

Anaemia and heart failure

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Anaemia has been found to be a common complication of chronic heart failure, reducing oxygen delivery to the periphery. Erythropoietin to correct anaemia has a long history in the management of renal failure with complicating anaemia, and the first reports of the use or erythropoietin in heart failure are coming through.

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Chronic heart failure (CHF) is frequently associated with poor exercise tolerance and debilitating symptoms despite optimal modern treatment. In the past we expected that this was due to the direct consequences of poor cardiac output and congested lungs. Other important pathophysiological disturbances in CHF occur as both short and long term consequences of the initial cardiac dysfunction. These include neurohormonal activation, cytokine release and trophic changes in skeletal muscle and the peripheral vasculature, and disturbances in reflex control systems.

The severity of symptomatic exercise limitation varies between patients, and bears little relation to the extent of the left ventricular systolic dysfunction measured at rest, or to markers of central haemodynamic disturbance.¹ Although there are several reasons for this, much recent research has suggested that changes which occur in the periphery as a consequence of the systemic effects of heart failure, may have become the principal factors limiting exercise.² Many changes have been described in skeletal muscle, peripheral arterial and endothelial function, and in reflex cardiopulmonary control systems. These have all been implicated in being limiting features to exercise tolerance in CHF patients. In its most severe form this can lead to cardiac cachexia.³ Major abnormalities in anabolic and catabolic hormones⁴ and in immune activation⁵ have been proposed to explain these developments in CHF. Therapeutic advances in managing heart failure have followed these pathophysiological studies, as neurohormonal blockade rather than positive inotropic treatment is now the mainstay of CHF therapy.

“HEART FAILURE SYNDROME”

One manifestation of the “heart failure syndrome” is the frequent finding of a form of non-iron deficient mild to moderate anaemia. This anaemia has much in common with the better recognised anaemia of chronic disorders which appears to be a defect in iron utilisation and which is a well known complication of chronic inflammatory conditions. Anaemia is more common in heart failure than could be accounted for

by age or the degree of renal dysfunction. It has also been realised that this anaemia could contribute importantly to exercise intolerance and is associated with a more advanced clinical severity, a more rapid deterioration in heart failure, and an increased mortality.

In normal subjects exercise is usually possible until maximal cardiac output is achieved, at which time a further increase in workload will produce extra carbon dioxide (CO₂) but with no commensurate increase in oxygen (O₂) uptake.⁶ This is termed maximal oxygen uptake ($\dot{V}O_{2max}$). At between 85–95% of $\dot{V}O_{2max}$ a point in exercise is reached where there is an excessive release of CO₂ for the rate of O₂ uptake due to a limitation in the rate of delivery of O₂ leading to the onset of anaerobic muscular metabolism with lactate production. This produces arterial acidosis and directly stimulates the chemoreceptors to produce relative hyperventilation. This point is called the anaerobic threshold. In most normal subjects exercise is limited by cardiac reserve, with lung function rarely being the limiting factor. Training status and genetic factors determine the overall fitness to exercise. A reduced oxygen carrying capacity, as caused by a reduction in haemoglobin concentration, reduces the effective maximal oxygen carrying capacity; this effect may be even more pronounced when the cardiopulmonary reserve is limited, such as it is in chronic heart failure.⁷

Increasing the haemoglobin concentration will inevitably increase maximum potential oxygen delivery, but at the cost of increased blood viscosity. Thus there is for each individual an optimal haemoglobin value that is a trade off between oxygen carrying capacity while avoiding excess viscous drag to blood flow. In heart failure this is probably above 12.5 g/dl in most patients. In confirmation of this theoretical effect we have recently described a significant association between haemoglobin concentration and peak O₂ consumption in 113 male patients with chronic heart failure.⁸ We found haemoglobin to be the single most powerful predictor of peak O₂ consumption in this cohort.

The frequency of anaemia in stable treated chronic heart failure has only recently received detailed study. An early report from Israel suggested the prevalence of anaemia (defined as a haemoglobin concentration < 12.0 g/dl) varied from 9.1% of patients in New York Heart Association (NYHA) class I to 79.1% of patients

Abbreviations: ACE, angiotensin converting enzyme; CHF, chronic heart failure; CRF, chronic renal failure; EPO, erythropoietin; GFR, glomerular filtration rate; PKV_{O₂}, peak oxygen consumption; SOLVD, studies of left ventricular dysfunction; TNF α , tumour necrosis factor α

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Table 1 Clinical outcomes by heamatocrit (Hct) quartile

	Quartile 1 (n = 66)	Quartile 2 (n = 54)	Quartile 3 (n = 63)	Quartile 4 (n = 56)	p Value
Patients hospitalised	53.0%	38.9%	38.1%	21.4%	0.005
Total per patient hospital days	7.84	7.22	2.00	1.48	0.0008
Cardiac per patient hospital days	2.77	5.53	1.55	1.05	0.03
Mortality	15.1%	18.5%	12.7%	3.6%	0.09

Quartile 1: Hct <35%; Quartile 2: Hct = 35–38%; Quartile 3: Hct = 39–42%; Quartile 4: Hct >42%.
Reproduced from McClellan *et al.*¹⁸

with NYHA class IV symptoms.⁹ These estimates are higher than those seen in subsequent reports, although no true population report of chronic heart failure has been published to date. Wisniacki and colleagues found prevalences going from 0.0% in class I, 36.4% in class II, 52.0% in class III, and 65.9% in class IV.¹⁰ In contrast, Tanner and colleagues found much lower estimates in 193 patients from a tertiary heart failure outpatient clinic (mean age 54 years) in Switzerland: 7% in class I, 9% in class II, 17% in class III, and 26% in class IV.¹¹ The frequency is of course dependent on the precise definition of anaemia. Although less than 12 g/dl is the most commonly used cut off this is of course arbitrary, and whether we should use different ranges for women (where the majority of heart failure patients are post-menopausal) is also not clear. The estimates of frequency nearly double in the lower symptomatic classes if a cut off of 12.5 g/dl is used.

CAUSE OF ANAEMIA IN CHF

The cause of anaemia in heart failure is not known. There are many recognised causes of anaemia such as iron, folate, or B12 deficiency, which should be looked for and, if found, treated. One report from Dundee of new heart failure cases with anaemia found that “simple” causes of anaemia such as iron B12 or folate deficiency were rare in heart failure, and that in most cases of anaemia in heart failure no specific aetiology could be found.¹² There may of course be other causative or contributory factors operative in heart failure that can cause anaemia by other routes. These include dysfunction of the bone marrow caused by low output failure¹³ as a result of the effects of cytokine activation. For example, tumour necrosis factor α (TNF α) can cause anaemia via known effects, including direct bone marrow depression, the induction of erythropoietin (EPO) insensitivity, and interference with the release and utilisation of iron.⁹ The TNF α /Fas pathway in lymphocytes has been shown to be activated in the bone marrow of a heart failure model in mice, suggesting one possible mode of effect.¹⁴ Within a severe heart failure population Bolger and colleagues recently showed that circulating concentrations of TNF, soluble TNF receptor-1, soluble TNF receptor-2, and soluble CD14—all

cytokine activation markers—all relate strongly to haemoglobin, suggesting that anaemia is related to inflammatory immune activation in severe CHF.¹⁵

Other factors include the known down regulation of EPO by angiotensin converting enzyme (ACE) inhibitors.¹⁶ Heart failure is frequently associated with a degree of functional chronic renal failure (CRF) with a relative deficiency of EPO production. It is not clear how much of the anaemia of heart failure can be explained by this mechanism, although if anaemia correction by EPO administration proves to be worthwhile this might remain a distinction of less practical importance. Although in heart failure EPO values are raised, they are still below what they should be, taking into account the level of anaemia, thus indicating a relative EPO deficiency.¹⁷

In addition to having an impact on exercise capacity, anaemia complicating heart failure has been shown in several reports to be associated, possibly causatively, with a worse outcome. In one retrospective survey of community hospital admissions for heart failure (665 eligible patients, mean (SD) age 75.7 (10.9) years), both haematocrit and serum creatinine were independently associated with an increased risk of death during follow up, after controlling for other patient risk factors (table 1).¹⁸ In one of the largest single centre reports the heart transplant assessment population of the University of California, Los Angeles (UCLA) was investigated. In a cohort of 1061 patients with advanced heart failure (NYHA functional class III or IV) with haemoglobin assessed at the time of initial evaluation, lower haemoglobin was associated with an impaired haemodynamic profile, higher blood urea nitrogen and creatinine, and also with the higher NYHA functional class ($p < 0.0001$), and a lower peak oxygen consumption (PKV_{O₂}) ($p < 0.0001$). Survival at one year was higher with increased haemoglobin quartile (55.6%, 63.9%, 71.4%, and 74.4% for quartiles 1, 2, 3, and 4, respectively). On multivariate analysis adjusting for known heart failure prognostic factors, low haemoglobin proved to be an independent predictor of mortality (relative risk 1.131, 95% confidence interval (CI) 1.045 to 1.224 for each decrease of 1 g/dl).¹⁹ In a confirmatory report on a larger multi-centre

Table 2 Interaction between chronic kidney disease, chronic heart failure anaemia and subsequent mortality

Patient group	Number of patients	2 year death rate (%)	RR (95% CI)
CHF(-)CKD(-)Anaemia(-)	848182	7.7	1.00 (reference)
CHF(-)CKD(-)Anaemia(+)	108926	16.6	1.90 (1.87 to 1.94)
CHF(-)CKD(+)Anaemia(-)	12031	16.4	2.05 (1.96 to 2.15)
CHF(+)CKD(-)Anaemia(-)	90886	26.1	2.86 (2.82 to 2.91)
CHF(-)CKD(+)Anaemia(+)	7381	27.3	3.37 (3.23 to 3.53)
CHF(+)CKD(-)Anaemia(+)	40364	34.6	3.78 (3.71 to 3.85)
CHF(+)CKD(+)Anaemia(-)	7131	38.4	4.86 (4.67 to 5.05)
CHF(+)CKD(+)Anaemia(+)	9404	45.6	6.07 (5.89 to 6.27)

CHF, chronic heart failure; CKD, chronic kidney disease; CI, confidence interval; RR, relative risk
Reproduced from Herzog *et al.*²²

trial the database of the SOLVD database was studied. Using a calculated glomerular filtration rate (GFR) the authors found both lower predicted GFR and lower haematocrit were risk factors for all cause mortality ($p < 0.001$ for both). After adjustment for other factors significant in univariate analysis, a 10 ml/min/1.73 m² lower GFR and a 1% lower haematocrit were associated with a 1.064 (95% CI 1.033 to 1.096) and 1.027 (95% CI 1.015 to 1.038) higher risk for mortality, respectively. At lower GFR and lower haematocrit, the risk was higher ($p = 0.022$ for the interaction) than that predicted by both factors independently, indicating a possible interaction between these two risk markers for heart failure mortality.²⁰

A similar effect of low haemoglobin being associated with increased mortality independent of conventional severity markers for heart failure was also seen in an analysis of the ELITE-II trial in moderate heart failure, although in this case a strong U shaped curve was seen with increased mortality in patients with haemoglobin concentrations above 15.4 g/dl, suggesting an optimal haemoglobin value of between 14.5–15.4 g/dl.²¹ In the largest report to date the claims records of 1 124 302 patients in the US General Medicare database (end stage renal disease excluded) were identified in a two year (1996–97) entry cohort. Chronic renal disease and anaemia were found independently to confer a twofold increased risk of death risk, and CHF a nearly threefold increased risk. The authors summarised that these data suggest a role for aggressive CHF treatment and anaemia correction in the elderly (table 2).²²

TREATMENT OF ANAEMIA IN HEART FAILURE

There have been only a very small number of reports on the treatment of anaemia in heart failure patients. In an early uncontrolled report 26 patients with heart failure and anaemia treated for an average of 7.2 months with EPO and intravenous iron were reported to show an increase in haemoglobin. from 10 to 12 g/dl, an increase in left ventricular ejection fraction from 27% to 35%, a decrease in hospitalisations for heart failure by 91%, an improvement in mean NYHA class from 3.6 to 2.6, and a reduction in the use of diuretics.⁹ Although these would be important benefits, limitations in trial design made them unreliable. Clearly further evidence from properly controlled trials was necessary.

In a second report with a control group (although not with a randomised double blind allocation) 16 patients with moderate to severe CHF and haemoglobin values persistently between 10.0–11.5 g/dl received subcutaneous EPO and intravenous iron to increase the concentration of haemoglobin to at least 12.5 g/dl. Over a mean (SD) period of 8.2 (2.6) months, the mean NYHA class improved by 42.1%, the left ventricular ejection fraction increased by 5.5%, and the need for oral and intravenous furosemide (frusemide) decreased by 51.3% and 91.3%, respectively. In addition the number of days spent in hospital compared with the same period of time before entering the study decreased by 79.0%.²³ A previous larger randomised controlled trial of recombinant human erythropoietin (epoetin) in 1233 dialysis patients, many with symptoms of heart failure, failed to show a benefit of aiming for higher rather than lower haematocrit values. Surprisingly the higher haematocrit group showed increased cardiovascular mortality and morbidity despite the fact that within each randomised group a higher haematocrit was associated with a lower cardiovascular event rate.²⁴ The explanation for this apparent conundrum remains unclear despite much analysis and discussion. What does remain attractive is that correcting anaemia with EPO or an erythropoietic agent could not only increase exercise tolerance but possibly also reverse the excess risk associated with the presence of anaemia in CHF.

CONCLUSION

Our increased understanding of the complex pathophysiology of heart failure has introduced a new era in the treatment of heart failure in which anti-neurohormonal and metabolic²⁵ treatments are tested for their ability to improve both functional capacity and survival of CHF patients. The era of trials on EPO in this effort looks imminent. Even if the strategy is successful its role in practice, given the high cost, may prove difficult to determine.²⁶

REFERENCES

- Franciosa JA, Baker BJ, Seth L. Pulmonary versus systemic hemodynamics in determining exercise capacity of patients with chronic left ventricular failure. *Am Heart J* 1985;110:807–13.
- Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol* 1996;28:1092–102.
- Anker SD, Sharma R. The syndrome of cardiac cachexia. *Int J Cardiol* 2002;85:51–66.
- Brink M, Anwar A, Delafontaine P. Neurohormonal factors in the development of catabolic/anabolic imbalance and cachexia. *Int J Cardiol* 2002;85:111–21.
- Conraads VM, Bosmans JM, Vrints CJ. Chronic heart failure: an example of a systemic chronic inflammatory disease resulting in cachexia. *Int J Cardiol* 2002;85:33–49.
- Clausen JP. Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and in patients with coronary artery disease. *Progress in Cardiovascular Diseases* 1976;18:459–95.
- Tanabe Y, Nakagawa I, Ito E, et al. Hemodynamic basis of the reduced oxygen uptake relative to work rate during incremental exercise in patients with chronic heart failure. *Int J Cardiol* 2002;83:57–62.
- Kalra PR, Bolger AP, Sharma R, et al. The relationship between hemoglobin and exercise capacity in patients with stable chronic heart failure (CHF). *Circulation* 2002;106(suppl):II-570.
- Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737–44.
- Wisniacki N. Is anaemia a cause or a consequence of heart failure in the elderly? [abstract] *Heart* 2001;85(suppl 1):P4.
- Tanner H, Moschoviitis G, Kuster GM, et al. The prevalence of anemia in chronic heart failure. *Int J Cardiol* 2002;86:115–21.
- Cromie N, Lee C, Struthers AD. Anaemia in chronic heart failure: what is its frequency in the UK and its underlying causes? *Heart* 2002;87:377–8.
- Chatterjee B, Nydegger UE, Mohacs P. Serum erythropoietin in heart failure patients treated with ACE-inhibitors or AT(1) antagonists. *Eur J Heart Fail* 2000;2:393–8.
- Iversen PO, Woldbaek PR, Tonnessen T, et al. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. *Am J Physiol Regul Integr Comp Physiol* 2002;282:R166–72.
- Bolger AP, Doehner W, Sharma R, et al. Anaemia in chronic heart failure: the relationship to inflammatory cytokine expression and prognostic importance. *Circulation* 2002;106(suppl):570–1.
- Volpe M, Tritto C, Testa U, et al. Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. *Am J Cardiol* 1994;74:468–73.
- Jensen J, Eiskjaer H, Bagger JP, et al. Elevated level of erythropoietin in congestive heart failure: relationship to renal perfusion and plasma renin. *J Intern Med* 1993;233:125–30.
- McClellan WM, Flanders WD, Langston RD, et al. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol* 2002;13:1928–36.
- Horwich TB, Fonarow GC, Hamilton MA, et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002;39:1780–6.
- Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;38:955–62.
- Anker SD, Sharma R, Francis D, et al. Anemia and survival in 3044 patients with chronic heart failure (CHF) in the ELITE II trial. *Circulation* 2002;106(suppl):472.
- Herzog CA, Li S, Collins AJ. The impact of congestive heart failure (CHF), chronic kidney disease (CKD), and anemia on survival in the Medicare population. *Circulation* 2002;106(suppl):471–2.
- Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001;37:1775–80.
- Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584–90.
- Harrington D, Chua TP, Coats AJ. The effect of salbutamol on skeletal muscle in chronic heart failure. *Int J Cardiol* 2000;73:257–65.
- Coats AJ. Making choices in cardiology: difficulties of rationing and equality of access. *Int J Cardiol* 2001;78:209–12.