Anemia and Congestive Heart Failure

To the Editor:

With great interest we read the article by Ezekowitz et al focusing on the high prevalence and possible causes of anemia in patients with congestive heart failure. Most patients in their cohort had anemia of chronic disease. In patients with cardiomyopathy, anemia obviously coincides with immune activation, given that raised concentrations of immune activation markers such as neopterin were found in patients, correlating with left ventricular functional tests and New York Heart Association classes. Neopterin is formed by human macrophages on stimulation with interferon-γ (IFN-γ) in scope with Th1-type immune response. IFN-γ, especially in cooperation with tumor necrosis factor α, is well known to suppress the growth of erythroid precursor cells and appears to be deeply involved in the pathogenesis of anemia of chronic diseases. The suppressive effect of IFN-γ on hematopoiesis is so far mainly attributed to direct cytokine interaction with bone marrow stem cells; still, the exact mechanisms underlying this process remain unclear. A possible explanation for hematopoietic suppression could be an accelerated tryptophan degradation, because IFN-γ induces enzyme indolamine-2,3-dioxygenase, which converts the essential amino acid tryptophan to kynurenine. Tryptophan is essential for indolamine-2,3-dioxygenase, which converts the essential amino
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Anemia has recently become an important issue in patients


Katharina Schroecksnadel, MD
Barbara Wirleitner, PhD
Dietmar Fuchs, PhD
Institute of Medical Chemistry and Biochemistry
University of Innsbruck
Innsbruck, Austria


To the Editor:

We read with great interest the study by Ezekowitz et al about the frequency, type, and prognostic impact of anemia in patients with chronic heart failure (CHF). It is important to know more about the frequency of anemia in the community, as anemia still is an underestimated risk factor in CHF. Ezekowitz et al used the International Classification of Diseases (9th revision) coding results to define the presence of anemia. Therefore, this analysis relies on physicians to consider anemia as a possible diagnosis when registering the coding. This may seem trivial, but one needs to consider that the database refers to data collected mostly before the year 2000. Before that time, knowledge about and awareness of anemia in CHF among cardiologists and other physicians treating these patients was low and probably mainly guided by information from nephrologists. Nephrologists generally consider anemia (requiring intervention) to be present when hemoglobin levels are below 8, 9, or 10 g/dL. Cardiologists aim to intervene at a much earlier stage and consider clinically relevant anemia to be present when hemoglobin level is <12.0, 12.5, or even 13.0 g/dL. Hence, the database presented may underestimate the prevalence of anemia in CHF.

Using coded data, it may be possible to analyze the frequency and prognostic impact of polycythemia (versus anemia) in CHF. Are such data available? Additionally, we wonder about the term “new-onset heart failure” used by Ezekowitz et al. How can the authors know this was new onset of heart failure, if—for instance—a patient had an episode of heart failure elsewhere or before 1993?

Finally, we wonder how to explain the great discrepancy between the data presented by Ezekowitz et al at the American Heart Association Scientific Sessions in November 2002 and the present paper. In the previous presentation, based on what seems to be the same database (with identical search dates, community area, and search codes), 29 302 CHF patients were found; in the present paper, there are only 12 065 patients.

Wolfram Steinborn
Piotr Ponikowski, MD, PhD, FESC
Stefan Anker, MD, PhD
Imperial College
National Heart and Lung Institute
London, United Kingdom


To the Editor:

Anemia has recently become an important issue in patients with heart failure, and in the January 21, 2003 issue of Circulation, 3 studies relating to this subject were published1–3 In one of these studies, Ezekowitz et al showed that anemia is common and is an independent prognostic marker for mortality in community-based patients with congestive heart failure (CHF). To determine the prevalence of anemia, the authors used the International Classification of Diseases, 9th revision (ICD-9). In using this method, however, the authors did not provide a cutoff value for when they considered patients to be anemic. In the recent literature, there is some controversy about the prevalence of anemia in patients with CHF, which not only depends on the severity of CHF, but also on the definition of anemia.4 Therefore,
it would have been important to know which hemoglobin values were used to define anemia.

Furthermore, the authors determined the prevalence as follows: ICD-9 codes 280 to 289 to capture "all anemia" and ICD-9 code 285.9 to capture "anemia of chronic disease." This method also has its limitations, because, for example, serum albumin levels may be decreased in CHF patients, indicating that malnutrition and malabsorption may also result in anemia.5 Also, many CHF patients use anticoagulants, and chronic (microscopic) blood loss may well play a role. Therefore, it would have added significant value if the authors had also evaluated the incidence of iron and vitamin deficiency anemias in their study.

**Response**

We appreciate the interest of Drs van der Meer, Fuchs, Steinborn, et al on anemia and congestive heart failure. We agree that the pathogenesis of anemia in congestive heart failure is complex and at least partly related to inflammatory mediators. Additionally, there are likely modulating roles for erythropoietin resistance,1 the renin-angiotensin axis,2 and medications such as angiotensin-converting enzyme inhibitors.3

Although early studies demonstrated a link between neopterin and cardiovascular disease,4 subsequent investigations have failed to confirm this.5 This complex pathway of tryptophan metabolism likely has many avenues that deserve exploration.

Interferon-γ directly inhibits erythroid progenitor cells' capacity for erythropoiesis; this may be mediated in part by nitric oxide, which blocks heme biosynthesis.1

Regardless of the underlying mechanistic cause(s) for anemia associated with congestive heart failure, treatment of the underlying heart failure with appropriate evidence-based therapies should be the primary goal. Ultimately, elucidation of the putative cellular mechanisms for the associated anemia may lead to more specific clinical strategies.

Steinborn and colleagues question the use of administrative data for examining the prevalence of anemia in the community. While they are correct that the recognition of anemia as a significant comorbidity in heart failure is relatively recent for cardiologists, the coding for anemia is (and has) been consistently done by trained health records abstractors in our locale throughout the entire study time period, and does not rely solely on recognition by the physician of record (see References 5 and 6 of the original paper).6 We did not analyze polycythemia in this cohort. The term "new-onset heart failure" relates to a 1-year "washout" to identify patients with recent onset of heart failure. Hence, patients admitted to hospital for heart failure within the preceding year were excluded; when we applied a 1-, 2-, or 5-year washout, the prevalence of anemia (and its prognostic significance) was unchanged.

Finally, the discrepancy in numbers between the 2 analyses relates to 3 factors, which were applied to create a more homogeneous dataset and permit examination between anemia and heart failure with minimum confounding (to obviate concerns that the heart failure diagnosis was secondary to the anemia, making any observed prognostic relationships spurious). First, we restricted our analysis to only those patients with incident heart failure (thus excluding anyone with a pre-existing diagnosis). Second, we analyzed only those patients with a more responsible diagnosis of heart failure, thus excluding any patients with a non–heart failure primary diagnosis and in whom heart failure was a secondary or complicating diagnosis. Third, we excluded patients transferred between hospitals because of concerns of double counting based on recoding pursuant to subsequent in-hospital events. Of note, the prevalence of anemia and its association with worsened outcome was similar in the heterogeneous cohort data previously presented7 and in the more homogeneous cohort data published in *Circulation*. This strengthens our belief that the relationship between anemia and prognosis in heart failure is real and, pending the results of ongoing trials, likely causal.

**Correspondence**

Peter van der Meer, MD
Wiek H. van Gilst, PhD
Dirk J. van Veldhuijzen, MD, PhD
Department of Cardiology
University Hospital Groningen
Groningen, the Netherlands


