CARDIOLOGY Rounds®

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Anemia and Heart Failure: Prevalence, Prognosis, Pathophysiology, and Treatment

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Heart failure (HF) is a disease associated with a poor prognosis. Anemia is common in patients with diastolic and systolic HF and is one of the many predictors of poor prognosis. Epidemiologic studies indicate that the prevalence of anemia varies from 10%-50% and increases with severity of HF, declining renal function, and increasing age. Chronic anemia leads to a wide variety of adaptive changes in the cardiovascular system, including ventricular dilation associated with increased preload and increased cardiac output. This increased workload on the heart is particularly detrimental in the setting of coronary artery disease. The pathophysiology of anemia associated with HF is likely multifactorial, involving hemodilution, angiotensin-converting enzyme (ACE) inhibitors, and/or angiotensin receptor blockers (ARBs), anemia of chronic inflammation, and chronic renal failure. Intervention studies in anemic HF patients to date have shown that optimal medical treatment of HF, together with correction of associated anemia using erythropoietin and supplemental iron, can improve cardiac function, patients' functional status, and quality of life, and reduce the frequency of hospitalization. There is a clear need for an improved and standardized definition of anemia and there is a growing demand for randomized controlled clinical trials to clearly establish the efficacy and safety of erythropoietin. This issue of *Cardiology Rounds* reviews the prevalence of anemia and its prognosis in patients with HF and also discusses the pathophysiology and potential for novel therapies, including erythropoietin and supplemental iron.

Introduction

HF is a condition associated with an adverse prognosis and a 1-year mortality of 35%-40% based on population-based studies. There are several important well-known prognostic factors, including clinical (advanced age, poor left ventricular [LV] function, hypotension, and co-morbidities) and biochemical (elevated serum creatinine, increased cytokines, and hyponatremia) variables. More recently, chronic anemia has been shown to be an important and common predictor of adverse outcomes in patients with HF.[1-3] Adequate tissue oxygen supply depends not only on cardiac output, but also on arterial blood hemoglobin concentration and oxygen saturation. This is of particular importance to the myocardium because of high oxygen demand and maximal oxygen extraction which, thereby, creates a critical dependence on oxygen supply.

Chronic anemia leads to a wide variety of adaptive changes in the cardiovascular system, including ventricular dilation associated with reduced systemic vascular resistance, increased preload, and enhanced cardiac output. Indeed, several recent studies have consistently shown that chronic anemia is a negative prognostic factor in patients with HF.[1-3]

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Table 1: Prevalence of anemia in selected heart failure studies

Population	Definition of anemia	N	Prevalence	Reference
LV dysfunction, +/- symptoms, clinical trial	Hct < 35%	6563	4%	6
Community-based patients with HF	Hb <130 men, <120 women	5888	8.5%	13
Tertiary care HF clinic	Hb <120	193	15%	7
New HF diagnosis, claims data	MD defined (ICD9 codes)	12,065	17%	1
Severe chronic HF, clinical trial	Hct <37.6%	1130	20%	8
Heart transplant referrals, single-centre	Hb <130 men, <120 women	1061	30%	9
Chronic HF, single-centre	Hb <130 men, <120 women	791	40% men 35% women	10
Diastolic HF (normal LVSF)	Hb <130 men, <120 women	210	46%	4
Medicare patients, claims data	Hct ≤37%	2281	48%	11
Acute decompensated HF, clinical trial	Hb <130 men, <120 women	949	49%	12
Chronic HF, single-centre	Hb <120	2142	50%	5

Hct = hematocrit; Hb = hemoglobin (g/L); HF = heart failure; LV = left ventricle; LVSF = LV systolic function; Hb = hemoglobin

Prevalence and prognosis of anemia in patients with heart failure

The most widely accepted definition of anemia is that of the World Health Organization (hemoglobin <130 g/L in men and <120 g/L in women).[2] The prevalence of anemia in patients with HF varies widely and ranges from 4% to 50% (Table 1). The reasons for this wide variation include differences in the HF population studied, as well as variations in study methods and definitions of anemia. Anemia is common in patients with diastolic[4] and systolic HF (Table 1).[1,5-13] Increasing age, New York Heart Association (NYHA) functional class, and renal impairment are all predictive of the presence of anemia in patients with HF.[2,5,14] The degree of anemia is independent of gender and the underlying etiologies of HF.[9] In addition to the absolute degree of anemia, a rapid fall in hemoglobin over time also predicts a worse clinical outcome.[15]

The presence of anemia is invariably associated with increased morbidity and mortality in patients with HF (Table 2). Increased mortality occurs with a graded response to increasing degree of anemia.[6,8,9,11] Anemia is also associated with worse symptoms, greater impairment in functional capacity, and an increased risk in hospitalizations for HF.[2,9] Several studies have also shown that higher than normal hemoglobin concentration is associated with worse outcomes, suggesting that increased blood viscosity can be detrimental as well.[13,16] In a Canadian population-based cohort of 12,065 patients with new-onset HF, the 1-year and 5-year mortality rates were 38% and 59%, respectively, in those with anemia compared with 27% and 50%, respectively, in those without the condition.[1] In a follow-up study, the same group demonstrated a gender-specific effect of anemia on mortality; they determined that anemia increases the mortality only in male patients with HF.[10] These observations may explain, in part, the better outcomes that have been observed in females with HF and also highlight the potential need for gender-specific distinction of anemia in future studies.

Pathophysiology

The pathogenesis of anemia in patients with HF is likely to be multi-factorial. Consistent with the activation of the neurohumoral system and expansion of the extracellular fluid compartment, hemodilution is common in patients with advanced HF and associated with a worse prognosis compared with patients with true anemia.[17] Since the early 1980s, it has been demonstrated that use of ACE inhibitors is associated with lower hemoglobin levels.[18-20] ACE inhibitors may cause a reduction in angiotensin II (Ang II) levels and Ang II stimulates the proliferation of erythroid progenitor cells, an effect inhibited by ARBs.[21] N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), a strong inhibitor of erythropoiesis, is also cleaved by ACE. Indeed, ACE inhibitors markedly increased Ac-SDKP levels 5- to 6- fold and may, therefore, reduce hematopoietic activity.[22] In ACE knockout mice, anemia is associated with lowered Ang II and increased Ac-SDKP levels. while chronic infusion with Ang II completely reverses the anemia, suggesting that lack of Ang II is the dominant cause for the anemia.[23] Therapeutic doses ACE inhibitors have been shown to decrease renal secretion of erythropoietin in

Table 2: Association of anemia and outcomes in selected heart failure studies

Population	Outcome	Initial change	Adj HR/OR	Reference
LV dysfunction, +/- symptoms, clinical trial	Mortality	1% Hct	1.027	6
New HF diagnosis, claims data	Mortality	Anemic vs non-anemic	1.34	1
Severe chronic HF, clinical trial	Mortality	10 g/L Hb	1.13	8
Heart transplant referrals, single-centre	Mortality	1% Hct	1.02	9
Chronic HF, single-centre	Mortality	Anemic vs non-anemic	1.7 (men) 1.2 (women)#	10
Diastolic HF (normal LVSF), single-centre	Mortality	Anemic vs non-anemic	2.7	4
Medicare patients, claims data	Mortality	1% Hct	1.03	11
Acute decompensated HF, clinical trial	Death or rehospitalization	10 g/L Hb	1.12	12
Community-based patients with HF	Mortality	Anemic vs non-anemic	1.38	13

Hct = hematocrit; Hb = hemoglobin (g/L); HF = heart failure; LV = left ventricle;
Adj HR/ORH = adjusted hazard/odds ratio; #P=0.84; * = relative risk

patients with hypertension, renal insufficiency, polycythemia, and chronic HF.[2] The role of Ang II in erythropoiesis has recently been supported by observations from the Valsartan in Heart Failure Trial (Val-HeFT), where valsartan use was associated with a significant and persistent decrease in hemoglobin concentration.[15]

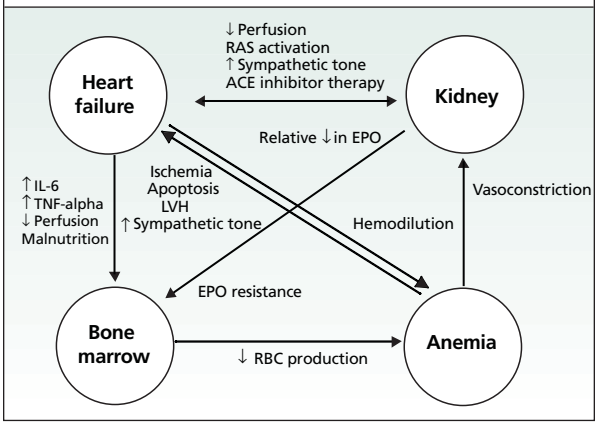
Anemia of chronic inflammation is particularly common in patients with HF in a pro-inflammatory state as reflected by persistently elevated serum cytokine levels.[24] Hepcidin is a small (20-25 amino acids) antimicrobial peptide that is expressed and secreted into the circulation by the liver in response to chronic inflammation.[25,26] Hepcidin inhibits iron excretion in macrophages and enterocytes by binding to a key iron export protein, ferroportin.[27] In HF, increased serum cytokine level has been well-documented, which may also play a key role in mediating anemia of chronic disease by reducing the availability of iron supply and inducing resistance to the actions of erythropoietin.[27] The concept of erythropoietin resistance is further supported by recent observations in HF patients, where elevated plasma erythropoietin levels are associated with an impaired prognosis and worse LV function independent of hemoglobin levels and other established markers of HF severity.[28,29]

HF and chronic kidney disease (CKD) often progress to end-stage disease, even with optimum medical therapy; CKD is present in about half of all HF patients. One factor that is common to both conditions is anemia. HF can cause or worsen both anemia and CKD, and CKD can cause or worsen both anemia and HF. Thus, a vicious circle exists between these 3 conditions, with each causing or worsening the other. This cycle has been called the "cardio-renal-anemia syndrome" (Figure 1).[3,24] CKD is well known to be associated with impaired renal production of erythropoietin. leading to a state of relative erythropoietin deficiency. In hospitalized patients, frequent blood sampling constitutes an important cause of iatrogenic anemia. Indeed, in patients admitted to a ward service or to intensive care units (ICUs), chronic blood sampling leads to significant anemia or worsening of preexisting anemia.[30,31] Clearly, patients with advanced HF and frequent hospital admissions are particularly susceptible to iatrogenic anemia.

Treatment of anemia

The physiological role of erythropoietin to stimulate erythropoiesis and increase hemoglobin concentration has been clearly linked to improved oxygen delivery to the tissues. However, erythropoietin and its receptor play a

Figure 1: Interaction between heart failure, renal function, and hematopoiesis, as part of the cardio-renal-anemia syndrome.



EPO = erythropoietin; RAS = renin-angiotensin system;
RBC = red blood cells; TNF = tumour necrosis factor;
IL = interleukin

significant biological role in tissues outside of the hematopoietic system and this has fueled significant interest in erythropoietin as a novel cytoprotective agent in both the neuronal and vascular systems.[32] Erythropoietin modulates a broad array of cellular processes that include progenitor stem cell development, cellular integrity, and angiogenesis. As well, erythropoietin is now considered to have applicability in a variety of disorders, including cerebral ischemia, myocardial infarction (MI), and chronic congestive heart failure.[32]

In a prospective study of 101 patients with first MI who underwent successful percutaneous coronary intervention (PCI) within 12 hours, peak creatine kinase level and cumulative creatine kinase release were significantly lower in those whose erythropoietin was above-median than in those whose levels were below-median. These data suggest that a high endogenous erythropoietin level can potentially lead to a smaller infarct size in patients with acute MI with successful PCI.[33] This might be attributed to the potentially protective effect of endogenous erythropoietin against ischemia-reperfusion injury in humans.

Since a low number of endogenous progenitor cells (EPCs) may help to identify patients at increased cardiovascular risk,[34] the role of erythropoietin in stabilizing and protecting EPCs may help to improve myocardial blood flow and function, thereby reducing adverse cardiovascular events.[35] Three erythropoietic agents are currently available: epoetin-alfa, epoetin-beta, and darbepoetin-alfa; each has different pharmacological and pharmacokinetic properties.[27]

Clinical studies in patients with NYHA class III/IV HF, who have hemoglobin levels <12 mg/dL and are refractory to maximal medical management, reveal that erythropoietin improves symptoms, exercise capacity, and LV function. In a study of 26 patients with HF, subcutaneous recombinant human epoetin (rHuEPO) and intravenous iron led to an increased hemoglobin level that was associated with improved NYHA functional class, increased LV ejection fraction, and reduced hospitalizations.[5] These authors subsequently conducted an open-label, randomized, clinical trial in 32 patients. Subcutaneous rHuEPO, coupled with iron supplementation, resulted in increased hemoglobin levels, improvements in NYHA functional class and LV ejection fraction, reduced hospitalizations, and reduced diuretic use.[36] In a small randomized trial, 26 patients were randomized to receive either placebo or rHuEpo; rHuEpo treatment resulted in a significant increase in hemoglobin levels and exercise capacity as measured by peak oxygen consumption and exercise duration over a 3-month period.[37]

To achieve and maintain target hemoglobin levels with erythropoietic agents, sufficient body iron stores are required. Supplemental iron should be administered, as needed, to maintain a transferrin saturation of 20% and a serum ferritin level of 100 ng/mL.[38] The use of blood transfusions should be avoided unless the hemoglobin is <80 g/L or in the setting of acute blood loss.

In patients with clinically overt HF or coronary artery disease who are receiving hemodialysis, administration of erythropoietin to raise their hematocrit to 42% is associated with potential harm and not recommended.[39] Adverse effects of erythropoietin therapy include pro-malignancy effects, hypertension, and vascular complications (thrombosis) that may limit its clinical applicability. Further studies are required to help clarify the link between anemia and HF and whether treating anemia with erythropoietin or darbepoetin-alfa will result in sustained improvement in clinical outcome for these patients.[2,40]

A multicentre, double-blind, placebo-controlled, randomized trial – Studies of Anemia in Heart Failure Trial (STAMINA HeFT) – was recently completed. In this trial, patients with HF with anemia were randomized to subcutaneous treatment with darbepoetin alfa or placebo over a 1-year period, with change in functional status being the main clinical endpoint.[40] A phase III trial was recently announced by Amgen Inc., which is being designed to examine the impact of darbepoetin-alfa on clinical outcomes in patients with HF.

Conclusion

In conclusion, anemia likely plays a role in the pathophysiology of HF. Preliminary studies indicate that erythropoietin therapy is well-tolerated and associated with short-term clinical benefit in patients with HF. The optimal target hematocrit, erythropoietin dosing regimen, iron supplementation regimen, as well as their impact on clinical outcomes for anemic patients with HF, remain to be determined. Ongoing randomized controlled trials will likely address to these issues.

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Abstract of Interest

Darbepoetin Alfa Improves Left Ventricular Function in Dogs with Advanced Heart Failure that are not Anemic

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BACKGROUND: Darbepoetin alfa (Aranesp™, Amgen, Inc.) is an erythropoietic protein used in the treatnent of anemia. In patients with chronic heart failure (HF) who are also anemic, erythropoietin type drugs have been shown to lead to significant clinical improvement. The present study tested the hypothesis that even in the absence of anemia, long-term monotherapy with darbepoetin alfa improves LV function and attenuates LV remodeling in dogs with advanced HF.

METHODS: Studies were performed in 14 dogs with intracoronary microembolization-induced HF (LV ejection fraction, EF ~25%). Dogs were randomized to a once a week subcutaneous injection of darbepoetin alfa (1.0 µg/kg, n = 7) or to no therapy at all (Controls, n = 7). At the time of randomization, the hematocrit (HCT) and hemoglobin (Hgb) were within normal limits. Heart rate (HR), LV end-diastolic pressure (LVEDP), LV end-systolic volume (ESV) and end-diastolic volume (EDV), EF, and cardiac index were measured in all dogs before (PRE) and 3 months after initiating darbepoetin alfa therapy or follow-up (POST).

RESULTS: Data are shown in the table. In Controls, HCT and Hgb increased modestly at 3 months. This increase was more marked and borderline significant in dogs treated with darbepoetin alfa. In Controls, HR was unchanged, EDV, ESV and LVEDP increased while EF and CI decreased after 3 months of follow-up. Treatment with darbepoetin alfa had no effect on HR, prevented the decline in EDV, decreased ESV and LVEDP and increased EF and CI.

CONCLUSIONS: Long-term monotherapy with the erythropoietic protein darbepoetin alfa improved LV systolic function and prevented progressive LV dilation in non-anemic dogs with advanced HF. These results indicate that darbepoetin alfa can elicit beneficial effects in HF that are independent of the presence of anemia.

Hemodynamic, Angiographic and Hemotological Findings

	HF-Controls		HF + Darbepoetin alfa	
	PRE	POST	PRE	POST
HCT (%)	45 ± 3	49 ± 1	44 ± 2	59 ± 5*
Hgb (g/dL)	15.4 ± 0.9	16.8 ± 0.3	15.1 ± 0.6	19.3 ± 2.0
LVEDP (mmHg)	16 ± 1	18 ± 1*	16 ± 1	11 ± 1*
CI (L/min/m²)	1.75 ± 0.08	1.63 ± 0.05	1.61 ± 0.15	1.93 ± 0.12*
EDV (ml)	67 ± 3	73 ± 3*	66 ± 4	66 ± 4
ESV (ml)	50 ± 2	57 ± 2*	50 ± 3	46 ± 4*
EF (%)	25 ± 1	22 ± 1*	25 ± 1	30 ± 1*

* = p < 0.05 PRE vs. POST

A presentation at the AHA, November, 2005.

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