THE PREVALENCE OF CARDIAC ARRHYTHMIAS AND ASSOCIATED RISK FACTORS AMONG PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT KENYATTA NATIONAL HOSPITAL

A

DISSERTATION SUBMITTED IN PART FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF THE MASTER OF MEDICINE IN INTERNAL MEDICINE OF THE UNIVERSITY OF NAIROBI SCHOOL OF MEDICINE:

By

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DECLARATION:

THIS DISSERTATION WAS SUBMITTED FOR EXAMINATION WITH OUR APPROVAL AS SUPERVISORS:

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TABLE OFCONTENTS:

LIST OF TABLES, FIGURES AND GRAPHS

FIGURES **PAGE**

TABLES

LIST OF ABBREVIATIONS

COPD - Chronic Obstructive Pulmonary Disease
AF - Atrial fibrillation
MAT - Multifocal Atrial Tachycardia
V.T - Ventricular Tachycardia
VPB - Ventricular Premature Beats
VPC - Ventricular premature Contractions
VES -Ventricular Extra-systole
PSVT - Paroxysmal Ventricular Tachycardia
ECG - Electrocardiogram
ABG - Arterial Blood Gases
ERS - European Respiratory Society
ATS - American Thoracic Society
GOLD - Global Initiative for chronic obstructive Lung Disease
BTS - British Thoracic Society
FEV1 - Forced Expiratory Volume at 1 second
FVC - Forced Vital Capacity
SADHS - South African Demographic and Health Survey
CCF - Congestive Cardiac Failure
AV-node - Atrio-ventricular node
SA-node - Sino atrial node
ESC - European Society of Cardiology
NASPE - North American Society of Pacing and Electrophysiology
WHO - World Health Organization
SABA - Short acting βeta-2 agonist
LABA - Long acting βeta-2 agonist
KNH - Kenyatta National Hospital
SATS - South African Thoracic Society
BPM - Beats per Minute
LVH - Left ventricular hypertrophy
Mg2+ - magnesium
U/E/Cr - urea, electrolyte and creatinine

ABSTRACT

Background

Cardiac arrhythmias are common in COPD patients and are a major cause of morbidity and mortality, especially the persistent supraventricular and ventricular rhythm disorders.

Multiple factors such as hypoxemia/ hypercapnia, acidosis, right heart failure and medication e.g. xanthene derivatives, steroids and β-2 agonists have been implicated.
Recently P wave dispersion and QTc wave dispersion have been reported to predict the development of atrial fibrillation and ventricular arrhythmias respectively.

Objective

To determine the prevalence of cardiac arrhythmias among patients with COPD, and describe the associated factors.

Study Design

Cross-sectional descriptive study done over a period of six months prospectively

Setting

Outpatient Chest clinic and chest ward, Kenyatta National Hospital.

Study Population

COPD patients who met the eligibility criteria.

Results

A total of 207 patients with COPD were studied. The male to female ratio was 2.3:1. The mean (SD) age of the study population was 66.7(8.5) years. The median duration of COPD diagnosis was 1 year (range- 0-6years) and the median duration of follow-up was also 1 year (range- 0-5 years). Past smokers accounted for 90.8% while only 1% were current smokers.The main occupation sited was agriculture at 72.9%.Most of the patients(97.1%) were on medication with majority (35.7%) on a combination of LABA, SABA, oral theophylline, and inhaled steroids. A minority (21.6%) used the medications regularly, the rest intermittently.

The prevalence of arrhythmia was 14% (95%CI 9.3-18.7). The commonest arrhythmia was VPB (51.7%). Atrial fibrillation accounted for 24%. Atrial fib +VPB accounted for 10.3%, while 13.8% had 3° heart block. Majority (96%) of those with arrhythmias were in stage III & IV of COPD.

A higher COPD stage, Hypokalemia, hypomagnesaemia, hypoxia, hypercapnia, acidosis, and longer QTc & P-wave dispersion was significantly associated with arrhythmias ($p<0.001$).

Conclusion

Arrhythmias are common among COPD patients at K.N.H. and a screening 12 lead ECG and regular electrolyte monitoring needs to be incorporated into the basic workup of COPD patients in order to identify potentially correctable rhythm disorders.

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic preventable & treatable multi-system disease whose pulmonary component is characterized by significant partially reversible progressive airflow limitation, often associated with an abnormal inflammatory response of the lung to noxious particles or gases.(1). Many international and national societies have recommended spirometric definition for COPD. The best known and widely accepted definition is that promulgated by the Global initiative for chronic obstructive lung disease (GOLD), in which a post bronchodilator cutoff point of FEV1/FVC ratio <70%, is considered diagnostic of COPD. (1).Spirometry has also been used to stage the severity of the disease into mild, moderate, severe and very severe on the basis of post bronchodilator FEV1 (see appendix iii).

The burden of COPD is difficult to ascertain as a result of variable and imprecise definitions. In Africa, The South African Demographic and Health Survey (SADHS) of 1998 (2), a national stratified household sample of over 14000 South African adults aged >15 years showed occurrence of bronchitis in 2.3% of males and 2.8% of females. A prevalence study in Latin America (3), a systematic review and meta-analysis of studies performed in 28 countries between 1990 and 2004 (4), and an additional study from Japan (5) provide evidence that the prevalence of COPD is appreciably higher in smokers and ex-smokers compared with nonsmokers, in those older than 40 years compared with those younger than 40 years, and in men compared with women. By the year 2020, it's estimated that COPD will be the third leading cause of death and disability worldwide (6, 7)

Arrhythmias are common in COPD and they tend to occur with increasing frequency especially in situations of acute exacerbation, respiratory failure and increasing co-morbidities. (8).The presence of arrhythmias in COPD confers a poor prognosis, especially in these situations. Hudson et al (9), reviewed E.C.Gs of 70 COPD patients during 148 admissions for acute respiratory failure, nearly one half (47%) had major supraventricular and ventricular arrhythmia. Ventricular tachycardia was associated with

very poor prognosis (70% in hospital mortality).Some of these arrhythmias may be preventable if detected early and the arrhythmogenic milieu altered favorably.

2: LITERATURE REVIEW

2.1: ARRHYTHMIAS AND COPD

Supraventricular and ventricular arrhythmias are common in COPD. The reported incidence varies widely because of variations in study populations e.g. stable disease versus acute exacerbations, the presence or absence of ventricular failure or underlying cardiac disease, the methodology used to record arrhythmias (a single ECG versus 24 hour recording), and the medication used in the management of the disease .

Kleiger et al, in a long term Electrocardigraphic (ECG) monitoring of 24 ambulatory patients with severe COPD found arrhythmias in 84% of stable ambulatory patients (10). 72% of these arrhythmias were ventricular in origin while 52% were supraventricular. Buch et al in the Copenhagen Heart Study noted that a reduced FEV1, a marker of airway obstruction, is an independent predictor of new onset atrial fibrillation in patients with stable COPD (11)

Shih et al in their study of 69 hypoxic COPD patients enrolled in the nocturnal oxygen therapy trial group found similar results with supraventricular tachycardia occurring in 69%, while atrial fibrillation was the basic rhythm in 8%. VPB (primarily multiform) and VT were present in 83% and 22% of the patients respectively. Both leg edema and hypercapnia were associated with an increased risk of ventricular arrhythmias. Using a resting 12-lead ECG, Shih and colleagues found a prevalence of ventricular and supraventricular arrhythmias ranging between 3 and 8% respectively, with sustained VT occurring in 0.3% of the patients (12). Hudson et al evaluated 70 patients with severe COPD admitted for acute respiratory failure and found that 47% of the patients had both major supraventricular and ventricular arrhythmias (9).

Fuso et al evaluated 90 COPD patients hospitalized for acute exacerbation and found atrial fibrillation and ventricular arrhythmias were independent predictors of death in addition to age and wide alveolar- arterial oxygen gradient (13).

2.2: PATHOGENESIS

A number of factors contribute to the development of arrhythmias in COPD patients. These factors include;

1) Medications
2) Cardiac autonomic dysfunction
3) Systemic arterial hypertension
4) Right and Left ventricular failure
5) Hypokalemia and hypomagnesaemia
6) Respiratory acidosis

2.2.1: Medications

a) **Theophylline**

Theophylline has numerous well documented cardiac side effects including dose dependent increase in heart rate, enhancement of atrial automaticity and acceleration of intracardiac conduction. (14)Theophylline has been associated with sinus tachycardia, premature atrial beats, supraventricular tachycardia, atrial fibrillation, unifocal and multifocal atrial tachycardia and ventricular arrhythmia. The frequency of atrial and ventricular arrhythmias increases as serum theophylline levels rise.

In a prospective study of theophylline toxicity, Sessler and Cohen found that sinus tachycardia and Ventricular Premature Beats (VPB) were the most common arrhythmias occurring in 85% and 80% of the subjects respectively (15).In a retrospective study of the arrhythmogenicity of theophylline, Bittar et al found a correlation between theophylline and the incidence of arrhythmia, with serum theophylline concentration being the strongest independent predictor of arrhythmias (16).

b) **Beta-adrenergic Agonists**

β2-agonists are the most common bronchodilators used in COPD.A study by Kallergis et al among 18 patients with asthma and mild COPD who received nebulized salbutamol (5mg), demonstrated that salbutamol affects sinus node activity (17). Specifically it shortened the sinus cycle length and the sinus node recovery time. In addition, administration of salbutamol enhanced AV-nodal conduction; reduced AV-node refractory time and reduced myocardial refractory time.Clinical studies, however suggest that inhaled β-adrenergic agonists may not cause serious arrhythmias in spite of their effect on cardiac conduction system. A meta-analysis of 33 randomized, placebo-controlled trials of patients receiving β- agonists for obstructive airway disease revealed that a single dose of beta agonist (SABA) increased the heart rate by 9.12 beats/ minute and decreased serum K+ by 0.6mmol/L compared to placebo. β- agonists were associated with an increased risk of adverse cardiovascular events overall (RR 2.54, 95% CI 1.25-4.05). However, most of this risk was for sinus tachycardia (RR 3.05, 95% CI 1.7-5.5). (18).

Sinus tachycardia is a supraventricular arrhythmia that can signal severe underlying pathology and is associated with poor prognosis in the presence of underlying ischemia; myocardial infarction or congestive heart failure (19). Tachycardia is not only a marker of sympathetic stimulation, which in itself is associated with poor cardiovascular prognosis, but also contributes to cardiac work and strain (19).Elevated heart rate has been shown to be a strong independent risk factor for the development of cardiomyopathy, coronary artery disease, fatal myocardial infarction and sudden death, cardiovascular and overall mortality (20, 21)

c) **Steroids**

The long term use of steroids has also been associated with arrhythmias. Huerta et al in evaluating the relationship of respiratory medications and arrhythmia found no increased risk of arrhythmia with use of inhaled steroids, but found a significant risk of

supraventricular tachycardia and ventricular arrhythmias with the use of oral steroids, with the relative risk being greater at the beginning of treatment (22).

d) **Anticholinergics**

Quaternary ammonium compounds such as ipratropium bromide and tiotropium which are the main anticholinergics used in COPD are highly hydrophilic and are poorly absorbed from mucus membranes. Though they are not without cardiovascular effects, their effects is negligible compared to sympathomimetics.

2.2.2: Cardiac Autonomic dysfunction

Alteration of cardiac autonomic function and prolongation of the QT interval are important in the development of arrhythmia in patients with COPD. Some patients with COPD lack the normal pattern of cardiac circadian rhythm changes and some have prolonged QT interval. Heart rate variability studies have reported mixed sympathetic and parasympathetic deterioration. The exact reasons for the deterioration of these nerves are unknown but chronic hypoxia/ hypercapnia have been implicated (23, 24).Furthermore, there is an association between the presence of ventricular arrhythmias and increased QT dispersion as shown by Yildiz, P et al (25).Tukek et al, in evaluating factors associated with atrial fibrillation also demonstrated that increased P wave dispersion was significantly related to atrial fibrillation among patients with COPD (26). The P wave dispersion and QT dispersion, both markers of arrhythmogenicity are thought to be related to cardiac autonomic changes in COPD patients (25, 26).

The QT dispersion (QTmax- QTmin) refers to the interlead and intercycle variability of the QT interval in a 12-Lead ECG, and is a reflection of heterogeneity of myocardial repolarization and has been proposed as a non invasive ECG parameter which may predict increased risk of malignant ventricular arrhythmias. (25).P-wave dispersion (Pmax- P.min) on the other hand refers to the intercycle variability of the P-wave

duration. It reflects the inhomogeneous and fractionated propagation of sinus impulse and predicts for the occurrence of atrial fibrillation in COPD. (26)

2.2.3: Ventricular Dysfunction and Respiratory Failure

The presence of arrhythmias in COPD has been associated with concurrent left ventricular diastolic dysfunction. Incalzi et al in a study in 1990 found that diastolic dysfunction was the only clinical variable predictive of ventricular premature beats (27). This physiologic abnormality may be related to the simultaneous presence of silent ischemia, ageing, or an overloaded right ventricle (based on ventricular interdependence). Co morbidities such coronary heart disease, cardiomyopathies, thyroid disorders and hypertension also contributes to arrhythmogenesis

The presence of respiratory failure may also be a determinant of arrhythmia formation. In Incalzi's study, atrial premature beats were related to hypoxemia and hypercarbia. Furthermore, the number of arrhythmias significantly decreased when respiratory failure improved.

2.3: TYPES OF ARRHYTHMIA IN COPD

The different forms of cardiac rhythm disorders so far reported include;

1) Sinus tachycardia
2) Sinus bradycardia
3) Atrial fibrillation
4) Atrial flutter
5) Multifocal atrial tachycardia
6) Ventricular premature beats
7) Sustained and non sustained Ventricular tachycardia

Out of these, sinus tachycardia and ventricular premature beats are the most common arrhythmias in COPD. However, multifocal atrial tachycardia (MAT) is the most characteristic cardiac arrhythmia in COPD.

2.3.1: MULTIFOCAL ATRIAL TACHYCARDIA (MAT)

The exact mechanism for the occurrence of MAT is not known but may be related to delayed after depolarization leading to triggered activities. MAT has been associated with theophylline toxicity in several studies (28). It is thought that by increasing cyclic AMP in myocardial cells, theophylline may promote catecholamine mediated delayed after depolarization (29). Theophylline may also be arrhythmogenic by causing increased urinary excretion of K+ and Mg+ and thereby hypokalemia and hypomagnesaemia (30). Other factors associated with MAT include hypoxemia, CCF, pulmonary embolism, electrolyte abnormalities and other physiologic factors related to respiratory dysfunction (31).MAT is a frequent transient arrhythmia and may spontaneously convert to sinus rhythm, atrial fibrillation or atrial flutter. The arrhythmia typically lasts one to ten days, but a few cases of chronic MAT have been documented (31).

MAT and other sustained atrial arrhythmias in patients with acute respiratory failure are associated with malignant ventricular arrhythmias (31). The prognosis in patients with COPD and MAT is poor, with one series reporting an in-hospital mortality of 46% (31). MAT is diagnosed from ECG or Holter by presence of p-waves of different morphologies.

2.3.2: ATRIAL FIBRILLATION (A.Fib)

Atrial fibrillation is characterized by rapid and irregular fibrillatory waves at a rate of 350-600 impulses/minute, and in the presence of normal AV-nodal conduction by an irregularly irregular ventricular response of 90 up to 140-170 beats/ minute, but may be higher in some patients.

Age and co morbid cardiac diseases predispose COPD patients to A.Fib. Atrial fibrillation increases the risk of stroke in these patients.(32)

2.3.3: ATRIAL FLUTTER

Atrial flutter is characterized by rapid, regular atrial depolarization at a rate of approximately 300 beats/minute. There is typically 2:1 conduction across the AV-node, as a result the ventricular rate is usually one half the flutter rate in the absence of AV-nodal dysfunction. (33).

2.3.4 :VENTRICULAR ARRHYTHMIAS

Ventricular arrhythmias can be considered under

1) Ventricular Premature Beats(VPB) and non sustained Ventricular Tachycardia(VT)
2) Life threatening ventricular tachyarrhythmia such as VT and ventricular fibrillation

Ventricular Premature Beats

VPBs are common and occur in a broad spectrum of populations including those with or without structural heart disease, irrespective of its severity.
The prevalence of VPBs is related to the age of study population, the detection method used and the duration of observation. VPBs increase with age, with reports of a 34% rise for every 5 year increase in age . The more an individual is observed the higher the number of VPBs. Finally, VPBs are also increased by hypokalemia, hypomagnesaemia, hypertension, structural heart diseases and COPD (34).

Non sustained Ventricular Tachycardia (NSVT)

NSVT is defined as ventricular tachycardia that is ≥ 5 consecutive beats, but lasts less than 30 seconds. It is found in 6% of patients with normal hearts and in up to 60-80% of patients with structural heart disease (35).

Ventricular Tachycardia (VT)

VT is defined as 3 or more successive ventricular complexes lasting longer than 30 seconds with a rate that is generally greater than 100 beats/minute. (35).Sustained VT is unusual, occurring in less than 5% of patients with heart failure of any etiology (36).Patients with spontaneous sustained VT are at a high risk of sudden cardiac death whatever the underlying aetiology (37).

2.4 EFFECT OF ARRHYTHMIAS

Arrhythmias have been associated with increased morbidity and mortality in COPD patients. Fuso L. et al in evaluating determinants of mortality in hospitalized acutely exacerbated COPD patients showed that atrial fibrillation and ventricular arrhythmias are independent predictors of death (13). Also among COPD patients with acute respiratory failure, the presence of sustained arrhythmia was associated with increased mortality (9).

MAT and other atrial arrhythmias in COPD patients with acute respiratory failure are associated with malignant ventricular arrhythmias. Payne reported an in-hospital mortality of 46% among very severe COPD with MAT (31).Both atrial and ventricular arrhythmias are also associated with increased hospitalization (12)

3: STUDY JUSTIFICATION

COPD is a leading cause of mortality and morbidity, with WHO estimating that it is expected to be third leading cause of death and disability by the year 2020 (6). The prevalence in Africa, though low. is expected to rise as a result of an increasingly ageing population and increasing prevalence of the habit of cigarette smoking (3).

Cardiac arrhythmias, contribute to the burden of mortality and morbidity among COPD patients, with a reported high in-hospital mortality and prolonged and recurrent hospitalization. (10). The identification and correction of some of the factors that predispose to these arrhythmias may help to forestall these consequences.

In a health care system grappling with competing priorities, the importance of preemptive and early identifications of amenable conditions cannot be overemphasized. It will enable appropriate and cost effective allocation of resources.

In this era of expensive gadgetry, it's gratifying to identify situations where simple tools like an ECG will provide key medical information. It's said that the first step to solving a problem is to know the problem. There is so far no study in our setup on the prevalence of the burden of cardiac arrhythmias among this often neglected patient group.

This study, therefore, will help in establishing the burden of the problem, form a basis for further research and possibly generate recommendations on how this problem should be approached.

4: STUDY OBJECTIVES

4.1. PRINCIPAL OBJECTIVE

- To determine the six month period prevalence of cardiac arrhythmias among COPD patients and describe the associated factors.

4.2. SPECIFIC OBJECTIVES

1). Determine the six month period prevalence of cardiac arrhythmias among COPD patients seen at outpatient chest clinic and chest ward.

2).Identify the types of cardiac arrhythmias among COPD patients seen at outpatient chest clinic and chest ward

3). Determine the presence of selected risk factors for cardiac arrhythmias in COPD patients i.e. COPD stage, hypoxemia/ hypercapnia, Hypokalemia, hypomagnesaemia, acidosis, COPD medications, P wave dispersion, QTc dispersion.

4) Correlate these risk factors with the presence of cardiac arrhythmias in the COPD patients.

5: METHODOLOGY

5.1. Study Design

Cross sectional descriptive study.

5.2. Study period and area

The study was conducted over six months between 28th January and July 30th 2008. The study was hospital based, conducted at the KNH chest ward and clinic. KNH is a tertiary level national referral hospital and the chest ward and clinic are part of the hospitals respiratory unit.

5.3. Study Population

COPD patients of any age who were being followed up at the chest clinic, or admitted in the chest ward, and who met the inclusion criteria.

COPD was defined as a functional disorder fulfilling the GOLD spirometric criteria (defined as FEV1/FVC ratio $\leq$ 70%).

5.4. Inclusion criteria

Any patient,

1. Bearing a diagnosis of COPD, confirmed by spirometry (FEV1/FVC $\leq$ 70%)
   And

2. Gave informed consent to participate

5.5: Exclusion criteria

1. Any patient who had mixed restrictive and obstructive pattern on spirometry

2. Any patient who had conditions predisposing to arrhythmia such as primary organic heart disease, thyrotoxicosis, hypertension

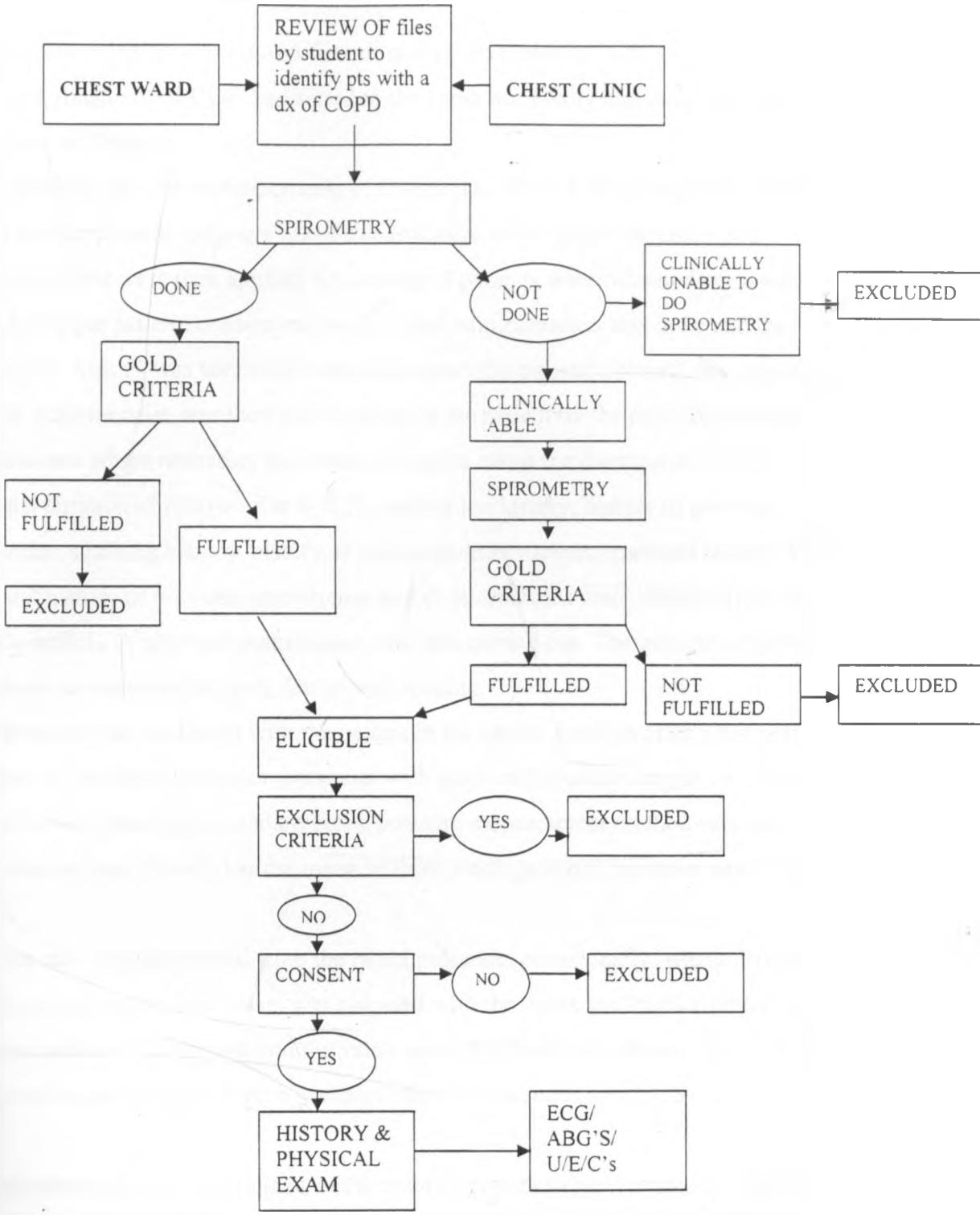
3. Patients who had been on anti-arrhythmic drugs

4. Any patient who declined to give consent.

5.6: Sample selection and size

Consecutive COPD patients who fulfilled the inclusion criteria were recruited prospectively over six month duration from the chest clinic and the chest ward.
It had been estimated that at the end of six months 312 COPD patients would have been recruited based on estimated clinic attendance of 10 COPD patients per week and admission rate of 3 COPD patients per week.

Figure 1. **RECRUITMENT FLOW OF PATIENTS**



5.7. Screening and Recruitment Method

The principal investigator reviewed files of consecutive patients with a clinical or spirometric diagnosis of COPD admitted to the chest ward daily and those attending the chest clinic on Fridays.

Those fulfilling the spirometric criteria of COPD (i.e. FEV1/FVC ratio) were deemed eligible for recruitment and were asked to participate in the study. Inclusion and exclusion criteria were then applied. On average 9 patients were recruited per week. For each eligible patient, consent explanation and administration was done and the demographic history was taken and where necessary the patient's record was consulted. A simple questionnaire was then administered to the patient by the principal investigator in English and where necessary kiswahili to enquire about the duration of COPD diagnosis, duration of follow up at K.N.H, medication history, history of previous arrhythmias, smoking history, history of co- morbidities and occupational history. Where necessary, history of previous arrhythmias and co-morbidities were inferred from the patient's records. A physical examination was then carried out. The general condition of the patient was assessed as good, fair or sick looking.

Blood pressure was measured with the patient in the supine position after a rest period of 5 minutes. A standard sphygmomanometer with adult cuff (bladder length 30-35 cm and width of 12 cm) was used. Standard blood pressure measurement method was used. The blood pressure was recorded as the mean of three readings taken 5minutes apart (38).

The pulse rate was determined from the radial pulse and occasionally, where difficult from the carotid pulse. The vessel was palpated with the index and middle finger and the beats counted for a full minute and the value entered as beats per minute. The pulse rate was entered as an average of three readings taken five minutes apart. (38)

The respiratory rate was determined as the number of breaths per minute, by observing the chest movements and counting each inspiratory movement for one minute .The rate was taken as an average of three readings taken five minutes apart and entered as breaths per minute (42).

Clinical procedures

Certain clinical investigations/ procedures were then carried out as follows:

Spirometry.

For those patients who had not had spirometric diagnosis of COPD done, their Forced Expiratory Volume at one second (FEV1), forced Vital Capacity (FVC) and FEV1/FVC ratio was measured using a spirometer (Autospirometer system 55, Minato Medical Science Co. Ltd, Osaka, Japan). The spirometry procedure was done according to the GOLD guidelines by a trained technician at KNH lung function laboratory. The FEV1 and FEV1/FVC ratio was then used to diagnose and stage COPD. The staging categorized patients into stage I, II, III and IV. (See appendix III)

Electrocardiography (ECG)

A standard resting supine 12-lead ECG was done for all patients using a standardized portable automated ECG machine (Model Marquette Pc 500, manufactured by Marquette electronics, USA). Prior to the study, validation of the measurements of QT interval and P wave duration was done by comparing the automated QTc and P wave duration and the manually calculated QTc and P wave duration of fifteen patients at KNH. Also two readings were obtained at intervals of five minutes to evaluate internal consistency of the ECG machine and intraobserver consistency of the manual readings. A paired t test was done to compare the QT and P wave duration and correlation obtained between the two readings. The ECG machine was found to be consistent with a correlation of 0.998. There was intraobserver consistency with a correlation of 0.987 between readings. The ECG paper was calibrated at paper speed of 25mm per second with 5mm representing 1mV.The same ECG machine was used throughout the study. The ECG was done by the principal investigator as stipulated in the ECG manual.

The readings were then analysed by the investigator in liaison with a cardiologist. The type of rhythm and/ or arrhythmia observed was recorded on the study proforma and the maximal and minimal QT interval and the maximal and minimal P wave duration was determined manually by the investigator from two contiguous leads and the values

entered on the proforma. The differences of the maximal and minmal values of the QTc interval and P wave durations were entered as QT and P wave dispersion respectively.

QT dispersion: - this refers to the intercycle variability of the QT interval measured from a minimum of 2 leads for at least 2 cycles per lead.

The QT interval was measured from onset of QRS complex to the end of the T-wave. This was done from at least 2 leads. The average of the two highest values was taken as the maximum QT duration and the minimum QT duration was determined as the average of the two lowest values.

The difference of the minimum and maximal duration of the QT (QTdispersion), was then calculated. Each QT interval was corrected for the patient's heart rate according to Bazzett's formula.

$$QTc = QT \sqrt{R\text{-}R\ interval}$$ where QT and R-R interval are expressed in seconds.

The values were then entered into the study proforma as milliseconds

P-wave dispersion: - Refers to the intercycle variability of the P wave duration as measured from a minimum of 2 leads for at least 2 cycles/ lead.

The P-wave duration was also measured manually under a magnifying glass from the beginning of the P-wave deflection from the isoelectric line to the end of the deflection returning to the isoelectric line.

The average of the two lowest values was taken as minimum p-wave duration and the average of the two highest values was taken as the maximum p-wave duration. The P-wave dispersion was then calculated as the difference between the maximal P-wave duration and the minimal P-wave duration as follows;

$$PWd = P_{max} - P_{min}\ (milliseconds)$$

The values were then entered into the study proforma as milliseconds

Arterial blood gases and urea, creatinine and electrolytes

The principal investigator then after explaining the process to the patients drew 5mls of arterial blood from either the femoral or radial artery in 2 separate heparinized 2.5ml syringes. One of the samples was delivered to the KNH ICU laboratory within 30 minutes for blood gas analysis using automated blood gas analyzer (Jaeger GMBH & Co.KG, Wuerburg. Germany). The other sample was delivered to KNH Renal laboratory within one hour for urea, creatinine, and magnesium assay using automated assay. Both laboratories had internal quality control, where the machines were recalibrated every morning and controls run with every test. The assay was run by well trained technicians who normally handle the machines for the hospital.

5.8: Definitions of outcome variables.

1. Arrhythmia- any rhythm that is not sinus
   A) VPB- any single ventricular premature complex seen on ECG
   B) Atrial fibrillation- irregular RR interval with absent P waves
   C) Mixed arrhythmia- presence of more than one arrhythmia on the ECG
2. Hypokalemia- serum potassium less than 3.5 mmol/l
3. Hypoxia- partial pressure of arterial oxygen less than 11.3 kPa
4. Hypercapnia- partial pressure of arterial carbon dioxide more than 6 kPa
5. Acidosis – arterial pH less than 7.35
6. Hypomagnesemia- serum magnesium less than 1.7mg/dl
7. Prolonged P-wave dispersion- difference between maximal and minimal p-wave duration more than 30ms
8. Prolonged QT dispersion- difference between maximal and minimal QT interval of more than 40ms

6. DATA ANALYSIS

The data gathered from the patients was entered continuously into a coded proforma, cleaned, verified and analyzed using the statistical package for social sciences version 14.2 (SPSS for Windows, 14.2; SPSS; Chicago, IL)

Descriptive statistics were applied to continuous and categorical data from which measures of central tendency and proportions were derived. Continuous variables such as K+, pH, PaCO2, PaO2, P wave dispersion and QT dispersion was analyzed into means (± SD) or medians (range) while categorical variables such as arrhythmia was analyzed into percentages with corresponding 95% CI.

Prevalence of arrhythmia was calculated as follows with 95% CI:

$$\frac{\text{No of patients with arrhythmias}}{\text{n (number recruited and analyzed)}} \times 100$$

Chi square was used to determine the association between COPD stage and arrhythmia while Mann whitney U test was used to determine the association between presence of arrhythmia and increasing QT and P-wave dispersion, hypoxia, hypercapnia, acidosis, hypokalemia and hypomagnesaemia.

Where comparisons were made, Statistical significance was defined as a P-value of less than 0.05.

7. ETHICAL CONSIDERATIONS

This study was carried out following the approval of the department of Internal Medicine of the University Of Nairobi School of medicine and the Kenyatta National Hospital ethics and research committee.

Patients received a written and oral explanation of what the study entailed, its potential benefits and dangers from the principal investigator. The patients also received an explanation of the study process and the tests done in lay terms

Appropriate interventions were offered to the study participants as indicated by clinical and laboratory parameters. At the end of each interview basic education regarding the illness was given and smoking cessation, good nutrition and compliance with medications reemphasized. The full cost of the study was met by the principal investigator.

8. RESULTS

A total of 218 subjects were screened between January and July 2008. 11 were excluded (3 had declined participation, 4 did not fulfill the diagnostic criteria for COPD and 4 did not honor further appointments for investigations).207 COPD patients were recruited and analyzed. Those who had study directed spirometry were 83(40%) while 124(60%) had spirometry prior.

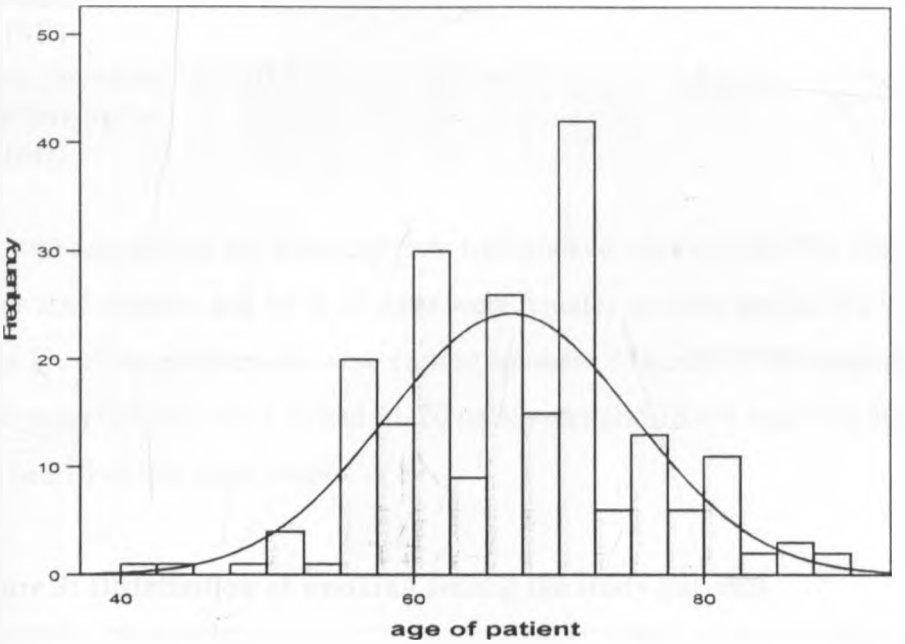
8.1. SOCIO-DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Table 1: socio-demographic profiles

Characteristic	Values
Age (mean±(SD))	66.7±(8.5)
Males	67.8±(8.3)
Females	64.0±(8.3)
Gender	
Males (n (%))	145(70)
Females (n (%))	62(30)
Current occupation	
Agriculture (n (%))	151(72.9)
Industrial (n (%))	23(11.1)
Office (n (%))	33(16)
Smoking status(in packs)	
0 (n (%))	19(9.2)
<5 (n (%))	2(1)
5-10 (n (%))	17(8.2)
11-20 (n (%))	61(29.5)
21-30 (n (%))	74(35.7)
>30 (n (%))	34(16.4)
Duration of COPD & follow up in years	
COPD duration; median (range)	1(0-6)
Follow up duration; median (range)	1(0-5)

A total of thirty three patients were recruited from the ward while 174 were recruited from the clinic. Their mean age was 66.7 ± 8.5 years (SD) and ranged from 40 to 90 years. The mean age of males was 67.8±8.3 years (SD) while that of females was 64.0±8.3 years (SD). 60.9% were 65 years and above. Overall there were more male patients with COPD (70%) than females giving a male to female ratio of 2.3:1.

Figure 2: Age distribution COPD patients



When subjects were categorized by age into the various stages of COPD, relatively younger patients tended to be in early stages with a mean age of 63.1 and 66.3 for those in stage I and II respectively while stage III and IV patients had mean age of 69 years. The difference was statistically significant (p=0.018)

Table 2: Age distribution in COPD stages.

COPD stage	I (n=46)	II (n=100)	III (n=52)	IV (n=9)
Mean Age± (SD) years	63.1±83	66.3±7.9	69.9±8.8	69.1±.6.9

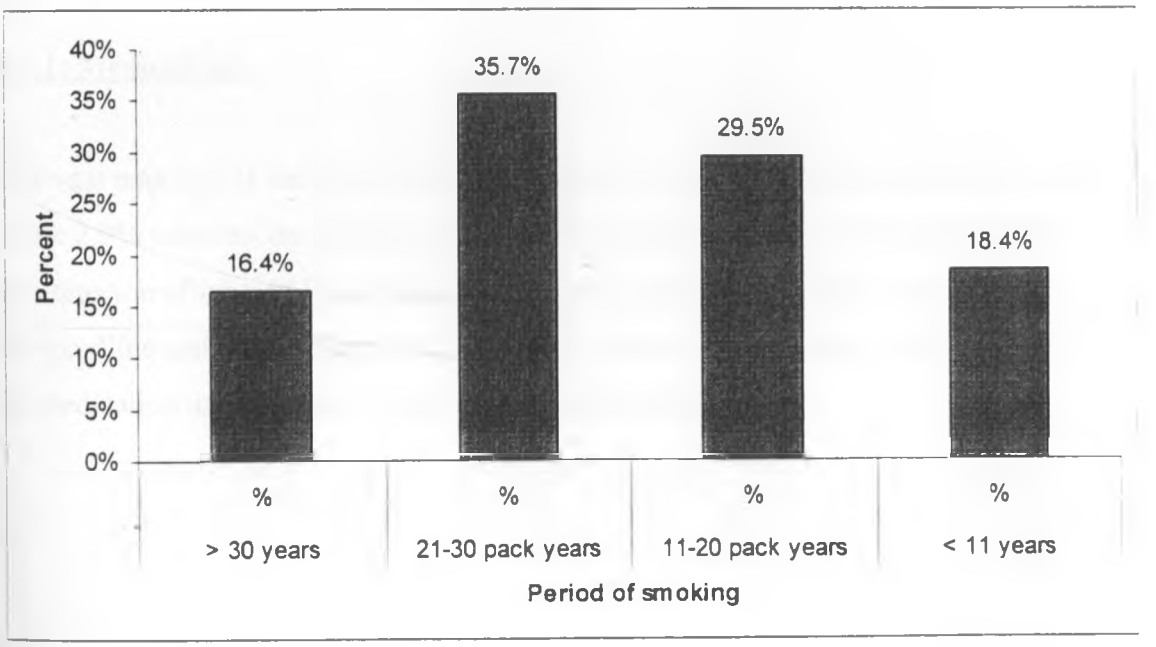
The mean duration of disease diagnosis and follow-up was on average longer for those with advanced disease (COPD stage III and IV) as opposed to those with mild disease (COPD stage I and II). However this was not statistically significant (p=0.068)

Table 3: Mean duration of disease and follow-up at various stages:

COPD stage	I (n=46)	II (n=100)	III (n=52)	IV (n=9)
Mean duration of COPD in yrs (SD)	1.2 ±0.8	1.4 ±0.9	1.9 ±1.2	2.3 ±1.3
Mean duration of follow-up in yrs (SD)	0.9 ±0.6	1.1 ±0.8	1.5 ±1.1	1.7 ±0.9

The vast majority of the study subjects had smoked tobacco (90.8%). Only 9.2 % had never used tobacco and 98 % of these were females as compared to 2% who were males. Only 1% of the participants were current smokers. Majority of the smokers had 21-30 pack years (35.7%), 29.5 % had 11-20 pack years and 16.4% had over 30 pack years. The rest had 10 or less pack years.

Figure 3: Distribution of smoking among the study patients



When the smoking status was assessed with respect to the various stages of COPD, it was apparent that all those in stage IV and 84.7% of those in stage III had more than 10 pack years of smoking while 80.1% and 79% of those in stage I and II respectively had more than 10 pack years. 13% of stage II patients, 8.6% of stage I patients and 3.8% of stage III patients had no smoking history.

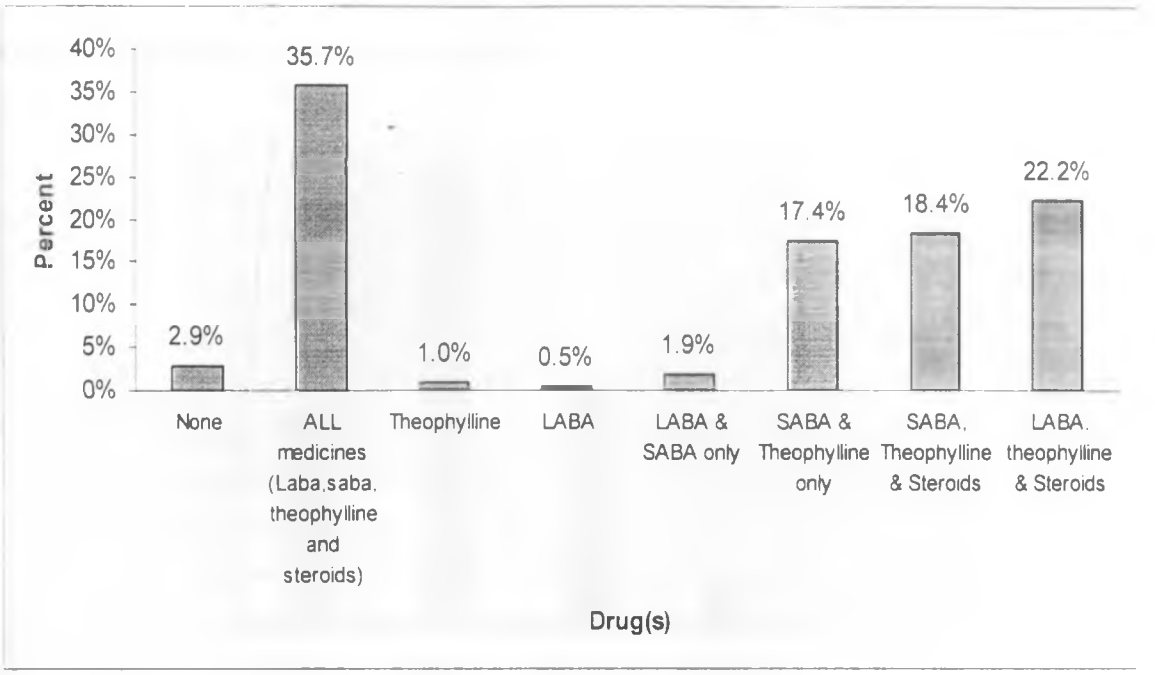
Table 4: cross tabulation of smocking versus COPD stage

	SMOCKING IN PACK YEARS					
COPD stage	**0 packs**	**<5 packs**	**5-10 packs**	**11-20 packs**	**21-30 packs**	**>30 packs**
I n=4(%)	4(8.6)	0(0.0)	5(10.8)	16(34.7)	16(34.7)	5(10.8)
II n=100(%)	13(13)	1(1)	7(7)	32(32)	33(33)	14(14)
III n=52(%)	2(3.8)	1(1.9)	5(9.6)	12(23.1)	20(38.5)	12(23.1)
IV n=9(%)	0(0.0)	0(0.0)	0(0.0)	1(11.1)	5(55.6)	3(33.3)

8.1.1: Medications

The vast majority of the study participants were on some form of medication (97.1%) while 2.9% were not on any medication. The majority of those on medication were on a combination of inhaled long acting β_2 agonist (LABA), short acting β_2 agonist, oral theophylline and inhaled steroid (35.7%). 1% were on theophylline alone. 21.6% of those on medication used regularly while78.4% used intermittently

Figure 4: Types of medications used by the COPD patients in the study



8.1.2: Blood pressure

The mean systolic blood pressure of the study subject was 113.51 ± 11.4 (SD), while the mean diastolic blood pressure was 67.27 ± 8.78.(SD). The mean systolic blood pressure of the females was 112.9 ±11.0 (SD) while that of the males was 114.8±12.6 (SD). The mean diastolic blood pressure was similar at 67.1±8.9 (SD) and 67.8±8.3 (SD) for females and males respectively.

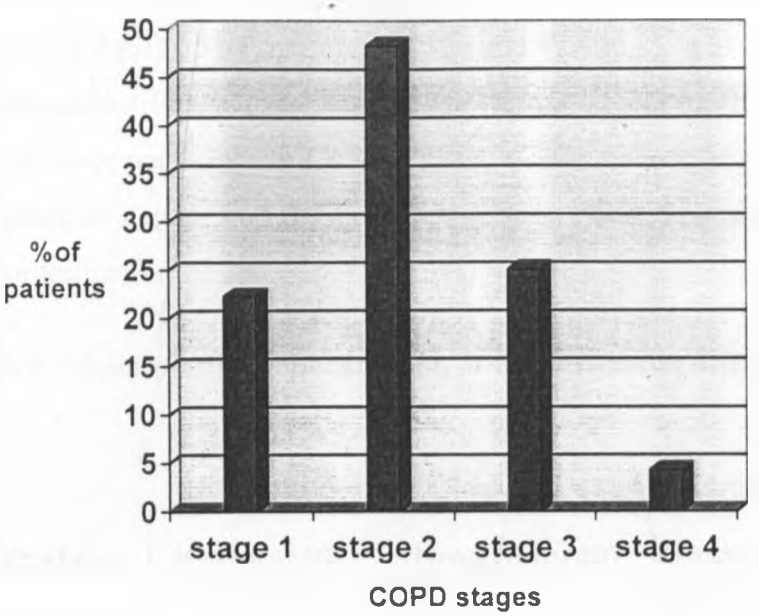
8.1.3. Co-morbidities

13% (27) of the study subjects had heart failure as a concurrent diagnosis. There was no study subject with Diabetes or previous diagnosis of arrhythmia.

8.1.4 COPD stage

Overall, among the study subjects, 48.3%(n=100) were in GOLD stage II, 25.1%(n=52) were in III, 22.3%(n=46) were in stage I and 4.3%(n=9) were in stage IV. Stage I and II accounts for over 70% of the subjects

Fig 5: COPD stages of the study subjects



8.1.5: Pulmonary function

The mean FEV1 of the study subjects was 60.4 ± (SD) 15.1, while the mean FVC was 3.0 ± (SD) 1.3L. The mean FEV1/FVC ratio was 0.65± (SD) 0.14. The distribution of FEV1 and FVC in various stages of the disease is in keeping with the respective cutoffs for the GOLD COPD stages, that is, percent predicted of FEV1 of more than 80 for stage one and less than 30 for stage IV.

8.1.6: Arterial blood gases, Urea, Creatinine & electrolytes

The mean pH of the subjects was 7.34± 1.05(SD), while the mean PaO2 and PaCO2 were 11.5Kpas ± 2.3(SD) and 4.8Kpas ± 1.6(SD) respectively. The mean bicarbonate concentration was 24mmol/ l± 5.7 (SD). The mean plasma concentration of potassium. magnesium. urea and creatinine in the study subjects were 3.84mmol/l±0.5 (SD, 1.8mg/dl±0.2 (SD), 3.91mmol/l±2.3 (SD) and 97.4µmol/l ±34.2 (SD) respectively. Categorization of the electrolytes into the various COPD stages reveals a tendency towards lower potassium and magnesium concentration among those in stages III and IV as opposed to stages I and II. The difference was statistically significant for potassium and borderline for the rest.

Table 6: Mean plasma concentration of electrolytes at different COPD stages

	Mean urea, creatininie and electrolyte concentration (SD)			
COPD stage	**K+(mmol/l)**	**Urea (mmol/l)**	**Creatinine (µmol/l)**	**Mg2+ (mg/dl)**
I(n=46)	4.0±0.57	3.3±1.1	92±19.4	1.9±0.19
II(n=100)	3.9±0.46	3.2±1.3	89.2±19.5	1.8±0.29
III(n=52)	3.6±0.52	4.8±2.4	108±38.8	1.7±0.29
IV(n=9)	3.6±0.5	3.9±2.3	97±34.2	1.8±0.2
P value	**0.045**	**0.055**	**0.052**	**0.05**

The distributions of the arterial blood gas concentration across the various stages reveals lower oxygen and higher carbon dioxide tension in stages III and IV as opposed to stages I and II. The difference was however not statistically significant (p=0.051).

Table 7: Mean arterial blood gases versus COPD stage

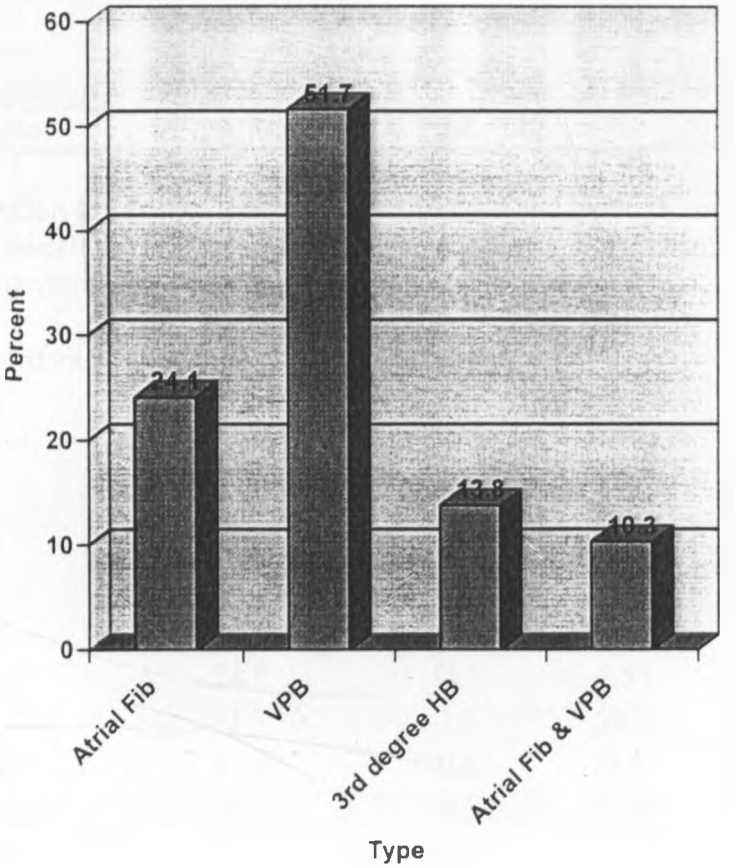
	Mean pH and blood gas concentrations in Kpas (SD)		
COPD stage	**pH**	**PCO2**	**PO2**
I(n=46)	7.34± (0.9)	4.8±(1.5)	11.8± (2.2)
II(n=100)	7.34±(1.0)	5.0± (0.85)	11.5±(2.03)
III(n=52)	7.32±(0.85)	5.2± (0.8)	11.0± (2.0)
IV(n=9)	7.32±(0.2)	5.5± (0.65)	10.5± (1.8)

8.2. PREVALENCE OF CARDIAC ARRHYTHMIAS

The prevalence of arrhythmia was **14% (95% confidence interval of 9.3% to 18.7%).** .The majority, 51.7% had ventricular premature beats (VPB) followed by Atrial Fibrillation at 24.1%. 10.3% had mixed Atrial Fibrillation and VPB while 13.8% had 3° heart blocks.

Of the 29 subjects with arrhythmia, 8 were females and 21 were males. 12.9% of the females had arrhythmias as opposed to 14.5% of the males.

Fig 6: Types of arrythmias



8.3: ARRHYTHMIA ASSOCIATED RISK FACTORS

The distribution of the median values of selected arrhythmia associated risk factors such as potassium, magnesium; P-wave and QT dispersion were significantly higher in the arrhythmia group than in those with sinus rhythm.

Table 8: distribution of median values of various variables

	Arrythmia			*Sinus*			
Variable	*n*	*median*	*Range*	*n*	*median*	*range*	*P-value*
Potassium in mmol/L	29	3.5	2.8 – 5.5	177	3.7	3.0 – 5.9	<0.001*
Magnessium concentration	29	1.6	1.0 – 2.2	178	1.8	1.2 – 2.3	0.018*
P-wave dispersion	28	37.5	7 – 70	173	10	0 – 43	<0.001*
QTc dispersion	28	47.5	10 - 112	177	20	0 – 81	<0.001*

The distribution of gender, regular medication use and heart failure were not significantly different between the two groups but those of hypoxia, hypercapnia, acidosis and hypokalemia were significantly different.

Table 9: odds ratios for dichotomous variables

Variable	**Arrythmia (n=29) %**	**Sinus (n=178) %**	**Odds ratio**	**95% Confidence interval**	
				Lower	**Upper**
Sex: males	72.4	69.7	1.14	0.48	2.74
Regular medication	31.0	19.8	1.83	0.76	4.37
Heart failure	24.1	11.2	2.51	0.95	6.63
Hypoxia	51.7	3.9	26.2	9.16	74.76*
Hypercapnia	31.0	0.6	79.65	9.58	661.64*
pH: Acidosis	34.5	0.6	93.15	11.30	767.91*
Hypokalemia	44.8	13.1	5.41	2.30	12.68*

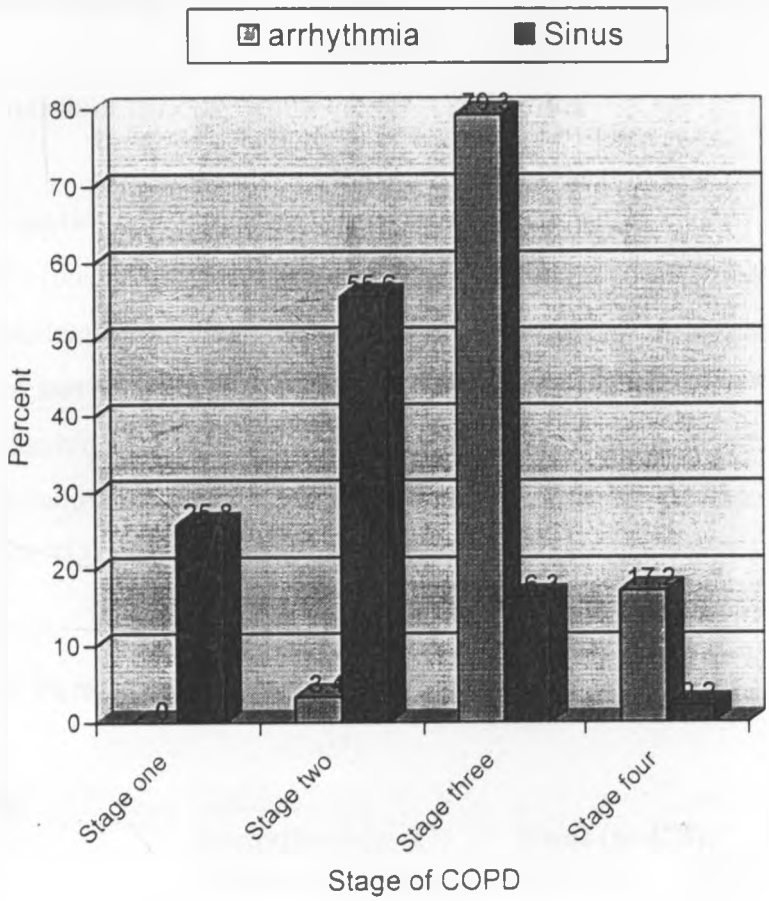
8.4: CORRELATION OF SELECTED FACTORS WITH ARRHYTHMIA.

8.4.1. COPD stage versus Arrhythmia

The majority of the study subjects with cardiac arrhythmia were in stages III and IV (79.3% &17.2% respectively) while the majority of those without arrhythmia were in stages II and I (55.6% & 25.8% respectively).

This difference was statistically significant ($X^2_3 = 73.86$; $p < 0.001$)

Fig 7; Stages of COPD versus Arrhythmia



8.4.2: Magnesium concentration versus Arrhythmia

The median blood concentration of magnesium among study subjects with arrhythmia was 1.6mg/dl while the median concentration among subjects without arrhythmia was 1.8mg/dl. This difference was statistically significant. (P- Value 0.018). The prevalence of overt hypomagnesaemia in the entire study subjects was 22.2%. 93.1% of those with arrhythmias had hypomagnesaemia as opposed to 10.7% of those with sinus rhythm.

Table 1o: Magnesium concentration in blood among study subjects

Variable	Arrhythmia(n=29)		Sinus (n=178)		
	Median	Range	Median	Range	P-value
Magnesium (mg/dl)	1.6	1.0-2.2	1.8	1.2-2.3	0.018

8.4.3: Potassium concentration versus Arrhythmia

The vast majority of study subjects had normokalemia (82.2%). 17.3% had hypokalemia and 0.48% (one subject) had hyperkalemia. Notably 44.8% of subjects with arrhythmia had hypokalemia while only 13% of those with sinus rhythm had hypokalemia. This difference was statistically significant. (P-value <0.001)

The median blood concentration of Potassium among study subjects with arrhythmia was 3.5mmol/l while the median concentration among subjects without arrhythmia was 3.7mmol/l. This difference was also statistically significant. (P- Value <0.001).

Table 11: Potassium concentration in blood among study subjects

Variable	**Arrhythmia(n=29)**		**Sinus (n=178)**		
	Median	**Range**	**Median**	**Range**	**P-value**
Potassium (Mmol/l)	3.5	2.8-5.5	3.7	3.0-5.9	<0.001

8.4.4: Hypoxia and hypercapnia versus arrhythmia

The great majority of the study subjects had normal oxygen tension (89.4%). 10.6% had oxygen tension in range of hypoxia. 51.7% of those with arrhythmia had hypoxia while only 4% of sinus group had hypoxia. This difference was statistically significant (P-value <0.001).

The vast majority of study patients had normal carbon dioxide tension in their blood (95.2%). 4.8% had carbon dioxide tension in the range of hypercapnia. 31% of those with arrhythmia had hypercapnia, while only 0.6% of those with sinus rhythm had hypercapnia. This difference was statistically significant (P-value<0.001)

Table 12: distribution of hypoxia and hypercapnia

Variable	Arrhythmia (n=29) %	Sinus (n=178) %	P-value
Hypoxia	51.7	3.9	<0.001
Hypercapnia	31.0	0.6	<0.001

8.4.5: Acidosis versus Arrhythmia

The vast majority of study patients had normal pH (94.7%). 5.3% had pH in the range of acidosis. 34.5. % of those with arrhythmias had acidosis as opposed to 0.6% of those with sinus rhythm. This difference was statistically significant (P-value<0.001).

Table 13: Distribution of acidosis among study subjects

Variable	Arrhythmia (n=29) %	Sinus (n=178) %	P-value
Acidosis	34.5	0.6	<0.001*

8.4.6. P-wave and QTc dispersion versus arrhythmia

The median p-wave dispersion among those study subjects with arrhythmia was 37.5ms as compared to 10ms among those subjects with sinus rhythm. This difference was statistically significant (p-value<0.001). Similarly the median QTc dispersion among those study subjects with arrhythmia was 47.5ms as compared to 20ms among those subjects with sinus rhythm. This difference was also statistically significant (p-value<0.001).

Table 14: P-wave and QTc dispersion among study subjects

	Arrhythmia			Sinus			
Variable	**n**	**median**	**Range**	**n**	**median**	**range**	**P-value**
P-wave dispersion (ms)	28	37.5	7 – 70	173	10	0 – 43	<0.001
QTc dispersion (ms)	28	47.5	10 – 112	177	20	0 – 81	<0.001

9: DISCUSSION

The mean age of the subjects in this study was 66.7± 8.5 years (range 40- 90 years) with over 60% of the subjects being older than 65years. This indicates that even in our setup COPD still remains a disease of the elderly. COPD was a predominantly male disease with a male to female ratio of 2.3:1. This may be due to the low prevalence of cigarette smoking among our female population which as of 2003 stands at 1.8 % (39).
The commonest occupation among these subjects was agriculture. The central bureau of statistics cites agriculture as the largest employer in Kenya with over 80% of Kenyans engaged in agriculture. Many retired Kenyans also engage in agriculture as source of income.

Currently there are no published data from Kenya and the rest of Africa on the epidemiology of COPD. Menezes AM et al (3) in a prevalence study of COPD in 5 Latin American cities (the PLATINO study), found a mean age of 68.5±5.5 years, but the male to female ratio was almost equal at 1.1:1. The difference in the gender is explained by the fact that the PLATINO study was carried out among highly urbanized people with high prevalence of female smokers (82% of females smoked) unlike our population where female smoking is still pretty low (39).However the findings of Menezes Am et al reflects international trends in which gender disparity is slowly disappearing as more and more women smoke. The extent to which African women are catching up with this trend is unknown.

The prevalence of cardiac arrhythmia in this study was 14%. Arrhythmia was assessed through one time 12- lead ECG Using the same tool as this study, Kleiger et al, (10) reported a prevalence of 20% among 25 patients with severe COPD, while Hudson et al (9) found a prevalence of 31% in 35 severely ill, hospitalized COPD patients. The higher prevalence of arrhythmia reported in these studies was due to a number of reasons; First, all of the patients in kleigers and Hudson's studies ware acutely ill and hospitalized, in fact, 50% of Hudson's patients had acute respiratory failure while all of Kleigers patients

had been admitted for acute exacerbation. Majority of the subjects in this study (84%) were stable ambulatory COPD patients. It's well known that acute exacerbation of COPD and respiratory failure are strong independent risk factors for arrhythmia. Most of the subjects in Kleigers and Hudson's studies had significant co-morbidities in the form of heart failure (55% and 53.2% respectively), as compared to 13% heart failure co-morbidity in this study.

The commonest arrhythmia in this study was ventricular premature beats (VPB) (51.7%), followed by atrial fibrillation (24%) while 10.3% had atrial fibrillation and VPB. While most of the VPB were single beats, the types of atrial fibrillation are difficult to discern from this study. Kleiger et al found similar results with the majority of the arrhythmias being ventricular in origin (72%) with VPB accounting for 53%; 24% were of atrial origin with the rest comprising conduction blocks and mixed arrhythmia. Hudson et al reported similar findings although the ventricular arrhythmia were of more severe forms(ventricular tachycardia and multiform NSVT), a finding that may be explained by the severity of the illness of his subject with over 50% of them in acute respiratory failure requiring ventilatory support. The relatively high prevalence of atrial fibrillation has adverse cardiovascular implications for these elderly subjects and may therefore warrant evaluation for this arrhythmia among this population so that appropriate measures may be taken.

GOLD stage III and IV of COPD was strongly associated with arrhythmia as compared to stage I and II. ($p<0.001$). In this study 79.3% and 17.2% of the subjects with arrhythmia were in stage III and IV respectively while the majority of those without arrhythmia were in stage II and I (55.6% and 25.8%). GOLD staging system is a reflection of the degree of airway obstruction as predicted by FEV1 and FVC. Both FEV1 and FVC are independent predictors of occurrence of arrhythmia. The manifestation of arrhythmias in those with more severe disease implies a double jeopardy in which the sicker ones suffer more.Both Kleiger et al and Hudson et al showed similar findings. Kleiger et al found 90% of those with arrhythmia were in stage IV and similarly 84% of Hudson's subjects with arrhythmia were in stage III and IV.

The median Magnesium concentration was significantly lower among subjects with arrhythmia (1.6mg/dl) as compared to subjects without arrhythmia (1.8mg/dl) (p-0.018).

The prevalence of overt hypomagnesaemia was 22.2% with over 90% of this having arrhythmia. Hypomagnesaemia has been associated with life threatening ventricular arrhythmias that may easily be forestalled by correcting the hypomagnesaemia with slow release oral preparations of magnesium or potassium sparing diuretics such as amiloride. Several studies have shown a co-relation between low magnesium concentration and the occurrence of arrhythmia. Kirby et al (40) co-related low magnesium concentration (<1.7mg/dl) with the occurrence of arrhythmia among COPD patients, with a reported prevalence of hypomagnesaemia of 6.3%.

Hypokalemia was also strongly associated with arrhythmia. 44.8% of subjects with arrhythmia in this study had hypokalemia as opposed to 13% of those with sinus rhythm ($p<0.001$). Hypokalemia in these patients may be driven by liberal use of β2 agonist and electrolyte disturbance that occur in the setting of acute illness. Kirby et al associated the occurrence of arrhythmia with significant hypokalemia. ($P=0.002$).

.The prevalence of hypoxia in this study was 10.6% while that of hypercapnia was 4.8%. Both hypoxia and hypercapnia were strongly associated with the occurrence of arrhythmia. ($p <0.001$).Several studies have shown the strong association between arrhythmia and respiratory failure. Kleiger et al and Hudson et al showed similar strong association between hypoxia/hypercapnia and arrhythmia, though the prevalence of hypoxia was higher in their study (22% and 18% respectively), a reflection of the severity of illness of their patients.

Both respiratory and metabolic acidosis has been associated with arrhythmia. The prevalence of acidosis in this study was 5.3% with 34.5% of those with arrhythmia having acidosis, while only 0.6 % of those with sinus rhythm had acidosis. This difference was significant. ($p <0.001$). . Kleiger and Hudson et al showed similar results. The acidosis in these patients may be contributed in part by anaerobic respiration in the setting of systemic hypoxia and persistent hypercapnia. Acidosis may be ameliorated by enhancing oxygen delivery.

The median P-wave dispersion was significantly longer among subjects with arrhythmia

as compared to those with sinus rhythm(37.5ms versus 10 ms)($p<0.001$). Tufan tukek et al (26) demonstrated similar longer p-wave dispersion among COPD patients with arrhythmia and further showed significant correlation between atrial fibrillation and longer p-wave dispersion. In this study, subjects with atrial fibrillation showed a trend towards longer p-wave dispersion but this was not analyzed further because the numbers were small.The median QTc dispersion was also significantly increased among subjects with arrhythmia as compared to those with sinus rhythm (47.5ms versus 10ms) ($p<0.001$). Pinar Yiditz et al (25) showed that QTc dispersion rates were significantly increased in patients with COPD as compared to healthy controls.(50 ±9ms versus 27±8.2ms) and that patients with ventricular arrhythmia had significantly longer QTc dispersion(67ms±10ms versus 55±8ms)($p<0.001$). The association of QTc dispersion and ventricular arrhythmia could not be analyzed because of the small numbers.

In summary, COPD at KNH remains a disease of the elderly like it is in the rest of the world, however while the male to female ratio in the developed world is equalizing and in some instances reversing, at KNH it still remains a predominantly male problem in part due to a preponderance of male smoking pattern in our society. While overall smoking in Kenya is still low, among this population it remains very high at 92%. This, in addition to high co morbidity predicts a poor cardiovascular health for this population. The occurrence of more complex ventricular premature complexes was not determinable from this study but the relatively high rate of atrial fibrillation poses important cardiovascular implications. Atrial fibrillation is associated with increased risk of stroke. Hypokalemia, hypomagnesaemia, hypoxia, hypercapnia and acidosis play a pathophysiologic role in arrhythmogenesis and are in part modifiable. Hypoxia, hypercapnia and in part acidosis may be corrected by oxygen therapy while hypokalemia and hypomagnaesemia are correctable by their oral salts. Prolonged QT and P-wave dispersion are touted as possible predictors and therefore markers of risk for arrhythmia. COPD stage and age are non modifiable and may be utilized in future to risk stratify patients.

10: CONCLUSIONS

1) The one time 12-lead ECG prevalence of arrhythmia among COPD patients at KNH is 14%.

2) Most of the arrhythmias are predominantly ventricular complexes. However one fourth (24%) of those with arrhythmia have atrial fibrillation

3) Advanced stage of COPD, hypomagnesaemia, Hypokalemia, hypoxia and hypercapnia, acidosis and increased QTc and P-wave dispersion are associated with arrhythmia.

11: RECOMMENDATIONS

1) Screening 12-lead ECG for all COPD to identify potentially treatable rhythm disorders should be done. While its not the ideal tool for detecting arrhythmias that may occur paroxysmaly, it remains an easily available relatively cheap tool for diagnosing arrhythmias.

2) Monitoring of electrolytes in COPD patients to identify and correct arrhythmogenic electrolyte derangement is necessary. The electrolyte to be monitored should include Mg2+ and K+. The frequency of monitoring and the elucidation of the pathophysiologic roles of these and other electrolytes in arrhythmogenesis needs to be established from a prospective study.

3) A longitudinal study to evaluate risk markers and possibly elucidate pathophysiologic mechanism linking these markers to arrhythmia among COPD patients is necessary

4) A holter study to elucidate the types and significance of VPB and the types of atrial fibrillation and their implication in terms of treatment strategy is important and necessary.

5) Long term Prospective studies should be carried out in this population to study the effects of arrhythmia on survival and quality of life.

12: STUDY LIMITATIONS

The huge financial implication and elaborate logistics required carrying out 24 hour or 72 hour Holter monitoring meant that this more accurate method of detecting arrhythmias was out of the reach of the principal investigator.

However, since the Holter is in practice inaccessible to many centers including K.N.H, the 12-lead ECG has become the initial investigation of choice. It was therefore reasonable to use the ECG as the primary tool. Much as some paroxysmal arrhythmias may be missed with the one time ECG, important sustained arrhythmias are hardly missed and it forms an important baseline investigation of choice.

Likewise all possible associated factors could not be studied. Since ultimately the objective is to benefit the patient, it was reasonable to study selected, possibly reversible, Arrhythmia associated factors. QT and p-wave dispersion were included because they were potential non invasive ways of predicting the occurrence of arrhythmias from a simple ECG.

A number of historical information like smoking history, history of previous arrhythmias, co-morbidities and medications history depended on the recall and good faith of these elderly subjects. This limitation, where necessary, was minimized by corroboration of the history from the patient's records, significant other relatives and by observation of the empty 'packs' of medication. Compliance was assumed.

The lack of a control group in this study may cast some doubt on the implications of the study for a clinical setting. A control group, however necessary, was not feasible because of the financial implications.

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14.APPENDICES

APPENDIX I STUDY PROFORMA

(Tick as applicable and insert appropriate code or figure)

Demographic data

Patient No.	Age	Gender Male=1 Female=2		Usual residence

Smoking in pack years			Occupation	Education level			
never	past	current		0	1^{oo}	2°	3°

Medical history

Year of COPD diagnosis	Duration of COPD in yrs	Duration of follow up in yrs	Medications currently used			
			SABA	LABA	Theophylline	Steroids

Frequency of use of this medication		Other medications		Previous history of arrhythmias	
Regular	intermittent	Yes	No	Yes	No

Other co-morbidities:

Heart failure	Diabetes	Pulmonary embolism	Asthma

Physical exam

Blood pressure(mmHg)	Pulse rate(beats/ minute)	Respiratory rate (breaths/ minute)

Clinical investigations

	FEV1	FVC	FEV1/FVC
Spirometry			

COPD stages			
Stage I (FEV1>80% predicted)	Stage II (FEV1 50-80% predicted)	Stage III(FEV1 30-50% predicted)	Stage IV(FEVI< 30% predicted)

Arterial blood gases

P02 in K/Pascal	PC02 in k/pas	HC03 in Meq/l	pH

Urea/ electrolytes and creatinine

K+	Mg2+	Urea	Creatinine

ECG

Rhythm

Rhythm	
Arrhythmia	Sinus

Types of arrhythmia

A fib	MAT	Atrial flutter	VPB	VT	NSVT	Others

P-wave and QT dispersion

Maximum p- wave duration (ms)		**Maximal QTc (ms)**	
Minimum p-wave duration (ms)		**Minimum QTc(ms)**	
p-wave dispersion(ms)		**QTc dispersion**	

APPENDIX II

PATIENT INFORMATION AND CONSENT FORM

Introduction:-My name is Dr Adam sheikh. I am currently undertaking postgraduate/ masters training in the department of internal medicine, School of Medicine University of Nairobi. As part of my training, I am expected to carry out a study and I intend to do a study on disorders of heart rhythm among patients with chronic obstructive lung disease.

Chronic obstructive lung disease is a common and increasing problem as our population ages. Heart rhythm disorders are very common among these patients because the disease itself and the medication used to treat it predispose to this.

. By doing this study I hope to establish the burden of this problem and possibly suggest modalities of reducing it.

The role of the study participant- if you bear a diagnosis of Chronic Obstructive Pulmonary Disease (COPD), I would like forthwith to request you to be my study participant since you may meet my entry criteria.

If you agree to participate, a medical history will be taken and physical examination done. This will entail inquiry about age, current medication, smoking, occupation any known chronic disease other than COPD.

A 5cc sample of blood will also be drawn from your artery and the blood will be used to measure your kidney function, blood oxygenation and electrolytes. The procedure involves drawing blood from either the femoral or radial artery(the p.i showed sites of these vessels).

You may also be required to avail yourself for pulmonary function test (spirometry), if you have not had one in the last year. This entails breathing through some tubes connected to a computerized machine. The purpose of this test is to determine how good or bad your lung is functioning.

Finally you will have an external assessment of your heart rhythm by a test called electrocardiogram (ECG), which maps the heart beat from different direction. Both ECG and spirometry posses no risk to you.

I will inform you about the result of any test done and these will be shared with your primary care physician(s) for intervention where appropriate.

All information obtained will be strictly confidential and will not be revealed to other persons, other than your primary care physician(s), without your prior consent.

The quality of care given to you in this hospital will not be compromised by your refusal to participate in this study.

Participation in this study is voluntary (at your own will) and you are free not to participate or to withdraw at anytime

Participant's benefits and risks :-some of the benefits expected to be passed onto the participant of this study include:

- having the cost of your kidney function test and blood gas covered by the investigator will reduce your treatment cost
- having the cost of your ECG covered by the investigator
- having the cost of your pulmonary function test covered by the investigator(only if you haven't had one done)
- the ECG may help in revealing other heart problems that were not diagnosed before.

On the other hand the risks involved are:

- during the drawing of blood you may feel some pain or discomfort in the area you are pricked

- swelling, reddening ,pain at the site of puncture(hematoma, thrombophlebitis) is a rare but possible complication even with standard bleeding practices that will be applied

This study is approved by my university department and the KNH ethics board.

Incase of any need to contact me, please call me on 0722384035
Incase of enquiries about the approval of the study, please contact the secretary of K.N.H ethics committee on extension 44102.

Please feel free to have a copy of this consent explanation, which I can provide free of charge.

Do you have any question about participating in this study?

I .....of ..... Understand the above (purpose, participant's role, procedures, risks and benefits of this study) and give my consent to participate in this study.

Signed..... Date .....

I confirm that I have adequately explained to the patient the above.

Investigator(signed)..... Date .....

APPENDIX III

SPIROMETRIC CLASSIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE SEVERITY BASED ON POST-BRONCHODILATOR FEV1

Stage I: mild FEV1/FVC, 0.70
FEV1 > 80% predicted

Stage II: moderate FEV1/FVC, 0.70
50% < FEV1, 80% predicted

Stage III: severe FEV1/FVC, 0.70
30% < FEV1, 50% predicted

Stage IV: very severe FEV1/FVC, 0.70
FEV1, 30% predicted or FEV1, 50%
predicted plus chronic respiratory failure*

Respiratory failure: arterial partial pressure of oxygen (PaO2), 8.0 kPa
(60 mm Hg) with or without arterial partial pressure of CO2 (PaCO2) . 6.7 kPa
(50 mm Hg) while breathing air at sea level

APPENDIX IV

DEFINITION OF TERMS

COPD Patient- patient on follow-up at chest clinic or admitted to chest ward with a diagnosis of 'COPD' made following standard GOLD spirometric criteria.

Arrhythmia:- any rhythm that is not sinus and includes

1) Atrial fibrillation – defined by all of the following.
   a) Absent P waves
   b) Fibrillatory f waves at a rate between 350-600 bpm, with the f waves varying in amplitude, morphology and interval.
   c) The R-R intervals are irregularly irregular
   d) Variable ventricular rate ranging between 90-170bpm
   e) Narrow QRS complex

2) Multifocal atrial tachycardia (MAT). - Defined by all of the following.
   a) Discrete P-waves with at least 3 different morphologies best seen in Lead I, II and V1
   b) An atrial rate of over 100bpm
   c) P-waves are separated by isoelectric intervals
   d) The P-P interval, the PR-duration and the R-R intervals vary

3) Atrial Flutter. – defined by all of the following.
   a) Absent P-waves
   b) Biphasic 'saw tooth' flutter waves at a rate of 240-440bpm
   c) f waves are regular with constant amplitude, duration and

morphology

d) no iso-electric interval between f-waves

e) The ventricular response (R-R interval) is usual one half the atrial rate giving even ratio of input to output

f) The QRS complex is narrow unless there is functional aberration

4) Ventricular Premature Beats. –defined electrocardiographically by all of the following.

a. QRS complexes without preceding P-waves
b. QRS complexes with bizarre morphology
c. Duration of more than 120seconds
d. T-wave in opposite direction to mean QRS vector
e. A fully compensatory pause

5) Ventricular Tachycardia. – defined electrocardiographically by all of.

a) A broad QRS complex (usually > 0.14seconds)

b) Atrioventricular dissociation

c) A bifid upright QRS with a taller first peak in V_1

d) Deep S- waves in V_6

e) concordant (same polarity) QRS vector in all chest leads

QT dispersion: - this refers to the intercycle variability of the QT interval measured from a minimum of 10 leads for at least 2 cycles per lead. The QT interval will be measured from onset of QRS complex to the end of the T-wave (if the end is indeterminate, it shall be taken as where the trace goes back to the isoelectric line between T and P wave ; incase of U-waves; end of T-wave is lowest point between the T-wave and U-wave;).

The minimum and maximal duration of the QT (QTmin and QTmax) and their difference (QTdispersion) will be calculated. Each QT interval shall be corrected for the patient's heart rate according to Bazzett's formula.

$$QTc = QT \sqrt{R\text{-}R\ interval}$$ where QT and R-R interval are expressed in seconds.

P-wave dispersion: - Refers to the intercycle variability of the P wave duration as measured from a minimum of 10 leads for at least 2 cycles/ lead.

The P-wave duration shall be measured manually under a magnifying glass from the beginning of the P-wave deflection from the isoelectric line to the end of the deflection returning to the isoelectric line.

The P-wave dispersion is then calculated as the difference between the maximal P-wave duration and the minimal P-wave duration as follows;

$$PWd = Pmax - Pmin\ (milliseconds)$$

Hypokalemia/hypomagnesaemia: - $K+ < 3.5$mmol/l; $Mg2+ < 1.7$mg/dl

Hypoxia/ hypercapnia: - Pa02 <11.3Kpa and PaC02> 6Kpa respectively

Acidosis: - pH < 7.35,

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Ref: KNH-ERC/ 01/ 72

24th January 2008

Dr. Mohamed Adam Sheikh
Dept. of Medicine & Therapeutics
School of Medicine
University of Nairobi

Dear Dr. Mohamed

RESEARCH PROPOSAL: "THE PREVALENCE OF CARDIAC ARRHYTHMIAS AND ASSOCIATED FACOTRS AMONG PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT KENYATTA NATIONAL HOSPITAL" (P325/11/2007)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above cited research proposal for the period 24th January 2008 – 23rd January 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M.Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Medicine & Therapeutics, UON
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2/11/07

TO: CHAIRMAN, KNH ETHICAL AND RESEARCH COMMITTEE

RE: PREVALENCE OF CARDIAC ARRHYTHMIAS AND ASSOCIATED FACTORS AMONG PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT K.N.H

RESEARCHER: DR. MOHAMED ADAM SHEIKH H58/7918/05

The above research proposal has been presented to the Department of Clinical Medicine and Therapeutics Academic Members of Staff meeting held on 2ND November 2007.

It has been fully discussed and passed. It can now be presented to your committee for approval on content and ethics.

Thank you.

Yours Faithfully,

DR. A.J.O. WERE.
CHAIRMAN, DEPARTMENT OF MEDICINE
RESEARCH COMMITTEE