REVIEW

Anaemia in heart failure

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Abstract

Despite modern treatment of chronic congestive heart failure, anaemia is associated with significant morbidity and mortality.
Anaemia commonly occurs in patients with heart failure. There is positive correlation between the severity of heart failure and the prevalence and severity of anaemia. Anaemia can play an important role in the natural course of chronic heart failure. Normalisation of haematological parameters in chronic heart failure patients may lead not only to symptomatic improvement but may provide therapeutic benefits. ***(Tab. 2, Ref. 39.)***
Key words: chronic heart failure, anaemia, erythropoietin.

Introduction to chronic heart failure

Congestive heart failure (CHF) is a common syndrome affecting more than 20 million people worldwide and approximately 7 million people in the European community (1). It is a complex syndrome that involves a disturbance of the function of the heart and circulation and which encompasses characteristic changes in endothelial function, neurohormonal activation and metabolic disturbances (2). The incidence and prevalence of CHF increases sharply with age (3).

Despite optimal use of modern, evidence-based treatments, CHF is associated with significant morbidity and mortality. Among patients with severe heart failure, some 60 % will die within one year in the absence of effective treatment. The prognosis for asymptomatic left ventricle dysfunction is considerably better, and approximately 5 % of these patients will die each year (4). Much recent research in this syndrome has been directed to understanding the factors that lead to disease progression, which determine symptomatic status and which predict a poor prognosis (2, 5).

Introduction to anaemia

Anaemia has been recognised to complicate a number of chronic inflammatory and degenerative diseases and to be particularly associated with chronic renal insufficiency (CRI) (Tab. 1) (6, 7). One feature of the syndrome of CHF that has received less attention until recently is the frequency of mild to moderate anaemia (1). Anaemia commonly occurs in patients with heart failure, with mean haemoglobin (Hb) levels at the lower limit of the range considered to be normal in healthy people. This anaemia becomes more prevalent and more severe as heart failure progresses. There is a positive correlation between the severity of heart failure and the prevalence and severity of anaemia (8, 9, 10). In addition, epidemiological studies show that anaemia is an independent risk factor for mortality in patients with heart failure (6, 11, 12, 13, 14). The Framingham Study has shown, that anaemia is an independent risk factor for the development of CHF (15). While anaemia is known to cause heart failure, CHF may also frequently cause anaemia. Furthermore, recent literature suggests a more important role of anaemia in the natural course of CHF. Despite this association of CHF with anaemia, its role is not mentioned in current guidelines and reviews and these documents do not include anaemia as a prognostic factor or as a treatment goal in CHF (16, 17, 18). One possible reason for resistance to treatment could be that anaemia, which is present in many cases of CHF, is not corrected.

About one third to one half of patients with heart failure are anaemic because they have Hb levels of less than 120 g/L. In

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Tab. 1. Prevalence of anaemia by degree of renal dysfunction in chronic renal insufficiency in different studies.

Study	Number of patients	Definition of anaemia	Renal function	Prevalence
Obrador et al., 1999	l55076	Htc < 30%	ESRD	67%
		Htc < 28%		51%
Levin et al.,1999	446	Hb < 13 g/dL	GFR ≥ 50 ml/min	25%
			GFR 35-49 ml/min	44%
			GFR 25-34 ml/min	51%
			GFR < 25 ml/min	87%
Astor et al., 2002	15625	Hb < 12 (11) g/dL in M (F)	GFR ≥ 90 ml/min per 1.73 m^2	1,8%
			GFR 60-89 ml/min per 1.73 m^2	1,3%
			GFR 30-59 ml/min per 1.73 m^2	5.2%
			GFR 15-29 ml/min per 1.73 m^2	44.1%
Hörl et al., 2003	4333	Hb ≤ 11 g/dL	GFR 18.2 ± 16.7 ml/min	71%

Legend: Htc — haematocrit, Hb — haemoglobin, ESRD — end stage renal disease, GFR — glomerular filtration rate, M — male, F — female (adapted from Locatelli et al, 2003)

addition, anaemia with CHF is associated with higher morbidity and mortality, higher rates of hospitalisation, lower quality of life, as well as signs of malnutrition (19).

There is no agreed level of Hb below which an anaemia complicating CHF can be diagnosed. In the general population the WHO recognises anaemia at less than 130 g/L in men and less than 120 g/L in women. Whether these levels represent the levels where separate complications or effects set in or where therapy may prove useful, remains to be determined (2). Whether we should in fact have different levels for men and post-menopausal women (who form the majority of females with CHF) is also not clear. The levels for anaemia in patients with CHF to be worth treating may be lower than the WHO levels.

Etiology of anaemia in chronic heart failure

There are many commonly recognised causes of anaemia such as iron, folate or vitamin B 12 deficiencies. These may occur in patients with heart failure as they do in other patient groups. They should therefore be looked for and treated. Some of these causes may be more likely present in CHF, such as iron deficiency in patients with heart failure secondary to ischemic heart disease where the chronic use of aspirin promoting gastrointestinal blood loss is common (2).

One report from Dundee (United Kingdom) of new heart failure cases with anaemia found, that “simple” causes of anaemia such as iron, vitamin B 12 or folate deficiency were rare in CHF and that in most cases of anaemia in CHF, no specific aetiology of anaemia could be found (20). It appears that CHF, like other chronic disorders, can be associated with poor utilization of seemingly adequate iron stores. CHF is also frequently associated with some degree of functional chronic renal failure with a relative deficiency of erythropoietin (EPO) production due to poor renal plasma flow. The following etiologic factors have to be considered:

1) Dysfunction of bone marrow as a result of reduced cardiac output (21).

2) Cardiac cachexia and malabsorption is often associated with reduced intestinal iron uptake (22).

3) Tumour necrosis factor (TNF) alpha, which is increased in patients with CHF (23, 24, 25). The damaged heart may secrete cytokines, such a TNF-alpha, which can cause anaemia in three ways: by reducing EPO production in the kidneys, by interfering with EPO activity at the level of the bone marrow, and by inhibiting the release of iron from the reticuloendothelial system, so it cannot get into the bone marrow to be utilized in Hb production (26). Within a severe heart failure population, Bolger and colleagues recently showed that circulating levels of TNF, soluble TNF receptor-1, soluble TNF receptor-2 and soluble CD 14 (all cytokine activation markers), all relate strongly to haemoglobin levels, suggesting that anaemia may be related to inflammatory immune activation in severe CHF (27).

4) CHF activates the renin-angiotensin-aldosterone system and vasopressin, which usually results in retention of sodium and water, leading to haemodilution and a fall in Hb (28). Patients with haemodilutional anaemia have a tendency for a worse outcome than patients with true anaemia (29).

5) CHF can lead to renal dysfunction due to renal vasoconstriction and ischemia causing in an increase in erythropoietin production. Although in heart failure EPO levels are elevated, the levels are still below the normal level, taking into account the level of anaemia, thus indicating a relative EPO deficiency. EPO levels are elevated in CHF subjects in proportion to the severity of symptoms (30). Renal anaemia usually develops in chronic renal dysfunction with serum creatinine over 310 μmol/L or a creatinine clearance below 30 ml/min.

Tab. 2. Prevalence of anaemia by degree of cardiac dysfunction among heart failure patients in different studies.

Study/survey	Number of patiens	NYHA class	Definition of anaemia	Prevalence
Silverberg et al., 2000	142		Hb < 120 g/L	55,6%
		I		9,1%
		II		19,2%
		III		52,6%
		IV		79,1%
Wisniacki et al., 2001		I		0,0%
		II		36,4%
		III		52,0%
		IV		65,9%
Tanner et al., 2002	193	I	Hb < 120 g/L	7,0%
		II		9,0%
		III		17,00%
		IV		26,0%
Cromie et al., 2002	269		Hb < 110 g/L	14,4%
Ezekowitz et al., 2003	12065		Htc < 30%	17,0%
ELITE II trial, 2000	3044		Hb < 125 g/L	16,90%
			Hb < 115 g/L	5,6%
Horwich et al., 2002	1061	III + IV	Hb < 130 g/L in men, Hb < 120 g/L in women	30,0%
Al-Ahmad et al., 2001	6635		Htc < 35%	
		I		37,0%
		II		43,0%
		III+IV		20,0%
COPERNICUS, 2001	2289		Hb < 125 g/L	19,0%
Val-HeFT, 2002	5010		Hb < 120 g/L in men, Hb < 110 g/L in women	9,0%
MacClelan et al., 2002	633		Htc < 30%	13,6%

Legend: Htc — haematocrit, Hb — haemoglobin

6) Diabetes as well as arterial hypertension can contribute to heart failure and are frequent concomitant diseases. Both can also contribute to further renal dysfunction and anaemia.

7) Therapy with angiotensin converting enzyme (ACE) inhibitors has been shown to inhibit the synthesis of endogenous EPO and ACE inhibitors also interfere with EPO activity in the bone marrow (31, 32, 33). These drugs are a standard therapy in CHF.

8) Chronic anaemia contributes to the development of CHF because an increased cardiac output is required to deliver oxygen to the tissues. This leads to an increase in myocardial oxygen demands and stimulates volume overload hypertrophy (34).

9) Treatment of the disease underlying CHF, principally coronary artery disease, with agents such as aspirin and warfarin can contribute to blood loss and anaemia due to gastrointestinal bleeding.

10) CHF is common in elderly patients. These patients use frequently NSAID (many times as OTCs) for pain-treatment and these drugs can also contribute to anaemia due to gastrointestinal bleeding.

11) A rightward shift of the oxyhemoglobin dissociation curve on exercise has been shown in patients with CHF. Erythropoietin treatment can further increase 2,3-diphospho-glycerate levels with a further increase in oxygen extraction (35).

12) Renal failure, anaemia, hypertension as well as left ventricular hypertrophy interact in various ways and contribute further to heart failure and vice versa to renal failure (36).

13) CHF patients often have proteinuria. EPO, iron and transferrin can be lost in significant amounts in the urine with proteinuria, thus also contributing to the anaemia (37). We suppose the same effect for folate and vitamin B12.

Despite all these potential reasons why CHF can cause anaemia, in most cases a specific reason cannot be found and anaemia is labeled as “anaemia of chronic disease”. In the Alberta database (12 065 patients), this accounted for 58 % of all cases of anaemia in CHF (11). This anaemia is characterised by normal red blood cell morphology and normal iron stores. Although the cause of anaemia complicating heart failure is not known, it is likely to be multi-factorial in many patients. The anaemia is probably due to a combination of renal failure and excessive production of cytokines, both of which interfere with EPO production and utilization.

Prevalence of anaemia in chronic heart failure and its relationship to severity of chronic heart failure

The prevalence of anaemia in CHF is extremely variable in the literature (Tab. 2) and ranges from around 10 % in some studies to around 60 % in others (10, 11, 13, 20). The differences in prevalence in the various studies are probably due to the different definitions of anaemia used, to the different exclusion criteria, and to the different nature of the populations studied. In general low Hb values and anaemia are about twice as frequent in women than in men (38). Prevalence rates of anaemia have been shown to be higher in older than in younger patients, higher in those hospitalized than in those seen in outpatient departments, and higher in those with more severe CHF and more severe chronic kidney insufficiency (CKI) (10, 11, 19).

The vicious circle of chronic heart failure, chronic kidney insufficiency and anaemia – the Cardio-Renal-Anaemia syndrome

Haemodynamic consequences of anaemia may contribute to the progression of heart failure symptoms and ventricular remodeling. Anaemia has been recognised to exacerbate pre-existing heart failure. In addition, a vicious cycle between anaemia, chronic renal failure and exacerbation of heart failure can be assumed (19).

CHF itself causes both anaemia and CKI. The CKI causes even more anaemia and the anaemia and CKI act back to further worsen the CHF which then further worsens the anaemia and CKI, etc. Wexler et al (2003) suggest calling this relationship the Cardio-Renal-Anaemia (CRA) Syndrome. The importance of this concept is that if the anaemia is not treated in CHF patients, there will likely be resistance to other forms of CHF therapy and there will be progression of both the CHF and the CKI. Thus correction of anaemia may therefore be crucial in the prevention of the progression of both CHF and CKI (19).

Treatment of anaemia in CHF

Silverberg et al (2001) suggested treatment with a combination of erythropoietin and intravenous iron. This combination has been shown to be safe and effective in patients with CHF before starting dialysis as well as in patients on dialysis. Intravenous iron administration seems to be more effective than oral administration, possibly because of iron absorption disturbances in CHF patients. Intravenous iron therapy can reduce the need for high erythropoietin doses, which might be preferable since this can lead to an increase in arterial pressure, which may not be desirable. Improvement of symptoms of CHF and exercise capacity has also been observed (8, 9).

Recent studies have investigated treatment with a novel erythropoiesis stimulating protein (NESP) which has a three-times longer half-life due to the addition of two extra carbohydrate chains than erythropoietin. NESP is a hyperglycosylated analogue of recombinant human erythropoietin that was used in 1500 patients for stimulation of erythropoiesis (39).

Anaemia is common in patients with CHF and appears to be a strong independent risk factor for poor survival and poor functional status in these patients. Despite the well-documented importance of anaemia in renal disease, underdiagnosis and undertreatment of anaemia in patients with chronic renal insufficiencies common and this is also a concern in patients with heart failure.

There is no uniform definition of anaemia in CHF. The prevalence of anaemia increases with the severity of heart CHF and is more frequent in women than in men. Several mechanisms may be involved in anaemia in CHF, however; most frequently, when Hb levels are low in CHF “anaemia of chronic disease” is diagnosed. Correcting anaemia in CHF may lead to symptomatic improvements and possibly also to improve prognosis. However, this approach needs to be tested and documented in prospective controlled interventional studies.

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