Anaemia among patients with congestive cardiac failure in Uganda – its impact on treatment outcomes

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Background: Anaemia increases morbidity and mortality in patients with congestive cardiac failure (CCF). Few studies have examined the prevalence of anaemia and its impact among patients with CCF in sub-Saharan Africa. We assessed the prevalence of anaemia and its influence on treatment outcome in patients with CCF attending a large referral hospital in Kampala, Uganda.

Methods: Echocardiography was done and haemoglobin levels were determined in 157 patients with CCF admitted to Mulago Hospital. The patients were followed up for 2 weeks and their treatment outcome was recorded.

Results: Of the 157 patients, 101 (64.3%) had anaemia (mean haemoglobin concentration ≤11.9 g/dl for women and ≤12.9 g/dl for men) at admission. Increasing age and hypertensive heart disease were significantly associated with anaemia (odds ratio (OR) 2.92, confidence interval (CI) 1.41 - 6.05, \( p < 0.01 \) and OR 0.31, CI 0.13 - 0.74, \( p < 0.01 \), respectively). In-hospital mortality at the end of the 2 weeks of treatment was 10.2% and was significantly higher among the anaemic patients than their non-anaemic counterparts (OR 4.9, CI 1.07 - 22.35, \( p < 0.03 \)). The mean duration of in-hospital stay was 7.5 (standard deviation 3.4) days. This did not differ significantly between anaemic and non-anaemic patients.

Conclusion: The prevalence of anaemia among patients with CCF attending Mulago Hospital was high. Anaemia in these patients was significantly associated with mortality by the end of 2 weeks of treatment.

on risk factors for cardiac disease (including rheumatic fever, cardiomyopathies, previous hospitalisation and cardiac-related surgery) were collected by questionnaire. Echocardiography was done using a digital Sonocor 9000 Echo Copier (Medison Co. Ltd, Serial SA 5500 100 – 120/200 – 00501), while Hb was measured on a haemolyser (CELL-DYN 1700 system 1995).

The prevalence of anaemia was calculated as the proportion of men and women who had low Hb levels (≤11.9 g/dl for women and ≤12.9 g/dl for men). Anaemia was categorised as mild (Hb 10 - 11.9 g/dl for women and 10 - 12.9 g/dl for men), moderate (Hb 7 - 9.9 g/dl for both genders) or severe (Hb <7 g/dl). Categorical variables including gender, causation of CCF and NYHA class were presented using frequencies and percentages and then cross-tabulated against the outcome variable (anaemia). Continuous variables such as age, urea, creatinine and fractional shortening were compared between the anaemic and non-anaemic patients using the independent-samples t-test for comparison of means. Levine’s test for equality of variances and the significance level corresponding to the assumption of equal variance was used. The value of the t-statistic for the equality of means was used as a measure of strength of association. Multivariate logistic regression was used to determine strength of association between the presence of anaemia and other variables found to be significantly associated with anaemia at bivariate analysis.

Results

Patient characteristics

Of the 157 patients studied, 104 (66.2%) were female. The mean age was 45 years (range 13 - 99).

Underlying causation of CCF

Rheumatic heart disease (28.2%), dilated cardiomyopathy (27.3%), hypertensive heart disease (25.1%) and endomyocardiofibrosis (EMF) (14.3%) were the most common underlying cardiac diseases, followed by degenerative valvular heart disease (1.9%), hypertrophic cardiomyopathy (1.3%) and ischaemic heart disease (1.9%), which was presumably due to ischaemic heart disease (Fig. 1). Most patients were admitted in severe CCF (NYHA classes III (59.9%) and IV (36.9%)). Only 5 (3.2%) were admitted in NYHA class II, and no patient was in NYHA class I.

Prevalence, severity and type of anaemia, and associations (Table I)

Anaemia was highly prevalent, occurring in 64.3% of the patients with CCF. The mean Hb was 11.2 g/dl (standard deviation (SD) 8.69). The prevalence of anaemia decreased along the scale from mild (31.2%) to severe (6.1%). The commonest type of anaemia was normocytic normochromic (88.2%).

Having hypertensive heart disease was significantly associated with anaemia (odds ratio (OR) 0.31, 95% confidence interval (CI) 0.13 - 0.74, p<0.01), as were increasing age (>50 years) (OR 2.92, CI 1.41 - 6.05, p<0.01) and raised creatinine (>133 µmol/l) (OR 0.17, 95% CI 0.08 - 0.37, p<0.01) and urea (>17.85 mmol/l) (OR 0.12, 95% CI 0.05 - 0.31, p<0.01).

Management outcomes

We examined mortality at the end of 2 weeks of hospitalisation and length of in-hospital stay.

<table>
<thead>
<tr>
<th>Table I. Severity and type of anaemia</th>
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<tr>
<td>Haemoglobin (g/dl)</td>
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<td>Severe anaemia (&lt;7.0)</td>
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<tr>
<td>Moderate anaemia (7.0 - 9.9)</td>
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<tr>
<td>Mild anaemia (10.0 - 11.9)</td>
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<td>Normal (≥12)</td>
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<tr>
<td>Total</td>
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*31 females were menopausal (15 did not have anaemia, 11 had mild anaemia, 4 had moderate anaemia and 1 had severe anaemia).

NN = normocytic normochromic; NH = normocytic hypochromic; MH = microcytic hypochromic.
Mechanisms of anaemia in CCF

Several mechanisms (Fig. 2) have been proposed to explain the occurrence of anaemia in CCF, and it is probable that individual patients have varying combinations of these. CCF plays an important role in the causation of anaemia, mainly due to the depressant effects of tumour necrosis factor alpha (TNFα), which is secreted from the damaged myocardium.

The overall prevalence of anaemia in CCF patients in a New York study was 61.0%, a finding similar to ours, as was the mean age of their patients (51.5 years). In our study, 72.4% of patients in NYHA class IV had anaemia compared with 57.4% in NYHA class III, which correlates with prevalences of anaemia of 79.1% and 52.6% in NYHA classes IV and III, respectively, in a study in Israel. This similarity in prevalence is surprising given the differences in mean age of the patients in the two studies – the patients in Israel were on average 70 years old. We found that the prevalence of anaemia in CCF increased with increasing patient age, as has been observed by others. This may be due to increasing co-morbidities with ageing.

On analysis of the causes of CCF, there was a statistically significant association between anaemia and hypertensive heart disease (OR 0.31, CI 0.13 - 0.74, p<0.01) that might reflect some underlying relative degree of hypertensive renal disease with concomitant relative erythropoietin deficiency in addition to the general mechanisms of anaemia causation in CCF.

While the prevalence of anaemia in our study is comparable to rates in the developed countries, the underlying causes of CCF are not. This may imply that the anaemia in our patients is occurring as an effect of CCF per se rather than an effect related to the underlying cause of the CCF. However, we might be dealing with some co-morbidities that have still to be identified.

Valvular heart diseases, EMF, dilated cardiomyopathy and hypertensive heart disease (probably because blood pressure control is poor) remain significant causes of CCF in our patients. This compares well with a South African study in which it was found that hypertensive heart disease and dilated cardiomyopathy are the major underlying causes of CCF, with few cases of ischaemic heart disease. However, we seem to have higher numbers of patients with CCF resulting from rheumatic heart disease and EMF, a finding attributed by some to differences in traditional diet, socio-economic status and unidentified infections (eosinophilia). Few patients (1.9%) had ischaemic heart disease ascribed to coronary artery disease, although we did not do coronary artery angiography. Similarly, Sliwa found only a small number of patients with ischaemic heart disease (9%) in their cardiac failure cohort, whereas ischaemic heart disease is the predominant underlying cause of CCF in developed societies. With epidemiological change the underlying causes of CCF in our setting will certainly continue to evolve.
Anaemia in patients with cardiac disease can also be iatrogenic, caused by drugs such as angiotensin-converting enzyme inhibitors and aspirin, which are thought to inhibit both erythropoietin production in the kidneys and its utilisation in the bone marrow and also cause gastro-intestinal bleeding.21,24

It is also important to note that anaemia is endemic in our community, with prevalences of 60.1% in children, 30.2% in women and 18.1% in men.27 Whether our high prevalence of anaemia reflects the generally high prevalence in the community requires further investigation.

Mortality
The all-cause in-hospital mortality rate in our study was 10.2%. This is comparable to mortality rates in other studies. A study in California reported an in-hospital mortality rate of 6.9%.6 Our rate may be slightly higher because our patients tend to present late with advanced disease. Furthermore, differences in the underlying cause of CCF may be partly responsible for differences in mortality rates. We established that the odds of dying in the first 2 weeks after admission for CCF patients with anaemia are 5 times higher than for CCF patients without anaemia. Early detection and appropriate management of anaemia in patients with CCF may improve their outcome.

Hospital stay
The mean length of hospital stay in our study was 7.5 days. The study was designed to follow up patients for a maximum of 2 weeks in hospital, yet some patients stayed longer than this. Our calculated mean duration of hospitalisation was therefore probably lower than would have been the case had patients been followed up until discharge. Nordyke and James found that their CCF patients spent a mean of 7.4 days in hospital, those with anaemia staying longer (p<0.01).20 In a Spanish study by Formiga, on the other hand, the mean length of stay for patients admitted with new-onset cardiac failure was 10 days.26 We suggest that this longer stay may in part be due to the time-consuming diagnostic work-up and counselling necessary for new patients. Our findings suggest that if we were to measure the Hb concentration on admission of every patient with CCF and treat anaemia if present, we could provide better care for these patients and reduce in-hospital mortality.

Limitations
We were unable to follow up all patients until discharge and therefore cannot come to accurate conclusions on the effect of anaemia on length of hospital stay. However, data obtained during the 2-week follow-up are sufficient for us to conclude that anaemia in CCF signifies an unfavourable outcome.

Recommendations
A long-term follow-up study in a setting similar to ours is recommended. Studies looking at optimal treatment of anaemia in CCF urgently need to be carried out in sub-Saharan settings.

The TNFα interferes with erythropoietin-induced bone marrow stimulation, reduces the production of erythropoietin in the kidneys and interferes with the release of iron from the reticuloendothelial system, depriving the bone marrow of this essential element for the production of Hb.26 Furthermore, the renal failure/damage that inevitably accompanies cardiac failure decreases erythropoietin production. In our study, where 95% of the participants had a structural cardiac disease (rheumatic heart disease, dilated cardiomyopathy, hypertensive heart disease or EMF, which lead to structural changes in the myocardium) as the underlying cause of CCF, this mechanism may have contributed significantly to the high prevalence of anaemia.

The reduced renal blood flow caused by CCF can lead to renal hypoxia, which can activate the renin-angiotensin axis and other growth factors, leading to glomerular and medullary damage and consequently proteinuria.27,28 In a vicious circle, proteinuria can further damage the renal tubules and reduce production of erythropoietin.29 Some degree of erythropoietin resistance occurs among CCF patients as a result of elevated plasma levels of inflammatory cytokines.20

In patients with chronic cardiac diseases, sequestration of iron in macrophages (consequent to chronic diseases) makes this nutrient unavailable for haematopoiesis. This would have applied to a large proportion of our patients and could have contributed to the high prevalence of anaemia.21 In addition, poor nutritional intake and gastro-intestinal malabsorption, which are common among patients with advanced CCF, could have played a role.22

On top of the mechanisms suggested above, the anaemia in cardiac failure patients may be due to haemodilution, which in one study was responsible for 46% of the anaemia.25 However, we did not assess patients for haemodilution.

Anaemia in patients with cardiac disease can also be iatrogenic, caused by drugs such as angiotensin-converting enzyme inhibitors and aspirin, which are thought to inhibit both erythropoietin production in the kidneys and its utilisation in the bone marrow and also cause gastro-intestinal bleeding.21,24

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Conflict of interest. None.

References