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ANAEMIA AND HEART FAILURE: A Retrospective Study at Charlotte Maxeke Johannesburg Academic Hospital

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A Research report submitted to the Faculty of Health Sciences, Department of Internal Medicine, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the Degree of Master of Medicine in the Branch of Cardiology.

Johannesburg 2012

DECLARATION

I declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine. It has not been submitted for any degree or examination at this or any other University.

Kershlin Naidu

23rd November 2012

DEDICATION

To my parents, Krish and Vigie, for giving me the opportunity to further my academic career.

To my wife, Ashana, for her constant encouragement, advice and support.

PUBLICATIONS AND PRESENTATIONS

The results of this study have not been published or presented at conferences or academic meetings.

ABSTRACT

ANAEMIA AND HEART FAILURE: A Retrospective Study at Charlotte Maxeke Johannesburg Academic Hospital

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INTRODUCTION

Anaemia has been associated with adverse outcomes in patients with chronic congestive cardiac failure in numerous international studies. There is a lack of local studies assessing the relationship between anaemia and heart failure.

AIMS

- To define the prevalence of co-morbid anaemia in patients attending the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital.
- To evaluate the relationship between anaemia and severity of heart failure.
- To compare anaemic and non-anaemic patient variables.
- To define the aetiology of heart failure in patients attending the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital.

METHODOLOGY

This is a single centre retrospective study of patients attending the Charlotte Maxeke Johannesburg Academic Hospital Heart Failure Clinic from January to June 2011. The patient files were analysed specifically for the presence of anaemia, New York Heart Association (NYHA) functional class, furosemide dose, six minute walk test and Minnesota Living with Heart Failure Questionnaire score. In addition, demographic data (age, gender) and the aetiology of heart failure were recorded.

Anaemia was defined by the World Health Organisation (WHO) criteria of a haemoglobin level <13 g/dl in men and < 12g/dl in women.

The control group consisted of participants attending the clinic who were not anaemic. The two groups were compared using:

a) Participant's symptom scores; using the Minnesota Living with Heart Failure Questionnaire (MLHFQ - Appendix B).
b) Objective measurements of the participant's state of health:
    - Six minute walk test
    - Dose of furosemide (Lasix)
    - New York Heart Association (NYHA) functional class

RESULTS

A total of 282 files were reviewed over 6 months from the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital. Sixty-two files were excluded from the study due to lack of study data recorded in the file. Data was collected and entered into a database which was analysed using the Statistics/Data Analysis Program (STATA) Version 10.0. Mean age of the study group was 59.8 years (SD±12.2), with the youngest subject aged 22 years and the oldest 91 years.

The mean haemoglobin concentration was 13.79 g/dl (SD±1.96). The mean haemoglobin in men was 13.83 g/dl (SD±1.97) and in females the mean haemoglobin was 13.79 g/dl (SD±1.96). The overall prevalence of anaemia in the sample population was 21.4% (47 anaemic patients). The prevalence of anaemia in

males and females was 15.8% and 26.1% respectively. Seventy-two patients (32.7%) had ferritin levels recorded and one patient (0.01%), who happened to be female, was iron deficient based on serum iron studies (Ferritin < 15 µg/L). None of the male subjects was iron deficient.

An insignificant inverse relationship between haemoglobin concentration and Minnesota score (p=0.452) was found. No correlation was found between haemoglobin concentration and furosemide dosage in this study (p=0.123). Analysis of haemoglobin concentration and the six minute walk test yielded a positive correlation which was statistically significant (p=0.001).

The Analysis of Variance Test (ANOVA) showed a significant association between the haemoglobin level across the different NYHA functional classes (p=0.03). The prevalence of anaemia in NYHA class I, II and III was 9.2%, 12.1% and 51.7% respectively. None of the subjects were documented as being NYHA functional class IV.

DISCUSSION

The overall prevalence of anaemia in this study was 21.4%, which is consistent with international studies.

Although an inverse relationship between haemoglobin concentration and Minnesota score was found, it was statistically insignificant (p=0.452). Lower haemoglobin levels are associated with higher Minnesota scores which reflect greater severity of heart failure based on patient's symptoms. Anaemic patients with heart failure are more likely to have poorer quality of life scores.

The finding of a positive correlation between haemoglobin concentration and the six minute walk test confirms that higher haemoglobin levels are associated with better effort tolerance and lower severity of heart failure, which is consistent with many international studies.

No correlation was found between haemoglobin concentration and furosemide dosage in this study (p=0.123). One would have expected higher doses of furosemide with lower haemoglobin levels as higher furosemide doses are associated with more severe heart failure. The reason for this discrepancy is probably due to the fact that many of the patients in the heart failure clinic are treated with other diuretics (eg. spironolactone, hydrochlorothiazide) in addition to furosemide.

The statistically significant association between NYHA functional class and haemoglobin supports the findings that anaemia is associated with poorer functional class. Patients classified as NYHA III had a mean haemoglobin of 11.9 g/dl, whereas NYHA I patients has a mean haemoglobin of 13.98 g/dl. The highest prevalence of anaemia (51.7%) was found in NYHA class III patients.

Dilated cardiomyopathy was the commonest cause of heart failure (34.1%) followed by hypertensive heart disease (21.4%), ischaemic heart disease (18.6%) and alcoholic cardiomyopathy (8.6%).

CONCLUSION

The findings of this study confirm that anaemia is common in heart failure patients. The study also found anaemia to be more prevalent in patients with more advanced heart failure, thus making anaemia a potential prognostic factor in patients with heart failure.

PREFACE

This study was approved by the Committee for Research on Human Subjects, University of the Witwatersrand.

Ethics Clearance Certificate Protocol Number: M111005

Reference number: R14/49 Dr Kershlin Naidu

LIST OF ABBREVIATIONS

µg/L	:	microgram per litre
g/dl	:	grams per decilitre
mg	:	milligrams
6MWT	:	Six minute walk test
ACD	:	Anaemia of Chronic Disease
ACE	:	Angiotensin Converting Enzyme
ACEi	:	Angiotensin Converting Enzyme Inhibitor
ANOVA	:	Analysis of Variance Test
CCF	:	Congestive Cardiac Failure
CIA	:	Chemotherapy-Induced Anaemia
CKD	:	Chronic Kidney Disease
CMO	:	Cardiomyopathy
DCMO	:	Dilated Cardiomyopathy
DMT1	:	Divalent Metal Transporter 1
EPO	:	Erythropoietin
ESA	:	Erythropoietin Stimulating Agent
Hb	:	Haemoglobin Concentration
HHD	:	Hypertensive Heart Disease
HIV	:	Human Immunodeficiency Virus
HAART	:	Highly Active Antiretroviral Therapy
IFN-γ	:	Interferon - gamma
IL	:	Interleukin
LPS	:	Lipopolysaccharide
N	:	Total number

No.	:	Number
NYHA	:	New York Heart Association
SD	:	Standard Deviation
STATA	:	Statistics/Data Analysis Program
TNF-α	:	Tumour Necrosis Factor - alpha
WHO	:	World Health Organisation

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Chapter 1: LITERATURE REVIEW

1.1 Background

Anaemia has been associated with adverse outcomes in patients with chronic congestive cardiac failure (CCF) in numerous international studies. There is a lack of local studies assessing the relationship between anaemia and heart failure. Cardiac failure is an extremely challenging condition to treat as a patient's quality of life is severely affected. Great advances have been made in this area over the recent past with the advent of beta-blockers and aldosterone antagonists. Despite the latter, mortality rates remain high. Therefore, the search for additional factors affecting prognosis and other treatment options continues.

1.2 Prevalence of Anaemia in Heart Failure

It has been noted that anaemia and CCF are common co-morbid conditions. The prevalence of anaemia depends on the sample selection and the definition used for anaemia. Data from many clinical trials and heart failure registries suggest that the prevalence of anaemia amongst hospitalised patients ranges between 14 and 70% (Anand, 2008b). The European Heart Failure Survey found 23% of women and 18% of men with chronic heart failure to be anaemic. In a large cohort of 12065 patients in Alberta, Canada the prevalence of anaemia was found to be 17%; 58% of which was due to anaemia of chronic disease, 21% was due to iron deficiency anaemia and 8% was due to other causes (Ezekowitz, McAlister and Armstrong, 2003). The SOLVD (Studies Of Left Ventricular Dysfunction), Val-HeFT (Valsartan Heart Failure Trial) and COMET (Carvedilol Or Metoprolol European Trial) trials found that newly diagnosed anaemia developed in 9.6%, 16.9% and 14.2% of their patients

respectively. A local study involving Black African patients with idiopathic dilated cardiomyopathy reported a prevalence of 13.5% (Inglis, et al., 2007).

1.3 Anaemia and Prognosis in Heart Failure

Current guidelines and reviews do not include anaemia as a prognostic factor or a treatment goal in the management of heart failure. Anaemia has consistently been shown to be associated with increased mortality in patients with acutely decompensated and chronic heart failure. The PRAISE (Prospective Randomised Amlodipine Survival Evaluation) study, which evaluated 1130 patients with CCF and ejection fractions <30%, found anaemia to be a major risk factor for death (Mozaffarian, Nye and Levy, 2003). A meta-analysis of more than 150 000 heart failure patients showed that mortality was twice as high in the anaemic group when compared to the non-anaemic group (Groenewald, et al., 2008). Importantly, anaemic patients in cardiac failure are also more likely to have severe heart failure as judged by higher NYHA functional class, reduced exercise capacity, lower quality of life scores, greater amount of peripheral oedema requiring diuretics and lower systolic blood pressures (Anand, 2008b). Many studies have concluded that there is an inverse linear relationship between haemoglobin levels and prognosis in heart failure. However, a few studies have found an increased risk with the highest haemoglobin level, also described as a U-shaped relationship (Sharma, et al., 2004; Mozaffarian, Nye and Levy, 2003).

1.4 Pathophysiological Mechanisms of Anaemia in Heart Failure

There are various mechanisms that link anaemia with increased morbidity and mortality. Reduced oxygen delivery to the tissues, leads to increased myocardial workload, which in turn results in left ventricular remodelling, hypertrophy and dilatation. Furthermore anaemia may be a marker of poor nutritional status. It is well recognised that poor nutritional status results in low albumin levels and body mass index (BMI), both of which are associated with increased mortality in heart failure patients (Guder, et al., 2009; Horwich, et al., 2008).

The reduced tissue oxygenation from chronic anaemia results in haemodynamic and non-haemodynamic compensatory responses, which enhance oxygen delivery to the tissues. The haemodynamic response results in tachycardia and a high output state which in turn will aggravate heart failure. These haemodynamic changes have deleterious effects on an already ailing heart. Non-haemodynamic responses include a right shift of the Haemoglobin-Oxygen Dissociation curve and enhanced erythropoiesis. Unfortunately, erythropoiesis is defective in heart failure.

1.5 Factors Contributing to the Development of Anaemia

1.5.1 Haematinic Abnormalities

Iron deficiency can be caused by poor nutrition and cardiac cachexia. Intestinal malfunction due to engorgement of the bowel with excess fluid results in malabsorption leading to iron, cobalamin and folate deficiencies. Iron absorption through the gastrointestinal system is impaired in chronic inflammatory diseases, including heart failure. Abnormal expression of the duodenal iron transporters cytochrome b, divalent metal transporter 1 and ferroportin was found in Dahl salt

sensitive rats with heart failure (Naito, et al., 2011). It is possible that similar mechanisms contribute to the iron deficiency anaemia in heart failure patients. Iron deficiency may be exacerbated by aspirin induced gastritis, a drug which is used commonly in the management of cardiovascular disease.

The prevalence of iron deficiency ranges between 5% - 73%, depending on the method used for diagnosis. (de Silva, et al., 2006; Nanas, et al., 2006; Witte, et al., 2004; Cromie, Lee and Struthers, 2002). A study performed on patients with heart failure found that 73% of patients had depleted iron stores on bone marrow, despite having normal iron and ferritin levels in the serum (Nanas, et al., 2006). This suggests that the incidence of iron deficiency anaemia may be underestimated in patients with heart failure.

Iron plays a central role in erythropoiesis, oxygen metabolism (iron forms part of oxidative enzymes and respiratory chain proteins) as well as oxygen uptake, distribution and storage (haemoglobin and myoglobin). Normal iron metabolism is essential for optimal function of haematopoietic cells, skeletal and cardiac myocytes (van Veldhuisen, et al., 2011). Chronic iron deficiency results in structural abnormalities in cardiac myocytes culminating in poor effort tolerance of heart failure patients (Brownlie, et al., 2004; Haas and Brownlie, 2001).

1.5.2 Abnormal erythropoietin metabolism

Erythropoietin (EPO) is produced by the kidney in response to hypoxia. It acts on the bone marrow, where it stimulates erythroid cell proliferation. In chronic kidney disease (CKD), the kidney is unable to produce adequate amounts of EPO due to damage of tubular, interstitial and vascular structures. Approximately half of heart failure patients have renal dysfunction, with reduced renal blood flow cited as a major contributing factor. Reduced EPO production secondary to renal dysfunction is one of the mechanisms of anaemia in heart failure (Anand, 2008a).

On the contrary, there are elevated EPO levels in heart failure patients without renal dysfunction (van der Meer, et al*.,* 2008b). Bone marrow resistance to EPO may be a contributory factor in anaemia in heart failure, as high EPO levels have been detected in patients with haemoglobin concentration slightly below the normal range (van der Meer, et al*.,* 2008b). Pro-inflammatory cytokines and certain drugs such as ACE inhibitors may be partially responsible for EPO resistance (Westenbrink, et al., 2010). Elevated plasma EPO levels have been associated with poorer prognosis in heart failure patients, a finding independent of haemoglobin concentration (van der Meer, et al*.,* 2004).

1.5.3 Bone marrow dysfunction

Higher EPO levels are required to stimulate sufficient erythropoiesis due to EPO resistance. Westenbrink, et al. (2010) discovered that the bone marrow of heart failure patients shows evidence of dysfunction along multiple haematopoietic lineages. The differentiation of haematopoietic progenitor cells of heart failure patients into erythroid and myeloid lineages was severely reduced (Westenbrink, et al., 2010). The degree of bone marrow dysfunction is proportional to the severity of heart failure. However the presence of anaemia did not correlate with the extent of bone marrow dysfunction (Westenbrink, et al., 2010).

1.5.4 Anaemia of chronic disease (ACD)

ACD can complicate many conditions including infections, malignancy, autoimmune diseases, heart failure, diabetes mellitus and chronic kidney disease. The anaemia is usually normochromic and normocytic with reduced serum iron levels and normal to increased ferritin levels. ACD occurs due to disturbances in iron homeostasis. Iron is diverted into the cells of the reticuloendothelial system resulting in reduced serum iron levels. As a result iron is unavailable for haemoglobin synthesis and erythropoiesis.

Hepcidin, a 25 amino acid acute phase protein that is produced in the liver, is the predominant negative regulator of iron absorption in the small intestine (Ganz, 2011). Hepcidin inhibits Ferroportin-1, duodenal iron absorption and erythropoiesis. Ferroportin is a transmembrane exporter of iron which is found in duodenal enterocytes, hepatocytes and macrophages of the reticuloendothelial system.

Hepcidin causes the internalisation and degradation of ferroportin, which results in iron being retained within the cell (Ganz, 2011). The reduced transfer of iron out of the duodenal enterocytes and macrophages causes accumulation of intracellular iron stores and reduced serum iron levels. Macrophage iron acquisition occurs via the phagocytosis of erythrocytes and the transmembrane transport of iron by the divalent metal transporter 1 (DMT1). The hepcidin–ferroportin axis is the chief regulator of extracellular iron homeostasis in health and disease (Weiss and Goodnough, 2005).

The major pathophysiologic mechanisms of ACD is Figure 1.5.4 (Weiss and Goodnough, 2005). In Panel A, microorganisms, neoplastic cells or autoimmune dysregulation results in T cell (CD_3+) and monocyte activation. Increased cytokine production results in elevated levels of tumour necrosis factor - alpha (TNF-α), interferon - gamma (IFN-γ) and interleukins (IL) 1,6,10. In Panel B, IL-6 and lipopolysaccharide (LPS) stimulate hepcidin production which inhibits duodenal absorption of iron. In Panel C, IFN-γ and LPS stimulate the expression of DMT1 which increases ferrous iron (Fe^{2+}) uptake. IL-10 stimulates the uptake of transferrin-bound iron into the monocytes. Activated macrophages phagocytose old erythrocytes for iron recycling. Hepcidin, IFN-γ and LPS inhibit ferroportin 1 expression resulting in decreased iron release from macrophages. Simultaneously, TNF-α, IL-1, IL-6 and IL-10 induce ferritin expression. These mechanisms cause reduced serum iron concentrations and accumulation of iron within the reticuloendothelial system. Panel D shows TNF-α and IFN-γ inhibition of EPO production by the kidney. In Panel E, TNF-α, IFN-γ and IL-1 directly inhibit erythroid progenitor cells.

In summary, IFN-γ inhibits EPO production, erythropoiesis and ferroportin 1. TNF-α causes increased degradation and phagocytosis of senescent erythrocytes and inhibits EPO production and erythropoiesis. Interleukin-6 stimulates production of hepcidin and ferritin (Weiss and Goodnough, 2005).

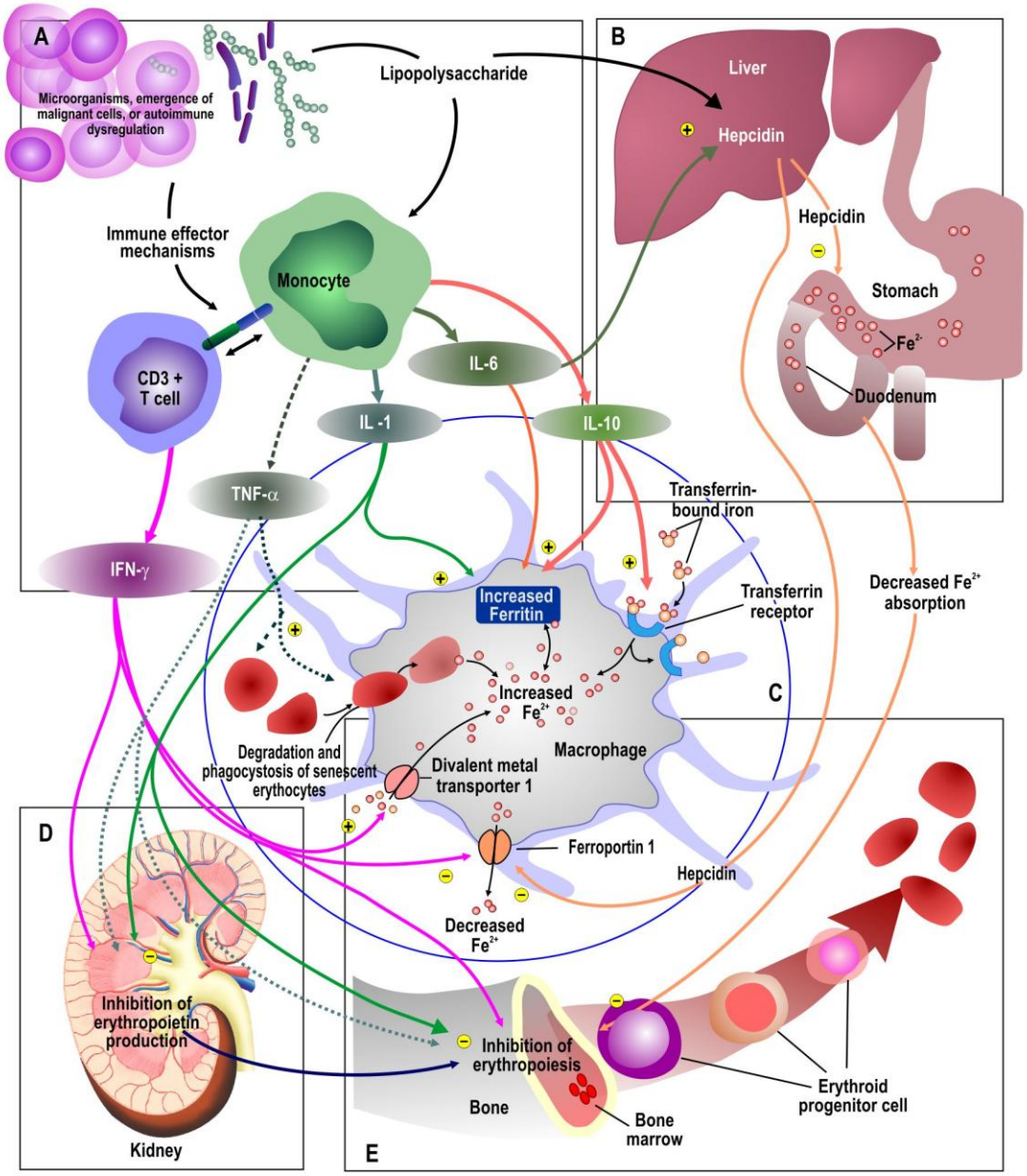


Figure 1.5.4: Pathophysiologic Mechanisms Underlying Anaemia of Chronic Disease
(Adapted from Weiss and Goodnough, 2005)

Anaemia of chronic disease may be the most significant cause of anaemia in heart failure patients. In a group of stable heart failure patients with anaemia, 43% had a demonstrable cause such as chronic kidney disease or iron, folate or cobalamin deficiency. The remainder of patients had elevated levels of pro-inflammatory cytokines, therefore they were considered to have ACD (Opasich, et al., 2005).

1.5.5 The Cardio-Renal Anaemia Syndrome

Reduced cardiac output and renal blood flow worsen renal function. Reduced EPO production and erythropoiesis cause anaemia. Anaemia exacerbates heart failure by increasing the heart rate and stroke volume. The patient then enters a vicious cycle known as the cardio-renal anaemia syndrome (Kazory and Ross, 2009). Figure 1.5.10 illustrates the pathophysiology linking heart failure, renal dysfunction and anaemia.

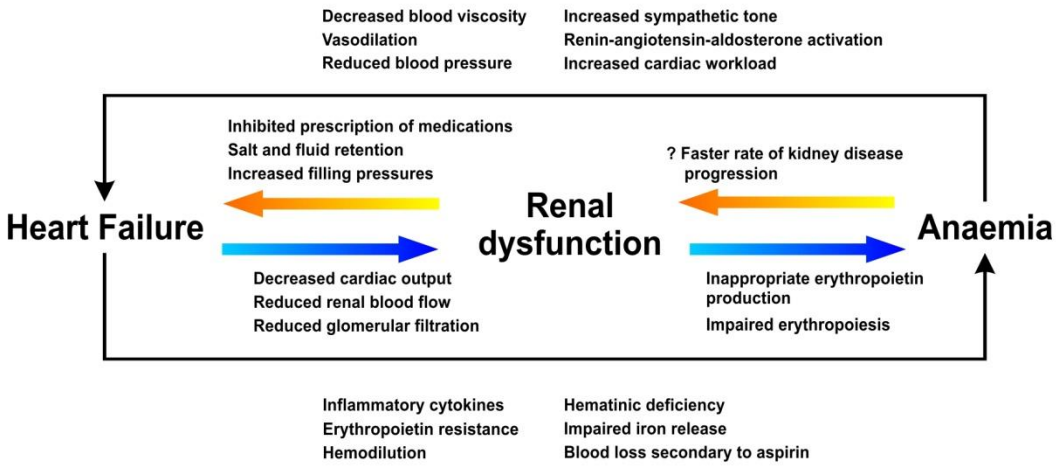


Figure 1.5.5: The Cardiorenal Anaemia Syndrome (Adapted from Kotecha, et al., 2011).

1.5.6 Renin-Angiotensin Blockade

Angiotensin II stimulates EPO production in the kidney, by causing vasoconstriction and resultant reduced oxygen tension. It also directly stimulates the bone marrow to produce erythroid progenitors. The use of angiotensin converting enzyme inhibitors (ACEi) block these pathways and this may contribute to the anaemia.

The impact of the above mechanism was evaluated in a report from combined SOLVD (Studies Of Left Ventricular Dysfunction) trials in which patients with left ventricular dysfunction were randomized to receive either Enalapril or placebo. At one year, the rate of anaemia was significantly higher in the Enalapril group. The difference was evident as early as six weeks of starting therapy (Ishani, et al., 2005).

1.5.7 Haemodilution-induced “pseudoanaemia”

Cardiac failure results in increased plasma volume due to fluid retention. As a result a relative reduction in red blood cell mass occurs. (Westenbrink, et al., 2007; Androne, et al., 2003).

1.5.8 Frequent blood testing

It has been suggested that frequent blood testing may also contribute to the anaemia associated with chronic congestive cardiac failure (Klutstein and Tzivoni, 2005).

1.5.9 Abnormal Adrenal Steroid Metabolism

A multitude of chronic illnesses can cause changes in adrenal steroid production. Chronic illness causes decreased Dehydroepiandrosterone (DHEA) production in favour of cortisol production. DHEA is an anabolic steroid hormone whereas cortisol is regarded as a catabolic hormone. This results in high cortisol/DHEA ratios. It is possible that selective inhibition of the cytochrome P450 17,20-lyase enzyme causes reduced DHEA levels (Okonko, et al., 2005).

Androgens enhance erythropoiesis (Shahidi, 1973) via various mechanisms which include stimulation of erythropoietin production and haem biosynthesis, increased erythroid progenitor erythropoietin sensitivity, and erythrocyte survival (Singer, Samuels and Adamson, 1976). However chronically elevated cortisol levels suppress erythroid progenitor cell proliferation (Hassan, Ibrahim and Rieder, 1982).

A study conducted on 92 men with chronic compensated heart failure found that higher cortisol/DHEA ratios were associated with lower haemoglobin levels (Okonko, et al., 2005). The study team concluded that abnormal adrenal steroid metabolism may contribute to the development of anaemia in heart failure patients (Okonko, et al., 2005). Androgen supplementation alters the cortisol/DHEA ratio and can correct the anaemia in heart failure patients (Silverberg, et al., 2004).

1.5.10 Telomere Length

Reduced leucocyte telomere length is considered to be a marker of cellular ageing. Wong, et al. (2010) discovered that shorter telomere lengths were associated with a greater risk of developing anaemia in heart failure patients. As a result the investigators concluded that cellular ageing plays a role in the pathogenesis of anaemia in this patient group (Wong, et al., 2010).

1.6 Treatment of Anaemia in Heart Failure

1.6.1 Iron supplementation in Heart Failure

Oral iron supplementation is associated with poor compliance, gastrointestinal side effects, reduced absorption and low efficacy (Macdougall, 1999). Intravenous iron therapy is more effective than oral iron therapy in treating iron deficiency anaemia in non-dialysis dependent chronic kidney disease patients (Van Wyck, et al., 2005). The IRON-HF trial, which is currently ongoing, will compare the efficacy of intravenous and oral iron therapy in heart failure patients (Beck-da-Silva, et al., 2007). The Ferinject® Assessment in Patients With IRon Deficiency and Chronic Heart Failure (FAIR-HF) Trial, which involved 459 patients, showed that intravenous iron (ferric carboxymaltose) therapy in iron deficient heart failure patients resulted in improved symptoms, exercise capacity and quality of life scores (Anker, et al., 2009). The European Effect of Intravenous Ferrous Sucrose on Exercise Capacity in Chronic Heart Failure (FERRIC-HF) trial, which involved 35 patients with heart failure, had similar outcomes with intravenous iron sucrose (Okonko, et al., 2008).

1.6.2 Erythropoietin Stimulating Agents in Heart Failure

As erythropoietin (EPO) may be central to anaemia in heart failure, a number of studies have assessed the effect of EPO in treating heart failure. The Study of Anemia in Heart Failure Trial (STAMINA-HeFT), in which patients were treated with darbepoetin alfa or placebo for 12 months, showed reduced all-cause mortality and hospitalization, however exercise duration did not improve (Ghali, et al., 2008). This study also showed that the adverse effects in the darbepoetin alfa group were very similar to placebo. The authors concluded that darbepoetin is a safe and well tolerated therapy. In 2009 Klapholz, et al. confirmed that darbepoetin therapy in heart failure patients was not associated with increased adverse effects.

A recent meta-analysis of 11 small randomised controlled trials has demonstrated the beneficial effects of erythropoietin stimulating agent (ESA) therapy in heart failure patients (Kotecha, et al., 2011). These effects include improved haemoglobin level, exercise capacity, left ventricular function and quality of life as well as reduced hospitalisation due to heart failure and all-cause mortality. Kotecha, et al. (2011) suggest that more large scale studies are necessary to confirm the safety of ESA therapy in heart failure.

Currently there is insufficient evidence to routinely use ESA's in heart failure patients with anaemia, however the available data from many studies appears promising (Lawler, Filion and Eisenberg, 2010). The results of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial which started in 2006 and is currently ongoing, are eagerly awaited (McMurray, et al., 2009).

On the contrary ESA therapy in chronic kidney disease (CKD) and chemotherapy-induced anaemia (CIA) has been associated with significant adverse effects. Three recent trials of anaemia and CKD patients treated with ESA's raise concerns. The Correction in Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction in Early Anemia Trial with Epoetin Beta (CREATE) showed that there may be increased risk of cardiovascular events when therapy was aimed at hemoglobin levels between 13.0–15.0 g/dl (Levin, 2007; Singh, et al., 2006). The Trial to Reduce Cardiovascular Events With Aranesp® Treatment (TREAT) that involved more than 4000 patients discovered an increased risk of stroke and venous thromboembolism (Pfeffer, et al., 2009). The participants of the CHOIR, CREATE AND TREAT trials were CKD disease patients. A 2009 meta-analysis by Bohlius, et al. reported increased mortality with ESA therapy in cancer patients. The study group concluded that risk versus benefit should be considered when contemplating ESA use in cancer patients.

ESA's in CKD and CIA are associated with greater adverse effects. However they have shown benefit in heart failure patients. The reason for this contradiction is unknown. Several hypotheses have been put forward. Klapholz, et al. (2009) hypothesise that heart failure patients usually receive antiplatelet and antithrombotic agents which may contribute to the lower incidence of thromboembolic events. Larger randomized controlled trials in heart failure and CKD are required to confirm the role of ESA's in these patients.

Figure 1.6.2 compares various heart failure therapies with ESA's and illustrates the potential clinical impact of ESA's when added to standard heart failure therapy. The graph is indicative as direct comparisons have not been made. Furthermore, the studies evaluating the individual heart failure therapies vary according to baseline demographics and follow-up. Graphs A demonstrates left ventricular ejection fraction compared with control. Graph B shows BNP change from baseline.

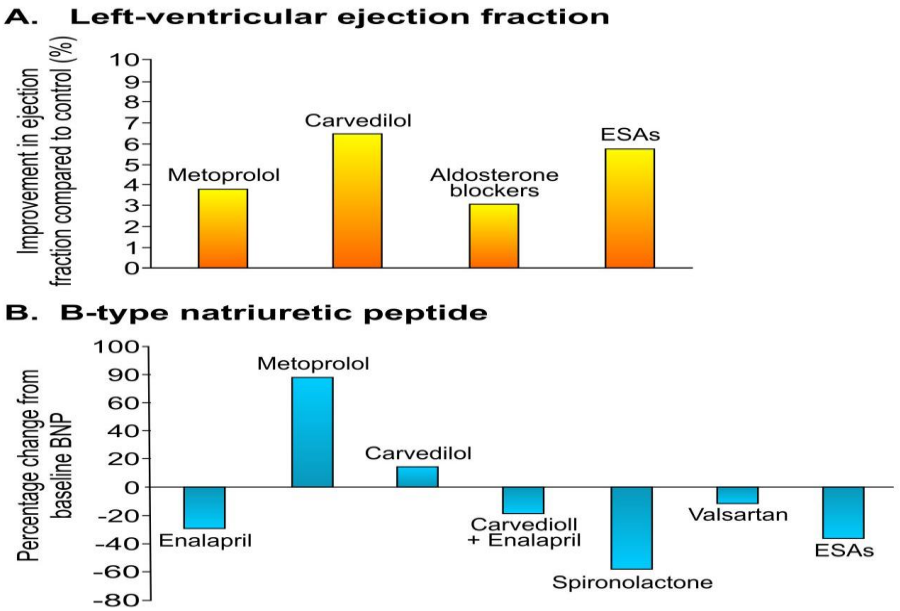


Figure 1.6.2: Indirect comparison of heart failure therapies with ESAs [when added to standard treatment] (Adapted from Kotecha, et al., 2011).

1.6.3 Pleiotropic Effects of Erythropoietin

Erythropoietin has numerous pleiotropic effects including neuro- and cardioprotection, anti-apoptotic, anti-inflammatory, mitogenic, pro-angiogenic and the protection of vascular integrity by stimulation of endothelial progenitor cells (van der Meer, et al., 2008a; Manolis, et al., 2005). Figure 1.6.3a is a schematic illustration of the effects of erythropoietin on target cells and organs. The EPO receptor is found in the cardiovascular system in endothelial cells, smooth muscle cells and cardiac myocytes.

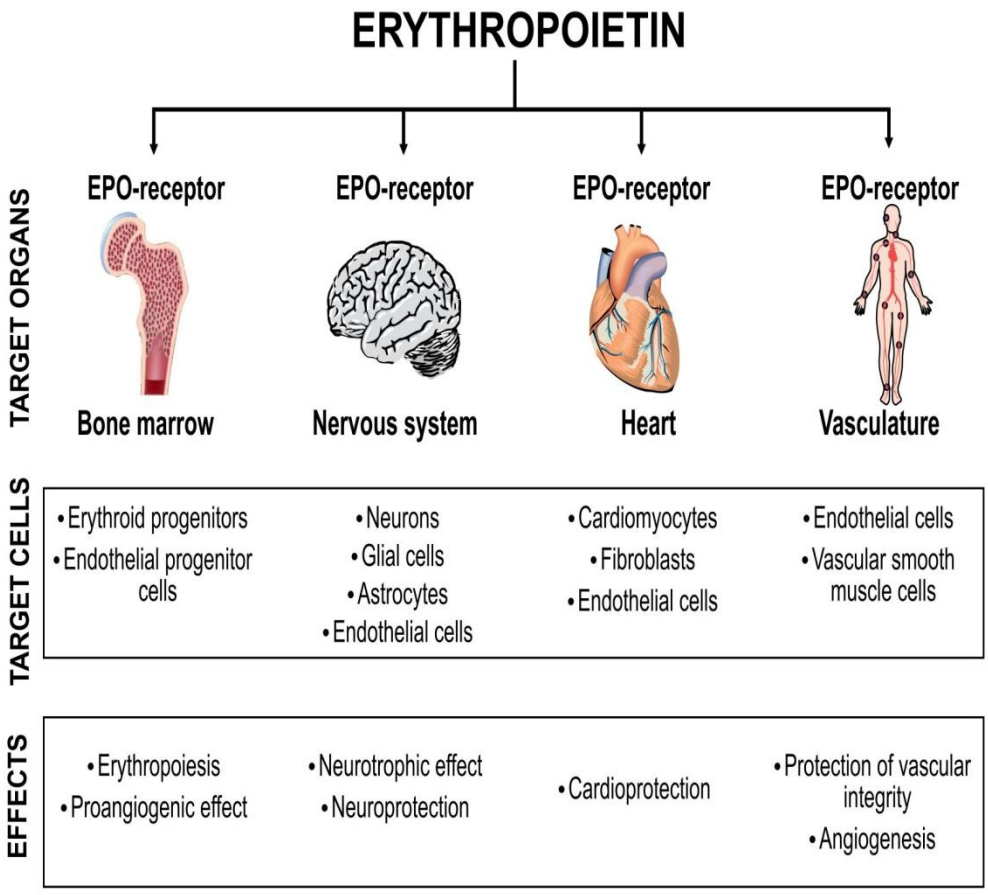


Figure 1.6.3a: Schematic illustration of the effects of erythropoietin on target cells and organs (Adapted from Manolis, et al., 2005).

Figure 1.6.3b shows the signaling pathways activated by EPO/EPO receptor complex that ultimately result in cardioprotection. The cardioprotective effect of EPO is due to the inhibition of the apoptotic signalling pathway which prolongs cardiac myocyte survival, protection of endothelial cell function and vascular integrity, stimulation of angiogenesis via the akt/PKB signal transduction pathway and attenuation of the myocardial inflammatory response following ischaemia and reperfusion. EPO may also improve myocyte contractility and stimulate undifferentiated stem cells migration into ischaemic myocardium (Manolis, et al., 2005). It is possible that the beneficial effects of ESA's found in heart failure patients is due to cardioprotection at a cellular level, in addition to the correction of anaemia.

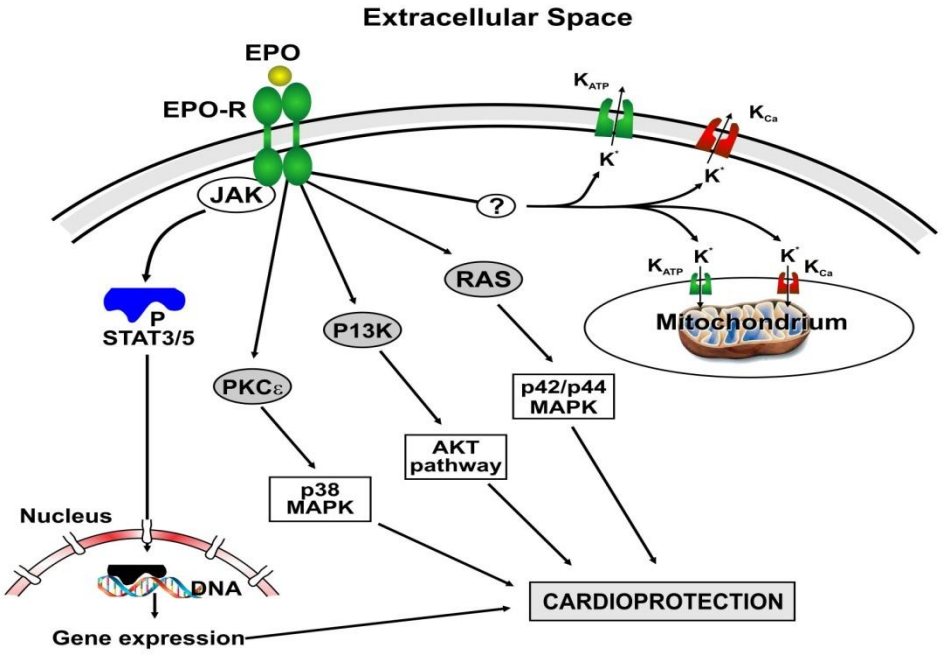


Figure 1.6.3b: Schematic representation of signalling pathways activated by erythropoietin (EPO) binding to erythropoietin receptor (EPO-R) which mediate the conferred cardioprotection (Adapted from Manolis, et al., 2005).

[JAK: Janus-tyrosine kinase; STAT: signal transducer and activator of transcription; PKC: isoform of protein kinase C; MAPK: mitogen activated protein kinase; PI3K: phosphatidylinositol-3-kinase; AKT: protein kinase B; KCA: calcium activated potassium channels; KATP: ATP-sensitive potassium channels]

1.6.4 Erythropoietin Stimulating Agents in Acute Myocardial Infarction

Recent studies have evaluated the use of ESA's in acute myocardial infarction. A study in 2009 by Ferrario, et al. found that short term high dose erythropoietin administered acutely in patients treated with percutaneous coronary intervention (PCI) resulted in smaller infarct size. Patients receiving erythropoietin had lower cardiac enzymes and better left ventricular remodelling. However the clinical significance of these findings needs to be confirmed (Ferrario, et al., 2009). In 2010 Voors, et al. found no improvement in left ventricular ejection 6 weeks after successful PCI for a ST-elevation myocardial infarction. To date, studies investigating ESA's in acute myocardial infarction have not conclusively established the role of ESA's in acute ischaemia (Kotecha, et al., 2011).

Chapter 2: STUDY DETAILS

2.1 Aims and Objectives

2.1.1 To define the prevalence of co-morbid anaemia in patients attending the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital.

2.1.2 To evaluate the relationship between anaemia and severity of heart failure.

2.1.3 To compare anaemic and non-anaemic patient variables.

2.1.4 To define the aetiology of heart failure in patients attending the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital.

2.2 Study Design and Methodology

This is a single centre retrospective study of patients attending the Charlotte Maxeke Johannesburg Academic Hospital Heart Failure Clinic from January to June 2011. The patient files were analysed specifically for the presence of anaemia, NYHA functional Class, furosemide dose, six minute walk test and Minnesota Living with Heart Failure Questionnaire score. In addition, demographic data (age, gender) and the aetiology of heart failure were recorded.

Anaemia was defined by the World Health Organisation (WHO) criteria of a haemoglobin level <13 g/dl in men and < 12g/dl in women.

The control group consisted of participants attending the clinic who were not anaemic. The two groups were compared using:

a) Participant's symptom scores; using the Minnesota Living with Heart Failure Questionnaire (MLHFQ - Appendix B).
b) Objective measurements of the participant's state of health:
    - Six minute walk test
    - Dose of furosemide (Lasix)
    - New York Heart Association (NYHA) functional class

2.2.1 Objective Assessment Measures

2.2.1.1 The Six Minute Walk Test

The six minute walk test (6MWT) was originally designed to test exercise tolerance in chronic respiratory disease and heart failure. However, recently it been used as a performance-based measure of functional exercise capacity in other populations including healthy older adults, people undergoing lower limb joint replacements, fibromyalgia, and scleroderma. The 6MWT measures the maximum distance in metres that an individual is able to walk in six minutes on a hard, flat surface. The test is simple to perform, requires inexpensive equipment, is safe and is fairly reproducible provided it is well standardized. The individual can walk at his or her own pace, resting intermittently if necessary. The 6MWT can be used to detect changes following therapeutic interventions and predict hospitalisation and mortality.

A lower score (reflecting less distance covered in 6 minutes) indicates worse function. The normal distance in healthy adults ranges from 400m to 700m. Walking less than 300 m during the 6MWT is a simple prognostic marker of subsequent cardiac death in patients with mild-to-moderate heart failure (Cleland, et al., 2003).

2.2.1.2 Furosemide dosage

Furosemide is used in patients with congestive cardiac failure to enhance urinary sodium excretion, thereby maintaining euvolemia and improving heart failure symptoms. The dosage of furosemide required to minimise symptoms can be used as an indicator of the severity of heart failure.

2.2.1.3 The New York Heart Association (NYHA) classification

The NYHA classification grades the severity of heart failure symptoms as one of four functional classes. It is widely used in clinical practice and in research because it provides a standard description of severity that can be used to assess response to treatment and to guide management. It is, however, less useful for assessing prognosis.

Table 2.2.1.3: The New York Heart Association (NYHA) Classification

NYHA Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

NYHA classification of heart failure symptoms [American Heart Association, 1994]

2.2.1.4 The Minnesota Living with Heart Failure Questionnaire (MLHFQ)

The Minnesota Living with Heart Failure Questionnaire, which was developed by Rector, et al. (1987), correlates highly with patients' global assessments of restrictions on their lives. The MLHFQ consists of 21 questions which measure the effects of heart failure and its treatment on an individual's quality of life. The MLHFQ incorporates key physical, emotional, social and psychological dimensions of quality of life. The answer for each question is assigned a numerical score from 0 to 5. The total score may vary from 0 – 105, with lower scores reflecting fewer heart failure symptoms and better quality of life.

2.2.2 Inclusion Criteria

Patients diagnosed with heart failure (systolic and/or diastolic dysfunction) attending the Heart Failure Clinic at Charlotte Maxeke Johanneburg Academic Hospital.

2.2.3 Exclusion Criteria

- Incomplete or missing data recorded in files
- Co-morbid respiratory disease
- Cor Pulmonale

2.2.4 Limitations of this study

- English is often not the first language of our patient study group. Therefore the Minnesota Living with Heart Failure Questionnaire (MLHFQ) may not accurately reflect the patient's quality of life score.
- Disadvantages of a retrospective analysis.

- A proportion of heart failure patients attending the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) are managed at a General Cardiology Outpatient Department. These patients are awaiting appointments or are in the process of being referred to the heart failure clinic. Therefore the results of this study may not be a true reflection of the total heart failure population attending the CMJAH.

2.2.5 Strengths of this study

- All the patients have been reviewed by a highly experienced heart failure study team that has been consistent for many years.
- The blood results are processed from the same laboratory (National Health Laboratory Service – NHLS).

2.2.6 Statistical analysis

Data was collected and entered into a database using Microsoft Office Excel 2007. The data was analysed using the Statistics/Data Analysis Program (STATA) Version 10.0.

2.2.6.1 Prevalence

Prevalence was calculated using the number of anaemic patients divided by the total number of patients included in the study – the ratio was multiplied by 100 and expressed as a percentage.

2.2.6.2 Minnesota Score, 6 Minute Walk Test, Furosemide Dose and Haemoglobin Concentration

The relationship between haemoglobin concentration and the variables listed above were analysed using the pairwise correlation statistical test.

2.2.6.3 NYHA and Haemoglobin Concentration

The relationship between NYHA functional class and haemoglobin concentration was assessed using the Analysis of Variance test (ANOVA).

Chapter 3: RESULTS

A total of 282 files were reviewed over 6 months from the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital. Sixty-two files were excluded from the study due to lack of study data recorded in the file.

3.1 Demographics

There were 119 females (54.1%) and 101 males (45.9%) in the sample group. The mean age of the study group was 59.8 years (SD±12.2), with the youngest subject aged 22 years and the oldest subject aged 91 years. Median age was 61 years. Mean age of males was 59.7 (SD±12.3) and females was 59.8 (SD±12.2) (Table 3.1).

Table 3.1 Patient Demographics

Parameter	**Results**
Number:	
Total no. of patients	220
Gender:	
Males	101 (45.9%)
Females	119 (54.1%)
Age (years):	
Mean ±SD	59.8 ±12.2
Median	61
Range	22-91
Male Mean ±SD	59.7 ±12.3
Female Mean ±SD	59.8 ±12.2

3.2 Haemoglobin and Anaemia

The mean haemoglobin concentration was 13.79 g/dl (SD±1.96). Male mean haemoglobin was 13.83 g/dl (SD±1.97) and the female mean haemoglobin was 13.79 (SD±1.96). The overall prevalence of anaemia in the sample population was 21.4% (47 anaemic patients), with male and female prevalence calculated at 15.8% and 26.1% respectively. Seventy-two patients (32.7%) had ferritin levels recorded in their files and 1 patient (0.01%) who happened to be female, was found to be iron deficient based on serum iron studies (Ferritin < 15 µg/L). None of the male subjects were iron deficient (Table 3.2).

Table 3.2 Haemoglobin and Anaemia

Parameter	**Results**
Mean Haemoglobin (g/dl):	
Males	13.83 ±1.97
Females	13.79 ±1.96
Overall	13.79 ±1.96
No. of Anaemic Subjects:	
Males (Hb < 13 g/dl)	16 (15.8%)
Females (Hb < 12 g/dl)	31 (26.1%)
Overall	47 (21.4%)
Ferritin (µg/L):	
Sample size	72 (32.7%)
Males (Ferritin < 25 µg/L)	0
Females (Ferritin < 15 µg/L)	1 (0.01%)

3.3 Aetiology of Heart Failure

The aetiology of heart failure is shown in Table 3.3. Dilated Cardiomyopathy was the commonest cause of heart failure (34.1%) followed by Hypertensive Heart Disease (21.4%), Ischaemic Heart Disease (18.6%) and Alcoholic Cardiomyopathy (8.6%). The prevalence of Peripartum Cardiomyopathy was 8.2%. Heart failure secondary to chemotherapy constituted 4.1% of the total population with Adriamycin (Doxorubicin) being the mostly commonly implicated drug. Thyrocardiac disease (3.6%), cardiomyopathy secondary to myocarditis (2.3%) and HIV related cardiomyopathy (0.9%) were among the less common aetiologies. The least common causes of heart failure included cardiomyopathy due to mitral valve disease (0.9%), Hypertrophic Obstructive Cardiomyopathy (0.5%) and Left Ventricular Noncompaction Syndrome (0.5%). One patient being followed up at the clinic was post cardiac transplantation (0.5%).

Table 3.3 Aetiology of Heart Failure

Aetiology	Results
Dilated Cardiomyopathy	75 (34.1%)
Hypertensive Heart Disease	47 (21.4%)
Ischaemic Heart Disease	41 (18.6%)
Alcoholic Cardiomyopathy	10 (8.6%)
Peripartum Cardiomyopathy	18 (8.2%)
Chemotherapy Related	9 (4.1%)
Thyrocardiac Disease	8 (3.6%)
Myocarditis	5 (2.3%)
HIV	2 (0.9%)
Other	5 (2.3%)

3.4 Prevalence of Anaemia According to Aetiology

The prevalence of anaemia according to the aetiology of heart failure is shown in Table 3.4.

Table 3.4 Prevalence of Anaemia According to Aetiology

Aetiology of Heart Failure	Prevalence (%)
Dilated Cardiomyopathy	17.3
Hypertensive Heart Disease	33.3
Ischaemic Cardiomyopathy	14.6
Alcoholic Cardiomyopathy	0
Peripartum Cardiomyopathy	38.9
Chemotherapy Related	0
Thyrocardiac disease	12.5
Myocarditis	40
Other	20

3.5 Analysis of Minnesota Score, 6MWT, Furosemide dose and NYHA Class

The mean Minnesota score was 26.29 (SD±22.51) and the median was 21. Evaluation of the 6 minute walk test (6MWT) yielded a mean of 412.89 metres (SD±91.69) and a median of 425 metres. The mean and median furosemide doses were 34.52 mg (SD±43.2) and 22.5 mg respectively. Mean NYHA Class was 1 (SD±0.5). (Table 3.5)

Table 3.5 Minnesota Score, 6MWT, Furosemide dose and NYHA Class

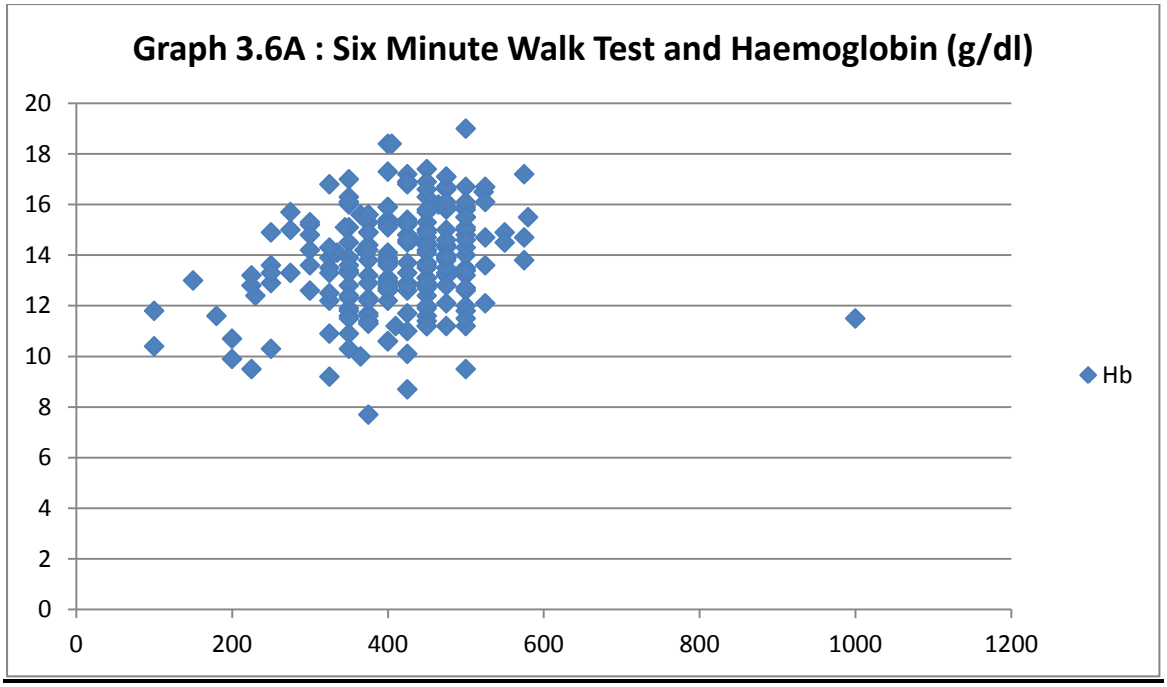
Parameter	**Results**
Minnesota score:	
Mean ±SD	26.29 ±22.51
Median	21
6 minute walk test (metres):	
Mean ±SD	412.89 ±91.69
Median	425
Furosemide dose (mg):	
Mean ±SD	34.52 ±43.2
Median	22.5
NYHA Class (I-IV):	
±SD	±0.5
Median	1

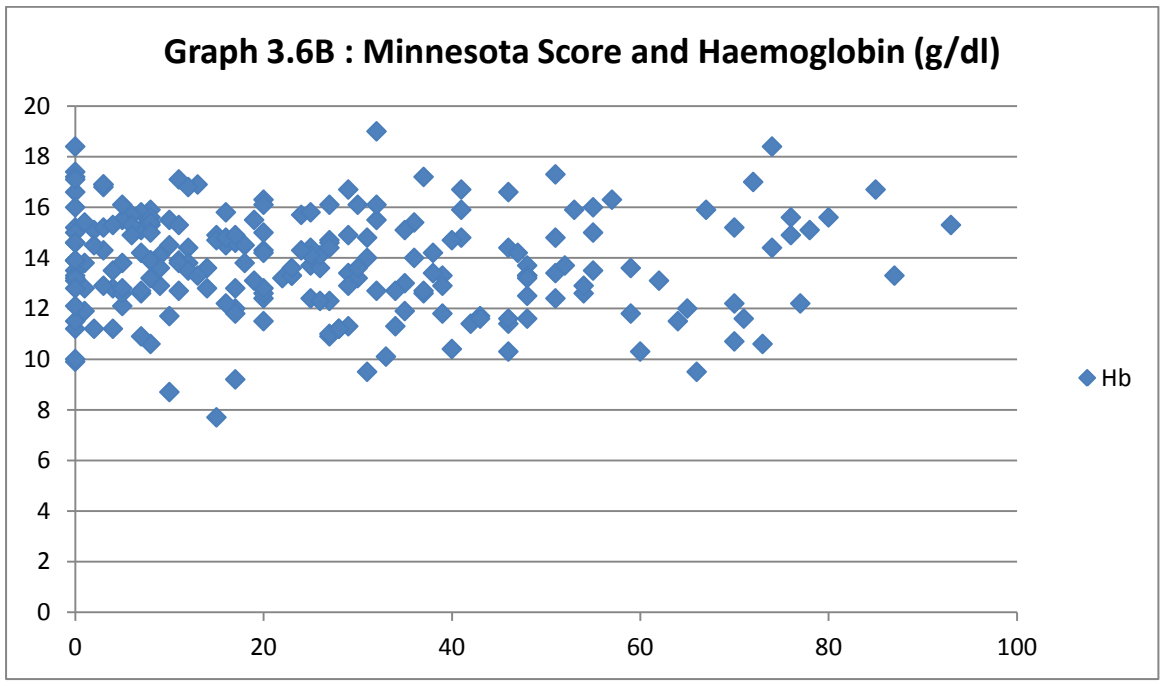
3.6 Pairwise Correlation of Variables with Haemoglobin (g/dl)

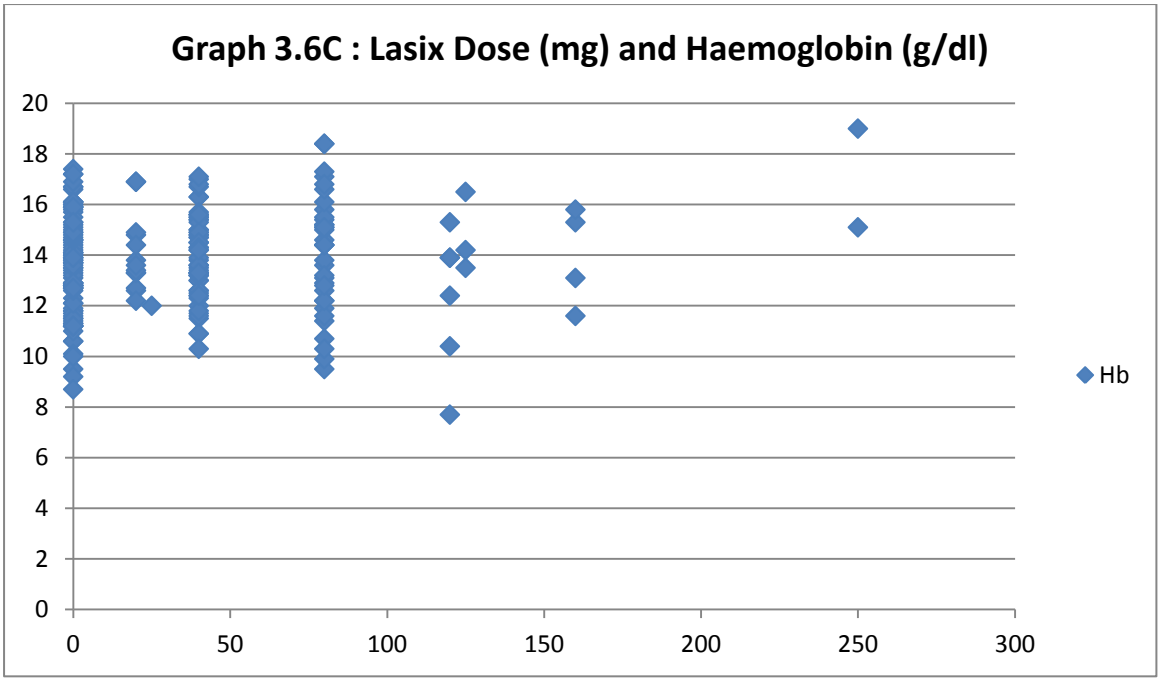
The study found no significant relationship between haemoglobin concentration and Minnesota score (r=-0.051; p=0.452). An insignificant correlation was found between haemoglobin concentration and furosemide dosage (p=0.123). Analysis of haemoglobin concentration and the six minute walk test yielded a statistically significant but weak positive correlation between the variables (p=0.001). (Table 3.6)

Table 3.6 Pairwise Correlation of Variables with Haemoglobin (g/dl)

Parameter	R value	P value
Minnesota score	-0.051	0.452
6 minute walk test	0.217	0.001
Furosemide dose	0.104	0.123

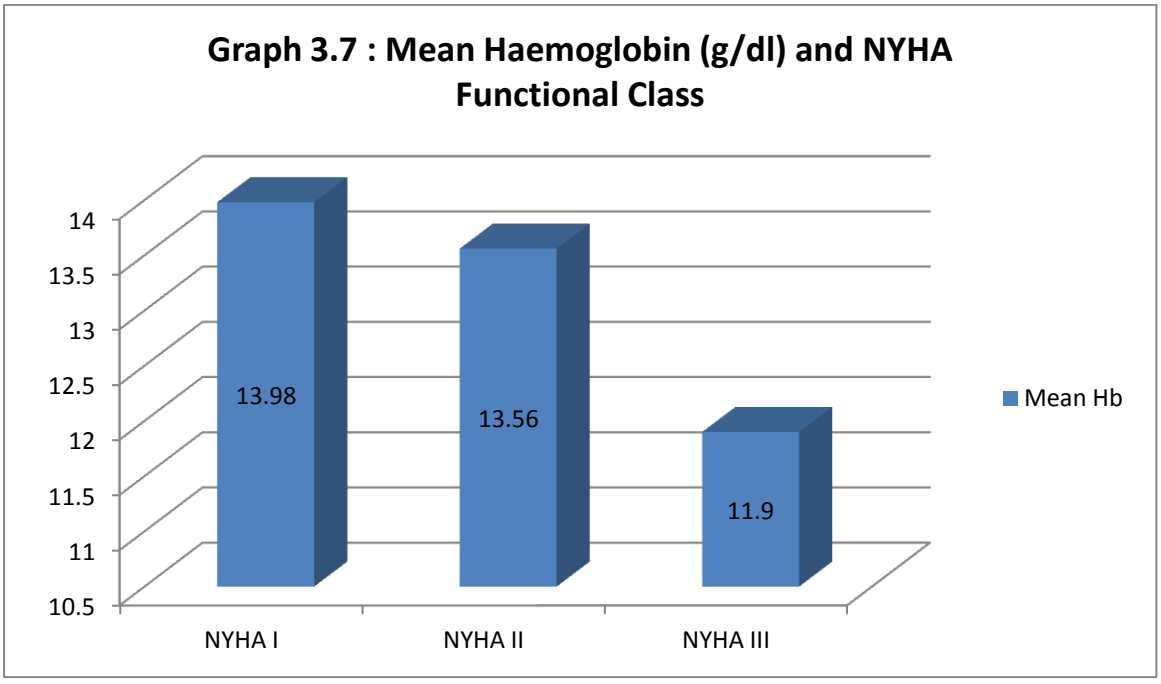

Graph 3.6A : Six Minute Walk Test and Haemoglobin (g/dl)
20
18
16
14
12
10
8
6
4
2
0
0
200
400
600
800
1000
1200
Hb


Graph 3.6B : Minnesota Score and Haemoglobin (g/dl)
20
18
16
14
12
10
8
6
4
2
0
0
20
40
60
80
100
Hb


Graph 3.6C : Lasix Dose (mg) and Haemoglobin (g/dl)
20
18
16
14
12
10
8
6
4
2
0
0
50
100
150
200
250
300
Hb

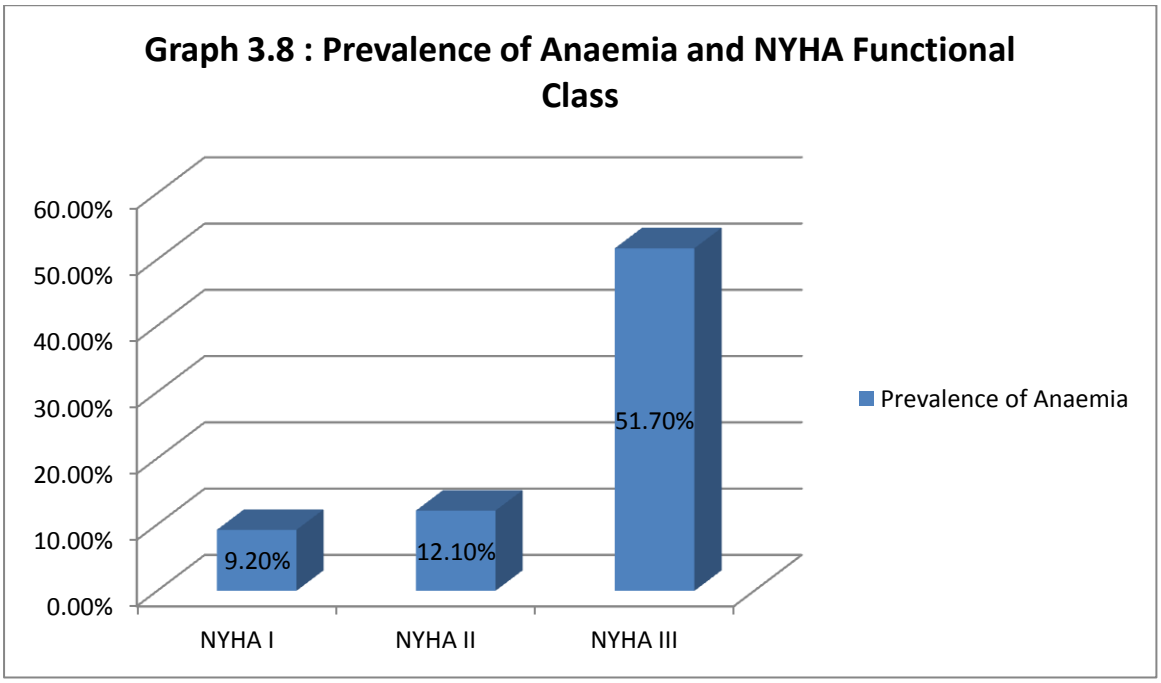
3.7 ANOVA Analysis of Haemoglobin (g/dl) and NYHA Functional Class

The Analysis of Variance Test (ANOVA) showed a significant association between the haemoglobin level across the different New York Heart Association (NYHA) Functional Classes (p=0.03). None of the subjects were documented as NYHA functional class IV. (Graph 3.7).



3.8 Prevalence of Anaemia and NYHA Functional Class

The prevalence of anaemia in NYHA class I, II and III was 9.2%, 12.1% and 51.7% respectively (Graph 3.8). The highest prevalence (51.7%) was found in NYHA class III patients.



Chapter 4: DISCUSSION

4.1 Demographics

The total number of subjects in the study was 220 (n=220). There was a higher proportion of females attending the clinic (54.1% vs. 45.9%). Peripartum cardiomyopathy constituted 8.2% of the study group and this may have accounted for the greater number of females attending the clinic.

In 2007 Inglis, et al. conducted a single centre retrospective study that included 163 Black African patients with newly diagnosed idiopathic dilated cardiomyopathy. The aim of the study was to assess the relationship between anaemia and renal dysfunction. Anaemia was defined according to WHO criteria and renal function was assessed using an estimated glomerular filtration rate (GFR). Inglis, et al. (2007) had 52% male patients in their study cohort whereas this study had 45.9% male patients. This difference can be explained by dissimilar demographic profiles in both studies. Furthermore, the mean age of the Inglis, et al. (2007) study cohort was 48 years (±11) compared to 59.8 years (±12.2) in this study.

4.2 Prevalence of Anaemia

The overall prevalence of anaemia in the study was 21.4%, which is similar to international studies. The prevalence of anaemia depends on the sample selection and the definition used for anaemia. Data from many clinical trials and heart failure registries suggest that the prevalence of anaemia amongst hospitalised patients ranges between 14 and 70% (Anand, 2008b).

A higher proportion of females fell within the anaemic range compared to male subjects (26.1% vs. 15.8%). A local study found 14.1% of females and 12.9% of males were anaemic according to WHO Criteria (Inglis, et al., 2007). Sharma, et al. (2004) found anaemia to be commoner in women than men. Mean haemoglobin in the male group of patients (13.83 g/dl, SD ±1.97) was higher than the female group (13.79 g/dl, SD ±1.96).

There are multiple reasons for the greater prevalence of anaemia in females. Cyclical menstrual blood loss may be major contributory factor. A study in Abu Dhabi which assessed 309 mothers reported a 16% prevalence of anaemia in non-pregnant women (Hossain, et al., 1995). A greater number of pregnancies and menorrhagia were associated with lower haemoglobin levels. The authors concluded that iron deficiency is probably the major cause of anaemia in women of child bearing age. McClung, et al. (2006) assessed 1216 female military personnel in the United States Army. They found an overall prevalence of iron deficiency of 13.4%. This prevalence almost doubled (32.8%) following basic combat training. Strenuous physical training diminishes iron stores, however the underlying pathophysiology is unknown (McClung, et al., 2006).

4.3 The Prevalence of Anaemia According to Aetiology

The prevalence of anaemia according to the aetiology of heart failure is shown in Table 3.4. The highest anaemia prevalence (40%) was found in patients with heart failure secondary to myocarditis. Many viruses have been implicated in myocarditis, the commonest of which are Coxsackie B, Human Herpes Virus 6 (HHV-6), Parvovirus B_{19}, Influenza (including the H_1N_1 strain), Adenovirus, Hepatitis C, Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Echovirus and HIV (Bowles, et al., 2003; Kindermann, et al., 2008; Kühl, et al. 2005).

All of the viruses listed above can cause anaemia of chronic disorder. However Parvovirus B_{19}, Hepatitis and HIV also directly affect the bone marrow resulting in anaemia (Kurtzman and Young, 1989; Brown, et al., 1997). Viral serology, polymerase chain reaction, in situ hybridisation, bone marrow aspiration and trephine and endomyocardial biopsy are not routinely performed at the heart failure clinic for the investigation of myocarditis. In a resource poor setting such as a public hospital these investigations may not be cost effective. Therefore it is difficult to confirm the degree to which viral involvement of the bone marrow causes anaemia in myocarditis patients.

The second highest prevalence of anaemia (38.9%) was found in the PPCMO group of patients. The period between delivery and assessment of haemoglobin was not documented. Postpartum haemorrhage, anaemia associated with pregnancy (haemodilution), blood loss from haemorrhoids or peptic ulcer disease, nutritional

deficiencies and helminthic infections may contribute to anaemia. Iron, folic acid and vitamin B_{12} deficiency cause nutritional anaemia in pregnancy. Iron deficiency is probably the commonest cause of anaemia in pregnant women (Hossain, et al., 1995). Anaemia is commoner in women who have repeated pregnancies within a short space of time (Hossain, et al., 1995).

The third highest anaemia prevalence (33.3%) was found in patients with hypertensive heart disease (HHD). Fifteen out of a total of 47 HHD patients (31.9%) had biochemical features of renal dysfunction with serum Creatinine < 90 µmol/l (reference range = 49 – 90 µmol/l). It is possible that concomitant chronic kidney disease and the cardio-renal anaemia syndrome contribute to the anaemia in these patients.

DCMO and ischaemic cardiomyopathy had an anaemia prevalence of 17.3% and 14.6% respectively. A local study by Inglis, et al. (2007) found an anaemia prevalence of 13.5% in idiopathic DCMO patients which is similar to this study. Undiagnosed viral infections discussed above may exacerbate the anaemia in DCMO patients. Seventy-one percent (40 of 56) of ischaemic cardiomyopathy patients had biochemical evidence of renal dysfunction. This suggests that chronic kidney disease and the cardio-renal anaemia syndrome may be major contributing factors in the pathogenesis of anaemia in this patient group.

4.4 Iron Deficiency Anaemia

Iron deficiency is common in heart failure. The prevalence of iron deficiency ranges between 20% - 73%, depending on the methods used for diagnosis (de Silva, et al., 2006; Nanas, et al., 2006; Witte, et al., 2004; Cromie, Lee and Struthers, 2002). Bone marrow aspiration performed on patients with advanced decompensated heart failure showed features of iron deficiency in 73% of patients (Nanas, et al., 2006). de Silva, et al. (2006) found that 15% of patients with normal haemoglobin levels had evidence of iron and/or folate deficiency. A study of 546 patients with stable systolic heart failure found that approximately 33% of patients with normal haemoglobin levels were iron deficient (Jankowska, et al., 2010).

Iron studies were not performed in the majority of patients that were in the study. At Charlotte Maxeke Johannesburg Academic Hospital iron studies are not routinely requested. Ferritin is an acute phase reactant and many conditions influence its serum level. These conditions include chronic inflammation, malignancy, liver disease, hyperthyroidism, diabetes mellitus, liver disease and repeated blood transfusions. Thus serum ferritin is not a reliable indicator of iron deficiency (Nanas, et al., 2006). In the current study serum ferritin was available for analysis in 72 of 220 (32.7%) patients. Of these only one patient, who happened to be female, (Ferritin < 15 µg/L) was found to be iron deficient.

Iron deficiency can lead to anaemia, but it can have clinical consequences even without anaemia. Iron plays a central role in erythropoiesis and oxygen uptake, metabolism, transportation and storage (van Veldhuisen, et al., 2011). Chronic iron deficiency results in structural abnormalities in cardiac myocytes culminating in poor effort tolerance of heart failure patients (Brownlie, et al., 2004; Haas and Brownlie, 2001).

Many patients at the heart failure clinic who are iron deficient could benefit from intravenous iron therapy (Anker, et al., 2009). However a large proportion of iron deficient heart failure patients have normal haemoglobin and ferritin levels which needs to be confirmed with an assessment of bone marrow iron stores. Good responses to intravenous iron therapy have been documented in many studies, the most recent of which is the FAIR-HF trial. The introduction of iron therapy in the heart failure clinic may be beneficial, but a more accurate assessment of iron deficiency needs to be performed. Furthermore cost versus benefit in investigating iron deficiency needs to be taken into consideration, especially in a resource poor environment such as a public hospital.

4.5 Haemoglobin and Minnesota Score

A very poor inverse relationship between haemoglobin concentration and Minnesota score (p=0.452) was found. Lower haemoglobin levels are associated with higher Minnesota scores which reflect greater severity of heart failure based on patient's symptoms (Anand, 2008b). Anaemic patients with heart failure are more likely to have poorer quality of life scores (Anand, 2008b). The poor relationship between haemoglobin and Minnesota score can probably be explained by the inaccurate completion of the MLHFQ forms. English is not the first language of most of our study patients. Many of the forms are completed with the assistance of translators which adds a further degree of inaccuracy when calculating the Minnesota score.

4.6 Haemoglobin and Six Minute Walk Test

Analysis of haemoglobin concentration and the six minute walk test (Graph 3.6A) yielded a weak positive correlation but which was statistically significant (p=0.001). This result is in keeping with international studies that higher haemoglobin levels are associated with better effort tolerance and less severe heart failure (Anand, 2008b).

It is postulated that the 6 minute walk test accurately assesses a patient's functional class / effort tolerance. In addition, the 6 minute walk test is a standardised protocol that can be performed by staff with minimal training. Patients that were not able to perform the test (eg. musculoskeletal abnormalities, neurological disorders, severe respiratory disease) were excluded from the study therefore the results are a good indicator of severity of heart failure based on effort tolerance.

4.7 Haemoglobin and Furosemide Dose

No correlation was found between haemoglobin concentration and furosemide dosage in this study (p=0.123). One would have expected higher doses of furosemide with lower haemoglobin levels as higher furosemide doses are associated with more severe heart failure. The reason for this discrepancy is probably due to the fact that many of the patients in the heart failure clinic are treated with other diuretics (spironolactone, hydrochlorothiazide) in addition to furosemide. Some patients were not taking furosemide, yet were on other diuretics.

A retrospective study of 1153 patients enrolled in the PRAISE study (Prospective Randomized Amlodipine Survival Evaluation) evaluated diuretic use in chronic heart failure patients (Neuberg, et al., 2002). They reported an independent association between high diuretic doses (furosemide > 80mg/day) and increased mortality in patients with advanced heart failure. Neuberg, et al. (2002) also suggest that diuretic resistance (patients requiring high dose diuretic therapy) should be considered as a prognostic factor in chronic heart failure. Retrospective analysis of 395 patients from the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness) trial database showed that furosemide doses in excess of 300mg/day may be associated with increased mortality (Hasselblad, et al., 2007).

The RALES (Randomized Aldactone Evaluation Study) study showed that spironolactone when added to conventional heart failure therapy is associated with better outcomes. Combination diuretic use with furosemide, spironolactone and hydrochlorothiazide is occasionally used for refractory heart failure to treat congestive symptoms. Thus the multiple diuretic combinations probably explain the inconsistency in the relationship between furosemide dosage and haemoglobin concentration in the current study.

4.8 Haemoglobin and NYHA Class

The Analysis of Variance Test (ANOVA) was used to assess the relationship between haemoglobin level and New York Heart Association (NYHA) Functional Class (Graph 3.7). The results illustrate a significant association ($p=0.03$) between the variables. Patients classified as NYHA III had a mean haemoglobin of 11.9 g/dl, whereas NYHA I patients had a mean haemoglobin of 13.98 g/dl.

Lower haemoglobin levels were associated with higher functional class which is indicative of more severe heart failure. The findings of this study are consistent with several other studies (Anand, et al., 2005; Anand, et al., 2004; Horwich, et al., 2002). Heart failure patients who are anaemic are more likely to have severe heart failure as judged by higher NYHA functional class, reduced exercise capacity, lower quality of life scores, greater amount of peripheral oedema requiring diuretics and lower systolic blood pressures (Anand, 2008b). Figure 4.7a below shows increased mortality and hospitalisation with anaemic heart failure patients.

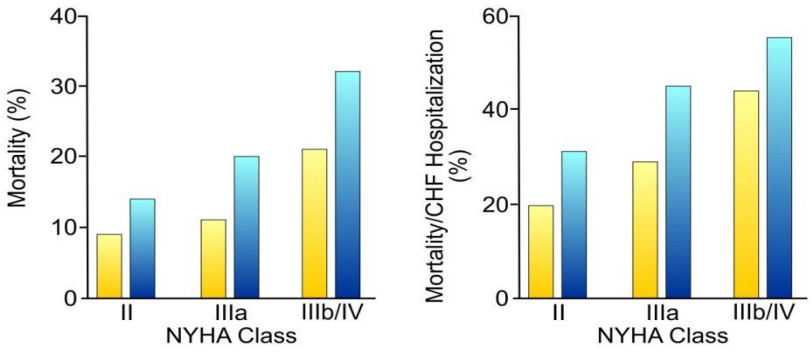


Figure 4.8a: Relationship between anemia and outcomes in various NYHA classes. Closed bars show mortality rate (A) or mortality/CHF hospitalization (B) at 1 year in subjects with Hb <12.0 g/dL (n=181). Open bars represent mortality rate (A) or mortality/CHF hospitalization (B) in subjects with Hb>12.0 g/dL (n=731) (Adapted from Anand, et al., 2004)

A single centre analysis of 1061 patients with advanced heart failure (NYHA III/IV) reported that lower haemoglobin is more likely to be associated with NYHA IV ($p<0.0001$) (Horwich, et al., 2002). Seventy-five percent of patients with NYHA IV heart failure had haemoglobin levels <12.3 g/dl.

A retrospective analysis of the Valsartan Heart Failure Trial (Val-HeFT) data, which comprised 1145 anaemic and 3857 non-anaemic patients, showed that NYHA functional class III and IV was commoner in the anaemic group [45 vs. 36%, $p<0.001$] (Anand, et al., 2005). Another retrospective analysis by Anand, et al. (2004) used data from the RENAISSANCE trial (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines). Nine hundred and twelve patients were enrolled in this multicentre, double-blind, placebo-controlled trial. Baseline Hb concentrations were compared among and between NYHA functional classifications with the Kruskal-Wallis and Wilcoxon rank tests. There was a significant correlation ($p=0.0017$) between lower baseline mean haemoglobin concentration and worse

NYHA functional class (Figure 4.8b). Table 4.8 shows the mean haemoglobin and anaemia prevalence in different NYHA classes.

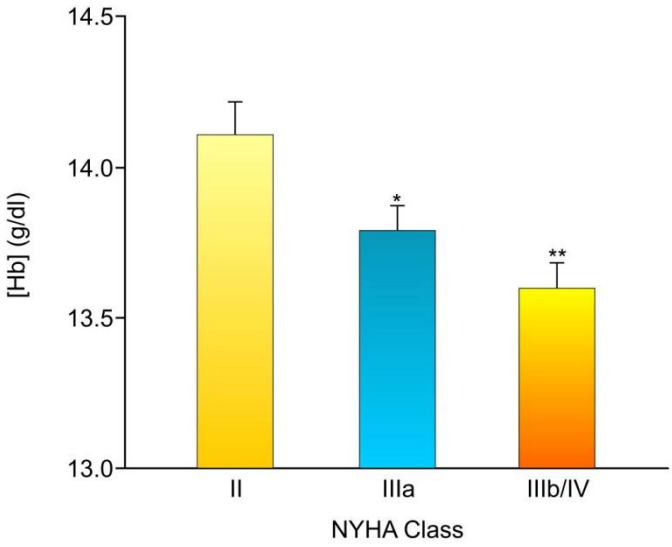


Figure 4.8b: Greater severity of CHF is associated with lower Hb concentrations ([Hb]). Mean ±SE baseline Hb concentration from subjects with NYHA class II (n=210), IIIa (n=428), and IIIb/IV (n=274) CHF. **P*=0.0186 vs NYHA class II; ***P*=0.0003 vs NYHA class II. (Adapted from Anand, et al. 2004).

NYHA Functional Class	**Mean Haemoglobin (g/dl)**	**Standard Deviation (SD)**	**Anaemia Prevalence**
II	14.1	±1.6	10%
IIIa	13.8	±1.6	13%
IIIb/IV	13.6	±1.5	17%

Table 4.8: Mean Haemoglobin, Anaemia Prevalence and NYHA Class (Anand, et al., 2004)

This study had a mean haemoglobin of 13.56 g/dl and 11.9 g/dl in NYHA II and III patients respectively, which differs from the RENAISSANCE trial (Anand, et al., 2004). In addition, the prevalence of anaemia according to NYHA class in this study is higher [NYHA II: 22.8% vs. 10%; NYHA III: 57.1% vs. 13/17%] (Table 3.8). The reason for these discordant results may lie in the demographics and size of the study cohort or it may be due to the altitude of Johannesburg. The RENAISSANCE Trial was conducted in North America and the sample size is larger than this study. The prevalence of iron deficiency anaemia is higher in Africa compared to the Americas [73% vs. 34] (Ramakrishnan, 2002). Furthermore the prevalence of HIV in sub-Saharan Africa is one of the highest in the world. It is possible that these factors contribute to the higher prevalence of anaemia in this study compared to the RENAISSANCE Trial.

4.9 Aetiology of Heart Failure

The top four causes of heart failure are dilated cardiomyopathy (DCMO), ischaemic cardiomyopathy, hypertensive heart disease and alcohol related cardiomyopathy in decreasing order of frequency. Female sex is associated with a better prognosis, especially in advanced heart failure (Ghali, et al., 2003; Adams, et al., 1999). Hypertension is a major cause of heart failure in women, whereas ischaemia is the predominate aetiology in male patients with heart failure (Levy, et al., 2002).

4.9.1 Dilated Cardiomyopathy

In 1995, the World Health Organisation (WHO) defined cardiomyopathy as a "disease of the myocardium associated with cardiac dysfunction". Dilated cardiomyopathy (DCMO) is characterised by dilatation and reduced systolic function of one or both ventricles. The list of underlying causes of DCMO is protean, with viruses and genetic defects being the commonest (Dec & Fuster, 1994). Felker, et al. (2000) calculated an incidence of 50% in their large study of 1230 patients. The DCMO prevalence in this study was 34.1%.

4.9.2 Ischaemic Cardiomyopathy

Coronary atherosclerosis results in myocardial ischaemia and ventricular dysfunction. Ischaemic cardiomyopathy and coronary artery disease is increasing in frequency globally - this increase parallels the increasing incidence of cardiovascular

risk factors. The metabolic syndrome, smoking, obesity and sedentary lifestyles are the commonest risk factors. Felker, et al. (2000) reported that the incidence of ischaemic cardiomyopathy was 7.4%. The prevalence of ischaemic cardiomyopathy in this study (18.6%) may be underestimated as a proportion of these patients attend the General Cardiology Clinic at Charlotte Maxeke Johannesburg Academic Hospital.

4.9.3 Hypertensive Heart Disease

Hypertensive heart disease occurs as a result of poorly controlled longstanding hypertension. Chronically elevated blood pressure can result in left ventricular hypertrophy, coronary artery disease, cardiac arrhythmias, and systolic and diastolic dysfunction of the myocardium.

Essential hypertension accounts for approximately 90% of cases of hypertension in adults, with the remainder being due to secondary causes. The Framingham study found that hypertension is the cause of heart failure in 25% of patients (Kannel and Cobb, 1992), with the prevalence as high as 68% in patients older than 65 years (Yamasaki, et al., 2003). The prevalence of hypertensive heart disease in this study was 21.4%.

4.9.4 Alcoholic Cardiomyopathy

There is a clear association between chronic alcohol consumption and cardiomyopathy, however the exact pathogenesis has not yet been elucidated. Proposed mechanisms include ethanol induced apoptosis of cardiac myocytes, direct toxicity to the myocardium, activation of the renin-angiotensin system and nutritional deficiencies, particularly thiamine (Fernandez-Sola and Nicolas-Arfelis, 2002). Women are more susceptible to alcohol induced cardiotoxicity due gender differences in alcohol metabolism (Fernandez-Sola and Nicolas-Arfelis, 2002).

The prevalence of alcoholic cardiomyopathy in international studies varies between 23% - 40% (Fauchier, et al., 2000; Gavazzi, et al., 2000; McKenna, et al., 1998). The prevalence in this study was 8.6%.

The mainstay of therapy is abstinence from alcohol. Nutritional supplementation with Vitamin B_{12} and folate is beneficial when added to heart failure treatment regimens. The 4 year mortality in patients who continue to consume alcohol is 50%. However the 1, 5 and 10 year survival rates of alcoholic cardiomyopathy is better than idiopathic dilated cardiomyopathy (Prazak, et al., 1996).

4.9.5 Peripartum Cardiomyopathy

Peripartum cardiomyopathy is defined as cardiomyopathy presenting in the last month of pregnancy or the first five months post delivery, with evidence of left ventricular systolic dysfunction and the absence of pre-existing cardiovascular disease. The aetiology remains unknown.

A study by Brar, et al. (2007) in California, USA found an overall incidence of 1 in 4025 deliveries with African-Americans being the most affected ethnic group. The incidence in Africa ranges from 1:100 - 1:1000 deliveries (Sliwa, 2005). This study yielded a prevalence of 8.2%.

Poor prognostic features include worse NYHA functional class at presentation, Black ethnicity, multiparity and left ventricular ejection fraction <30%. The likelihood of recovery depends on the degree of left ventricular dysfunction at presentation (Goland, et al., 2011). Future projects can assess the response of peripartum cardiomyopathy to heart failure therapy in South Africa.

4.9.6 Chemotherapy Related Cardiomyopathy

Anthracyclines and related compounds (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone), are the most frequently implicated chemotherapeutic agents causing cardiotoxicity (Singal and Iliskovic, 1998). Some of the cardiovascular complications related to anthracycline therapy include hypertension, arrhythmias, pericarditis, myocarditis, myocardial necrosis resulting in dilated cardiomyopathy and myocardial ischaemia. Doxorubicin is the most commonly used anthracycline in our setting and is frequently used to treat lymphomas, leukaemias and Kaposi's sarcoma, amongst others.

The incidence of heart failure is directly proportional to the cumulative dose of Doxorubicin (>160 mg/m^2), with prior drug exposure being a major risk factor. (Posner, et al., 1985). The incidence of anthracycline induced cardiotoxicity is <1% in the acute phase (immediately after infusion), between 1.6-2.1% less than a year after therapy and >36% from 1-30 years after completion of treatment (Bovelli, Plataniotis and Roila, 2010). The prevalence of chemotherapy induced cardiomyopathy (4.1%) may be underestimated by our study, as a proportion of patients may not be referred to heart failure. A joint study between the Departments of Cardiology and Medical Oncology would probably give a better indication of prevalence.

4.9.7 Thyrocardiac Disease

Hyperthyroidism results in positive inotropic and chronotropic cardiac effects resulting in a hyperdynamic state. Cardiac output can increase up to 2.5 times normal. Hyperthyroidism can also cause atrial fibrillation, pulmonary hypertension and exacerbate ischaemic heart disease. Heart failure is most commonly seen associated with atrial fibrillation.

A study of 591 hyperthyroid patients reported that 5.8% of patients presented initially with heart failure. Two thirds of patients reported no heart failure symptoms 3 months after thyroid function tests normalised. The remaining one third of patients developed features of dilated cardiomyopathy requiring long term anti-failure therapy (Siu, et al., 2007). 3.6% of this study group were diagnosed with thyrocardiac disease.

A prospective study assessing outcome in this group of patients and documenting the cause of the hyperthyroidism should yield interesting results.

4.9.8 HIV Related Cardiomyopathy

There are numerous cardiovascular manifestations in advanced HIV patients, the commonest of which are pericarditis, myocarditis, cardiomyopathy, valvular disease, diseases of the pulmonary vasculature, pulmonary hypertension and coronary artery disease (De Castro, et al., 1992; Himelman, et al., 1989). Myocardial disease includes focal myocarditis, left ventricular systolic dysfunction (diagnosed on echocardiography) and dilated cardiomyopathy. Cardiomyopathy can be due to the direct effect of HIV on the cardiac myocytes or an autoimmune process precipitated by HIV (Barbaro, et al., 1998).

The prevalence of HIV infection in Sub Saharan Africa is staggering. HAART has improved survival and reduced the incidence of AIDS related cardiac disease. The incidence of HIV related Cardiomyopathy with evidence of depressed left ventricular function in international studies ranges from 8-32% (Barbaro, et al., 1998; Cardoso, et al., 1998; Roy, et al., 1999). The prevalence of HIV related Cardiomyopathy in this study (0.9%) is likely to be underestimated for the following reasons:

- HIV is not routinely tested at the heart failure clinic
- Informed consent is required for the test and a large number of patients refuse to be tested
- Patients may attend other outpatient departments, despite being diagnosed with HIV related cardiomyopathy.

Future studies can investigate the prevalence of HIV related Cardiomyopathy in our setting, response to HAART and overall prognosis.

4.10 Conclusion

Anaemia is a common comorbidity in heart failure patients. In this retrospective survey of heart failure patients in a public hospital in South Africa the overall prevalence of anaemia was found to be 21.4%. Furthermore, this study confirmed that anaemia was associated with worse effort tolerance as measured by the six minute walk test as well as a poorer NYHA functional class. Of note was the finding that more than half of NYHA class III patients were anaemic by WHO Criteria. The results of this study, which are consistent with international studies, confirm that anaemia is associated with greater severity of heart failure, making anaemia a potential prognostic factor in the management of heart failure patients.

4.11 The Future

The aetiology of anaemia needs to be investigated because up to one third of patients with normal haemoglobin are iron deficient. Iron deficiency can exacerbate heart failure symptoms via various mechanisms. The Anker FAIR-HF Trial demonstrated the benefit of intravenous iron supplementation in heart failure patients. However the role of erythropoietin stimulating agents is less clear - the outcome of the RED-HF trial could shed light on this subject. I hope that the results of this study can be used to justify the investigation and correction of anaemia at our heart failure clinic.

Potential future studies at the heart failure clinic include:

- investigation of diuretic use, looking specifically at the type of agent used, efficacy and side effects
- peripartum cardiomyopathy prevalence, management and outcome
- thyrocardiac disease prevalence, management and outcome
- HIV related cardiomyopathy prevalence, management, response to HAART and outcome.

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APPENDIX

APPENDIX A: Patient Data Sheet

Gender
Age
Haemoglobin
Ferritin
Minnesota Score
NYHA Functional Class
6 Minute Walk Test
Furosemide dosage (mg)
Aetiology of Heart Failure

APPENDIX B: Minnesota Living With Heart Failure Questionnaire (MLHFQ)

MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**	**Very Little**				**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

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