A STUDY OF ANEMIA AND IRON DEFICIENCY IN CHRONIC SYSTOLIC HEART FAILURE

BY

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Dr. Tan Kok Leng

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
ARB	Aldosterone receptor blocker
ASA	Acetyl salicylic acid
CAD	Coronary artery disease
CCB	Calcium channel blocker
CI	Confidence interval
EF	Ejection fraction
GFR	Glomerular filtration rate
HF	Heart failure
ID	Iron deficiency
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction

OR	Odds ratio
RCT	Randomized control trial
SD	Standard deviation
TSAT	Transferrin saturation

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Introduction: Iron deficiency (ID) is an emerging problem in patients with chronic systolic heart failure and can be a potential therapeutic target. However, not much is known about the frequency, predictors of iron deficiency and anemia in patients with chronic heart failure.

Objectives: The primary objective of this study was to determine the frequency of iron deficiency in chronic systolic heart failure patients who were follow up in Hospital Universiti Sains Malaysia. The secondary objectives included were to determine the frequency of anemia in the same study population, correlation between ejection fraction and blood parameters and determining risk factors for anemia in chronic systolic heart failure.

Methods: A total of 81 patients who were followed up in Hospital Universiti Sains Malaysia were recruited into this cross sectional study using purposive sampling method. These patients had history of chronic systolic heart failure for more than 6 months with left ventricular ejection fraction less than 45% as assessed by echocardiography using Simpson's planimetric method. 10mls of venous blood was drawn from each participant and analyzed.

Result: Thirty three patients were anemic (40.7%) as compared to 48 patients (59.3%) who did not. Sixteen patients were iron deficient (19.8%). All iron deficiency patients were anemic patients. There were positive correlation between serum ferritin ($r=0.624$, $p<0.001$), transferrin saturation ($r= 0.346$, $p<0.001$) and hemoglobin ($r=0.528$, $p<0.001$) with ejection fraction, respectively. Anemia in chronic systolic heart failure was independently associated with serum ferritin (OR 0.974, 95% CI 0.959, 0.988), transferrin saturation (OR 0.831, 95% CI 0.726, 0.952), and diabetes mellitus (OR 6.680, 95% CI 1.599, 27.897) based on multiple logistic regression analysis.

Conclusion: This study demonstrated high frequency of anemia in chronic systolic heart failure patients. Majority of anemic patients were iron deficient. Besides that, serum hemoglobin and serum ferritin and transferrin saturation were positively correlated with left ventricular ejection fraction. It is recommended in future, an appropriately powered randomized trials with correction of anemia using erythropoietin and intravenous iron be carried out to validate the study findings.

Professor Dato' Dr Zurkurnai Yusof : Supervisor
Dr. Ng Seng Loong : Co-Supervisor

ABSTRAK

Latar belakang: Kekurangan zat besi adalah masalah baru yang dikaitkan dengan penyakit kegagalan jantung kronik dan ia berpotensi sebagai sasaran perawatan. Malah, pengetahuan mengenai kekerapan kes kekurangan zat besi dan kekurangan sel darah merah di kalangan pesakit kegagalan jantung kronik masih kurang.

Objektif : Objektif pertama kajian ini adalah untuk mengenalpasti kekerapan kes kekurangan zat besi dikalangan pesakit kegagalan jantung kronik. Objektif sekunder adalah untuk menentukan kekerapan kes kekurangan sel darah merah pada populasi yang sama. Hubungan antara kekuatan sistolik jantung dan keputusan darah juga dikenalpasti. Pada masa yang sama, faktor risiko untuk menghidap kekurangan sel darah merah di dalam kes kegagalan jantung kronik juga dianalisa.

Kaedah: Satu kajian keratan rentas yang melibatkan sejumlah 81 orang pesakit dari Hospital Universiti Sains Malaysia yang menghidap penyakit kegagalan jantung kronik telah terlibat dalam kajian ini. Pesakit-pesakit tersebut mempunyai kekuatan sistolik jantung kurang dari 45% mengikuti ukuran Simpson dan disah menghidapi kegagalan jantung melebihi 6 bulan. Sebanyak 10 mls darah diambil daripada setiap pesakit and dihantar ke makmal untuk analisa.

Keputusan : Enam belas orang pesakit didapati mengalami kekurangan zat besi (19.8%). Tiga puluh tiga pesakit disahkan mengalami kekurangan sel darah merah (40.7%) berbanding dengan 48 pesakit (59.3%) yang normal kandungan sel darah merah.

Semua pesakit kekurangan zat besi adalah dari golongan kekurangan darah merah. Terdapat hubungan positif antara kandungan ferritin, zat besi dan sel darah merah dengan kekuatan sistolik jantung. Kandungan ferritin (OR 0.974, 95% CI 0.959, 0.988), ketepuan transferrin (OR 0.831, 95% CI 0.726, 0.952), dan penyakit kencing manis (OR 6.680, 95% CI 1.599, 27.897) merupakan risiko untuk menhidapi penyakit kekurangan darah merah.

Kesimpulan : Kajian ini menunjukan bahawa kes kekurangan sel darah merah dalam kes kegagalan jantung kronik mempunyai kekerapan yang tinggi. Kebanyakan pesakit kekurangan sel darah merah terdiri daripada pesakit yang kekurangan zat besi. Selain daripada itu, kandungan hemoglobin, ferritin dan ketepuan transferrin berkait dengan kekuatan sistolik jantung. Pada masa depan, disarankan kajian mengenai rawatan kekurangan sel darah merah dengan ubat erythropoietin dan pengambilan zat besi perlu dijalankan untuk mengesah keputusan kajian ini.

ABSTRACT

Background: Iron deficiency (ID) is an emerging problem in patients with chronic systolic heart failure and can be a potential therapeutic target. However, not much is known about the frequency, predictors of iron deficiency and anemia in patients with chronic heart failure.

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Conclusion: This study demonstrated high frequency of anemia in chronic systolic heart failure patients. Majority of anemic patients were iron deficient. Besides that, serum hemoglobin and serum ferritin and transferrin saturation were positively correlated with left ventricular ejection fraction. It is recommended in future, an appropriately powered randomized trials with correction of anemia using erythropoietin and intravenous iron be carried out to validate the study findings.

CHAPTER 1

INTRODUCTION

1.1 Chronic systolic heart failure; epidemiologic perspective

Heart failure (HF) is the end stage of most diseases of the heart. The prevalence of HF varies between 3-20 per 1000 population, but for those over the age of 65 years, it could be as high as 100 per 1000 population (Davis *et al.*, 2000).

The prognosis for HF is poor, far worse than some of the common cancer (Kannel *et al.*, 1982). The one year mortality rate varies between 5% to 52% depending on the severity and the presence of co-morbidity (Investigators, 1992). In a large community based study, about 40% of individuals with HF died within a year of initial diagnosis (Cowie *et al.*, 2000). About half of all deaths are sudden and may occur at any stage of the syndrome (Cleland *et al.*, 2001). Heart failure is an important cause of hospitalization accounting for about 10% of all medical admissions in Malaysia (Teh BT, 1999). About 45% of patients with HF are readmitted at least once within 12 months for acute decompensation (Krumholz *et al.*, 1998). More recent epidemiological studies from the West seem to indicate that the prognosis has improved slightly with earlier detection of the condition and improved treatment strategies (MacIntyre *et al.*, 2000; Schaufelberger *et al.*, 2004).

Heart failure is a clinical syndrome characterized by symptoms of breathlessness and fatigue, with signs of fluid retention and supported by objective evidence of cardiac dysfunction (systolic and/or diastolic). The severity of the symptoms may be graded according to the New York Heart Association (NYHA) Functional Class. These symptoms may fluctuate in severity with time and may completely disappear following therapy.

Heart failure is due to the inability of the heart to pump blood at a rate to meet the needs of various organs of the body or its ability to do so only at high filling pressures. It may be the result of any disorder of the endocardium, myocardium, pericardium or great vessels although commonly it is due to myocardial dysfunction. Myocardial contractility is most often reduced resulting in Left Ventricular (LV) systolic dysfunction.

In LV systolic dysfunction, cardiac output is reduced due to depressed myocardial contractility. This initiates a complex pathophysiological process which includes hemodynamic alterations and structural changes within the myocardium and vasculature. Activation of neuro-hormones such as catecholamine and the renin-angiotension-aldosterone system play a pivotal role in this process.

1.2 Definition of chronic systolic heart failure

Heart failure can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (Dickstein *et al.*, 2008). HF is defined clinically as a syndrome in which patients have typical symptoms (e.g. breathless, ankle swelling and fatigue) and signs (e.g., elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function. Demonstration of an underlying cardiac cause is therefore central to the diagnosis of HF. This is usually myocardial disease causing systolic ventricular dysfunction.

The main terminology used to describe HF is historical and is based on measurement of LV ejection fraction (EF). Mathematically, EF is the stroke volume (which is the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume. In patients with reduced contraction and emptying of the left ventricle, stroke volume is maintained by an increase in end-diastolic volume. The more severe the systolic dysfunction, the more the EF is reduced from normal and generally the greater the end-diastolic and end-systolic volumes. The EF is considered important in HF, not only because of its prognostic importance, but also because most clinical trials selected patients based upon EF. The major trials in patients with HF and a reduced EF or systolic HF mainly enrolled patients with an EF < 45%, and it is only in these patients that effective therapies have been demonstrated to date (Guidelines, 2012).

A patient who has never exhibited the typical signs or symptoms of HF is described as having asymptomatic LV systolic dysfunction. Patients who have had HF for some time are often said to have ‘chronic HF’. A treated patient with symptoms and signs, which have remained generally unchanged for at least a month, is said to be ‘stable’. If chronic stable HF deteriorates, the patient may be described as ‘decompensated’ and this may happen suddenly ‘acute’, leading to hospital admission (Dunlay *et al.*, 2009; McMurray *et al.*, 2010; Chen *et al.*, 2011). Symptoms can also change rapidly and an acutely unwell patient with pulmonary edema with NYHA class IV symptoms may improve rapidly with administration of a diuretic. Deterioration in symptoms indicates heightened risk of hospitalization and death and is an indication to seek prompt medical attention and treatment.

1.3 New York Heart Association functional classification

The NYHA functional classification has been used to select patient in almost all randomized treatment trials in HF. Patients in NYHA class I have no symptoms attributable to heart disease, those in NYHA classes II, III or IV are said to have mild, moderate or severe symptoms respectively.

1.4 Role of echocardiography in the evaluation of heart failure

Imaging plays a central role in the diagnosis of HF and in guiding treatment. Among the several imaging modalities available, echocardiography is the method of choice in patients with suspected HF for reasons of accuracy, availability, safety and cost.

Echocardiography is a term used to refer to all cardiac ultrasound imaging techniques, including two-dimensional/ three-dimensional echocardiography, pulsed and continuous wave Doppler, color flow Doppler and tissue Doppler imaging. Echocardiography provides information about cardiac anatomy and function.

Left ventricular ejection fraction (LVEF) is not the same as stroke volume. Stroke volume may be maintained by LV dilation in patient with reduce EF. The recommended echocardiographic method for measurement of EF is the apical biplane method of discs (the modified Simpson's rule). The Teichholz methods of calculating EF from linear dimensions may result in inaccuracies, particularly in patients with regional LV dysfunction (Kirkpatrick *et al.,* 2007; Rudski *et al.,* 2010; Dokainish *et al.*, 2011).

1.5 Management of chronic systolic heart failure

Drug therapy is the mainstay of management of chronic systolic heart failure. The most effective therapy is combination of diuretic, angiotension-converting enzyme inhibitor, beta-blocker and aldosterone receptor antagonist.

a) Angiotensin-Converting Enzyme Inhibitors (ACEI)

ACEI improve survival and quality of life in all classes of heart failure (SOLVD, 1992). ACEI are first-line drugs for the treatment of HF and should be given to all patients in whom there is evidence of left ventricular (LV) systolic dysfunction as reflected by an LV ejection fraction of < 45%.

b) Angiotensin II Receptor Blockers (ARB)

ARB should be considered in patients intolerant to ACEI. In post myocardial infarction (MI) patients with impaired LV function, the ARB Valsartan was found to be as effective as captopril (Cohn and Tognoni, 2001). In patients with severe HF, the combination of ACEI and ARB may be considered to reduce hospitalization due to HF (Granger *et al.*, 2003).

c) Beta-Blockers

Large clinical trials have shown that beta-blockers reduce morbidity and mortality in heart failure patients with NYHA II-IV, regardless of ischemic or non-ischemic aetilogy. Beta-blockers therapy should be initiated when pulmonary congestion is absent and the patients is clinically stable. All stable patients with current or prior symptoms of HF and reduced LV ejection fraction should be given β-blockers unless contraindicated (Merit-HF, 1999; Poole-Wilson *et al.*, 2003; Doughty *et al.*, 2004).

A recent trial indicated that initiating therapy with beta-blockers first is non-inferior to the standard approach of starting with an ACEI. The benefits seen with both these drugs are additive (Poole-Wilson *et al.*, 2003).

Patients who decompensate and are admitted in acute heart failure may need reduction or temporary discontinuation of their beta-blockers. After the patient has been stabilized and is no longer in overt HF, an attempts should be made to reinstitute beta-blockers starting with low doses.

d) Aldosterone Receptor Antagonists

The addition of spironolactone to ACEI, loop diuretics and digoxin in patients with severe HF reduces mortality and hospitalization (Pitt *et al.*, 1999). Another aldosterone receptor antagonist, eplerenone when added to beta-blockers and ACEI has been shown to be beneficial when given to post MI patients with impaired LV function and mild HF (Pitt *et al.*, 2003).

Care should be exercised in patients with renal impairment. Serum potassium should be monitored regularly. Potassium supplements may need to be reduced or stopped.

e) Digoxin

Digoxin is indicated in patients with HF and atrial fibrillation (Cleland *et al.*, 2002). Combination of digoxin and beta-blockers is superior to either agent alone in patients with atrial fibrillation (Khand *et al.*, 2003).

In patients with HF and normal sinus rhythm, digoxin may be added if symptoms persist despite diuretics, ACEI, beta-blockers and low dose spironolactone. Digoxin has no effect on mortality but reduces hospitalization (Uretsky *et al.*, 1993; Digitalis, 1997).

f) Antiplatelet agents

Antiplatelet therapy consists of acetylsalicyclic acid (ASA), an cyclo-oxygenase inhibitor and clopidogrel and ticlopidine, both adenosine diphosphate receptor (ADP) antagonists. Antiplatelet is the main treatment regime for ischemic heart disease, which is the main etiology for systolic heart failure.

ASA acts by inhibiting cyclooxygenase-1 with platelets, hence preventing the formation of thromboxane A2 which inhibits platelet aggregation. Additionally, ASA may also reduce plague rupture and its sequalae (Ridker *et al.*, 1997). Antiplatelet Trialists Collaboraton 1994, a collaborative overview of randomized trials of antiplatelet therapy noted significant reduction of death, myocardial infarction and stroke in various categories of patients by 25% (Collaboration, 1994).

ADP antagonists blocks adenosine diphosphate receptor resulting in inhibition of platelet aggregation. CAPRIE steering committee 1996, reported relative risk reduction in incidence of ischemia, myocardial infarction (MI) or vascular death by 8.7% in favor of clopidogrel when patients were randomized to receive either ASA 325mg/day or clopidogrel 75mg/day (Gent *et al.*, 1996). CURE trial showed significant reduction in incidence of cardiovascular death, nonfatal MI or stroke by 9.3% in patients who were given clopidogrel (300mg immediately followed by 75mg/day) within 24 hours after onset of acute coronary syndrome (ACS) (Yusuf *et al.*, 2001).

g) Diuretics

Diuretics are indicated in all patients with HF in whom there are signs and symptoms of fluid retention (Hampton, 1994). The dose of diuretic used is wide and dependent on individual requirements. Diuretic therapy must be used with care because overdiuresis can cause severe intravascular dehydration and deteriorating renal function. Thiazide diuretics may be preferred in patients with hypertensive HF and mild fluid retention. For most patients, a loop diuretic is often required. Responsiveness to loop diuretics diminished as HF progresses. In this situation, combination of thiazides and loop diuretics are useful as these drugs work synergistically to improve diuresis (Dormans *et al.*, 1998).

1.6 Risk factors and co-morbidities associated with chronic systolic heart failure

Co-morbidities are important in patients with HF for four main reasons. First, co-morbidities may affect the use of treatments for HF. Secondly, the drugs used to treat co-morbidities may cause worsening of HF. Thirdly, the drugs used to treat HF and those used to treat co-morbidities may also interact with one another and reduce patient adherence. Lastly, most co-morbidities are associated with worse clinical status and are predictors of poor prognosis in HF. This has led to some co-morbidities themselves becoming targets for treatment (McMurray *et al.*, 2009).

a) Anemia

Anemia (defined as hemoglobin concentration <13g/dL in men and <12g/dL in women) is common in HF, particularly in hospitalized patients. It is more frequent in women, the elderly and in patients with renal impairment (Felker *et al.*, 2003).

Anemia is associated with more symptoms, worse functional status, greater risk of HF hospitalization and reduce survival. A standard diagnostic work-up should be undertaken in anemia patients. Although no definite etiology is identified in many patients, correctable causes should be treated in the usual way. Correction of iron deficiency using intravenous iron has been specifically studied in patients with HF. The value of erythropoietin-stimulating agents as a treatment for anemia of unknown etiology is unknown but is currently being tested in a large mortality-morbidity randomized control trial (RCT) (McMurray *et al.,* 2009).

b) Diabetes mellitus

Hyperglycemia and diabetes mellitus are very common in HF and diabetes mellitus is associated with poorer functional status and worse prognosis (Bauters *et al.,* 2003). Diabetes may be prevented by treatment with ARBs and possibly ACE inhibitors (McMurray *et al.,* 2010). Beta-blockers are not contraindicated in diabetes and are as effective in improving outcome in diabetic patients as well as in non-diabetic individuals (Jonas *et al.,* 1996). Different beta-blockers may have different effects on glycemic indices (Bakris *et al.,* 2005). Thiazolidinediones cause sodium and water retention and increased risk of worsening HF and hospitalization and should be avoided. Metformin is not recommended in patients with severe renal or hepatic impairment because of the risk of lactic acidosis but is widely used in other patients with HF (MacDonald *et al.,* 2010). The safety of newer antidiabetic drugs in HF is unknown.

c) Hyperlipidemia

Elevated low-density lipoprotein cholesterol is uncommon in HF, Patients with advanced HF often have low concentrations of low-density lipoprotein, which is associated with a worse prognosis (Horwich *et al.*, 2002). Rosuvastatin did not reduce the primary composite mortality-morbidity endpoint in two large RCTs in heart failure (Tavazzi *et al.*, 2008).

d) Hypertension

Hypertension is associated with an increased risk of developing HF, antihypertensive therapy markedly reduces the incidence of HF (Furberg *et al.*, 2000). Negatively inotropic calcium channel blockers (CCB) should not be used to treat hypertension in patients with HF, and moxonidine should also be avoided in patients with HF as it increased mortality in patients in one RCT (Cohn *et al.*, 2003). If blood pressure is not controlled with an ACE inhibitor, a beta-blocker, aldosterone receptor antagonist, diuretic, hydralazine and amlodipine, are additional blood pressure-lowering agents shown to be safe in systolic HF. The blood pressure targets recommended in hypertension guidelines are applicable to HF (Myat *et al.*, 2012).

e) Iron deficiency

Iron deficiency may contribute to muscle dysfunction in HF and causes anemia if continually depleted. In a single RCT, 459 patients with systolic HF whose hemoglobin concentration range between 9.5 and 13.5g/dL plus iron deficiency were randomized 2:1 to iv ferric carboxymaltose or saline.

Over 6 months of treatment, iron therapy improved patients' functional class compared to placebo (Anker *et al.*, 2009b). In that trial, iron deficiency was diagnosed when serum ferritin was < 100 μg /L or when the ferritin concentration was between 100 and 299 μg/L and transferrin saturation was < 20%. Iron therapy may be considered as a treatment for these patients. However the long-term safety of iron therapy in HF is unknown.

f) Kidney dysfunction and cardiorenal syndrome

The glomerular filtration rate (GFR) is reduced in most patients with HF, and renal function is a powerful independent predictor of prognosis in HF. Renin-angiotensin-aldosterone blockers frequently cause a fall in GFR. Conversely an immediate and large fall in GFR should raise the suspicion of renal artery stenosis. Sodium and water depletion and hypotension are well recognized causes of renal dysfunction. There are also less well known causes for renal dysfunction which are volume overload, right heart failure and renal venous congestion. Other causes of kidney dysfunction are prostatic obstruction and nephrotoxic drugs such as NSAIDs and certain antibiotic. All of these causes should be considered in HF patients with worsening renal function. Thiazide diuretics may be less effective in patients with a very low GFR, and certain renally excreted drugs may accumulate in patients with renal impairment. Sometimes the term 'cardiorenal syndrome' is used to describe concurrent heart and renal failure (Ronco *et al.*, 2009).

g) Obesity

Obesity is a risk factor for HF and complicated its diagnosis because it cause dyspnea, effort intolerance and ankle swelling and may result in poor-quality echocardiography images. Obese individuals also have reduced natriuretic peptide levels. Obesity is more common in HF-preserve ejection fraction (HF-PEF) than in HF-reduce ejection fraction (HF-REF). Although it is possible that misdiagnosis may explain at least some of this difference in prevalence.

CHAPTER 2

LITERATURE REVIEW

2.1 Iron deficiency and anemia in chronic systolic heart failure

Despite improvements in chronic heart failure (HF) treatment over the years, normal daily activities of many patients remain restricted . Anemia, a common comorbidity in HF is associated with increased disease severity and may contribute to a worse outcome (Groenveld *et al.*, 2008; Ghali, 2009; Jankowska *et al.*, 2010; Haehling *et al.*, 2011). The mechanism where anemia contributes to adverse outcome in chronic HF patients is complex and multifactorial (van der Meer and van Veldhuisen, 2009). Important factors include renal failure, bone marrow resistance to erythropoietin, chronic inflammation, and iron deficiency (ID) (van der Meer *et al.*, 2005; Westenbrink *et al.*, 2007; van Veldhuisen *et al.*, 2011). Traditionally, the presence of ID is only considered clinically relevant in the presence of anemia. However, a reduced hemoglobin levels can be viewed as the end result of a process beginning with gradual depletion of iron stores (Semba, 2003). Even if patients are not anemic, ID may already be common in chronic HF (Jankowska *et al.*, 2010; Silverberg, 2011). ID with or without anemia is associated with decreased aerobic performance and exercise intolerance (Pinhas-Hamiel *et al.*, 2003). ID recently also shown in chronic HF (Klip *et al.*, 2013).

In recent years, a number of studies have shown that correction of ID through intravenous iron supplementation in patients with chronic HF may improve functional status and quality of life (Toblli *et al.*, 2007; Usmanov *et al.*, 2008; Okonko *et al.*, 2011). This was observed in both anemic and non-anemic patients with chronic HF, shifting the focus for anemia in HF away from hemoglobin and toward iron (Anker *et al.*, 2009b). The prevalence and potential importance of ID per se, irrespective of hemoglobin are currently a subject of interest in HF. However, data on this topic are scarce and only a few studies have reported on ID as a predictor of outcome in chronic HF.

2.2 Prevalence and definition of iron deficiency (ID)

In recent years, the prevalence and prognosis of ID in chronic HF have received greater attention. Despite this, there is no standard definition of ID in chronic HF, leading to a wide variation in reported prevalence.

Opasich et al (2005) reported that among 148 patients with chronic HF and anemia, impaired iron supply was the cause in nearly all patients with anemia of chronic disease. In a large observational trial by Jankowska et al (2010), ID was present in 37% of all chronic systolic HF patients. In another recent study, Parikh et al (2011) reported a prevalence of 61% among community-dwelling HF patients.

Chronic HF is a cardiovascular syndrome with a high mortality, and iron deficiency has been shown to be an independent risk factor for mortality in HF (Pitt *et al.*, 2003).

About half of all patients with HF have either absolute iron deficiency (ferritin < 100µg/L and TSAT <20%) or functional iron deficiency (serum ferritin 100-300µg/L and TSAT <20%) respectively. This finding is only partly associated with the presence of anemia. Indeed, many HF patients present with iron deficiency, many with anemia, and some of these with both. Iron deficiency independently relates to exercise intolerance expressed as reduced peak oxygen uptake and augmented ventilator response to exercise in patients with chronic HF (Okonko *et al.*, 2008). The absence of iron in the blood of patients with HF may be also reflected as reduced iron load in the bone marrow and in the myocardium. At the level of the bone marrow, the dominant regulatory protein that controls synthesis of new erythrocytes is erythropoietin. Erythropoietin is synthesized predominantly in the peritubular endothelium cells of the kidney (Lacombe *et al.*, 1988). During anemia, caused by either reduced iron intake or blood loss, the healthy kidney can increase erythropoietin production by at least 10-fold. The symptoms and signs of iron deficiency are partially explained by the presence of anemia, but experimental evidence suggests that iron itself improves muscle function and exercise capacity in animals without changes in hemoglobin levels. This finding emphasizes the role of iron as a co-factor in skeletal and cardiac muscle function. The reason why iron may have an effect on HF irrespective of anemia and hemoglobin values is that iron is an essential constituent of myoglobin, which is found in the cytoplasm and avidly binds and releases oxygen. Mitochondrial function needs iron since iron is a co-factor for heam proteins that are involved in electron transfer of ATP and energy production in the cells (Rouault and Tong, 2005). In recent years, different therapeutic possibilities embrace iron replacement by oral or intravenous routes.

Serum iron markers, however, may be inadequate to detect decreased iron status. Only 1 study conducted by Nanas et al (2006) used the criterion standard of bone marrow iron staining to determine the prevalence of ID in patients with chronic HF. They found that 73% of patients with advanced HF and anemia had depleted iron stores. Nonetheless, the criteria most commonly used for detecting ID in chronic HF are a ferritin level <100 μg/L or ferritin 100 to 299 μg/L in combination with a TSAT <20% (Klip *et al.*, 2013).

2.3 Pathophysiology of ID in chronic HF

Iron is a metabolically active micronutrient. One of its crucial properties is the ability to shuttle between two oxidative states (ferric and ferrous iron), which makes it an efficient cofactor for several enzymes and the catalyst of numerous biochemical reactions. Iron plays a crucial role in oxygen transport (as a component of hemoglobin), oxygen storage (as a component of myoglobin), oxidative metabolism in the skeletal and heart muscle (as a component of oxidative enzymes and respiratory chain proteins, and also is involved in the synthesis and degradation of lipids, carbohydrates, DNA, and RNA. The maintenance of normal iron metabolism is particularly important for cells that are characterized by high mitogenic potential (neoplastic cells, hematopoietic cells, including immune competent cells) and high energy demand (hepatocytes, adipocytes, renal cells, immune cells, skeletal myocytes, and cardiomyocytes). Iron deficiency (ID) is the most common nutritional disorder, affecting more than one-third of the general population (Zimmermann and Hurrell, 2007).

Iron deficiency has been also recognized to complicate chronic diseases (e.g. inflammatory bowel disease, Parkinson's diseases, rheumatoid diseases, and chronic renal failure) with or without concomitant anemia (Weiss, 2009). The presence of ID may have multifaceted clinical consequences, not only directly related to impaired erythropoiesis but also to marked impairment of oxidative metabolism, cellular energetics, and cellular immune mechanisms (Jankowska *et al.*, 2010).

It was recently shown that patients with chronic HF are more susceptible to become iron deficient. This could be explained by gradual depletion of iron stores due to low iron intake, gastrointestinal blood loss, or iron malabsorption.

Patients with chronic HF are prone to become iron deficient as a consequence of a depletion of iron stores (absolute ID) or more frequently as a result of impaired iron metabolism in the course of inflammatory processes characterizing chronic HF (functional ID). In chronic HF, there is an activation of proinflammatory cytokines that block intestinal absorption of iron and divert iron from the circulation into the reticuloendothelial system, causing reticuloendothelial block. Hepcidin, a small hepatic peptide secreted in response to proinflammatory cytokines, seems to play a key role in the control of these processes. Decreased intestinal iron absorption together with its accumulation within the reticuloendothelial stores reduces iron availability to its target tissues and organs. Thus, functional ID may occur despite adequate iron stores in the body, in contrast to absolute ID, when the body iron stores are significantly depleted.

In human, intracellular iron is stored as ferritin and in times of iron overload, as hemosiderin whose excessive presence in macrophages is responsible for the color of hematoma. Values of serum ferritin are a clinically meaningful proxy to reflect body iron stores as this protein spills over from intracellular stores into the bloodstream. Ferritin is also an acute phase reactant whose levels may increase during inflammatory process. Transferrin saturation reflect the relative amount of transferrin that is loaded with iron. In contrast to ferritin, transferrin is a negative acute phase reactant, its levels decrease during times of inflammation. Neither serum iron nor serum transferrin alone should be used as indicators of iron status. Chronic inflammation, commonly observed in chronic HF may also play a role. Inflammation causes reduced iron absorption and availability of iron recycled in the reticuloendothelial system (functional ID) (Weiss and Goodnough, 2005; Weiss, 2009). Therefore, functional ID may occur despite adequate iron stores, whereas iron stores are depleted in absolute ID.

CHAPTER 3

OBJECTIVES

3.1 Primary Objective

To determine the frequency of iron deficiency in patients with chronic systolic heart failure.

3.2 Secondary Objectives

3.2.1 To determine the frequency of anemia in patients who diagnosed chronic systolic heart failure.

3.2.2 To determine the correlation between left ventricular ejection fraction with selected hematological parameters.

3.2.3 To determine factors associated with anemia in chronic systolic heart failure.

CHAPTER 4

METHODOLOGY

3.1 Study design

This is a cross sectional study of patients who have chronic systolic heart failure in Hospital USM.

3.2 Study approval

This study was approved by the Research and Ethic Committee, Universiti Sains Malaysia on 27th October 2014. Study protocol code USM/JEPeM/14080293.

3.3 Study setting and population

This study was conducted in Hospital Universiti Sains Malaysia (HUSM). Patients diagnosed with chronic systolic heart failure were recruited from echocardiography room and cardiology clinic.

3.4 Inclusion criteria

1. Patients with chronic systolic heart failure attending outpatient cardiology clinics and echocardiography room.
2. A documented history of chronic heart failure more than 6 months
3. Left ventricular ejection fraction (LVEF) less than 45% as assessed by echocardiography (performed at the time of screening using Simpson's planimetric method to determine LVEF)
4. Clinical stability and unchanged medications for more than 1 month preceding the study.