Original Research Article

Clinical Factors associated with Atrial Fibrillation in Congestive Heart Failure patients admitted at the University Teaching Hospital, Lusaka, Zambia

Abstract

Introduction: Atrial fibrillation (AF) and Heart failure (CHF) have emerged as major global epidemics. These two conditions share common risk factors and frequently coexist. Each condition predisposes to the other, and the concomitant presence of the two has additive adverse effects. This study examined the clinical factors associated with AF in CHF patients admitted at the University Teaching Hospital (UTH), Lusaka, Zambia.

Method: A hospital-based cross-sectional study was conducted at UTH adult medical wards. Data was done from June 2014 to August 2014. A structured interview schedule was used to capture the socio-demographic; an Omron HEM 780 automated Blood Pressure machine was used to measure Blood Pressure and pulse. Schiller AT-102 ECG machine was used to identify participants with AF. Those participants without AF, had 24-hours ECG DR180+ Digital Recorder applied to detect those with paroxysmal AF. All participants with any form of AF were assessed for clinical factors. Binary logistic regression analysis of the data was carried out using IBM® SPSS® Statistics for Windows version 20.0 to predict clinical factors associated with AF in CHF patients.

Results: A total of 49 patients were sampled and out of these 13 (26.5%) had AF. Atrial fibrillation was associated with excessive alcohol intake, hypertension and diabetes mellitus.

Conclusion: These findings suggest the need for clinicians taking care of the congestive heart failure patients to consider full scale use of ambulatory ECG monitors in all CHF patients with the above conditions.

Keywords: Atrial fibrillation; ambulatory ECG monitors; congestive heart failure; Lusaka, Zambia

1.0. INTRODUCTION

1.1. Background

Atrial fibrillation (AF) and Congestive Heart failure (CHF) have emerged as major global epidemics [1]. These two conditions share similar risk factors, frequently coexist, and have additive adverse effects when occurring in conjunction [2]. The risk factors include hypertension (HTN), coronary artery disease (CAD), structural heart disease (non-ischaemic, valvular), diabetes mellitus (DM), obesity and obstructive sleep apnoea [3]. The co-prevalence also increases with advancing age and each predicts/compounds the course of the other [1,4].

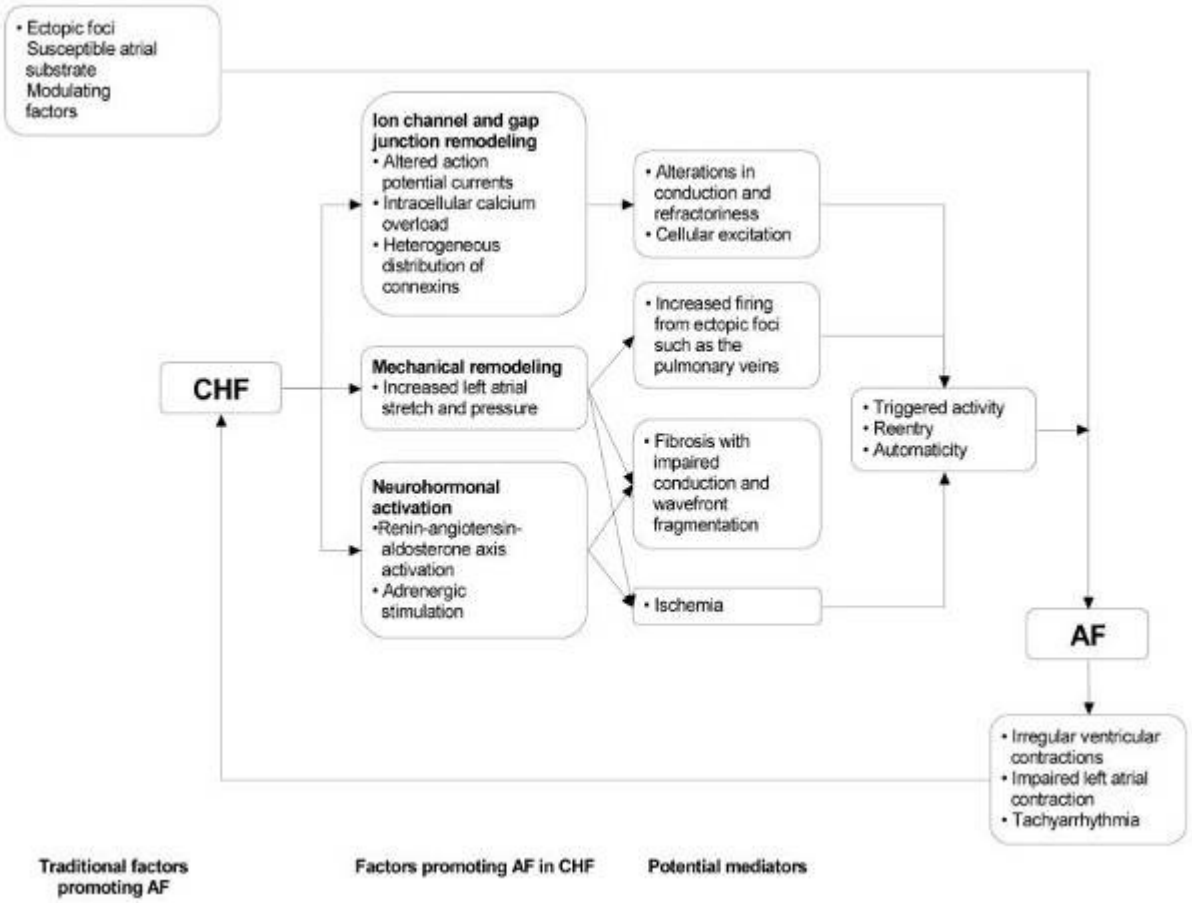
There has been increasing evidence regarding the adverse role of AF in patients with CHF both in terms of morbidity as well as prognosis [1]. Most of the studies done have revealed that AF through the loss of organized atrial activity and absence of coordinated atrial mechanical function, is associated with clinical and hemodynamic deterioration which may predispose the patient to systemic thromboembolism and poorer prognosis [1]. 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 [5].

1.1.1. Pathoetiology of Atrial Fibrillation in Congestive Heart Failure

The pathoetieological interplay between CHF and AF is complex. CHF predicts the development of AF and conversely AF predisposes to CHF [1]. The mechanisms, through which CHF provides arrhythmogenic atrial substrate include; elevated left-sided filling pressures, mitral regurgitation, atrial

enlargement, interstitial fibrosis and electromechanical remodelling [4]; activation of autonomic and renin-angiotensin axis; as well as changes in the intracellular calcium [6].

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 [1]. Irregularity in the RR interval can also have a potentially deteriorating influence on cardiac output irrespective of the heart rate [7]. Moreover, deterioration of sinus rhythm in AF patients with CHF can lead to acute decompensation.



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

Figure 1:A. Pathoetiological inter-relationship between AF and CHF

1.2. Statement of the problem

Most of the studies done 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 [1]. 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 [5].

Furthermore, 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. It was therefore, hoped that the ability to define clinical factors associated with AF in CHF patients would have important clinical relevance. It was further assumed that this study will provide the basis for many studies in the area of AF and CHF. Hence, the need that this study be done.

MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY

1.3. *Population and sampling procedures*

This was a hospital based cross-sectional study carried out in adult medical wards run at the UTH, Lusaka, Zambia. The UTH is the national referral health centre that treats and reviews patients with various diseases, including CHF.

1.3.1. Inclusion criteria

All known congestive heart failure patients aged 18 years and above who consented to take part in the study were included.

1.3.2. Exclusion criteria

However, CHF patients below the age of 18 years, acute patients who were not able to get out of bed, congestive heart failure patients who refused to consent to the study and those who were recruited in the previous month(s) were excluded from the study.

1.3.3. Participants enrolment

Participants who met the inclusion criteria were enrolled into the study between July to September 2014.

1.4. *Data collection*

A structured interview schedule was used to capture data on demographic characteristics, clinical factors and laboratory measurement results. The interview schedule was developed based on the World Health Organization (WHO) stepwise survey (STEPS) instrument [8]. The same instruments were used on all the patients to ensure reliability and validity. The data on demographic and clinical factors were obtained by interview, review of medical records and anthropometric measurements.

The weight and height of the patients were measured using a ZT-160 adult weighing mechanical scale model 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 left hand of the patient in a lying position using an Omron HEM 780 automated Blood Pressure machine (Omron HEALTHCARE Co. Ltd, Vietnam). A standard 12-lead Electrocardiogram (ECG) was done using Schiller AT-102 ECG machine on all participants to identify those with and without atrial fibrillation. Then those who had no atrial fibrillation on Schiller AT-102 ECG machine, had a holter monitor (DR180+ Digital Recorder, 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.

1.5. *Data analyses*

Using IBM® SPSS® version 20.0, analyses included: descriptive and binary logistic regression. A 95% confidence interval (CI) and *P*-value of < 0.05 were set.

1.6. *Ethics approval*

This non-interventional study was approved by ERES CONVERGE IRB (Reference number 2014-Mar-003) and permission was granted by the Hospital authority to carry out the study. All subjects were older than 18 years and gave written consent prior to their participation.

2.0. RESULTS

2.1. Socio-demographic data

Table 2: Socio-demographic characteristics of 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 atrial fibrillation in congestive heart failure patients admitted the UTH. A total of 49 Congestive Heart Failure patients who met the inclusion criterion were enrolled into the study. There were almost equal number men and women; 49% vs. 51% respectively. However, the majority of patients (42.9%) were aged 65 years and above. The majority (53.1%) of the patients had a normal BMI (18.5 – 24.9). About 20.4% of the patients were smokers; and about 30.6% of the patients were consumers of alcohol.

2.2. 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		
Yes	40	81.6
No	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 of the patients (81.6%) were in the New York Heart failure Association (NYHA) class IV; 26.5% of the patients had hypertension; 18.4% had dilated cardiomyopathy; 14.3% had chronic lung disease; 14.3% had diabetes mellitus; and 6.1% had coronary artery disease.

2.3. Electrodiagnosis of Atrial Fibrillation

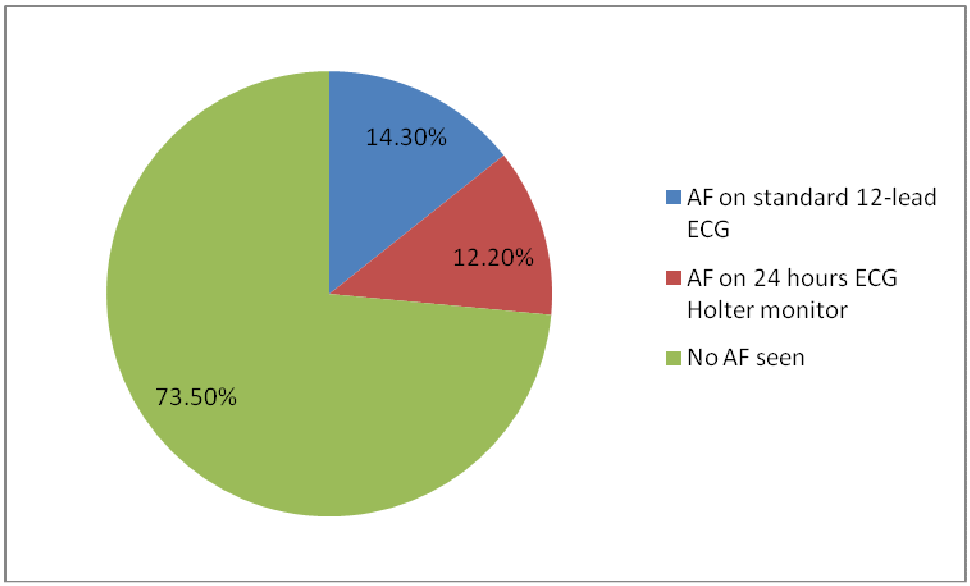


Figure 1:B. Electrodiagnosis of Atrial Fibrillation (N=49)

Figure 1 shows the modality utilsed to diagnose AF. Standard 12-lead ECG done on the patients indicated that (7) 14.3% had atrial fibrillation. The ambulatory monitor showed atrial fibrillation waves in another (6) 12.2% of patients, giving a combined prevalence of AF of 26.5% in this study population.

2.4. Univariate Logistic Regression of the Factors Associated with AF in CHF patients

Binary logistic regression analysis was used to determine the clinical factors associated with atrial fibrillation in congestive heart failure patients.

Table 4: Univariate Logistic Regression Determining Factors Associated with AF in CHF patients

	Atrial Fibrillation			
	No AF seen	AF seen		
Clinical Factor	**No (%)**	**No (%)**	**OR (95%CI)**	**P-value**
Sex				
Female	20 (80.0)	5 (20.0)	2.00 (.55 – 7.31)	.295
Male	16 (66.7)	8 (33.3)		
Age				
35 - 44 Years	2 (100.0)	0 (0.0)	.00 (.00 – 1.85)	.999
45 - 54 Years	10 (100.0)	0 (0.0)	.00 (.00 – 1.85)	.999
55 - 64 Years	12 (75.0)	4 (25.0)	.44 (.00 - 1.85)	.264
65 Years and above	12 (57.1)	9 (42.9)	Ref (1.0)	
Body Mass Index				
18.5 - 24.9	26 (100.0)	0 (0.0)	.00 (.00 - .56)	.998

25 - 29.9	8 (72.7)	3 (27.3)	.08 (.01 - .56)	**.012***
30 and above	2 (16.7)	10 (83.3)	Ref (1.0)	
Smoking				
No	33 (84.6)	6 (15.4)	.08 (.02 - .39)	**.002***
Yes	3 (30.0)	7 (70.0)	Ref (1.0)	
Alcohol intake				
No	33 (97.1)	1 (2.9)	.01 (.00 - .08)	**.000***
Yes	3 (20.0)	12 (80.0)	Ref (1.0)	
NYHA Class				
Class III	7 (77.8)	2 (22.2)	.75 (.14 – 4.20)	.746
Class IV	29 (72.5)	11 (27.5)	Ref (1.0)	
Hypertension				
No	34 (94.4)	2 (5.6)	.01 (.00 - .09)	**.000***
Yes	2 (15.4)	11 (84.6)	Ref (1.0)	
Coronary Artery Disease				
No	35 (76.1)	11 (23.9)	.16 (.01 – 1.90)	.146
Yes	1 (33.3)	2 (66.7)	Ref (1.0)	
Dilated Cardiomyopathy				
No	34 (85.0)	6 (15.0)	.05 (.00 - .30)	**.001***
Yes	2 (22.2)	7 (77.8)	Ref (1.0)	
Diabetes Mellitus				
No	35 (83.3)	7 (16.7)	.03 (.00 - .32)	**.003***
Yes	1 (14.3)	6 (85.7)	Ref (1.0)	
Chronic Lung Disease				
No	35 (83.3)	7 (16.7)	.03 (.00 - .32)	**.003***
Yes	1 (14.3)	6 (85.7)	Ref (1.0)	

***Indicates significant *p*-value at $p < 0.05$. (2-tailed)**

Table 4 above shows a binary logistic regression analysis of the variable factors. Smoking, alcohol intake, hypertension, dilated cardiomyopathy, diabetes mellitus and chronic lung disease were shown to be strongly associated with atrial fibrillation in congestive heart failure. However, the analysis showed that sex, age, body mass index, NYHA class and coronary artery disease were not associated with atrial fibrillation in congestive heart failure.

The multivariate logistic regression model was the final analysis performed. All the significant factors from the univariate logistic regression were considered for entry into the multivariate logistic regression model. The results of the multivariate binary logistic regression analysis to establish whether six variable factors; that is smoking, alcohol intake, hypertension, dilated cardiomyopathy, diabetes mellitus and chronic lung disease are associated with atrial fibrillation in congestive heart failure.

2.5. Factors associated with AF in CHF patients

Table 5: Multivariate Logistic Regression Determining Factors Associated with AF in CHF patients

Clinical Factor	Atrial Fibrillation		OR (95%CI)	P-value*
	No AF seen	AF seen		
	No (%)	No (%)		
Smoking				
No	33 (84.6)	6 (15.4)	.11 (.00 - .17)	
Yes	3 (30.0)	7 (70.0)	Ref (1.0)	.106
Alcohol intake				
No	33 (97.1)	1 (2.9)	.02 (.00 - .27)	
Yes	3 (20.0)	12 (80.0)	Ref (1.0)	**.004***
Hypertension				
No	34 (94.4)	2 (5.6)	.02 (.00 - .21)	
Yes	2 (15.4)	11 (84.6)	Ref (1.0)	**.002***
Dilated Cardiomyopathy				
No	34 (85.0)	6 (15.0)	.64 (.03 - 13.24)	
Yes	2 (22.2)	7 (77.8)	Ref (1.0)	.773
Diabetes Mellitus				
No	35 (83.3)	7 (16.7)	.01 (.00 - .17)	
Yes	1 (14.3)	6 (85.7)	Ref (1.0)	**.002***
Chronic Lung Disease				
No	35 (83.3)	7 (16.7)	.09 (.00 - 3.52)	
Yes	1 (14.3)	6 (85.7)	Ref (1.0)	.198

*Indicates significant *p*-value at $p < 0.05$.

The multivariate binary logistic regression model was tested for factors associated with atrial fibrillation in congestive heart failure. The dependent variable was AF in CHF patient: present (1), absent (0). The results of the multivariate binary logistic regression analysis to predict the clinical factors associated with AF in CHF patients showed that there is no correlation between the presence of atrial fibrillation in congestive heart failure and sex, age, body mass index, NYHA class, smoking, coronary artery disease, dilated cardiomyopathy and chronic lung disease; and a strong association was noted between atrial fibrillation in congestive heart failure and excessive alcohol intake, hypertension, and diabetes mellitus.

3.0. DISCUSSION

The major finding of our study is a demonstration of a 26.5% prevalence of atrial fibrillation in congestive heart failure patients; and that hypertension, diabetes mellitus and excessive alcohol intake are strong, independent clinical factors associated with atrial fibrillation in congestive heart failure patients.

The prevalence of atrial fibrillation in congestive heart failure patients admitted to UTH during the period of study; on standard 12-lead ECG was 14.3%. However, the 24-hour ECG holter monitor revealed an additional 12.2% (Figure 1). This indicates that the standard 12-lead ECG misses some of the cases of atrial fibrillation probably because these cases may be having paroxysmal atrial fibrillation which may not be active at the time a standard 12-lead ECG is being taken. This may also be the case with 24-hour ECG holter monitor because sometimes paroxysmal atrial fibrillation 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 atrial fibrillation may also be picked.

This high prevalence rate of AF may be attributed partially to the advancing age of the study population [9]; increase in the prevalence of non-communicable diseases such as hypertension, heart failure, and diabetes mellitus; as well as the increase in the chronic lung diseases [10]. However, this prevalence rate is similar to the 30% prevalence rate reported in the Acute Decompensated Heart Failure National Registry in the United Kingdom [11]. It is also similar to what the Framingham Heart Study [12] reported of AF after the age of 40 in the United States. They reported a prevalence of 26% for men, and 23% for women.

The study also revealed that there is a strong association between atrial fibrillation in congestive heart failure and excessive alcohol intake (OR .02, p=.004). Similarly, several case-control studies [13,14,15,16] found relatively similar odds of AF among abstainers and moderate drinkers, and significantly higher odds of AF among heavier drinkers, a finding confirmed in a prospective analysis of the Copenhagen City Heart Study [17]. Furthermore, Satoru K et al (2011) [18] also found that the AF risk increases with increasing levels of alcohol consumption. However, these studies did not address whether

179 the type of alcoholic beverage consumed (beer, wine, or spirits) made a difference to AF risk. Atrial
180 fibrillation in alcohol is probably due to the fact that heavy, long-term drinking damages the heart by
181 weakening the heart muscle leading to a condition known as alcoholic cardiomyopathy; which provide
182 favourable conditions for the genesis and maintenance of atrial fibrillation.

183 The study also found a strong association between atrial fibrillation and hypertension (OR .02, p= .002).
184 This result is similar to the findings of Psaty BM et al [19] and Hennersdorf MG et al [20]. Several
185 pathophysiologic mechanisms in hypertension may be implicated in the initiation and maintenance of
186 atrial fibrillation. These include structural changes, neurohormonal activation, fibrosis, atherosclerosis,
187 etc. They have all been advocated to explain the onset and sustainance of atrial fibrillation. Untreated or
188 suboptimally treated hypertension leads to the development of left ventricular hypertrophy (LVH), which is
189 one of the most important expressions of subclinical organ damage, and is an independent risk factor for
190 cardiovascular events, including the development of atrial fibrillation. In the presence of LVH, left
191 ventricular compliance is reduced, left ventricular stiffness and filling pressure increase, coronary flow
192 reserve is decreased, wall stress is increased and there is activation of the sympathetic nervous system
193 and of the renin–angiotensin–aldosterone system. In the atria, proliferation and differentiation of
194 fibroblasts into myofibroblasts and enhanced connective tissue deposition and fibrosis are the hallmarks
195 of this process. Structural remodelling results in electrical dissociation between muscle bundles and in
196 local conduction heterogeneities facilitating the initiation and perpetuation of atrial fibrillation. This
197 electroanatomical substrate permits multiple small re-entrant circuits that can stabilize the arrhythmia.
198 Over time tissue remodelling promotes and maintains atrial fibrillation by changing the fundamental
199 properties of the atria [21]

200 Some studies [22,23] have implicated diabetes mellitus in the initiation and perpetuation of atrial
201 fibrillation. This study also found a strong association (OR .01, p= .002) between diabetes mellitus and
202 atrial fibrillation. Diabetes mellitus has also been implicated as an independent risk factor for atrial
203 fibrillation in that glucose and insulin disturbance can directly affect the myocardium in the atrium and/or
204 ventricle, e.g. by causing left ventricular hypertrophy leading to AF. Prospective data from large
205 population based studies established the relationship between LA size and risk of developing AF [24].

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 [24]. 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 the diabetes animal model. The heterogeneous increase in sympathetic innervation was proved to be associated with the promotion of AF in several studies [25,26].

4.0. CONCLUSION

To the best of our knowledge, this is the first study at UTH to look at clinical factors associated with AF. The main findings of this study include a relatively high prevalence of atrial fibrillation in congestive heart failure patients of 26.5%. Only 54% of this diagnosis was made using the standard 12 Lead ECG. Almost half of the patients with AF would have been missed without the use of the holter ECG monitor. This study also demonstrates a strong association between atrial fibrillation in congestive heart failure and excessive alcohol intake, hypertension, and diabetes mellitus. These results suggest that clinicians should carefully evaluate patients in congestive heart failure to exclude AF especially in patients with history of excessive alcohol intake, hypertension, and diabetes mellitus which diagnosis would be enhanced by the use of ambulatory ECG monitoring devices.

REFERENCES

1. Caldwell JC, & Mamas MA., ***Heart failure diastolic dysfunction and atrial fibrillation; mechanistic insight of a complex inter-relationship***, Heart Failure Review Journal 2012; No. **17**: 27-33

2. Lubitz SA, Benjamin EJ, and Ellinor PT., ***Atrial Fibrillation in Congestive Heart Failure.*** Heart Fail Clin. Apr 2010. 6(2): 187-200.

3. Nazario B., ***Atrial Fibrillation and Stroke – Symptoms of Atrial Fibrillation***. Cardiology Journal. 2013, Vol. 18, No. 3, pp. 356–364.

4. Deedwania PC, & Lardizabal JA., ***Atrial fibrillation in heart failure: a comprehensive review***. American Journal of Medicine 2010; No. 123: 198-204

5. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin E, ***Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study.*** Circulation. 2003;107:2920–5. [PubMed]

6. Anter E, Jessup M and Callans DJ., ***Atrial Fibrillation and Heart Failure Treatment Considerations for a Dual Epidemic,*** Circulation. 2009; 119: 2516-2525.

7. Clark DM, Plumb VJ, Epstein AE, Kay GN., ***Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation.*** J Am Coll Cardiol. 1997;30:1039–1045. [PubMed]

8. World Health Organization. ***World Health Organization STEPwise approach to chronic disease risk factor surveillance (STEPS) instrument. Version 3. 2007***. Geneva. World Health Organization. **Google Scholar**

9. Mapoma CC, (2013), **Population Ageing in Zambia:** ***Magnitude, Challenges and Determinants*****,** University of Zambia, Lusaka.

10. Ministry of Health – Zambia and World Health Organization Country Office (Zambia) (2008), ***STEPS Report Zambia: Prevalence rates of the common non-communicable diseases and their risk factors in Lusaka district, Zambia 2008***, Ministry of Health World Health Organization.

11. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP., ***Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first***

100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). American Heart Journal; 2005, No.149: 209-216.

12. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D., ***Lifetime risk for development of atrial fibrillation: the Framingham Heart Study***. Circulation. 2004; 110:1042–6.

13. Djoussé L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham study. Am J Cardiol. 2004;93:710–713. [PubMed]

14. Ruigómez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. J Clin Epidemiol. 2002;55:358–363. [PubMed]

15. Koskinen P, Kupari M, Leinonen H, Luomanmäki K. Alcohol and new onset atrial fibrillation: a case-control study for a current series. Br Heart J. 1987;57:468–473. [PMC free article] [PubMed]

16. Rich EC, Siebold C, Campion B., ***Alcohol-related acute atrial fibrillation. A case-control study and review of 40 patients.*** Arch Intern Med 1985;145:830 -3.

17. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women - the Copenhagen City Heart Study. Circulation. 2005;112:1736–1742. [PubMed]

18. Satoru K, Kazumi S, Shiro T, Chika H, Aki S, Yoriko H, Yui A, Yukako N, Yoko Y, Kaoruko TI, Yasuo O, Nobuhiro Y, Hirohito S., ***Alcohol Consumption and Risk of Atrial Fibrillation: A meta-Analysis,*** Journal of the American College of Cardiology, 25 January 2011, Vol.57(4):427-436, doi:10.1016/j.jacc.2010.08.641

19. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM;, ***Incidence of and risk factors for atrial fibrillation in older adults***, Circulation, 96 (1997), pp. 2455–2461

20. Hennersdorf MG, Schueller PO, Steiner S, Strauer BE., ***Prevalence of Paroxysmal Atrial Fibrillation Depending on the Regression of Left Ventricular Hypertrophy in Arterial Hypertension,*** Science Journal, *Hypertension Research* (2007) 30, 535–540; doi:10.1291/hypres.30.535

21. Healey JS and Connolly SJ. **Atrial fibrillation: hypertension as a causative agent, risk factor for complications, and potential therapeutic target.** Am J Cardiol. 2003 May 22;91(10A):9G-14G.

22. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, MacIntyre K, McMurray JJ., ***A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland.*** *Heart*. 2007;93:606-12.

23. Movahed MR, Hashemzadeh M, Jamal MM., ***Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease***. *Int J Cardiol*. 2005 Dec 7; 105:315-8.

24. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS., ***Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study.*** *Circulation*. 2003; 107: 448-54.

25. Schmid H, Forman LA, Cao X, et al. (1999), ***Heterogeneous cardiac sympathetic denervation and decreased myocardial nerve growth factor in streptozotocin induced diabetic rats: implications for cardiac sympathetic dysinnervation complicating diabetes.*** *Diabetes*. 1999; 48:603-8.

26. Olgin JE, Sih HJ, Hanish S, et al. (1998), ***Heterogeneous atrial denervation creates substrate for sustained atrial fibrillation.*** Circulation. 1998; 98: 2608-14.