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Scientific Update™

Heart Failure: Canadian Perspectives on the Management of Cardiorenal Syndrome and Acute Decompensated Heart Failure

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A Review of a Presentation at a Satellite Symposium at the Canadian Cardiovascular Congress

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The cardiorenal syndrome has recently drawn significant attention from investigators, government agencies, and the industry. In 2004, the National Heart, Lung, and Blood Institute (NHLBI) convened a working group to "evaluate the current state of knowledge regarding interactions between the cardiovascular system and the kidney, to identify critical gaps in our knowledge, understanding, and application of research tools, and to develop specific recommendations for the NHLBI in cardiorenal interactions related to heart failure." This issue of *Cardiology Scientific Update* discusses two conditions that are closely associated with the cardiorenal syndrome – the cardiorenal-anemia syndrome and acute heart failure syndromes.

Cardiorenal anemia syndrome and chronic heart failure

Anemia is a common finding in patients with chronic kidney and heart failure (HF). Across the spectrum of heart and kidney disease, anemia is independently associated with an impaired quality of life, poor outcomes, reduced survival, a reduced exercise capacity, the development of left ventricular hypertrophy (LVH), and increased severity of congestive HF. For both chronic kidney disease (CKD) and HF, deterioration in kidney and cardiac function, respectively, are accelerated by anemia. Diabetes appears to amplify both the adverse prognostic relationship and the severity of the anemia for any given degree of renal dysfunction.[1] Consequently, anemia has been a target for therapy in the management of patients with heart and kidney disease.

Pathogenesis of anemia in HF and kidney disease

Cardiac and renal functions are closely coupled, such that a deterioration in one organ impacts on the other. The reduction in cardiac output in the failing heart is sensed by the kidney as a volume-depleted state and results in vasoconstriction and sodium retention, which further exacerbates HF. Anemia influences outcomes by a complex interaction between the impairment in cardiac and renal function and the bone marrow (Figure 1).[2] In CKD, anemia commonly results from a relative deficiency in renal erythropoietin (EPO) and impaired iron utilization.[3] Renal impairment may also develop during the more severe stages of HF and becomes an important factor in the development of anemia. Chronic inflammation is increasingly recognized as a contributory factor to the development of anemia in both CKD and heart disease.

Elevated pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin (IL)-6 impair erythropoesis by reducing the iron supply and erythropoietin production and shortening red blood cell survival time (Figure 2). Diabetes is also associated with a relative deficiency of EPO and, therefore, exacerbates the development of anemia in patients with CKD and heart disease. Malnutrition, chronic gastritis, and urinary protein loss can also contribute to the depletion of iron, folate, and vitamin B_{12} stores in CKD and HF.[4,5] An expanded plasma volume, resulting in hemodilution, is a reflection of the severity of the HF and is

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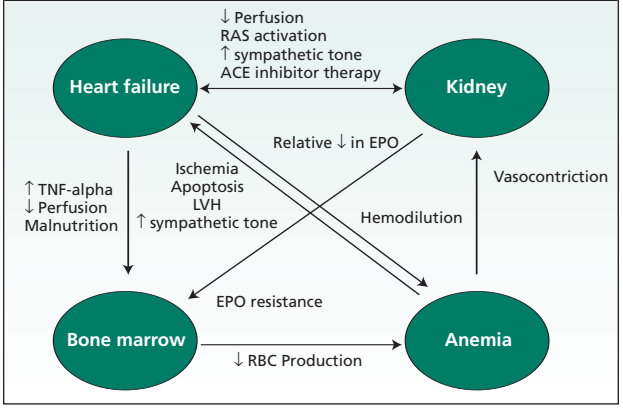
Figure 1: The complex interaction between the heart, kidney, and anemia[2]



EPO = erythropoietin; LVH = left ventricular hypertrophy;
RAS = renin-angiotensin system; TNF-alpha = tumour necrosis factor-alpha

associated with a worse prognosis.[6] Anemia increases both renal and myocardial hypoxia, not only increasing demands on the failing heart, but also stimulating processes that lead to reduced cell survival and increased fibrosis in both the myocardium and kidney.

Prevalence of anemia

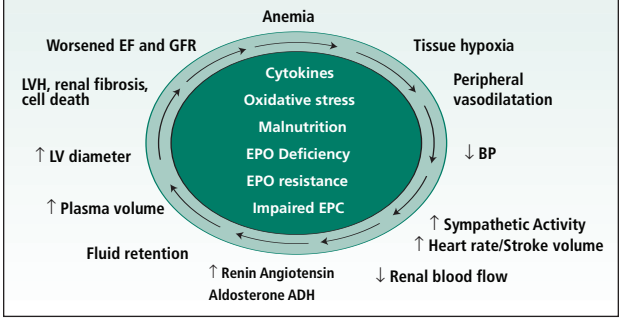
More than 90% of patients with end-stage renal disease (ESRD) have anemia and 80% of patients with HF and New York Heart Association (NYHA) class IV symptoms have hemoglobin (Hgb) levels <120 g/L.[7] In the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) program that included NYHA functional class II-IV patients, 25% had anemia (defined as Hgb levels <120 g/L in women and <130 g/L in men).[8] Anemic patients were older, thinner, more likely to be black, had worse renal function, and tended to have worse HF symptoms, as well as signs of congestion. Patients with HF and preserved ventricular systolic function were as likely to have anemia as those with impaired LV systolic function.

Reduced renal function is a common finding in the patient with HF. In the Studies Of LV dysfunction (SOLVD) database of 6427 patients with HF, impaired renal function (defined as eGFR <60 mL/min) was found in 39% of subjects. The degree of anemia in patients with HF correlates with the severity of renal dysfunction.[9]

The impact of anemia in heart disease

Symptoms and clinical outcomes are worse in patients with anemia and heart disease because anemia impacts on cardiac function and adverse remodeling of the left ventricle. Anemia is an independent predictor of survival and need for hospitalization in the patient with chronic HF.[8,10] CKD, HF, and anemia have an incremental and synergistic impact on clinical outcomes.[11,12]

Figure 2: Cycle of worsening HF, CKD, and anemia



EF = ejection fraction; GFR = glomerular filtration rate;
EPO = erythropoietin; EPC = endothelial progenitor cells

Although multiple prospective clinical trials have shown anemia to be an independent predictor of mortality, population-based studies have not uniformly revealed such a relationship. A study of 13,000 patients with HF in Alberta demonstrated anemia to be an independent predictor of mortality.[13] However, a recent single hospital experience in >50,000 older patients with HF showed that a lower hematocrit was strongly associated with increased 1-year mortality. When corrected for non-cardiac co-morbidity and HF severity, however, the increased mortality was largely explained by the severity of comorbid illness.[14]

Management

Correction of anemia in both CKD and heart disease might be expected to improve quality of life, exercise capacity, and improve outcomes. However, the benefits may depend on anemia severity, its cause, and the mode of therapy used. As anemia is likely a marker of more serious underlying disease with a worse prognosis, it is unclear if correction of anemia *per se* will impact survival. There are also potential hazards associated with erythropoietin (EPO) treatment, such as thrombosis,[15] platelet activation, and hypertension.[16] Although it appears intuitive that correction of anemia leads to improved outcomes, only randomized clinical trials can determine the true benefit, especially when agents such as erythropoietin are used.

The management of anemia in patients with CKD and heart disease should include an investigation for other causes of renal anemia. Iron deficiency due to inadequate intake or absorption, or from blood loss, is the most common nonrenal cause and should be sought by measurement of ferritin and transferrin saturation. Folate or Vitamin B_{12} deficiency should also be sought. Blood transfusion may be necessary; however, in patients with acute coronary syndromes, blood transfusion has been associated with an

increase in mortality and recurrent acute coronary events.[17] Erythropoietin-alfa has additional effects that may be beneficial in the failing heart, including protecting the heart from ischemia/reperfusion injury,[18] and enhanced myocardial cell repair by recruiting endothelial progenitor cells.[19] In a small observational study of 26 patients with severe HF and a mean Hgb of 102 g/L,[20] erythropoietin-alfa treatment for 7 months increased the Hgb to 121 g/L and significantly reduced the need for hospitalization when compared to values prior to treatment. Results from small randomized trials indicate that erythropoietin-alfa, given for 3-8 months, increases Hgb, improves functional class, increases exercise duration, increases LV ejection fraction, decreases diuretic requirements, and reduces the need for hospitalization due to HF.[21,22]

The Study of Anemia in Heart Failure Trial (STAMINA-HF) was a placebo-controlled clinical trial that examined the value of darbepoetin-alfa in 319 patients with NYHA class II-IV HF, creatinine >3 mg/dL, and Hgb 90-125 g/L.[23] Unpublished preliminary results reveal that there was no significant improvement in the primary endpoint of exercise duration, functional class, or quality of life scores associated with darbepoetin-alfa treatment for 27 weeks. In addition, all-cause mortality and HF hospitalization were not significantly reduced. However, the point-estimates were in favour of the darbepoetin-alfa treatment (hazard ratios, 0.68 and 0.74, respectively). The change in exercise duration on treatment was related to the increase in hemoglobin. In a pre-planned pooled analysis of 2 randomized trials examining treatment with darbepoetin-alfa in 165 patients, there was a trend towards a reduction in HF-related hospitalization and a significant reduction in the combined endpoint of all-cause mortality and HF-related hospitalization. The ongoing Reduction of Events with Darbepoetin-alfa in Heart Failure (RED-HF) trial and the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) are large-scale randomized-controlled trials that will assess the effect of treatment of anemia with darbepoetin-alfa on mortality and morbidity in patients with HF and those with diabetes and CKD, respectively.

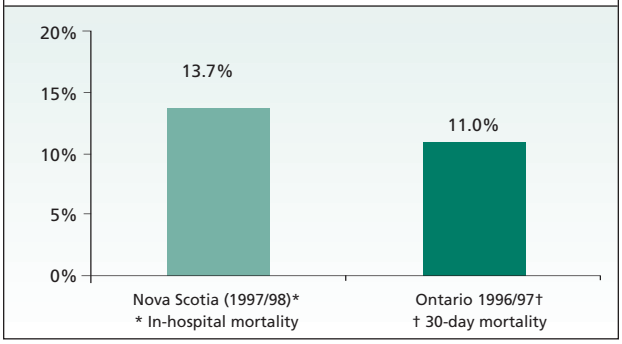
Recent clinical experience with EPO in patients with CKD calls for caution. Although EPO treatment to increase Hgb from <100 g/L to 120 g/L improves functional class and peak oxygen consumption, an increase of hemoglobin (target 135 g/L) results in an increase in cardiovascular events.[24] Another study demonstrated that treatment with EPO to a target hemoglobin of 130-150 g/L did not reduce clinical events or shorten the time to the requirement of dialysis.[24,25]

In conclusion, most studies demonstrate that anemia is an independent predictor of mortality in patients with HF. However, co-morbid conditions likely have an important impact on clinical outcomes and may limit the therapeutic benefits of anemia correction. Although early clinical trials with EPO showed some promise for improved outcomes, randomized trials in patients with CKD have thus far shown no survival benefits. However, symptoms and the need for re-hospitalization appear to be reduced by EPO treatment. As there are currently no other treatments to resolve the debilitating effects of chronic anemia in patients with severe HF, EPO may have a therapeutic role for symptomatic patients. Evidence for the reversal of LVH by correction of anemia in patients with chronic renal failure (CRF) provides a rationale for the potential benefits of such treatment in patients with CHF. Although small short-term studies suggest clinical benefit by correction of anemia, there are still unanswered questions that need to be addressed in large, randomized clinical trials.

Acute HF syndromes: new guidelines and treatment strategies

Heart failure is an increasingly important source of morbidity and mortality in Canada and the rest of the world. Although advances in the understanding and treatment of chronic HF have improved survival, the prognosis for patients hospitalized with acute HF syndromes (AHFS) remains poor.[26] As shown in Figure 3, the short-term mortality for patients admitted with HF in Nova Scotia and Ontario exceeds 10%.[27,28] Acute HF is not a disease entity, but rather a complex syndrome with various etiologies and distinct clinical conditions as a result of systolic and/or diastolic left and/or right ventricular dysfunction that is accompanied by neurohormonal and cytokine activation and impaired function of vital organs, including the kidney. Indeed, renal insufficiency is one of the most important predictors of mortality

Figure 3: Mortality of patients admitted with heart failure in Nova Scotia and Ontario



Nova Scotia data based on 3261 discharges (2509 patients) from October 15, 1997 – October 14, 1998
Ontario data from Cardiovascular Health & Services in Ontario: An ICES Atlas, 1999

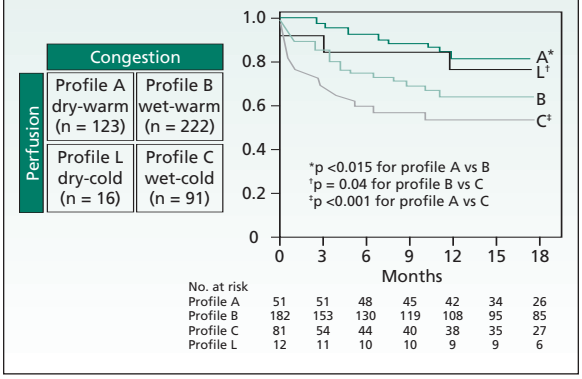
in both patients with chronic HF,[29] as well as those admitted to hospital with AHFS.[30] Recent data from the Acute Decompensated Heart Failure Registry (ADHERE), Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), and the EuroHeart Failure survey have shown that most AHFS hospitalizations are caused primarily by volume overload, rather than by low cardiac output.[31-33] Clinical presentations of patients with AHFS include:

- HF with SBP >140 mm Hg (50%)
- HF with SBP 90-140 mm Hg (48%)
- HF with SBP <90 mm Hg (2%)
- Cardiogenic shock (<1%)
- Pulmonary edema (<3%)
- Radiographic pulmonary congestion (74%)
- Isolated right-sided HF
- ACS with HF

The majority of patients have normal to elevated systolic blood pressure, while only a minute proportion have low systemic blood pressure. On the other hand, pulmonary and systemic congestion is very common. The most common presenting signs and symptoms are dyspnea, rales, and peripheral edema.

There are increasing data to suggest that each acute episode of exacerbation of HF may contribute to the loss of myocytes and, therefore, progression of HF.[34] Rapid and accurate diagnosis, risk stratification, and implementation of therapy are essential in the management of patients with AHFS. The relationship between the clinical assessment and clinical outcomes in patients with advanced HF are shown in Figure 4. In this study,[35] profiles based on clinical assessment of congestion and tissue perfusion at the time of admission were compared with subsequent clinical outcomes. Survival analysis

Figure 4: Clinical assessment and outcomes of patient with severe heart failure[35]



revealed that clinical profiles predict outcomes in HF. Patients in hemodynamic Profiles B and C with increased congestion and reduced tissue perfusion have an increased risk of death plus urgent transplantation. Failure to recognize and adequately address circulatory congestion has also been known to increase the risk of morbidity and mortality in these patients.[36] Recent studies suggest that the use of biomarkers such as B-type natriuretic peptide (BNP) or N-terminal fragment of the prohormone (NT-proBNP) provide incremental value to the diagnosis and prognostic stratification in patients presenting with AHFS.[37] These blood tests are most useful in patients presenting with acute dyspnea whose diagnoses are not clinically obvious.

Recently published guidelines for the management of HF include discussions on the management of patients with AHFS.[38-40] Recommendations for the management of acute HF from the European Society of Cardiology, the Heart Failure Society of America, as well as the Canadian

Table 1: Guidelines on the management of acute heart failure: diagnosis

	HFSA	ESC	CCS
Timing of diagnosis and treatment		As soon as possible after arrival at ED	Within 2 hours of presentation to ED Response determined within 2 hours Disposition within 8 hours
Primary diagnostic tools	Clinical history, physical examination, chest X-ray, ECG, routine biochemical studies	Clinical history, physical examination, chest X-ray, ECG, routine biochemical studies	Clinical history, physical examination, chest X-ray, ECG, routine biochemical studies
Secondary diagnostic tools	Echocardiography, BNP or NT-proBNP when there is clinical uncertainty about the diagnosis	ECG, chest x-ray, plasma BNP/NT-proBNP and other laboratory tests, and echocardiography	BNP if clinical uncertainty about diagnosis,echocardiography if available

HFSA = Heart Failure Society of America; ESC = European Society of Cardiology; CCS = Canadian Cardiovascular Society; ED = Emergency Department

Table 2: Guidelines on the management of acute heart failure: therapy

	HFSA	ESC	CCS
Primary Treatment Goal	Symptom relief (especially congestion and low output symptoms)	Symptom relief and stabilization of hemodynamic status	Symptom relief and stabilization of hemodynamic status
Initial Treatment	Loop diuretics (furosemide, bumetanide, torasemide) at adequate dose to achieve optimal volume status,	Loop diuretics when symptoms are secondary to fluid retention.	IV diuretic (furosemide) bolus (for those with predominant volume overload)
Vasodilators	In patients with acute pulmonary edema or hypertension, IV vasodilators (nitroglycerin or nitroprusside or nesiritide) in combination with diuretics	In most if acceptable BP and with congestion Improve hemodynamics with nesiritide with fewer adverse effects	If inadequate response to diuretics, administration of combined IV diuretics and vasodilator therapy (IV nitroglycerin infusion) If there is moderate-to-severe volume overload or inadequate response to IV diuretics
Inotropes	For relief of symptoms, to improve end organ function in patients with evidence of fluid overload unresponsive to IV diuretics or vasodilators or poor perfusion	When peripheral hypoperfusion as evidenced by hypotension and decreased renal function, is present.	In patients with low cardiac output and systolic BP < 90 mmHg.
Monitoring	Invasive hemodynamic monitoring not recommended unless patient is refractory to initial therapy, unclear hemodynamics with deterioration	Arterial line as needed – when patients not responding in predictable ways to traditional treatments	Arterial line ± pulmonary artery catheter when there is evidence of low cardiac output and poor perfusion

Cardiovascular Society (CCS) on the diagnosis and treatment of AHFs are shown and compared in Tables 1 and 2. The CCS recommendations, in particular, emphasize early diagnosis and initiation of therapy.[39] All guidelines recommend the use of intravenous loop diuretics as initial therapy. It should be noted, however, that there may be important limitations associated with the utility and tolerability of diuretic use, including additional activation of the neurohormonal cascade,[41] electrolyte depletion, and worsening renal function.[42] All of the treatment guidelines recommend the addition of intravenous vasodilator agents in patients who are not responsive to diuretics. In countries where recombinant human BNP is available for clinical use, the use of nesiritide is recommended on the basis of its documented clinical benefits and hemodynamic benefit over nitroglycerin.[43] Inotropic agents, on the other hand, are not recommended unless patients show signs of low cardiac output or poor tissue perfusion. These recommendations are consistent with recent observations from the AHFS Registry, ADHERE, demonstrating lower in-hospital mortality in patients who received vasodilators compared to those who received inotropes.[44]

Conclusion

Patients admitted to a hospital for AHFS experience high mortality and frequently have co-morbid conditions, including renal insufficiency, which influences both treatment and outcome. Unfortunately, evidence-based data to guide management decisions in these patients are lacking. There is a compelling need for additional studies in this population to create alternative methods for fluid removal in volume-overloaded patients, to develop better strategies to manage existing and prevent future renal insufficiency (including development of renal-protective medications), and to reduce the morbidity and mortality associated with AHFS.

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