0.95	0.88–1.03	0.24	1.04	0.97–1.11	0.28
Absolute hematocrit value during follow-up†	1.21	1.12–1.32	<0.0001	1.10	1.02–1.20	0.02	1.15	1.08–1.23	<0.0001
Baseline GFR‡	0.96	0.92–1.00	0.045	1.01	0.97–1.05	0.69	1.02	0.98–1.05	0.30
Absolute GFR during follow-up‡	1.14	1.09–1.19	<0.0001	1.03	0.99–1.08	0.13	1.04	1.00–1.07	0.04
Model 2									
Hematocrit variations§	1.07	1.01–1.14	0.03	1.05	0.99–1.11	0.11	1.04	0.99–1.09	0.12
GFR variations¶	1.07	1.04–1.10	<0.0001	1.02	0.99–1.05	0.18	1.01	0.99–1.03	0.28

The relative variations of hematocrit were calculated as follows: (follow-up_i count – baseline count)/baseline count, where *i* = samples at follow-up visits. *After adjusting for demographics, past medical history, baseline evaluation and medication use; †For each 5% in hematocrit decrement; ‡For a 10 mL/min/1.73 m² decrement in estimated glomerular filtration rate (GFR); §For each 10% diminution in hematocrit during follow-up; ¶For each 10% diminution in estimated GFR during follow-up

death. Furthermore, we provided the first data demonstrating a relationship between temporal variations in hematocrit and cardiac ischemic events. Our results are consistent with those of the CHARM program and the risks of anemia, with the exception of sudden death, for which the investigators observed a significant association (8).

In addition, absolute hematocrit was the strongest predictor of non-CV death and non-CV hospitalization, along with age. Again, these results are consistent with the observations of the CHARM investigators (8). Whether these relationships reflect a direct effect of anemia or the presence of comorbidities remains uncertain, but nonetheless, they demonstrate that an important number of adverse events related with low hematocrit levels in HF patients are non-CV.

Finally, our results confirm previous findings regarding the powerful prognostic value of renal function in patients with HF for CV events (16–19), as absolute estimated GFR during follow-up was related to CV, HF and arrhythmic mortality, and HF hospitalization.

Possible mechanisms

The mechanisms linking low hematocrit values to worse clinical outcomes have not been fully identified. On one hand, low hematocrit levels can have a direct influence on the evolution of HF by modifying ventricular mass (20), promoting myocardial ischemia or neurohumoral activation (21), or by increasing circulating concentrations of free radicals, because erythrocytes contain a significant amount of antioxidant enzymes (22). On the other hand, low hematocrit levels may also reflect other underlying phenomena. Iron, folate or vitamin B₁₂ deficiencies secondary to poor nutrition or malabsorption are possible factors contributing to the development of anemia in HF

patients, although previous reports have demonstrated that nutrient deficiencies are responsible for only a minority of the cases of anemia found in patients with HF (30% or fewer) (5,23).

Decreased hematocrit levels may also reflect hemodilution. In one study (1), almost one-half of anemic HF patients had normal red blood cell volume with excess plasma volume, leading to low hematocrit values and high pulmonary wedge pressure. Nonetheless, in a large HF cohort (*n*=1061), Horwich et al (2) demonstrated that the prognostic value of hemoglobin was independent of pulmonary wedge pressure, suggesting that the prognostic value of hematocrit goes beyond the plasma volume status.

Because impaired renal function is associated with decreased erythropoietin production by the kidneys and, subsequently, anemia, some advocate that the prognostic importance of hematocrit in HF patients may only reflect the presence of renal dysfunction, an established risk factor for mortality and morbidity in this population (16–19). Our findings and the results from others (2,6,7,14) have shown that the prognostic value of hematocrit level as a time-dependent variable is independent of the presence of renal dysfunction. More importantly, the prognostic value of hematocrit in our study was independent of the changes in renal function over time, which have also been shown to be a powerful predictor of outcomes (24,25).

Similar to what is observed in the anemia of chronic diseases, low hematocrit levels or anemia may also be the consequence of high levels of immune markers, such as tumour necrosis factor- α (26), a predictor of mortality in HF patients (27). Indeed, tumour necrosis factor- α and other cytokines (26) interfere with both erythropoietin production by the kidney and its effects on the bone marrow, in addition to reducing red cell survival (28).

Limitations

The SOLVD trials may not reflect current practice, because pharmacological and nonpharmacological treatment of HF has greatly evolved in the past two decades. Although we adjusted for drug treatment and known predictors of mortality, we cannot exclude that residual confounders may explain some of our results, particularly changes in comorbidities during the study follow-up. Although we included an extensive number of variables in our multivariate model, we cannot exclude that the worse prognosis found in anemic patients may reflect a higher prevalence of other comorbid conditions not fully evaluated in the present study, such as depression, uncontrolled diabetes or neoplasms. This might have been particularly relevant with regard to non-CV events. Finally, it is important to highlight that there was no adjudicating committee as part of SOLVD and that the classification of the mode of death relied solely on the local investigators. Therefore, the classification of death in this population may be imprecise (29).

CONCLUSIONS

Low hematocrit levels are associated with an increased risk of CV, non-CV and HF mortality, HF and non-CV hospitalization, and cardiac ischemic events. Our results highlight that absolute hematocrit values over time are more clinically relevant to monitor than are relative variations. Additional investigations are required to pinpoint the exact mechanisms responsible for the relationship between anemia and prognosis in HF patients. The hypothesis that therapies directed toward increasing hematocrit levels are potentially life-saving is appealing (30) but awaits confirmation from large clinical trials.

ACKNOWLEDGEMENTS: Drs Ducharme and White were supported by the Fonds de recherche en santé du Québec. Dr Tardif holds the Pfizer and Canadian Institutes of Health Research position of Chair in Atherosclerosis.

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