CHAPTER ONE

1.0. Introduction

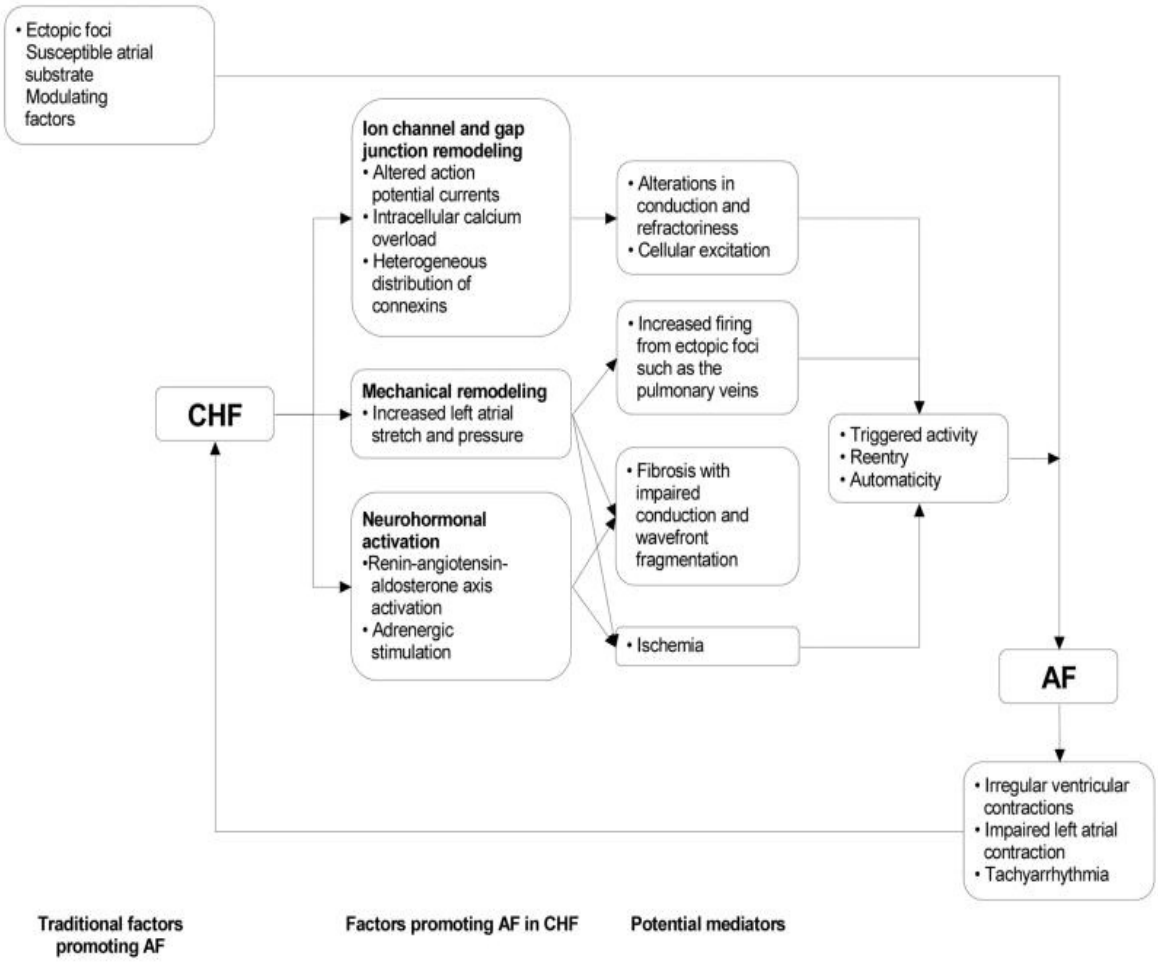
1.1. Background

Atrial fibrillation (AF) and congestive heart failure (CHF) have emerged as major global epidemics (Caldwell & Mamas, 2012). These two conditions share similar risk factors, frequently coexist, and have additive adverse effects when occurring in conjunction (Lubitz, Benjamin & Ellinor, 2010). The risk factors include hypertension (HTN), coronary artery disease (CAD), structural heart disease (non-ischaemic, valvular), diabetes mellitus (DM), obesity and obstructive sleep apnoea (Nazario, 2013). The co-prevalence also increases with advancing age and each predicts/compounds the course of the other (Caldwell & Mamas, 2012; Deedwania & Lardizabal, 2010).

1.1.1. Pathoetiology of Atrial Fibrillation in Congestive Heart Failure

The interplay between CHF and AF is complex. CHF predicts the development of AF and conversely AF predisposes to HF (Caldwell & Mamas, 2012). The mechanisms, through which CHF provides arrhythmogenic atrial substrate include; elevated left-sided filling pressures, mitral regurgitation, atrial enlargement, interstitial fibrosis and electromechanical remodelling (Deedwania & Lardizabal, 2010); activation of the autonomic and renin-angiotensin axis; as well as changes in the intracellular calcium levels (Anter et al, 2009).

Conversely, AF can lead to CHF through multiple adverse effects including loss of atrial systole, functional mitral/tricuspid regurgitation, tachycardiomyopathy, and reduced ventricular diastolic filling time (Caldwell & Mamas, 2012). Irregularity in the RR interval can also have a potentially deteriorating influence on cardiac output irrespective of the heart rate (Clark et al, 1997). Moreover, deterioration of sinus rhythm into AF in patients with CHF can lead to acute decompensation.



Source: **Lubitz, Benjamin & Ellinor (2010)**

Figure 1: Pathoetiological inter-relationship between AF and CHF

1.1.2. Diagnosis of atrial fibrillation

The pattern of AF can be classified as paroxysmal, persistent, or permanent. Paroxysmal AF is self-terminating, usually within 48 hours, but may continue for up to 7 days. Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion. Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient and physician. Notably, paroxysmal AF carries the same risk of stroke as permanent or persistent AF (Camm et al, 2010).

AF is often undetected because many individuals with AF are asymptomatic or have few symptoms (Kannel & Benjamin, 2008). Although some patients with AF may have minimal to no symptoms, others may have severe symptoms. These symptoms include palpitations, fatigue, light-headedness, dyspnea with exertion, and acute pulmonary edema (Kannel & Benjamin, 2008). Some patients experience symptoms only during paroxysmal AF and over time as AF becomes permanent, symptoms such as palpitations disappear (Medi et al 2007).

Because many individuals with AF lack symptoms, AF is often diagnosed by routine electrocardiography (ECG) examination, in the course of a stroke or myocardial infarction (MI), on implanted pacemaker, or during ambulatory ECG monitoring (Kannel & Benjamin, 2008). On ECG, AF is detected by the replacement of consistent P-waves with rapid oscillations varying in amplitude, shape, and timing, and an irregular ventricular response. There is also an irregular RR interval; as well as, an irregular, sustained wide QRS complex (Lu et al, 2005).

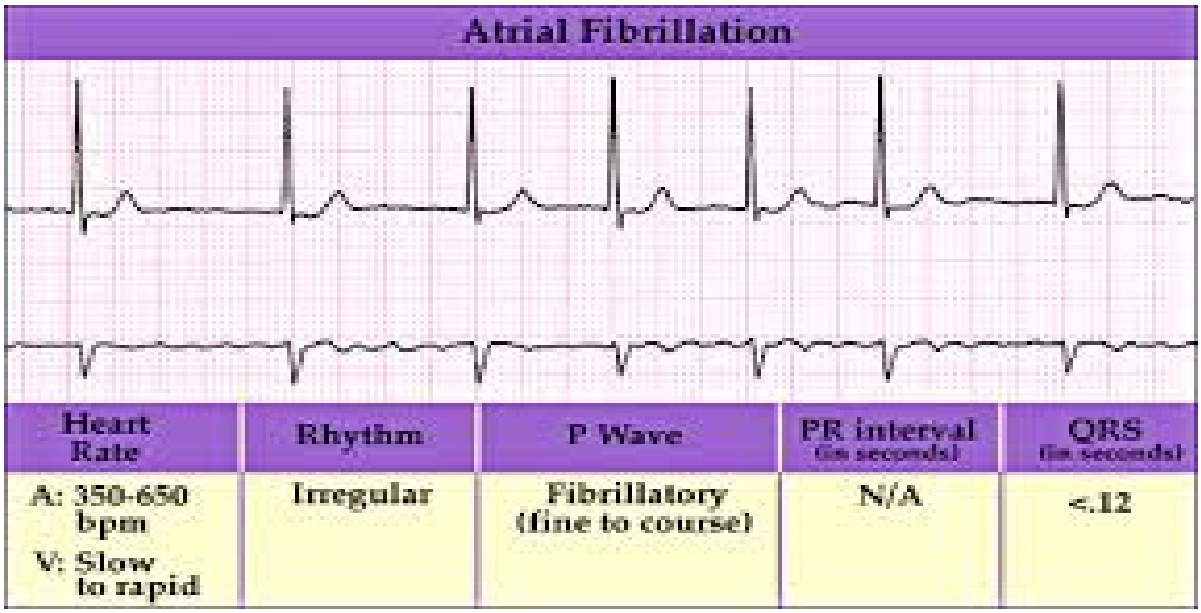


Figure 2: An illustration of an ECG with atrial fibrillation

1.2. Statement of the Problem

The presence of AF in CHF has been shown to be independently associated with an adverse effect on mortality as well as prognosis (Rivero-Ayeza et al, 2008; Dries et al, 1998). Most of the studies done (Caldwell & Mamas 2012, Lubitz, Benjamin & Ellinor 2010, Deedwania & Lardizabal 2010, Wang et al 2003, Anter et al 2009, Clark et al 1997) have revealed that AF through the loss of organized atrial activity and absence of coordinated atrial mechanical function, is associated with clinical and hemodynamic deterioration which may predispose the patient to systemic thromboembolism and poorer prognosis. Impaired contraction of the atria may cause blood stasis and the potential for thrombus formation, particularly in the left atrial appendage, especially in CHF as there is already presumed stagnation of blood (Wang et al 2003).

Data from Acute Decompensated Heart Failure National Registry demonstrated a 30% prevalence of AF among patients admitted with acute decompensated HF (Adams et al, 2005). The EuroHeart survey looked at HF hospitalisation data from 24 countries over a 6-wk duration. It revealed that out of a total of 10701 patients, 34% were known to have AF previously while 9% developed new onset AF (Rivero-Ayerza et al, 2008). The prevalence of AF also correlates directly with the severity of HF symptoms. It can vary from under 10% in those with functional New York Heart Association (NYHA) class 1 to as high as 50% in those in NYHA class 4 (Maisel & Stevenson, 2003).

The impact of AF on patients in Africa is not well characterized. Moran et al (2013) noted that the largest relative increase in cardiovascular disease burden between 1990 and 2010 in Sub-Saharan Africa was in AF; and Rahman et al (2014) estimated that by 2050, the prevalence of AF in Africa will be greater than in any other region of the world. Anderson et al (2007) and Baker et al (2009) found that even in developed regions of Africa, where high-quality health care is readily accessible, AF is under diagnosed and patients with AF are undertreated with anticoagulant therapy. Therefore, additional attention and resources are needed for the prevention and treatment of AF and its associated complications on the African continent and the developing world in general.

Similarly, in Zambia, much less is known of atrial fibrillation and heart failure apart from what Chansa et al (2011) reported, that the proportion of hospital deaths due to heart failure in our setting is approximately two to three times higher than in North America and Europe respectively. They also reported a 35% mortality rate among patients of heart failure. This mortality rate is among the highest mortality rates in the world. Despite this high mortality rate, the factors associated with atrial fibrillation and heart failure have not been investigated in our patient population. Furthermore, Goma (2014) established that arrhythmias and conduction defects are quite common in HF patients in Zambia, the most common being Atrial Fibrillation (AF) which has serious consequences.

At the University Teaching Hospital (UTH), CHF continues to be a significant burden causing considerable mortality as indicated in table 1. Furthermore, CHF is ranked number six among the top ten causes of morbidity and mortality at the UTH (UTH, 2014).

Table 1: Congestive Heart Failure Admissions and Deaths UTH

Year	Medical Conditions Admissions	Congestive Heart Failure Admissions	Congestive Heart Failure Deaths
2011	6, 026	298 (5.0%)	82 (13.7%)
2012	7, 374	349 (4.7%)	78 (22.3%)
2013	5, 832	258 (4.4%)	63 (24.4%)

(Source: UTH, 2014)

Therefore this study will investigate the clinical factors associated with AF in CHF patients admitted at UTH.

1.3. Justification of the study

In clinical practice, the use of clinical risk factors in predicting disease development, prognosis as well as the probability of death is very important; because early recognition and treatment of reversible factors indicative of poor outcome could aid in early identification and better management of patients. Therefore, the ability to define clinical factors associated with AF in CHF patients would have important clinical relevance.

Furthermore, this study will also provide the basis for many studies in the area of AF and CHF. Hence, the need that this study be done.

1.4. Literature Review

The prevalence of both CHF and AF is steadily increasing (Gaetano et al, 2007). Since the two conditions are said to share common risk factors they frequently coexist (Khand et al, 2000). The common risk factors for these two conditions include the following:

1.4.1. Socio-demographic Factors Affecting Atrial Fibrillation

1.4.1.1. Age

It has become clear over recent years that pre-existing alterations, such as autonomic dysbalance, degenerative tissue changes and fibrosis, can provide an electrophysiological and morphological substrate, which increases the likelihood of AF. In particular, alterations of the interstitial matrix in atrial tissue seem to be significant contributory factors (Nattel, 2002). Increased amounts of fibrous tissue in fibrillating human atria were reported as early as 30 years ago (Davies & Pomerance, 1972) and it is known to impair cell-to-cell coupling, thus causing heterogeneity in intra- and inter-atrial conduction. Initially, subsequent changes in atrial conduction may be subtle. However, isolated atrial amyloidosis has been found to be of importance for the development of atrial conduction disturbances and AF (Rőcken et al, 2002).

Amyloidosis represents a diverse group of diseases characterized by the presence of extracellular proteinaceous deposits showing characteristic structural and tinctorial properties. Amyloidoses are classified on the basis of the amyloid protein deposited and the clinical presentation (Rőcken & Sletten, 2003) and may affect the heart as part of a systemic disease, as in immunoglobulin-derived amyloid light-chain amyloidosis. In senile cardiovascular amyloidosis, the fibril protein consists of transthyretin (non-hereditary ATTR amyloidosis), and amyloid is observed in cardiac vessels, in the interstitium of the ventricles and in atria. Most commonly, the heart is affected by a strictly localized or organ-limited variety called isolated atrial amyloidosis. The incidence of isolated atrial amyloidosis increases with age, reaching more than 90% in the 9th decade (Rőcken & Sletten, 2003).

1.4.1.2. Sex

Gender-related differences in AF have not been well examined, although it has long been known that women have a higher mean heart rate and a longer QT interval (Bazett, 1920). In all age groups, men have a higher incidence of AF than women (Humphries et al, 2001). However, because the incidence of AF increases dramatically with age and because there are more women in the population older than the age of 75 years, the absolute number of women and men with AF in this age group is equal (Hnatkova et al, 1998).

Women are more symptomatic than men, possibly because of faster heart rates and small body habitus (Humphries et al, 2001; Rienstra et al, 2005). In the Canadian Registry of Atrial Fibrillation (CARAF), women experienced a significantly increased frequency of symptomatic recurrences, although there was no difference in electrocardiographically documented occurrences (Humphries et al, 2001).

Studies also have demonstrated differences in the clinical characteristics. The CARAF investigators demonstrated that, at the time of initial presentation of AF, men have a higher burden of ischemic heart disease whereas women have a higher prevalence of hypertension and a history of thyroid dysfunction (Humphries et al, 2001). The Framingham study cohort suggested that there were higher incidences of CHF, valvular heart disease, and diabetes (Benjamin et al, 1994). Although women have a lower incidence of AF, some studies have demonstrated a worse outcome and a higher rate of recurrence after cardioversion (Benjamin et al, 1998; Suttorp et al, 1993).

1.4.1.3. Smoking

Cigarette smoking is an important risk factor for several cardiovascular diseases, including AF. In general, smoking causes or aggravates endothelial dysfunction and atherosclerosis and causes cardiac rhythm disorders through the combined effects of nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons (Ambrose & Barua, 2004). Thus, tobacco smoking may change the myocardial substrate as well as action potentials; of which both processes provoke and facilitate AF.

In Holland, Heeringa et al (2008), in the Rotterdam Study, a population-based cohort study among subjects aged ≥55 years; the association between cigarette smoking and the

risk of AF was examined. In their study they revealed that current smokers and former smokers had increased risks of AF as compared to never smokers. No differences were found between men and women.

Similarly, Chamberlain et al (2011) in their study "Smoking and incidence of AF: results from the Atherosclerosis Risk in Communities (ARIC) study", in which they wanted to determine the association of cigarette smoking with incident AF in a population-based cohort of blacks and whites. They found that compared to never smokers, the incidence of AF was 2.10 times greater than in those who never smoked. They also noted that individuals who quit smoking exhibited a trend indicating a slightly lower risk of developing AF compared to those who continued to smoke. They also noted that associations were similar by gender and race.

1.4.1.4. Excessive alcohol consumption

Heavy alcohol consumption has been implicated as a trigger of AF. Atrial fibrillation in alcohol is probably due to the fact that heavy long-term drinking damages the heart by weakening the heart muscle leading to a condition known as alcoholic cardiomyopathy; which provide favourable conditions for the genesis and maintenance of AF (Lowenstein et al, 1983).

In America, Mukamal et al (2005), in their study "Alcohol Consumption and Risk and Prognosis of AF among older adults" found that compared with long-term abstainers, the risk for AF was greatest among former drinkers. They also noted that mortality among participants with AF was highest among former drinkers.

However, Satoru et al (2011) in a meta-analysis of Alcohol Consumption and Risk of AF, on a spline regression model noted that the AF risk increased with increasing levels of alcohol consumption.

1.4.2. Clinical Factors Associated with Atrial Fibrillation

1.4.2.1. Heart Failure

Heart failure can increase the risk for the development of AF in several ways, including elevation of cardiac filling pressures, dysregulation of intracellular calcium, and autonomic and neuroendocrine dysfunction. Atrial stretch results in activation of stretch-activated ionic currents, leading to increased dispersion of refractoriness and alterations

in anisotropic and conduction properties, facilitating atrial fibrillation (Solti et al, 1989). Heart failure has been associated with increased interstitial fibrosis (Li et al, 1999). This increase in fibrosis can lead to abnormal conduction through the atria, creating a substrate for AF in animal models (Li et al, 1999; Guerra et al, 2006: Lee et al, 2006). Dysregulation of intracellular calcium, an important feature in the pathophysiology of heart failure, also has been found to be associated with AF. The key regulators of intracellular calcium metabolism, the ryanodine receptor and the sarcoplasmic reticulum Ca^{2+}-ATPase, are downregulated in AF (Beuckelmann et al 1992; Ohkusa et al, 1999). In addition, heart failure is characterized by neurohormonal activation, with elevated concentrations of catecholamine and angiotensin II; the degree of neurohormonal activation correlates with the severity of heart failure and has become a target of pharmacological inhibition. Interestingly, neurohormonal activation also promotes structural remodeling and atrial fibrosis, thus altering atrial conduction properties and promoting AF (Li et al, 1999; Cha et al, 2003).

Gaetano et al (2007) in their study "prevalence and clinical correlates of AF among HF patients in everyday clinical practice", on a logistic model found that AF was associated with a 2.5 OR of being in NYHA class III–IV vs. I–II while accounting for age, gender, left ventricular ejection fraction (LVEF), and aetiology of HF. Furthermore, Targoński et al (2013) also showed that the increase in the NYHA class is an independent risk factor for both forms of AF.

1.4.2.2. Hypertension

Hypertension is the most important risk factors for AF. To explain the onset of AF several pathophysiologic mechanisms in hypertension may be implicated in the initiation and maintenance of AF such as structural changes, neurohormonal activation, fibrosis, atherosclerosis, etc. Untreated or suboptimally treated hypertension leads to the development of Left Ventricular Hypertrophy (LVH), which is one of the most important expressions of subclinical organ damage, and is an independent risk factor for cardiovascular events, including the development of AF. In the presence of LVH, left ventricular compliance is reduced, left ventricular stiffness and filling pressure increase, coronary flow reserve is decreased, wall stress is increased and there is activation of the

sympathetic nervous system and of the renin–angiotensin–aldosterone system. In the atria, proliferation and differentiation of fibroblasts into myofibroblasts and enhanced connective tissue deposition and fibrosis are the hallmarks of this process. Structural remodelling results in electrical dissociation between muscle bundles and in local conduction heterogeneities facilitating the initiation and perpetuation of AF. This electroanatomical substrate permits multiple small re-entrant circuits that can stabilize the arrhythmia. Over time tissue remodelling promotes and maintains AF by changing the fundamental properties of the atria (Healey & Connolly, 2003).

Krahn et al (1995), in the Manitoba Follow-up study, found that the risk of AF was 1.42 times higher in hypertensive subjects as compared with normotensive subjects. Meanwhile Kannel et al (1998) revealed that because of its high prevalence in the population, hypertension independently accounts for more AF cases than any other risk factor (Kannel et al, 1998). Furthermore, Verdecchia et al (2003), in their study "Atrial Fibrillation in Hypertension Predictors and Outcome", noted that in hypertensive subjects with sinus rhythm and no other major predisposing conditions, the risk of AF increases with age and left ventricular mass. Increased left atrial size predisposes to chronicization of AF.

1.4.2.3. Dilated Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by unexplained LV hypertrophy and ventricular myocyte disarray (Keren et al, 2008; Nishimura & Holmes, 2004). Electrophysiological features associated with left atrial dilation include shortening of the refractory period and prolongation of conduction time (Lindsay & Smith 1996). Both these alterations may lead to the development of multiple reentrant wave fronts starting and possibly perpetuating AF (Lindsay & Smith 1996).

In Cameroon, Ntep-Gweth et al (2010) in their study "Atrial fibrillation in Africa: clinical characteristics, prognosis, and adherence to guidelines in Cameroon", noted that the prevalence of paroxysmal, persistent, and permanent AF was 22.7, 21.5, and 55.8%, respectively and the underlying cardiac disorders, present included hypertensive heart disease (47.7%), valvular heart disease (25.6%), dilated cardiomyopathy (15.7%), and

coronary artery disease (6%). They noted also that AF in Cameroon is much more severe than in developed countries.

In South Africa, a study by Sliwa et al 2010 entitled "Predisposing factors and incidence of newly diagnosed atrial fibrillation in an urban African community: insights from the Heart of Soweto Study", revealed that the most common concurrent diagnosis was any form of HF (56%), seconded by primary valve disease and/or valvular dysfunction secondary to another cardiac etiology (e.g. cardiomyopathy) which was also common affecting 43% of cases. The study also revealed that Women with AF were more likely to present with hypertensive heart failure but less likely to present with a dilated cardiomyopathy or coronary artery disease, than men.

1.4.2.4. Coronary Artery Disease

The relationship between AF and coronary artery disease is more complex. The mechanism through which coronary artery disease may lead to AF is thought to be that a partially occluded artery might cause an imbalance of nutrient flow to an area of downstream heart muscle (ischemia) (Lokshyn et al, 2000). Atrial ischemia plays an important pathophysiological role in the genesis of AF. Hence, significant stenosis in the proximal right coronary artery and the circumflex artery prior to the takeoff of the atrial branches increase the likelihood of AF in these patients (Galrinho et al, 1993).

In India, a study by Thakkar & Bagarhatta (2014) where they were looking at detection of paroxysmal AF or flutter in patients with acute ischemic stroke or transient ischemic attack by holter monitor. All patients free of AF or flutter on presentation underwent 24 h Holter monitoring within 7 days of admission. The study revealed that 5.8% of the patients with Transient Ischemic Attack had paroxysmal AF and all these patients were older than age 60 years.

Lokshyn et al (2000) in the USA in their study 'atrial fibrillation in coronary artery disease' found that in patients with coronary artery disease, systolic heart failure may be more important than atrial ischemia in causing AF.

1.4.2.5. Diabetes Mellitus

Diabetes mellitus has also been implicated as an independent risk factor for AF in that glucose and insulin disturbance can directly affect the myocardium in atrium and ventricle, by causing left ventricular hypertrophy leading to AF. Prospective data from large population based studies established the relationship between LA size and risk of developing AF (Rutter et al, 2003). Analysis of the Framingham study subjects showed that left ventricular (LV) mass increased with the worsening of glucose tolerance and the trend was more striking in women than in man. There were also close relationship between insulin resistance and LV mass, as well as LV wall thickness, in women both with normal and abnormal glucose tolerance (Rutter et al, 2003). Furthermore, several observations suggest that the autonomic nervous system plays an important role in both the initiation and/ or the maintenance of AF in humans. In the animal model of DM, the occurrence of AF was enhanced by adrenergic activation in diabetic heart. The intra - atrial conduction delay and fibrotic deposition in atria play a major role in producing atrial tachyarrhythmia in diabetes animal model. The heterogeneous increase in sympathetic innervations was proved to be associated with the promotion of AF in several studies (Schmid et al, 1999; Olgin et al, 1998).

Benjamin et al (1994), in the early 1990s, in the Framingham study found diabetes mellitus to be an independent risk factor for AF with OR of 1.4 for men and 1.6 for women after 38 years follow-up. Movahed et al (2005) showed that DM is an independent factor associated with AF. In addition, Iguchi et al (2008) noted that the prevalence of AF in diabetic patients is higher than in controls (20% vs. 12%). They also demonstrated that diabetes mellitus is independently associated with AF (OR, 1.46); and even after adjustment for other risk factors, diabetes mellitus was associated with a 26% increased risk of AF among women (HR, 1.26), but not a statistically significant factor among men. Furthermore, a cross sectional survey in mainland China, found that the prevalence of AF in participants with self-reported DM was higher than those without known diabetes mellitus (1.29% vs. 0.88%) after adjustment for age and sex (Zhou & Hu, 2008).

1.4.2.6. Chronic lung disease

Atrial fibrillation in chronic lung disease is thought to result from changes in blood gases, abnormalities in pulmonary functions, and hemodynamic changes resulting from pulmonary hypertension (Lopez and House-Fancher, 2005) as well as structural remodelling. Hypoxaemia (Khokhar, 1981; Sideris et al 1975), acidosis (Levine & Klein 1976), corpulmonale and coexisting ischaemic heart disease (IHD) (Thomas & Valabhji, 1969; Holford & Mithoefer, 1973) have been proposed as major causes for the relationship between COPD and arrhythmias. Hypoxiemia and hypercapnia is associated with over-compensatory fluctuations in autonomic tone, intrathoracic pressures and cardiac haemodynamics, with possible atrial stretch and remodeling, each of which could lead to AF, particularly when hypercapnia causes a significant decrease in pH values (Stevenson et al, 2010). Morphological abnormalities associated with chronic obstructive pulmonary disease (COPD) include signs of right atrial enlargement, and right ventricular hypertrophy. Structural remodeling results in an electrical dissociation between muscle bundles and local conduction heterogeneities, facilitating the initiation and perpetuation of AF. This electro-anatomical substrate allows multiple small re-entrant circuits that may trigger the arrhythmia (Stevenson et al, 2010).

Buch et al (2003) in the Copenhagen City Heart Study in Denmark which was investigating the relationship between forced expiratory volume in one second (FEV_1) and risk of first episode of AF in a prospective study, revealed that the Risk of new AF at re-examination was 1.8-times higher for FEV_1 between 60–80% compared with FEV_1 ≥80% after adjustment for sex, age, smoking, blood pressure, diabetes and body mass index. The study further revealed that the risk of AF hospitalization was 1.3-times higher for FEV_1 between 60–80% and 1.8-times higher for FEV_1 <60% compared with FEV_1 ≥80%, when additional adjustment was made for education, treatment with diuretics and chest pain at activity.

1.4.2.7. Sleep apnoea

AF is exceedingly prevalent in patients with obstructive sleep apnea (OSA) (Gami et al, 2004). Mechanisms by which obstructive sleep apnea increases the risk of AF include: 1) intermittent nocturnal hypoxemia and hypercapnia; 2) enhanced sympathetic tone

with surges in blood pressure during apneic episodes leading to left atrial stretch through pressure and volume overload; 3) increased oxidative stress and inflammatory processes contributing to left atrial remodeling and fibrosis (Somers et al, 1995; Otto et al, 2007; Romero-Corral et al, 2007). These mechanisms may act as both triggers and perpetuators of AF.

Obstructive Sleep Apnoea is characterized by repeated episodes of nocturnal hypoxemia. Intermittent hypoxemia causes mitochondrial dysfunction by altering redox state of cytochrome oxidase and results in repetitive oxidative stress (McGown et al, 2003; Peng et al, 2003). Hypoxemic episodes induce transcription factors like nuclear factor kappa-B leading to increased production of inflammatory cytokines such as tumor necrosis factor α and interleukin 6. These cytokines, in concert with increased oxidative stress, lead to endothelial dysfunction, insulin resistance, hypercoagulability, and adverse myocardial remodeling (Lurie, 2011). Furthermore, hypoxemic episodes induce sympathetic surges leading to vasoconstriction, hypertension and tachycardia (Somers et al, 1995; Tilkian et al, 1976), and ultimately increased myocardial oxygen demand. This increased stress on myocardium results in adverse myocardial remodeling, which is a substrate for cardiac arrhythmias (Probhakar, 2002; Lévy et al, 2008).

Autonomic tone instability seen in OSA also contributes to pathogenesis of AF. Increases in parasympathetic and sympathetic tone are known to trigger AF (Fuster et al, 2006). During normal sleep, afferent inputs from stretch receptors in lung tissue inhibit the paroxysmal parasympathetic discharges that occur during rapid eye movement sleep (Kara et al, 2003; Cooper et al, 2005). These receptors are activated due to lung expansion during normal ventilation. However, in apneic patients, this response is attenuated due to pauses in breathing. Uninhibited paroxysmal parasympathetic discharges lead to marked paroxysmal bradycardia. Bradycardia is associated with decrease in atrial effective refractory period (AERP). The reduction in AERP promotes rapid electrical firing from atrial tissue in pulmonary vein ostia, thereby leading to AF (Fuster et al, 2006; Caples & Somers, 2009; Chen & Shen, 2007). Hypoxemia and hypercapnea associated with apneic episodes promote chronically heightened sympathetic activity (Somers et al, 1995; Somers et al, 1989; Somers et al, 1989).

Heightened sympathetic tone induces focal discharges from pulmonary veins, which have high concentration of adrenergic and vagal nerve endings (Tan et al, 2008; Chen & Douglas, 2006). Hypoxemia may exert an effect on cardiac arrhythmias that is independent and additive of sleep apnea. This hypothesis is supported by increased rates of ventricular ectopy among chronic obstructive pulmonary disease patients who have nocturnal hypoxemia without sleep apnea (Zipes et al, 2006).

Obstructive Sleep Apnoea is also associated with sudden and frequent changes in intrathoracic pressures, which are transmitted to thin walled atria and cause atrial stretch. Repetitive stretch may result in atrial enlargement and structural changes in pulmonary vein ostia, predisposing to development of AF (Fuster et al, 2006; Caples & Somers, 2009).

The first insight into a potential link between obstructive sleep apnea and AF came from an observational study which reported episodes of AF seen on ambulatory electrocardiographic monitoring among 3% of subjects with obstructive sleep apnea (Guilleminault et al 1983). This association was supported by the complete resolution of paroxysmal AF episodes among those who were successfully treated for obstructive sleep apnea (Guilleminault et al 1983). Furthermore, Naruse et al (2013) noted that left atrial volume, concomitant obstructive sleep apnea, and usage of continuous positive airway pressure (CPAP) therapy were associated with AF recurrences during the follow-up period.

CHAPTER TWO

2.0. RESEARCH FOCUS

2.1. Research Question

What are the clinical factors associated with AF in CHF patients admitted to the University Teaching Hospital?

2.2. Research Objectives

2.2.1. General Objective

To determine the clinical factors associated with atrial fibrillation in congestive heart failure patients admitted to the University Teaching Hospital.

2.2.2. Specific objectives

i. To describe the socio-demographic characteristics of the patients with atrial fibrillation in congestive heart failure admitted to the University Teaching Hospital.

ii. To establish the clinical factors associated with atrial fibrillation in congestive heart failure patients admitted to the University Teaching Hospital.

CHAPTER THREE

3.0. METHODS AND MATERIALS

3.1. Study Design

This was a hospital-based, cross-sectional study.

3.2. Study Setting

The study was conducted in the six (6) adult medical wards (E01, E02, E11, E12, E21 and E22) at UTH, Lusaka, Zambia. The site was selected purposively because it is a referral hospital, and for ease accessibility of equipment such as the standard 12-lead Electrocardiogram.

3.3. Target Population

The target population included all the heart failure patients who were admitted to the six (6) adult medical wards at UTH during the study period. The study took place from June - August 2014.

3.4. Study population

The study population composed of 49 CHF patients who had consented to the study

3.5. Selection of Participants

3.5.1. Sample size calculation

The sample size was calculated using the prevalence formula as shown below.

Formula:

$$\mathbf{n} = \frac{\mathbf{z^2 \times p(1-p)}}{\mathbf{d^2}}$$

Description:

n = required sample size

z = confidence level at 95% (standard value of 1.96)

p = estimated prevalence of AF

d = margin of error at 5% (standard value of 0.05)

Using the AF prevalence of 10% for South Africa the sample size calculated is 138. With this sample size and the admission rate of at least 6 patients per week (72 patients

in three months), it would have taken me at least 8 months to finish data collection from 138 participants. Therefore, to find a manageable sample size within the stipulated time frame, I used the formula for finite population as shown below:

Formula: nr = n/(1+((n-1)/N))

Description: nr = Sample size required

n = Sample size (138)

N = Population (72)

Calculation: **nr = n/(1+((n-1)/N))**

nr = 138/ (1+ ((138-1)/72)

47.54

48 participants

Adding 10% drop out rate the total sample size is **53 participants**

3.5.2. Inclusion Criteria

All consenting known CHF patients aged 18 years and above who were available during the study period were invited to participate.

3.5.3. Exclusion Criteria

CHF patients below the age of 18 years; acute patients who were not able to get out of bed and; congestive heart failure patients who refused to consent were excluded from the study.

3.6. Methodology

3.6.1. Socio-demographic information

A structured questionnaire was administered to collect socio-demographic and related historical data; and the participants health records were also reviewed to obtain additional health information.

3.6.2. Clinical assessment

Weight and height of the patients were measured using a ZT-160 adult weighing mechanical scale with a height rod (Wuxi Weigher Factory Co., Ltd, Zhejiang, China) whose values were used to compute the body mass index (BMI).

Blood Pressure and pulse rate were measured on the non-dominant hand of the patient in a lying position using an Omron HEM 780 automated Blood Pressure machine.

A standard 12-lead ECG was done on all participants using Schiller AT-102 ECG machine to identify those with and without atrial fibrillation. Then those who had a normal ECG, had an ECG holter monitor (Holter LX Remote Northeast Monitoring Inc, USA) applied for 24 hours in trying to pick up some paroxysmal arrhythmias which were not detected on a standard 12-lead ECG. All electrocardiograms were assessed by an experienced cardiologist for interpretation according to the UTH criteria.

Patients found with AF of any type were assessed for the clinical factors such as sex, age, NYHA class, diabetes, high blood pressure, Coronary artery disease, prior heart attacks, structural heart disease (valve problems or congenital defects), prior open-heart surgery, untreated atrial flutter, chronic lung disease, obstructive sleep apnea, excessive alcohol or stimulant use, and any other serious illness or infection; using information from the patient's health files.

3.6.3. Data storage

Once collected, data on hard copies was kept in a lockable cupboard to promote confidentiality and, as soft copies; the data was stored on a computer protected with a password which was only known by the principal investigator.

3.7. Ethical considerations

Participation in this study was voluntary, with participants free to withdraw from the study at any time. Patients found to have atrial fibrillation were counseled and referred to the cardiologist for specialized treatment. All procedures used to collect data were normal routine procedures done in the routine care of patients, within the patient's natural environment, and nothing was done to the discomfort of the patient. Ethical clearance was obtained from ERES CONVERGE IRB (Reference number 2014-Mar-003) and permission was also sort from UTH Management and the department of Medicine before starting data collection.

CHAPTER FOUR

4.0. RESULTS

A total of 49 Congestive Heart Failure patients who met the inclusion criteria were enrolled into the study. The results have been presented in frequency tables, figures and contingency tables according to the sequence and sections of the interview schedule.

4.1. Socio-demographic Characteristics of the participants

Table 2: Socio-demographic characteristics of with AF in CHF patients admitted to UTH (N=49)

Variable	Frequency	Per cent
Sex		
Female	25	51
Male	24	49
Total	**49**	**100**
Age		
35 - 44 Years	2	4.1
45 - 54 Years	10	20.4
55 - 64 Years	16	32.7
65 Years and above	21	42.9
Total	**49**	**100**
Body Mass Index		
18.5 - 24.9	26	53.1
25 - 29.9	11	22.4
30 and above	12	24.5
Total	**49**	**100**
Smoking		
No	39	79.6
Yes	10	20.4
Total	**49**	**100**
Alcohol consumption		
No	34	69.4
Yes	15	30.6
Total	**49**	**100**

Table 2 shows the socio-demographic characteristics of with atrial fibrillation in congestive heart failure patients admitted the UTH. There were almost equal number of men and women; 49% vs. 51% respectively. The majority 21 (42.9%) of patients were aged 65 years and above and the majority 26 (53.1%) of the patients had a normal BMI

(18.5 – 24.9). There were 10 (20.4%) patients who were smokers in the study. 15 (30.6%) of the patients reported that there were consumers of alcohol.

4.2. Clinical Factors Data

Table 3: Clinical characteristics of patients with AF in CHF patients (N=49)

Variable	Frequency	Per cent
NYHA Class		
Class III	9	18.4
Class IV	40	81.6
Total	**49**	**100**
Hypertension		
No	36	73.5
Yes	13	26.5
Total	**49**	**100**
Coronary Artery Disease		
No	46	93.9
Yes	3	6.1
Total	**49**	**100**
Dilated Cardiomyopathy		
No	40	81.6
Yes	9	18.4
Total	**49**	**100**
Diabetes Mellitus		
No	42	85.7
Yes	7	14.3
Total	**49**	**100**
Chronic Lung Disease		
No	42	85.7
Yes	7	14.3
Total	**49**	**100**

Table 3 shows the clinical characteristics of AF in CHF. The majority 40 (81.6%) of the patients were in the NYHA class IV. Just over a quarter, 13 (26.5%) of the patients had hypertension; 9 (18.4%) had dilated cardiomyopathy; 7 (14.3%) had chronic lung disease; 7 (14.3%) had diabetes mellitus; and 3 (6.1%) had coronary artery disease.

4.3. Electrodiagnosis of Atrial Fibrillation

The modalities used in diagnosing atrial fibrillation in this study were by the use of a standard 12-lead ECG and a 24 hour ECG holter monitor.

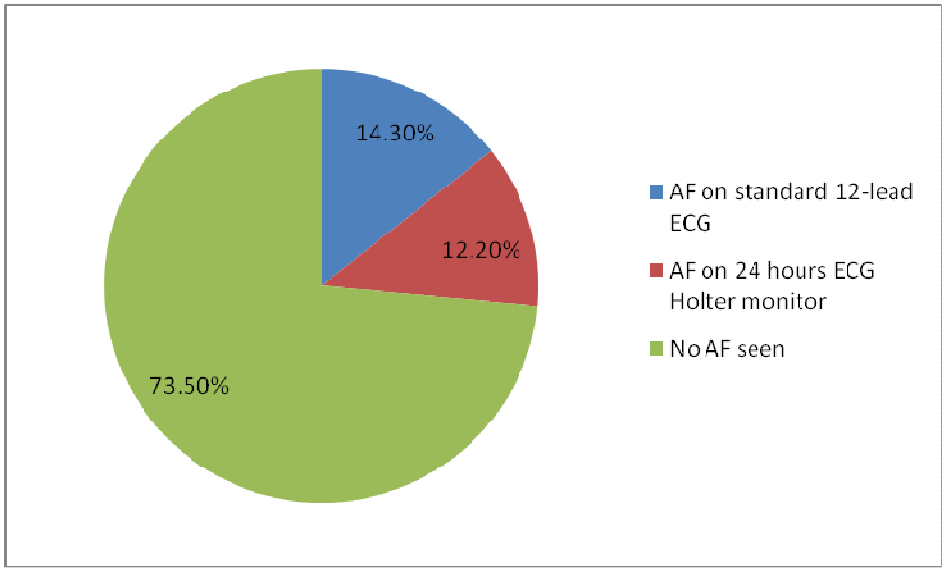


Figure 3: Electrodiagnosis of Atrial Fibrillation (N=49)

Figure 3 shows the modalities utilised to diagnose AF. Only 7 (14.3%) of the 49 patients had atrial fibrillation on standard 12-lead ECG done on them on admission. Another 6 (12.2%) of the patients who had no AF on standard 12-lead ECG, had atrial fibrillation on 24 hours ECG holter monitoring. Thus a total of 13 (26.5%) of the 49 patients enrolled had atrial fibrillation either on standard 12-lead ECG or 24 hours ECG holter monitor.

4.4. Atrial Fibrillation by the socio-demographic characteristics and clinical factors

Using Pearson chi-square of independence test, the association between atrial fibrillation in congestive heart failure patients and the socio-demographic characteristics as well as the identified clinical factors was measured. The results obtained are presented in tables 3 and 4 below.

Table 4: Atrial Fibrillation by the socio-demographic factors

	Atrial Fibrillation			
	No AF seen	**AF seen**		
Clinical Factor	**N (%)**	**N (%)**	**X^2**	**P-value**
Sex[a]				
Female	20 (80.0)	5 (20.0)	1.12	.291
Male	16 (66.7)	8 (33.3)		
Age[a]				
35 - 44 Years	2 (100.0)	0 (0.0)		
45 - 54 Years	10 (100.0)	0 (0.0)		
55 - 64 Years	12 (75.0)	4 (25.0)	5.03	**.025***
65 Years and above	12 (57.1)	9 (42.9)		
Body Mass Index[a]				
18.5 - 24.9	26 (100.0)	0 (0.0)		
25 - 29.9	8 (72.7)	3 (27.3)	22.59	**<0.001***
30 and above	2 (16.7)	10 (83.3)		
Smoking[a]				
No	33 (84.6)	6 (15.4)	9.54	**.002***
Yes	3 (30.0)	7 (70.0)		
Alcohol intake[a]				
No	33 (97.1)	1 (2.9)	27.88	**<0.001***
Yes	3 (20.0)	12 (80.0)		

[a]Fisher's Exact Test. *Indicates significant *p*-value at $p < 0.05$.

Table 4 shows the cross tabulations of AF by the socio-demographic factors. The incidence of AF was higher in males 8 (33.3%) than the females 5 (20.0%); though no statistical significance was noted in relation to gender. The presence of AF in CHF patients increased with age from 4 (25%) below 65 years to 9 (42.9%) in those above 65 years, and the Fisher's exact test showed that there is a statistical significance between age and the presence of AF in CHF patients. Furthermore, the incidence of AF increases with the increase in the BMI from 3 (27.3%) in the overweight to 10 (83.3) in the obese. 7 (70%) of the smokers in CHF had AF and Fisher's exact test showed that there is a statistically significant association between atrial fibrillation in congestive heart failure and smoking. The majority 12 (80.0%), of the patients who reported taking alcohol had atrial fibrillation.

Table 5: Atrial Fibrillation by the Clinical Factors

	Atrial Fibrillation			
	No AF seen	**AF seen**		
Clinical Factor	**N (%)**	**N (%)**	**X^2**	**P-value**
NYHA Class[a]				
Class III	7 (77.8)	2 (22.2)	0.00	1.000
Class IV	29 (72.5)	11 (27.5)		
Hypertension[a]				
No	34 (94.4)	2 (5.6)	26.71	**<0.001**
Yes	2 (15.4)	11 (84.6)		
Coronary Artery Disease[a]				
No	35 (76.1)	11 (23.9)	0.90	.342
Yes	1 (33.3)	2 (66.7)		
Dilated Cardiomyopathy[a]				
No	34 (85.0)	6 (15.0)	11.81	**.001**
Yes	2 (22.2)	7 (77.8)		
Diabetes Mellitus[a]				
No	35 (83.3)	7 (16.7)	11.35	**.001**
Yes	1 (14.3)	6 (85.7)		
Chronic Lung Disease[a]				
No	35 (83.3)	7 (16.7)	11.35	**.001**
Yes	1 (14.3)	6 (85.7)		

[a]Fisher's Exact Test. *Indicates significant *p*-value at $p < 0.05$.

Table 5 above shows the Pearson chi-square of independence test of AF in CHF by the clinical factors. The test showed that there was a strong association between AF and hypertension, dilated cardiomyopathy, diabetes mellitus as well as chronic lung disease. However, the test showed that there was no significant association between AF and NYHA class and Coronary Artery Disease.

CHAPTER FIVE

5.0. DISCUSSION

Atrial fibrillation is said to be the most common arrhythmia seen in clinical practice and is responsible for significant morbidity (Fuster et al, 2006). The presence of AF confers a five-fold increased risk of stroke (Kannel et al, 1998), a significantly increased risk of dementia (Otto et al, 1997) and an almost two-fold increased risk of death (Kannel et al, 1998). The clinical consequences of AF are derived from the loss of organized atrial activity and absence of coordinated atrial mechanical function. Impaired contraction of the atria may cause blood stasis and the potential for thrombus formation, particularly in the left atrial appendage, with a resultant risk of stroke. This risk of stroke is increased in patients with CHF (Gage et al, 2001). The concomitant presence of AF and CHF identifies individuals with a higher risk for death than with either condition alone (Lubitz, Benjamin & Ellinor, 2010). The current study examined the clinical factors associated with AF in CHF patients admitted at UTH in the city of Lusaka, Zambia.

5.1. Prevalence of Atrial Fibrillation in Congestive Heart Failure

There were 49 participants in the study. The prevalence of AF in CHF patients admitted to UTH during the period of study was 26.5%. This prevalence was quite high; though almost half of the patients in this group were missed by routine ECG. The routine standard 12-lead ECG missed some of the cases of AF probably because these cases may have had paroxysmal AF which may have not been active at the time a standard 12-lead ECG was being taken. This may also be the case with 24-hour ECG holter monitor because sometimes paroxysmal AF may take more than 24 hours before it may resurface. However, this shows that there is need to use ambulatory diagnostic equipment such as ECG holter monitors in the diagnostic investigations so that even those with paroxysmal AF may also be picked. This prevalence rate is similar to the 30% prevalence rate reported in the Acute Decompensated Heart Failure National Registry (Adams et al, 2005) in the United States in 2005; and Lloyd-Jones et al (2004) also reported that AF after the age of 40 in the United States being 26% for men, and 23% for women. This high prevalence rate may be attributed partially to the advancing

age of the Zambian population (Mapoma, 2013); increase in the non-communicable diseases such as hypertension, heart failure, and diabetes mellitus; as well as the increase in the chronic lung diseases (MOH-WHO, 2008).

Six (46.2%) among patients who had AF (shown by ECG holter monitor) had paroxysmal AF. However, this study could not discriminate persistent from permanent atrial fibrillation because the patients who had AF on a standard 12-lead ECG did not wear the ECG holter monitor so much so that we did not know whether these arrhythmias were going to terminate in 48 hours or not. Therefore, there is need that a more detailed study be done to characterize the types of AF in our CHF patients. This was different from what Ntep-Gweth et al (2010) reported in their prospective study of AF patients in Cameroon, where the prevalence of paroxysmal, persistent, and permanent AF was 23%, 22%, and 56%, respectively.

5.2. Socio-demographic Characteristics of the patients

There were almost equal numbers of males 24 (49%) and females 25 (51%) in the study. Although, we did not find any statistical difference (X^2= 1.12, p= .291) between males and females, in the prevalence of AF in CHF, the majority 8 (61.5%) of patients with AF in CHF were males. Among the male CHF patients, the prevalence of AF was higher (33.3%) compared to 20% among the female CHF patients. Similarly, Humphries et al, (2001) reported that in all age groups, men have a higher incidence of AF than women. Furthermore, Nazario (2013) also reported that males are more likely to suffer from AF than their female counterparts. This is probably because males are more exposed to other risk factors for AF like smoking and excessive alcohol intake. However, although women have a lower incidence of AF, some studies have demonstrated a worse outcome and a higher rate of recurrence after cardioversion (Benjamin et al, 1998; Suttorp et al, 1993).

Most 21 (42.9%) of the patients in the study were aged 65 years and above. Of those who had AF in CHF, the majority 9 (69.2%) were within the 65 years and above age group, 4 (30.8%) were with the 55 years – 64 years age group, while no cases of AF were recorded in the age groups below 55 years. The study also revealed that age 65

years and above was statistically (X^2= 5.03, p= .025) associated with AF in CHF. This result was similar to what was reported by Psaty et al (1997), in a cohort study which found that the development of AF increases with advancing age. Nazario (2013) also reported that advancing age is a risk factor for the development of AF. Advancing age is implicated in the development of AF probably because pre-existing alterations, such as autonomic dysbalance, degenerative tissue changes and fibrosis, can provide an electrophysiological and morphological substrate, which increases the likelihood of AF. In particular, alterations of the interstitial matrix in atrial tissue seem to be significant contributory factors (Nattel, 2002).

The majority 26 (53.1%) of the patients in the study had a normal body mass index (18.5 – 24.9) (Table 2). Of the 13 (26.5%) patients who had AF, the majority 10 (76.9%) were obese with a body mass index of 30 and above, 3 (23.1%) were overweight and no case was found among the CHF patients who had a normal body mass index. The study also revealed that body mass index is significantly (X^2= 22.59, p= < .001) associated with AF in CHF. Similarly, Guilian et al (2013) and Overvad et al (2013) reported that obesity is associated with the development of AF and may impact AF-related outcomes. However, it is worthy to note that it is very difficult to calculate body mass index in CHF patients because of the exaggerated patient's weight resulting from fluid retention.

There were 10 (20.4%) patients who were smokers in the study. Among the smokers, majority 7 (70%) of them had AF compared to 6 (15.4%) among the non-smokers. The study also showed that smoking is statistically (X^2= 9.54, p= .002) associated with AF in CHF. This result is in agreement with what was reported by Heeringa et al (2008) in their prospective, population-based study, that current and former cigarettes smokers have an increased risk of AF; as well as Chamberlain et al (2011) who also reported that smoking was associated with the incidence of AF, with more than a two-fold increased risk of AF attributed to current smoking. Smoking may harm the heart through causing or aggravating endothelial dysfunction and atherosclerosis as well as causing cardiac rhythm disorders through the combined effects of nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons (Ambrose & Barua, 2004). Thus, smoking may

change the myocardial substrate as well as action potentials; of which both processes may provoke and facilitate AF.

Compared to non-consumers of alcohol, 1 (2.9%) with AF, the majority 12 (80%) of the consumers of alcohol in CHF had AF. The current study has shown that excessive alcohol intake is strongly (X^2= 27.88, p= <.001) associated with AF in CHF. Similarly to several case-control studies (by Djousse et al 2004; Ruigomez et al 2002; Koskinen et al 1987; and Rich, Siebold & Campion 1985) reported a relatively lower odds of developing AF among abstainers and significantly higher odds of developing AF among heavier drinkers. Furthermore, Mukamal et al (2005) in the Copenhagen City Heart Study and Satoru et al (2011) also found that the risk of developing AF increases with increasing levels of alcohol consumption. Although, this result was anticipated there has been much controversy over the exact mechanism by which alcohol induces AF. Engel and Luck (1983) postulated that alcohol-induced atrial arrhythmias were related to intramyocardial catecholamine release in response to the toxic effects of acetaldehyde. Other studies (Mäki et al, 1998; Steinbigler et al, 2003) have suggested that an increase in sympathetic reaction could be related to the production of AF based on the increased density of beta-adrenergic receptors in lymphocytes. Balbão et al (2009) proposed multiple mechanisms for the acute and long-term consumption of alcohol resulting in AF. They thought that alcohol consumption acutely affected catecholamine release, metabolic acidosis, electrolyte disturbances, and increased oxidative distress. In the long term, this resulted in myocardial fibrosis/dilatation, structural heart disease, metabolic disturbances, and increased sympathetic tone. The combination of these effects contributed to the increase in atrial arrhythmias.

5.3. Clinical Factors

The patients in this study were in NYHA classes III/IV because this study was conducted at a tertiary hospital where critically ill patients (usually in NYHA class III/IV) are referred to from primary health care centres and second-level hospitals. The majority 40 (81.6%) of the patients were in NYHA class IV. Compared to patients with NYHA class IV 11 (84.6%), the incidence of AF was lower 2 (15.4%) in patients with

NYHA class III. Although, there was no statistical difference (X^2= 0.00, p= 1.000) between the two groups, there were more AF cases in NYHA class IV compared to the cases in NYHA class III. However, findings from other previous studies by Wright et al (2003); Nicol et al (2008); Rogers et al (2002); Mwandolela (2007); and Fofana et al (1988); have revealed that the prevalence of AF increases with the increase/severity in the NYHA class. Our results turned out otherwise probably due to the bias that only hospitalized patients in NYHA classes III/IV were involved in the study. Congestive heart failure may be implicated in the initiation and perpetuation of AF through elevated left-sided filling pressures, mitral regurgitation, atrial enlargement, interstitial fibrosis and electromechanical remodelling (Deedwania & Lardizabal, 2010); activation of autonomic and renin-angiotensin axis; as well as changes in the intracellular calcium (Anter et al, 2009).

Slightly a quarter, 13 (26.5%) of the patients had hypertension in the study. The majority 11 (84.6%) of these patients had AF compared to non hypertensive 2 (5.6%). This study revealed that hypertension in congestive heart failure is strongly associated with (X^2 = 26.71, p= <.001) associated with AF. Similarly, Psaty et al (1997) as well as Hennersdorf et al (2007) reported that hypertension is a strong independent risk factor for AF. Hypertension may be implicated in the initiation and maintenance of AF through structural changes, neurohormonal activation, fibrosis, atherosclerosis, etc. Untreated or suboptimally treated hypertension leads to the development of Left Ventricular Hypertrophy (LVH), which is one of the most important expressions of subclinical organ damage, and is an independent risk factor for cardiovascular events, including the development of AF. In the presence of LVH, left ventricular compliance is reduced, left ventricular stiffness and filling pressure increase, coronary flow reserve is decreased, wall stress is increased and there is activation of the sympathetic nervous system and of the renin–angiotensin–aldosterone system. In the atria, proliferation and differentiation of fibroblasts into myofibroblasts and enhanced connective tissue deposition and fibrosis are the hallmarks of this process. Structural remodelling results in electrical dissociation between muscle bundles and in local conduction heterogeneities facilitating the initiation and perpetuation of AF. This electroanatomical substrate permits multiple small re-

entrant circuits that can stabilize the arrhythmia. Over time, tissue remodelling promotes and maintains AF by changing the fundamental properties of the atria (Healey & Connolly, 2003).

The current study showed that only 3 (6.1%) of the patients had coronary artery disease and out of these 2 (66.8%) had AF. Thakkar & Bagarhatta (2014) reported that transient ischemic attack as may be found in coronary artery disease is a risk factor for AF. However, Lokshyn et al (2000) reported, that in patient with coronary artery disease, systolic heart failure may be more important than atrial ischemia in causing AF. Lokshyn et al (2000) explained that coronary artery disease is thought to cause AF in that a partially occluded artery might cause an imbalance of nutrient flow to an area of downstream heart muscle (ischemia). Atrial ischemia plays an important pathophysiological role in the genesis of AF. Hence, significant stenosis in the proximal right coronary artery and the circumflex artery prior to the takeoff of the atrial branches increases the likelihood of AF in these patients (Galrinho et al, 1993).

Only 9 (18.4%) of the patients had dilated cardiomyopathy and the majority 7 (77.8%) of these patients had AF. The study revealed that dilated cardiomyopathy in CHF is strongly ($X^2 = 11.81$, $p= 0.001$) associated with AF. Similarly, Aleksova et al (2010) and Anter et al (2009) reported that AF is relatively frequent in patients with idiopathic dilated cardiomyopathy. Luchsinger & Steinberg (1998) also reported that tachycardia-induced cardiomyopathy may be a more common mechanism of LV dysfunction in patients with atrial arrhythmia than expected, and aggressive treatment of this arrhythmia should be considered. Electrophysiological features associated with left atrial dilation in dilated cardiomyopathy include shortening of the refractory period and prolongation of conduction time (Lindsay & Smith 1996). Both these alterations may lead to development of multiple reentrant wave fronts starting and possibly perpetuating AF in dilated cardiomyopathy (Lindsay & Smith 1996).

Like most of the studies (Murphy et al 2007; Movahed et al, 2005) have implicated diabetes mellitus in the initiation and perpetuation of AF, this study also revealed that 6 (85.7%) diabetic patients with CHF had AF. The study revealed that diabetic patients

were strongly (X^2 = 11.35, p= 0,001) associated with AF when compared to non-diabetics in CHF. Diabetes mellitus may be implicated as an independent risk factor for AF in that glucose and insulin disturbance can directly affect the myocardium in atrium and ventricle, by causing atrial and ventricular hypertrophy leading to AF. Prospective data from large population based studies established the relationship between LA size and risk of developing AF (Rutter et al, 2003). Analysis of the Framingham study subjects showed that left ventricular (LV) mass increased with the worsening of glucose tolerance and the trend was more striking in women than in men. There were also close relationship between insulin resistance and LV mass, as well as LV wall thickness, in women both with normal and abnormal glucose tolerance (Rutter et al, 2003). Furthermore, several observations suggest that the autonomic nervous system plays an important role in both the initiation and/ or the maintenance of AF in humans. In the animal model of diabetes mellitus, the occurrence of AF was enhanced by adrenergic activation in the diabetic heart. The intra-atrial conduction delay and fibrotic deposition in atria play a major role in producing atrial tachyarrhythmia in diabetes animal model. The heterogeneous increase in sympathetic innervations was proved to be associated with the promotion of AF in several studies (Schmid et al, 1999; Olgin et al, 1998).

6 (85.7%) of the patients with chronic lung disease in CHF had AF. The current study revealed that chronic lung disease in CHF is strongly (X^2 = 11.35, p= 0.001) associated with AF in CHF. This is in agreement to what was reported by Shibata et al 2011, who reported that impaired pulmonary function is an independent risk factor for AF in the Japanese general population. Furthermore, Kang et al (2009) reported that reduced FEV_1%, which represents the severity of airway obstruction, was associated with chronic AF and the greater the pulmonary function impairment, the greater the co-existence with AF. Atrial fibrillation in chronic lung disease is thought to result from changes in blood gases, abnormalities in pulmonary functions, and hemodynamic changes resulting from pulmonary hypertension (Lopez and House-Fancher, 2005) as well as structural remodelling. Hypoxemia and hypercapnia are associated with over-compensatory fluctuations in autonomic tone, intrathoracic pressures and cardiac haemodynamics, with possible atrial stretch and remodeling, each of which could lead to

AF, particularly when hypercapnia causes a significant decrease in pH values (Stevenson et al, 2010). Morphological abnormalities associated with chronic obstructive pulmonary disease (COPD) include signs of right atrial enlargement, and right ventricular hypertrophy. Structural remodeling results in an electrical dissociation between muscle bundles and local conduction heterogeneities, facilitating the initiation and perpetuation of AF. This electro-anatomical substrate allows multiple small re-entrant circuits that may trigger the arrhythmia (Stevenson et al, 2010).

CHAPTER SIX

6.0. Conclusions and Recommendations

6.1. Conclusions

The prevalence of AF in CHF patients at 26.5% was quite high. The prevalence was high in males compared to females. However, almost 50% of these cases were missed by routine 12-lead ECG. The study revealed that obesity, smoking, excessive alcohol intake, hypertension, dilated cardiomyopathy, diabetes mellitus and chronic lung disease in CHF was strongly associated with AF. There was also a weak statistical difference between AF in CHF among different age groups, with those 65 years and above seem to be associated with AF. However, there was no any statistical difference found in relation to sex, NYHA classes as well as coronary artery disease and the prevalence of atrial fibrillation in congestive heart failure.

6.2. Recommendations

All patients with heart failure need to have an ECG done when they come to the hospital. Further care needs to be taken for those patients whose standard 12-lead ECG would be normal as there is a possibility that they may have paroxysmal arrhythmias. Therefore, the ministry of health need to supply ECG machines to general and district hospitals throughout the country. The ministry should also supply ambulatory ECG monitors to UTH and all the general hospitals to enable clinicians taking care of patients with cardiovascular diseases make quick and appropriate diagnoses for prompt treatment. The ministry must also ensure the promotion of public education on the heart benefits of a healthy lifestyle to reduce on prevalence of HF and other cardiovascular diseases.

Clinicians also need to start using ambulatory ECG monitors on all congestive heart failure patients whose baseline standard 12-lead ECG is normal; especially those with obesity, history of excessive alcohol intake, hypertension, dilated cardiomyopathy, diabetes mellitus and chronic lung disease; as well as those patients aged 65 years and above. Furthermore, the cardiology team to take into consideration the findings of this study when formulating guidelines for the management of HF.

6.3. Limitations of the Study

The study setting was a tertiary hospital which offers services to severely ill patients so much that only patients in NYHA classes III/IV were included in the study.

Limited diagnostic tools such as a holter monitor. Therefore, the ECG holter monitoring duration was limited to 24 hours only, so much so that paroxysmal arrhythmia which took more than 24 hours to resurface could not be picked. Furthermore, the ECG holter monitor did not come with the software for us to analyze the patient's information so that we had to transmit the patient's information to USA for them to analyze the patient's information and give us a report. This had a cost and time implication on the study.

The sample size was small due to the time frame in which the study had to be done and more importantly limited diagnostic equipment.

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