

**ELECTROCARDIOGRAPHIC MEASUREMENTS IN A COHERENT SAMPLE OF
HEALTHY ADULT URBAN AFRICANS IN KENYA**

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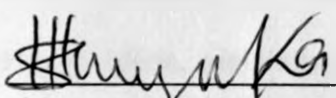


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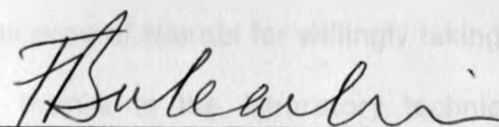
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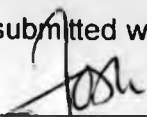
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ABBREVIATIONS AND ACRONYMS

AMI	Acute Myocardial Infarction
ANOVA	Analysis of Variance
BP	Blood Pressure
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
ECG	Electrocardiogram
EKG	Elektrokardiogram
HIV/AIDS	Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome
IHD	Ischaemic Heart Disease
HR	Heart Rate
LAFB	Left Anterior Fascicular Block
LVH	Left Ventricular Hypertrophy
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease
Ms	Milliseconds
NCDs	Non- communicable Diseases
QRS axis	Electrocardiographic electrical axis
QTc	QT interval corrected for heart rate
SD	Standard Deviation
SEM	Standard Error of the Mean
SPSS	Statistical Package for the Social Sciences
SSA	Sub-Saharan Africa
WHO	World Health Organization

ABSTRACT

Background: Electrocardiogram (ECG) measurements (intervals, amplitudes, heart rate, and QRS axis) are known to differ with age and sex. Most available data have been collected in Caucasian populations, yet evidence exists for racial differences in ECG findings. Studies of ECG parameters in the black African population are few and have their limitations such as those performed in hypertensive, HIV/AIDs, ischaemic heart disease and heart failure patients. This study describes changes in major ECG measurements with normal ageing in a population of healthy adult Africans.

Objective: To determine the ECG parameter differences with age and gender in a sample of healthy adult urban Africans in Kenya.

Design: Descriptive cross-sectional study.

Setting: The city of Nairobi and its environs.

Subjects: The study included 151 men and 224 women, all apparently healthy, with a relatively even spread of ages between 18 and 90 years.

Methods: Standard 12-lead ECGs were recorded and manually processed using digital callipers in and around Nairobi, Kenya. Volunteers were recruited from the University of Nairobi and from the surrounding estates of Nairobi city. ECGs were reviewed to exclude any that were technically unsatisfactory and others that had an unexpected abnormality. Data was empirically divided into six age groups; Group 1 (18-30 years), Group 2 (31-40 years), Group 3 (41-50 years), Group 4 (51-60 years), Group 5 (61-70 years) and Group 6 (70 years and above). The medians, lower limits (2nd percentile) and upper limits (98th percentile) of various ECG measurements were determined and age and sex comparisons examined. Data were expressed as mean (SD).

Results: Significant differences in numerical ECG values based on age and sex were observed. Heart rate was higher in women than men in all age groups ($P < 0.05$) and did not differ with age. The other study findings were as follows when the young, middle and older age groups, median (2nd and 98th percentile) were compared. Group 1 (18-30 years), Group 3 (41-50 years) and Group 5 (61-70 years)) were compared: *P duration:* Group 1, 110 (78,136) ms vs. Group 3, 114 (96,136) ms and Group 5, 125 (105,145) ms, $P < 0.001$, respectively. *PR interval:* Group 1, 171 (125,213) ms vs. Group 3, 187 (135,247) ms and Group 5, 199 (149,216) ms $P < 0.001$, respectively. *QRS duration:* Group 1, 63 (52, 84) ms vs. Group 3, 70 (47, 93) ms $P < 0.01$; Group 1, 63 (52, 84) ms vs. Group 5, 98 (65,117) ms $P < 0.001$. *QT interval:* Group 1, 362 (364, 458) ms vs. Group 3, 386 (320,429) ms $P < 0.01$; Group 1, 362 (364, 458), vs. Group 5, 403 (342,469) ms, $P < 0.001$. The mean QRS axis in degrees: Group 1, 62 (-72,108) vs. Group 3, 30 (-7, 82), $P < 0.01$; Group 1, 62 (-72,108) vs. Group 5, 11 (-35, 89), $P < 0.001$. Moreover, there were marked sex differences in the PR and QT intervals whereby men had higher mean PR interval (199 vs.192, $P < 0.01$) than women and on the other hand women had higher QT intervals than men (397 vs.403, $P < 0.05$).

Conclusions: The study showed marked age and sex differences in the ECG parameters measured in the black African population. This merits the definition and use of age- and sex-specific ECG criteria for the African population.

Keywords: Electrocardiogram; Age; Sex; African population; Developing countries.

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CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 GLOBAL TRENDS OF CARDIOVASCULAR DISEASES

Cardiovascular disease (CVD) is no longer just a problem of the affluent countries. In developing countries, it causes twice as many deaths as HIV, malaria, and tuberculosis combined and the economic implications of this problem are equally important for the sustainability of many developing countries (Lopez et al, 2006). Cardiovascular disease is the leading cause of death in those over the age of 45 years in Africa. The economic toll from CVD is equally devastating, leading to billions of dollars lost due to healthcare costs and reduced productivity from the disabling and fatal outcomes related to diabetes, hypertension, stroke, valvular heart disease, and heart failure. Much of it is preventable. In Sub-Saharan Africa (SSA), the prevention of CVDs is rarely on the public health agenda, as the region is plagued by infectious and parasitic diseases, nutritional deficiencies, and excessive maternal and perinatal morbidity and mortality (Twagirimukiza et al, 2011). Thus, with reasonable screening programmes and judicious use of scarce resources much of the suffering can be alleviated (Thomas, 2007).

This epidemic has the potential to place a large social and economic burden on developing countries, where CVD tends to strike those in their prime working years. In addition, the risk of CVD increases with advancing age. Since resources for managing CVD are limited, it is important that interventions be guided by cost-effective results for

low- and middle-income countries (Thomas, 2007). Despite the burden, cost-effective strategies such as smoking cessation, reduction in alcohol consumption, reducing fat intake and avoiding use of unsaturated fats while preparing meals, engaging in meaningful physical exercise coupled with sound health education exist at the population and individual levels for reducing CVD. Integral to all personal intervention strategies is an adequate assessment of the underlying risk of disease (Lopez et al, 2006).

According to Bovet et al (2006), CVD have become a leading cause of mortality and morbidity in developing countries and rates are expected to rise further over the next few decades. In particular, it has been estimated that high blood pressure, which may be as high as 15-25% in Africa, accounts for as much as 5.0% of the total mortality in middle-income countries (Mensah et al, 2005). According to this study, tobacco accounts for 4.0%, high cholesterol for 2.1% and obesity for 2.7% mortality.

The World Health Report (1999) estimates that in 1998, 78% of the burden of non communicable diseases (NCDs) and 85% of the CVD burden arose from the low and middle-income countries. The CVD burden afflicts both men and women, with cardiovascular deaths accounting for 34% of all deaths in women and 28% in men in 1998. As the epidemics advance, the social gradient also reverses with the poor becoming the most vulnerable victims in both developed and developing countries (WHO, 1999).

The high burdens of CVD in the developing countries are attributable to the increasing incidence of atherosclerotic diseases, perhaps due to urbanization and higher risk factor levels (such as obesity, diabetes, dyslipidaemia, hypertension, smoking, physical inactivity and excessive alcohol consumption, among others). This suggests that the increases in CVD rates based purely on demographic shifts are likely underestimates. The relatively early age at which they manifest, the large sizes of the population, and the high proportion of individuals who are young adults or middle-aged in these countries demonstrate the seriousness of the problem. For example, about half of the deaths attributable to CVD in the developing countries in 1990 occurred below the age of 70 years, in contrast to about a quarter in the developed countries (Murray et al, 1996). Such a pattern of premature CVD mortality is likely to haunt the developing countries even more in the future. Between 1990 and 2020, the increase in ischaemic heart disease (IHD) mortality (120% in women and 137% in men) in the developing countries is expected to be much greater than among developed countries (29% and 48% in both sexes), respectively. A similar pattern of increase in cerebrovascular disease mortality is predicted (124% and 107% increases among men and women) in developing countries, versus (78% and 56% increase), in the developed countries), respectively (Chockalingam et al, 1999). These projections are largely based on the expected changes in the demographics of the population and does not account for potential increases in risk factor levels (Reddy and Yusuf, 1998). More recently, a study by Yusuf et al (2004) identified nine easily measured risk factors (smoking, lipids, hypertension, diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors) that account for over 90% of the risk of acute myocardial infarction (AMI). These risk

factors are the same in almost every geographic region and every racial/ethnic group worldwide and are consistent in men and women.

Therefore, efforts must be made to reduce the CVD burden in developing countries as it has been done in the developed world. The largest effort to date to combine clinical and epidemiological knowledge with policy instruments to address CVD in low- and middle-income countries was made through the recent publication of *Disease Control Priorities in Developing Countries* (Jamison et al, 2006). This paper briefly reviewed those findings and extended them by detailing the central importance of the overall risk assessment in managing the CVD epidemic cost-effectively in developing countries. Cost-saving measures require appropriate diagnostic and therapeutic interventions. In addition, the role of advancing age, a known CVD risk factor, needs to be understood well particularly in developing countries.

1.2 Normal ageing

Ageing is the accumulation of changes in an organism or object over time. Ageing in humans refers to a multidimensional process of physical, psychological, and social change. Some dimensions of ageing grow and expand over time, while others decline. Reaction time, for example, may slow with age, while knowledge of world events and wisdom may expand (Melvin, 2003). Ageing is also thought to be a gradual, continuous process of spontaneous change that begins at conception and continues throughout all stages of life. It involves maturation and development for children, adolescents, and young adults. Then, during middle and late age, many bodily functions begin to be

altered. Thus, ageing has positive and negative aspects. The process of ageing is a continuum progressing throughout an individual's life. Unlike pathologic conditions, the ageing process affects all individuals. It is a process that is genetically programmed but modified by environmental influences, so the rate of ageing can vary widely among people. Therefore, physiologic ageing in any given individual may occur more rapidly or more slowly than the chronologic age, giving rise to people who are "old" at age 60 and others who are "young" at age 75. The status of physical conditioning of the individual can radically affect the measurements of cardiovascular function in the elderly and changes in physical activity can profoundly change cardiovascular function (Melvin, 2003). "Normal" ageing is ageing which occurs without disease, that is, there are a number of physiological changes, that do not involve a pathological process, and though there may be bodily changes in the person, the person enjoys good function of mind and body, and is able to live independently, and with a good quality of life (Mark, 2006).

The following is a description setting out five criteria for ageing, as proposed by Strehler (1962).

Cumulative: Effects of ageing increase with time.

Universal: All members of a species display signs of ageing.

Progressive: Ageing is a series of gradual changes.

Intrinsic: Changes would take place even in a "perfect" environment.

Deleterious: Changes that occur compromise normal biological functions.

1.3 THE EFFECT OF AGEING ON THE CARDIOVASCULAR SYSTEM

Ageing is associated with complex and diversified changes of cardiovascular structure and function. There are several cardiovascular changes associated with physiologic ageing namely, cardiac, vascular and blood pressure changes.

Cardiac changes

The heart becomes slightly hypertrophied and hyporesponsive to sympathetic (but not parasympathetic) stimuli, so that the exercise-induced increases in heart rate and myocardial contractility are blunted in older hearts. Thus, for cardiac output to be increased in proportion to the body's metabolic needs despite inadequate contractile and chronotropic reserves, the ageing left ventricle mainly engages the Frank-Starling mechanism, that is, it undergoes marked increases in volume, both end-diastolic and end-systolic. Via such haemodynamic pattern, the ageing heart can significantly increase its maximum output and allow elderly subjects to perform vigorous exercise, although not up to the same intensity as a younger individual can sustain. Overall, the peak cardiac output attained in response to maximal effort is blunted by some 20–30% in elderly compared with young healthy subjects; the blunting being largely attributable to a lesser degree of effort tachycardia rather than to altered stroke volume (Fleg et al, 1995).

Physiological age-related alteration in left ventricular diastolic function is a predisposing factor to the development of diastolic heart failure, which is indeed highly prevalent in elderly patients, accounting for up to 50% of all heart failure patients in this age range

(Alberto et al, 2003). Altered endothelial function in ageing coronary vessels is a further element that causes advanced age to be listed among coronary risk factors. Likewise, there is now convincing evidence that increased carotid intima or media thickness (by ultrasound) predicts occurrence of cardiovascular events (O'Leary et al, 1999)

Vascular changes

The aorta and major elastic arteries become elongated and stiffer, with increased pulse wave velocity, evidence of endothelial dysfunction, and biochemical patterns resembling early atherosclerosis. The arterial baroreflex is sizeably altered in ageing, but different components are differentially affected: there is a definite impairment of arterial baroreceptor control of the heart but much better preserved baroreceptor control of peripheral vascular resistance. The age-associated increased arterial stiffness result from several factors, including fragmentation of the elastic membrane, intimal thickening, increases in collagen content and linking, decreased baroreflex sensitivity, and diminished endothelium-dependent vaso-relaxation (Challah et al, 1997). These changes increase the vascular load faced by the left ventricle and exert a significant influence on cardiovascular performance in healthy subjects (Lakatta and Schulman, 2004). Although the above-mentioned age-related functional alterations have been observed in atherosclerosis-free normotensive individuals, most of them are also present in atherosclerotic vessels, which are also known to be stiffer than normal but in which, unlike in ageing, focal lesions, vessel stenosis, and plaque rupture eventually develop. Thus, because ageing and atherosclerosis run along very similar biochemical pathways and determine many similar vascular alterations, vessel ageing may be

viewed as representing the prodromal stage of atherosclerotic disease or, conversely, atherosclerosis may be viewed as a form of accelerated arterial ageing, probably favoured by coexisting noxious stimuli (e.g. dyslipidaemia, smoking, and hypertension) (Alberto et al, 2003).

Blood pressure changes

The fundamental age-related change in arterial function is impairment of distensibility and thus of the cushioning function of the aorta and its major branches, associated with an enhancement in pulse wave velocity; such changes have been suggested to be nonuniform throughout the arterial tree with more marked alterations in elastic-type versus muscle-type arteries (Roach and Burton, 1959). Increased stiffness is not solely dependent on structural alterations but also is majorly affected by humoral and endothelial regulation of vascular smooth muscle tone. Aged vessels show an increased endothelial permeability and a reduced nitric oxide-dependent vasodilator response to acetylcholine. Also the vasodilator responses to beta-adrenoceptor agonists are clearly attenuated because of reduced number and affinity of specific receptors. Albeit to a probably lesser extent, vasoconstrictor responses to alpha-receptor stimulation are also diminished in aged arteries. The systemic haemodynamic consequences of age-related vascular hypertrophy and stiffness include a moderate increase in total peripheral resistance and the well known tendency to increased systolic and pulse pressure. In turn, elevated pressure is a stimulus for further development of vessel wall hypertrophy and stiffness, so that adverse phenomena beget each other and a more or less rapidly progressing vicious circle is established (Egashira et al, 1993).

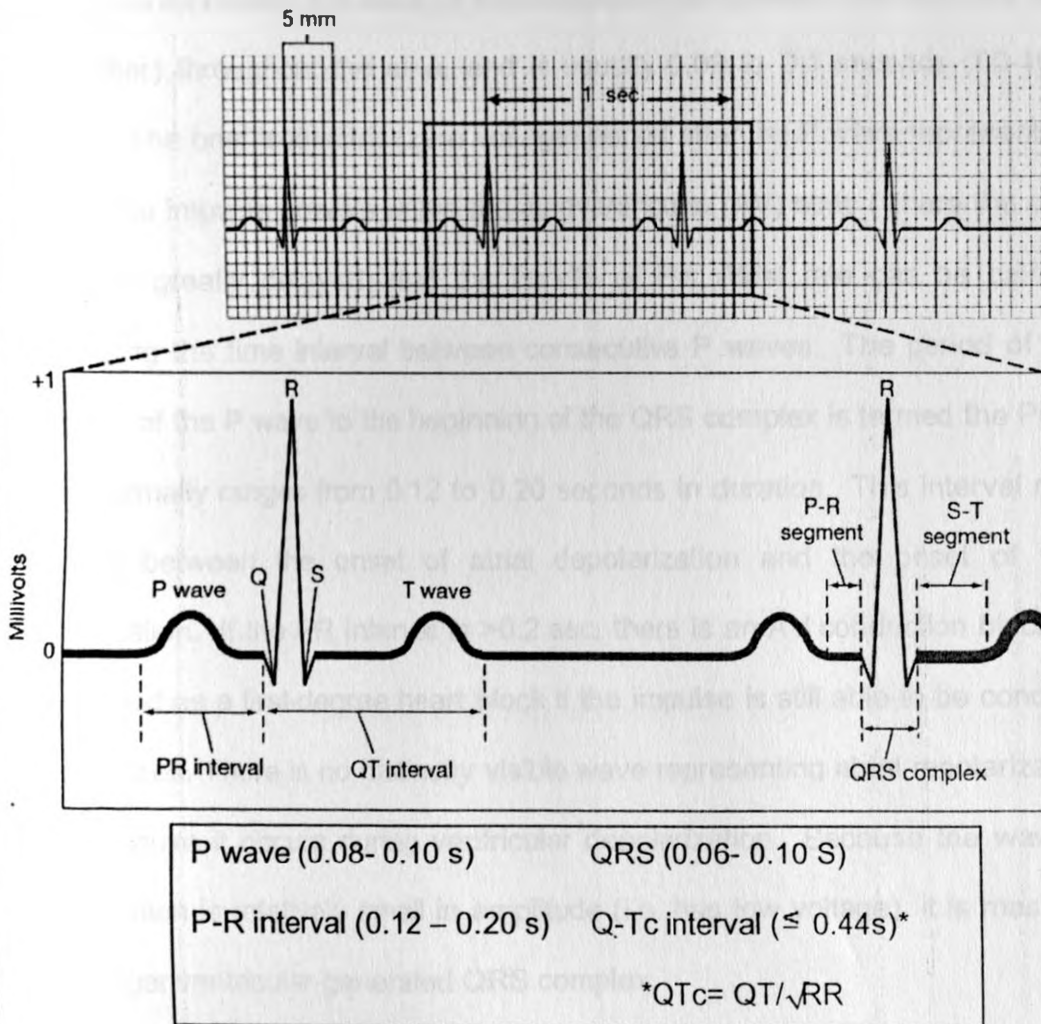
Combined occurrence of enhanced pulse wave velocity and prolonged ejection time critically facilitates summation of anterograde and retrograde arterial waves, which may contribute to elevation of systolic blood pressure and pulse pressure in aged subjects. This has obvious implications as a powerful mechanism favouring onset and/or progression of vascular damage and increased risk of adverse physiological or clinical outcomes, including excessive cardiac workload and oxygen demand, left ventricular hypertrophy, further arterial stiffening itself, cerebrovascular events, and decline of renal function. In summary, cardiovascular ageing encompasses such a wide and complex range of phenomena at the structural, functional, and molecular levels. It is therefore important to determine ageing changes of the heart function before considering any abnormality as significant, especially in the elderly.

1.4 GENERAL DESCRIPTION OF THE ELECTROCARDIOGRAM

1.4.1 PHYSIOLOGY OF ELECTROCARDIOGRAPHY

When the cardiac impulses pass through the heart, electrical current also spreads from the heart into the adjacent tissues surrounding the heart. A small portion of the current spreads all the way to the surface of the body. Because body fluids are good conductors (that is, because the body is a volume conductor), fluctuations in potential that represent the algebraic sum of the action potentials of myocardial fibers can be recorded extracellularly. This electrical activity generated by the heart can be measured by an array of electrodes placed on the body surface. The recorded tracing is called an Electrocardiogram (ECG, or EKG). A "typical" ECG tracing is shown in Figure 1. The different waves that comprise the ECG represent the sequence of depolarization and repolarization of the atria and ventricles. If an electrode is placed so that the wave of depolarization spreads towards the recording electrode, the ECG records a positive (upward) deflection. On the other hand, if the wave of depolarization spreads away from recording electrode, a negative (downward) deflection occurs. When myocardial muscle is completely polarized or depolarized, the ECG will not record any electrical potential but rather a flat line, isoelectric line (Meek and Morris, 2002). Accordingly, the ECG has three waves, P, QRS and T, and two clinically relevant time intervals, QRS and QT.

ELECTROCARDIOGRAM



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Figure 1: Various ECG parameters and waves commonly measured

(amplitudes like P, R and T and intervals e.g. PR, QRS and QT). Amplitudes are measured in millivolts (mV) while intervals are measured in seconds (sec) or milliseconds (ms). One small square represents 0.1 mV vertically and 0.04 seconds horizontally.

The P wave and PR interval

The P wave represents the wave of depolarization that spreads from the sino atrial node (pacemaker) throughout the atria, and is usually 0.08 to 0.1 seconds (80-100 ms) in duration. The brief isoelectric (zero voltage) period after the P wave represents the time in which the impulse travels within the atrioventricular (AV) node (where the conduction velocity is greatly delayed) and the bundle of His. Atrial rate can be calculated by determining the time interval between consecutive P waves. The period of time from the onset of the P wave to the beginning of the QRS complex is termed the PR interval, which normally ranges from 0.12 to 0.20 seconds in duration. This interval represents the time between the onset of atrial depolarization and the onset of ventricular depolarization. If the PR interval is >0.2 sec, there is an AV conduction block, which is also termed as a first-degree heart block if the impulse is still able to be conducted into the ventricles. There is no distinctly visible wave representing atrial repolarization in the ECG because it occurs during ventricular depolarization. Because the wave of atrial repolarization is relatively small in amplitude (i.e. has low voltage), it is masked by the much larger ventricular-generated QRS complex.

The QRS complex

The QRS complex represents ventricular depolarization. Ventricular rate can be calculated by determining the time interval between consecutive QRS complexes. The duration of the QRS complex is normally 0.06 to 0.1 seconds (60 to 100 milliseconds). This relatively short duration indicates that ventricular depolarization normally occurs very rapidly. If the QRS complex is prolonged (>0.12 sec), conduction is impaired within

the ventricles. This can occur with bundle branch blocks or whenever a ventricular focus (abnormal pacemaker site) becomes the pacemaker driving the ventricle. Such an ectopic focus nearly always results in impulses being conducted over slower pathways within the heart, thereby increasing the time for depolarization and the duration of the QRS complex. The shape of the QRS complex in the Figure 1 above is idealized. The shape changes depending on which recording electrodes are being used. The shape will also change when there is abnormal conduction of electrical impulses within the ventricles.

ST segment

The isoelectric period (ST segment) following the QRS is the time at which the entire ventricle is depolarized and roughly corresponds to the plateau phase of the ventricular action potential. The ST segment is important in the diagnosis of ventricular ischaemia or hypoxia because under these conditions, the ST segment can become either depressed or elevated.

T wave

The T wave represents ventricular repolarization and is longer in duration than depolarization (i.e. conduction of the repolarization wave is slower than the wave of depolarization). Sometimes a small positive U wave may be seen following the T wave. This wave represents the last remnants of ventricular repolarization. Inverted or prominent U waves indicate underlying pathology or conditions affecting repolarization.

QT interval

The QT interval represents the time taken for both ventricular depolarization and repolarization to occur and therefore roughly estimates the duration of an average ventricular action potential. This interval can range from 0.2 to 0.4 seconds depending upon heart rate. At higher heart rates, ventricular action potentials shorten in duration, which decreases the QT interval. Because prolonged QT intervals can be diagnostic for susceptibility to certain types of tachyarrhythmias, it is important to determine if a given QT interval is excessively long. In practice, the QT interval is expressed as a "corrected QT (QTc)" by taking the QT interval and dividing it by the square root of the RR interval (interval between ventricular depolarizations). This allows an assessment of the QT interval that is independent of heart rate. Normal corrected QTc intervals are less than 0.44 seconds. The ECG is recorded at a speed of 25 mm/sec, and the voltages are calibrated so that 1 mV = 10 mm in the vertical direction. Therefore, each small (1 mm square) represents 0.04 sec (40 ms) in time and 0.1 mV in voltage, as shown in Figure 1. Because the recording speed is known, one can calculate the heart rate and various ECG intervals between different waves. (Cooper, 1986).

1.4.2 ECG CHANGES WITH AGEING

The ageing process is known to affect ECG measurements. The cardiovascular system of ageing people exhibits a number of morphological, functional and special clinical features. Alterations in shape, size and weight of the heart, alterations of coronary arteries, valves and aorta are accompanied by typical changes in several hemodynamic variables (Franke et al, 1976). As age is a determinant of cardiac refractory periods, the

younger age group tends to have shorter values than the older age groups. Knowledge of interpretation of the basics of ECG changes with normal ageing is helpful in differentiating normal from abnormal findings during interpretation. These basics include familiarity with the age-related normal findings in heart rate, intervals, axis, and waveform morphologies. For those dealing with very young and older children, an understanding of cardiac physiologic changes associated with age and maturation, particularly the adaptation from right to left ventricular predominance is very important (Sharieff and Rao 2006).

Electrocardiographically or echocardiographically detected left ventricular hypertrophy (LVH) is a manifestation of preclinical cardiovascular disease and a strong predictor of cardiovascular morbidity and mortality (Verdecchia et al, 1998). The Framingham heart studies clearly highlighted that the diagnosis of LVH should preferably be made using echocardiography because it is more sensitive in detecting LVH (Crow et al, 1998). However, technical difficulties and economic considerations restrict the large-scale use of Echo for this purpose. Resting ECG, on the other hand, is a low-cost, non-invasive, easy-to-acquire method that is widely available for clinical use.

Many studies have been conducted to improve electrocardiographic criteria for the identification of this condition in patients with different cardiovascular diseases. The major criterion for the identification of LVH is the increased QRS-complex voltage, and several criteria have been proposed for this purpose. Reports of superiority of the Cornell criterion over the classic Sokolow-Lyon criterion have previously been published

(Casale and Devereux, 1985). The Sokolow-Lyon-Rappaport (SLR) index (SV_1 or V_2+RV_5 or $V_6 \geq 3.5$ mV or 35 mm) and the Cornell criteria ($RaVL+SV_3 \geq 2.8$ mV or 28 mm, and/or 2.4 mV or 24 mm for males and ≥ 2.0 mV or 20 mm for females), hereafter called "external criteria", are used to assess LVH (Casale et al, 1987).

Electrocardiographic R and S wave amplitudes increase with age in females, especially in the left precordial leads. The upper limits of normal for the T wave amplitudes decrease with age in men. Values for the Sokolow-Lyon and 12-lead summed voltages as well as products with their voltage durations are lower in women than in men up to the age of 75 years, from where these lines cross. This is because these values increase with age in women, whereas in men, they decrease with age. The Cornell voltage and voltage duration product criteria only slightly increase with age in both sexes. There is a clear link between age and QRS duration, which increases linearly from about one year of age to adolescence. In the adults, the principal differences seem to be increased QRS duration in men compared with women both in the standard and signal-averaged ECG. Upper limits of normal heart rate also tend to be higher in women than in men in the adult populations (Macfarlane et al, 1994).

Age-associated changes in the QRS complex observed by ECG are caused by increased electric resistance and not by the heart current itself (Macfarlane et al, 1994). According to Rijnbeek et al (2006), the QRS duration is longer in men than in women but does not show significant changes with age. With advancing age in men, there is a narrowing of QRS, a leftward QRS axis shift, and a loss of SV_1 and RV_5 amplitude. In

women, a leftward QRS axis shift is associated with advancing age. These changes should be considered in defining normal age- and sex-specific reference values. These findings underscore theoretical limitations of commonly used criteria for the ECG diagnosis of conditions such as LVH (Levy et al, 1987). Previous studies have reported that the prevalence of nonspecific ECG findings differs by race. Among individuals free of clinical CHD, African-Americans reportedly have more T wave abnormalities, prolonged PR intervals, high amplitude R waves, and ECG defined LVH than whites (Lori et al, 1998). Sex has been considered for many years to be a factor that may influence the ECG pattern of cardiac repolarization. A longer duration of repolarization, reflected by a longer QT interval and small T-wave amplitude, is present in the surface ECGs of women compared with men (Bidoggia et al, 2000).

Previous research findings show that the higher incidence of nonspecific ST-T changes, prolonged PR intervals, and left-axis deviation occur more frequently in older people (Rajala et al, 1984; Mihalick MJ and Fisch C, 1974). It is difficult to assess whether such changes in the geriatric population are due to the normal ageing process or a reflection of underlying subclinical heart conditions, namely CAD, congestive heart failure (CHF), and age-related cardiac amyloidosis.

Dispersion of QT intervals has been proposed as a measure of repolarization process inhomogeneity (and thus refractoriness inhomogeneity) of ventricular myocardium. Recently, other possible explanation for this phenomenon has been intensively discussed (Karjalainen et al, 1997). According to this concept, QT dispersion is

explained by different projections of the heart repolarization vector. Moreover, the reproducibility of the measurement of QT dispersion is rather low as it could be influenced both by intrinsic (e.g. amplitude of the T wave or U wave) and extrinsic (e.g. noise, amplitude and time parameters of recording) factors. Only markedly prolonged QT dispersion must therefore be interpreted as a sign of abnormal course of the repolarization. Nevertheless, according to all mentioned facts the only serious interpretation of increased QT dispersion is that it reflects nonspecific repolarization changes. Explanation that is more specific is currently not available. The QT interval is longer in men than in women and increases in both sexes with age (Balaji et al, 1997).

Commonly accepted reference ranges for the ECG have been in use, with little change, for many years. A reexamination of established reference values based on age and sex is needed. ECGs are now recorded and read differently from when the time-honoured upper and lower limits of normal for heart rate, PR interval, QRS duration, QT interval, and frontal plane axis were being defined decades ago (Hiss and Lamb, 1962). Populations throughout the world have different age and ethnic compositions from time immemorial, and the nature, incidence, extent, and medical treatment of cardiac and noncardiac diseases that influence these intervals has changed (Macfarlane et al, 1994). Reference ranges for ECG intervals, heart rate, and QRS axis in general use by medical personnel and ECG readers are unrepresentative of true age- and sex-related values in large populations (Mason et al, 2007). It would thus seem imperative that normal ECG parameters for the African population based on age and sex be available

to assist in the development and application of specific diagnostic criteria for ECG interpretation.

A Study by Lori et al (1998) showed that the age-adjusted prevalence of high-amplitude R wave, ST elevation, T wave findings, and prolonged PR interval were significantly higher in African-Americans than in whites. As for continuous ECG measurements, the R wave in leads V₅ and V₆, the S wave in V₁, the J-point amplitude in leads V₂ and V₅, the P-R interval, and the Cornell voltage (SV₃ + RaVL) for LVH were all significantly greater in African-Americans than in whites. However, in both men and women, the heart rate corrected QT interval was shorter in African-Americans than in whites. These results suggest that racial differences in ECGs may not be explained entirely by differences in established CHD risk factors, and because current diagnostic ECG criteria are largely based on data from middle-aged white men and women, race should be considered in the interpretation of ECG findings.

1.4.3 ECG IN DIAGNOSIS OF HEART DISEASE

The ECG or Electrocardiogram (EKG) is a diagnostic tool that measures and records the electrical activity of the heart in exquisite detail. Interpretation of these details allows diagnosis of a wide range of heart conditions. These conditions can vary from minor to life threatening. The information obtained from an ECG can be used to diagnose different types of heart disease. It may be useful for seeing how well the patient is responding to treatment. The ECG is used to measure the rate and regularity of heartbeats as well as the size and position of the chambers; the presence of any

damage to the heart; and the effects of drugs or devices used to regulate the heart (e.g. pacemakers). Further, it reveals rhythm problems such as the cause of a slow or fast heartbeat and to demonstrate hypertrophy of a heart muscle, for example, due to long-standing elevated blood pressure.

The resting ECG permits to suspect or diagnose a large number of cardiac disorders like CHF, cardiac arrhythmias, myocardial ischaemia, ventricular and atrial fibrillations. As a noninvasive, inexpensive, risk-free and simple technique, ECG may be even more useful in developing countries where resources are limited and cardiovascular diseases are rapidly emerging as a major health problem.

It is useful to record an ECG in the case of symptoms like dyspnoea, chest pain, fainting and palpitations or when someone feels that their own heartbeat is abnormal. The test can show evidence of disease in the coronary arteries. Unfortunately, in many people who have significant narrowing of the arteries supplying the heart muscle, the ECG recording made at rest is often normal. Therefore, if a significant narrowing is suspected, an ECG recording is often made when the patient is exercising (an exercise stress test), as this is more likely to reveal the problem.

An ECG can be used to assess if the patient has had a heart attack (myocardial infarction) or evidence of a previous heart attack. An ECG can be used to monitor the effect of medicines used for CAD. Significant age trends are present in, for example, P-wave duration, QTc interval, and frontal QRS axis, with concomitant changes of R amplitudes in the extremity leads. Sex differences exist for heart rate, interval durations,

the Sokolow and Cornell indices (indices for LVH), and QRS and ST-T amplitudes in different leads. Notably, left-precordial R wave amplitudes in women increases with age; the Sokolow index shows a clearer age trend for men than for women, the reverse being true for the Cornell index. Some of these findings are at odds with established diagnostic ECG criteria (Wu et al, 2003). The mean frontal QRS-axis shifts to the left with advancing age, but the shift is significant only in men. In both men and women there is a leftward shift of the mean frontal QRS-axis with increased weight, increased chest circumference and increased obesity index which should put into consideration as one can be erroneously diagnosed with left posterior bundle branch block (Lundh, 1984). There has been reported elevation of the ST segment in anterior chest leads of African-Americans. Several mechanisms, including subepicardial injury, pericarditis, cardiac tumor and abnormal atrial repolarization producing an upright T wave have been proposed to explain ST elevation in the precordial leads. However, in healthy individuals, especially young adults and African-Americans, the most likely explanation is early repolarization of the subepicardial regions (Wasserburger and Alt, 1961).

The present study was therefore undertaken to determine the ECG parameter differences with age from a sample of black African subjects. Most of the ECG intervals, heart rate and QRS axis in general use by medical personnel and ECG readers may be unrepresentative of true age- and sex-related values in the African population (Mason et al, 2007; Wu et al, 2003) . Accurate reading and interpretation of the ECGs is the basis on which diagnostic criteria are developed. The ECG, however, is subject to age- and sex-variations and may also be racially determined (Rautaharju et al, 1994). Studies of

normal ECG limits for the Africans, especially sub-Saharan Africa, are few (Niakara et al, 2002; Odeku and Ikeme, 1967; Lodha and Makene, 1976; Seedat et al, 1993; Olubodun et al, 1991; Odia, 1990) and have their limitations for example, Electrocardiograms (ECG) obtained from patients and subjects with HIV disease, hypertension, congestive heart failure and CAD. Typical examples of normal ECG recordings from both men and women are illustrated in Appendices 5.1-5.4.

1.5

BROAD OBJECTIVE

To determine the ECG parameters in representative age group and gender from a sample of healthy African subjects.

SPECIFIC OBJECTIVES

1. To determine the ECG variables in various age groups.
2. To determine gender differences in various ECG measurements.
3. To determine the relationship between ECG measurements and anthropometric measurements.

1.6

JUSTIFICATION

1. Studies in normal ECG values for the Africans, especially sub-Saharan Africa, are few and have their limitations.
2. Accurate normal limits of the ECG are the basis on which diagnostic criteria are developed, but these vary with normal ageing.
3. Reference ranges for ECG intervals, heart rate, and QRS axis in general use by medical personnel and ECG readers are unrepresentative of true age- and sex-related values in large populations.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 Study design

Descriptive cross-sectional study.

2.2 Study area

The study was conducted in Nairobi and its environs. The study subjects were recruited from Chiromo Campus of the University of Nairobi which included members of staff, students and visitors, selected Health Centres of Nairobi City Council (Kangemi, Karen and Umoja). Additional volunteers were recruited from the Little Sister's Charity for Wazee's home for the Elderly, based in Kasarani, Nairobi; and the Presbyterian Church of East Africa (PCEA) Social Hall, Ongata Rongai. Local advertisements inviting volunteers to come for the study on specified days were conducted through public notice boards, and announcements in local churches. The researcher and trained assistants went to these designated venues to perform the standard 12-Lead ECGs.

2.3 Sample size and study population

Healthy volunteer adult subjects aged 18 to 90 years were selected for the study. The study included a single baseline ECG. The study subjects were empirically categorized into six subgroups according to age, namely: Group 1 (18-30 years), Group 2 (31-40 years), Group 3 (41-50 years), Group 4 (51-60 years), Group 5 (61-70 years) and Group 6 (70 years and above). A Convenient non-probability sampling technique was applied to recruit the study participants and target sample size of 400 participants was determined. The sample size was calculated using the formula shown below (Daniel, 1999):

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where, n = sample size.

Z = Z statistic for a level of confidence, 1.96 (1.96 for 95% confidence level).

P = Expected prevalence or proportion (in proportion of one; if 20%, P = 0.2), and

d = precision ((in proportion of one; if 5%, d = 0.05). P here stands for prevalence of CVD, expressed as a decimal, and which stands at approximately 10% in the Kenyan population.

Z statistic (Z): for the level of confidence of 95%, which is conventional, Z value is 1.96.

Results are presented with 95% confidential intervals (CI)

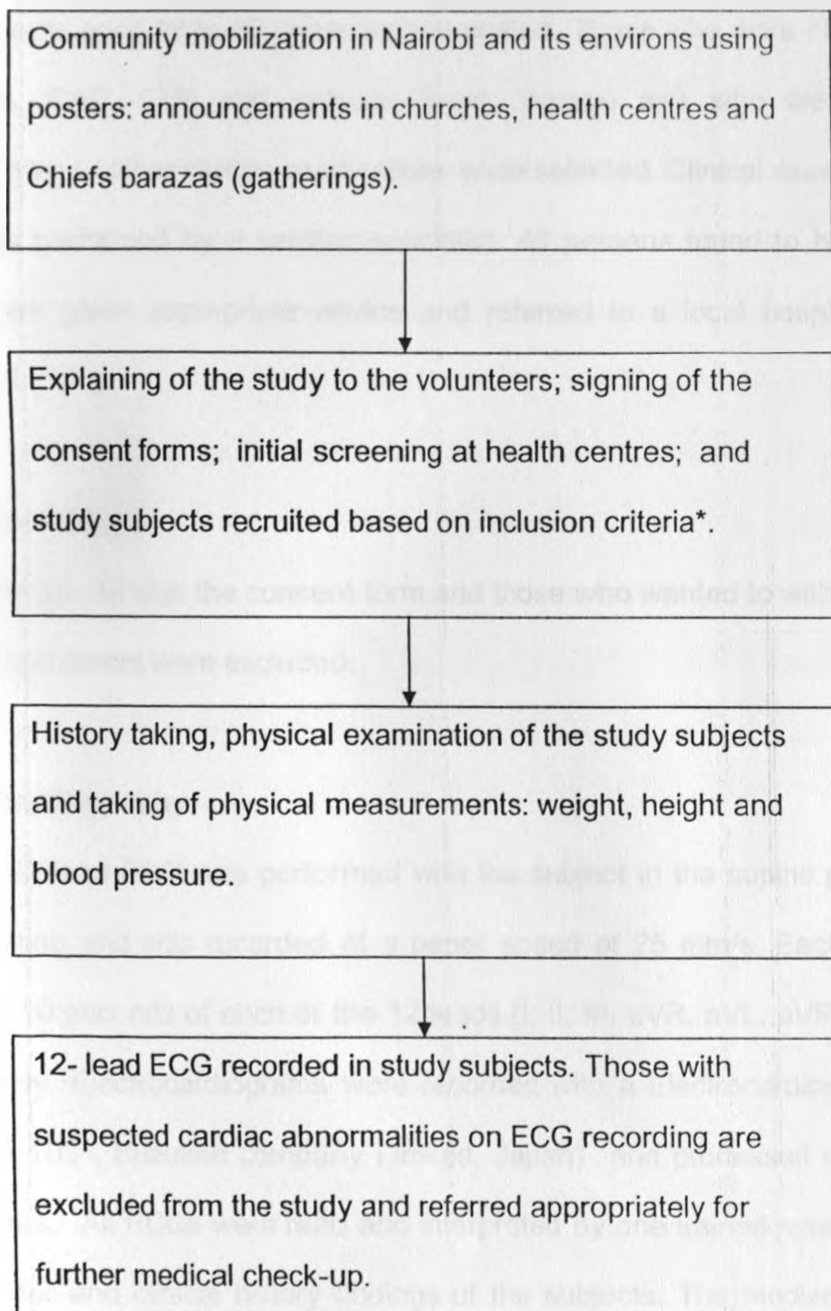


Figure 2: Selection of the study subjects. *inclusion criteria are explained in the text.

2.4 Inclusion criteria

Healthy subjects aged 18 to 90 years were recruited. Those who were clinically free of hypertension, CAD, CHF and valvular heart disease and who were not taking antihypertensive or other cardiac medications were selected. Clinical examination of the subjects was performed by a cardiac specialist. All persons found to have a cardiac condition were given appropriate advice and referred to a local hospital for further management.

2.5 Exclusion criteria

Subjects who did not sign the consent form and those who wanted to withdraw from the study after recruitment were excluded.

2.6 Electrocardiography

A standard 12-lead ECG was performed with the subject in the supine position during quiet respiration and was recorded at a paper speed of 25 mm/s. Each ECG tracing consisted of 10 seconds of each of the 12 leads (I, II, III, aVR, aVL, aVF and V1 to V6) simultaneously. Electrocardiograms were recorded with a Electrocardiograph machine (KENZ-ECG 103 , Suzuken company Limited, Japan) and processed manually using digital callipers. All ECGs were read and interpreted by one trained researcher blinded to age, gender and clinical history findings of the subjects. The medians, lower limits (2nd percentile) and upper limits (98th percentile) of various ECG measurements were measured and age and sex differences examined. Various interval measurements were determined, including QRS duration, heart rate, PR interval, frontal plane QRS axis, QT

interval, QTc-Bazett and QTc-Fridericia (QT intervals corrected for heart rate according to Bazett and Fridericia formulas) (Lundh, 1984).

QT-interval analysis was performed on 12-lead ECGs. The QT interval was taken from the onset of the QRS to the end of T wave (the end of the T wave was defined as the intersection of the iso-electric line and the tangent of the maximal slope on the downward limb of the T wave) (Figure 1). If U waves were present, the QT interval was measured to the nadir of the curve between T and U waves. QT intervals were corrected with Bazett's formula ($QTc=QT/\sqrt{RR}$), where QTc is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds, (Bazett, 1920). Fridericia's formula ($QTc=QT/RR^{0.33}$) was also used as it is more accurate than Bazett's (Fridericia, 1920).

2.7 Blood Pressure and Anthropometric measurements

Measurements of blood pressure (BP), body weight, and height were in accordance with the guidelines of the WHO-MONICA (monitoring trends and determinants of cardiovascular disease) project (WHO-MONICA project, 1989). Anthropometrics were taken with the subjects wearing "light" clothing and no shoes. Height, measured to the nearest centimetre, and weight, measured to the nearest kilogram, was used to calculate body mass index (kilograms per square meter). Three seated BP were measured using a random-zero sphygmomanometer, and the average of the last two was used.

2.8 Definition of various ECG measurements

Various ECG waves are illustrated in figure 1 above:

P wave: the sequential activation (depolarization) of the right and left atria

QRS complex: right and left ventricular depolarization (normally the ventricles are activated simultaneously).

The Q wave: represents the initial negative deflection before an R wave.

The R wave: first positive deflection after a Q wave.

The S wave: first negative deflection after an R wave.

ST-T wave: ventricular repolarization.

U wave: origin for this wave is not clear - but probably represents "afterdepolarizations" in the ventricles.

PR interval: time interval from onset of atrial depolarization (P wave) to onset of ventricular depolarization (Q wave).

QRS duration: duration of ventricular muscle depolarization.

QT interval: duration of ventricular depolarization and repolarization.

RR interval: duration of ventricular cardiac cycle (an indicator of ventricular rate).

PP interval: duration of atrial cycle (an indicator of atrial rate).

2.9 Orientation of the 12 Lead ECG

The 12-lead ECG provides spatial information about the heart's electrical activity in approximately three orthogonal directions. It consists of three bipolar limb leads: I, II, and III; three augmented voltage leads: aVR, aVL, aVF; and six chest or precordial

leads: $V_1 - V_6$. All limb leads lie in the frontal plane. Chest leads circle the heart in the transverse plane.

Each lead provides a different electrical angle or picture of the heart. Anterior part of the heart is pictured by looking at $V_1 - V_4$, lateral view of heart the by I, aVL, V_5 and V_6 while Inferior view of the heart is pictured by II, III, and aVF. Limb lead II shows large QRS amplitude because left ventricular vector lies in parallel with electrode placement. While chest lead V_1 has large S wave because left ventricle current vector is directed away from the electrode. Each of the 12 leads represents a particular orientation in space, as is shown Figure 3 below:

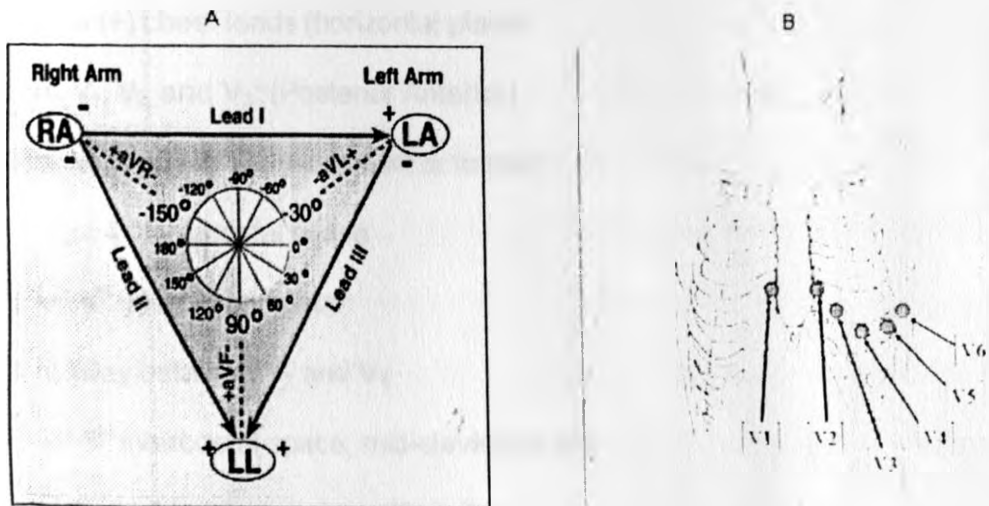


Figure 3A: Einthoven's Triangle. Each of the 6 frontal plane leads has a negative and positive orientation (as indicated by the '+' and '-' signs). Lead I (and to a lesser extent Leads aVR and aVL) are right \leftrightarrow left in orientation. Lead aVF (and to a lesser extent Leads II and III) are superior \leftrightarrow inferior in orientation. **Figure 3B:** Shows the precordial leads V_1 to V_6 and their positions as they are normally placed on the chest (Reproduced with permission from Intermountain Healthcare's "Introduction to ECG Interpretation," by Frank Yanowitz, M.D. ©2010, Intermountain Healthcare).

RA = right arm; LA = left arm, LL = left leg.

Bipolar limb leads (frontal plane):

Lead I: RA (-) to LA (+) (Right Left, or lateral)

Lead II: RA (-) to LF (+) (Superior Inferior)

Lead III: LA (-) to LF (+) (Superior Inferior)

Augmented unipolar limb leads (frontal plane)

Lead aVR: RA (+) to [LA and LF] (-) (Rightward)

Lead aVL: LA (+) to [RA and LF] (-) (Leftward)

Lead aVF: LF (+) to [RA and LA] (-) (Inferior)

Unipolar (+) chest leads (horizontal plane)

Leads V₁, V₂, and V₃: (Posterior Anterior)

Leads V₄, V₅, and V₆: (Right Left or lateral).

V₁: right 4th intercostal space

V₂: left 4th intercostal space

V₃: halfway between V₂ and V₄

V₄: left 5th intercostal space, mid-clavicular line

V₅: horizontal to V₄, anterior axillary line

V₆: horizontal to V₅, mid-axillary line

2.10 Ethical considerations

All participants were adults. Informed consent was obtained from all of them (Appendix 2). Ethical approval was obtained from the Kenyatta National Hospital Ethics and Research Committee.

2.11 Reproducibility (Repeatability and reliability)

Intra-observer and inter-observer variabilities were tested in ten recorded ECG strips selected randomly. Two trained observers measured the ECG strips independently and measurements, particularly of QT interval, PR interval and QRS duration were taken and repeated at different times to determine both intra- and inter-observer variability. Results were analysed using the method of agreement as described by Bland and Altman (1986) and presented as the coefficient of variation.

2.12 Statistical Analysis

Descriptive statistics using SPSS version 13.0, were used for this analysis. The mean values, standard deviation, the median, 2nd and 98th percentiles for the continuous measurements and the values for categorical ECG findings were calculated. Differences between two sets of continuous data (e.g. men vs. women) were compared by using nonparametric Wilcoxon's rank-sum test. Comparisons in various age groups (taken as a continuous variable) were quantified with the Cuzick's test (a nonparametric extended Wilcoxon's rank-sum test). Bivariate analysis was used to test the independence of the association between ECG findings and several clinical variables (i.e., age, body mass index, systolic BP, diastolic BP and mean QRS axis). Data were expressed as mean \pm S.D. Differences between the ECG subgroups were assessed by ANOVA and post hoc tests, Tukey and Bonferroni. A P-value less than 0.05 was considered significant.

CHAPTER THREE

3.0

RESULTS

Between February and June 2009 a total of 600 subjects were invited and screened for inclusion. Four hundred and ten (410) subjects were recruited for the study and 12-lead resting ECGs obtained. However 20 ECG strips were excluded from analysis because they were technically faulty and therefore were ineligible. Another 15 ECG strips were excluded from the study due to detected ECG abnormalities such as left ventricular hypertrophy, tachycardia (above 100 beats per minute) and myocardial ischaemia.

3.1 General characteristics

Electrocardiograms for three hundred and seventy five (375) subjects were analysed, 151 (41.3 %) males and 224 (59.7%) females. The mean age of the study population was 42.7 (SD 17.7) years ranged between 18 and 90 years. All subjects were empirically categorized into six prespecified subgroups according to age, namely: Group 1 (18-30 years), Group 2 (31-40 years), Group 3 (41-50 years), Group 4 (51-60 years), Group 5 (61-70 years) and Group 6 (70 years and above) as depicted in Table 1.

The general characteristics across age group and by gender are depicted in Table 1. The number of subjects in each age group exceeded thirty and there were more women than men in group 1 to 4. The number of men in groups 2 to 6 and number of women in group 5 and 6 were less than thirty. Although both systolic and diastolic blood pressure measurements were within the normal range as a result of exclusion criteria, the mean systolic and diastolic blood pressure measurements showed significant increase with

age ($P < 0.001$). Height and Weight did not differ between age groups with mean sample height and weight of 1.63 SD 0.08 cm and 67.67 SD 14.22 kilograms, respectively. Weight, height, and age distribution of the study population was approximately normal. Body Mass Index was higher in groups 3, 4 and 5 and lower in group 1 and group 6 ($P < 0.001$) as shown in Table 1 and Figure 4 and 5.

Table 1: General characteristics: Mean (SD) by Age group and Gender

Characteristics Mean (SD)	Group 1 18-30 years (n = 107)	Group 2 31-40 years (n = 72)	Group 3 41-50 years (n = 69)	Group 4 51-60 years (n = 56)	Group 5 61-70 years (n = 39)	Group 6 >70 years (n = 32)	*P Values
Age (years)							
All	24 ± 3	36 ± 3	46 ± 3	55 ± 3	65 ± 3	78 ± 6	
Male	23 ± 3	36 ± 3	46 ± 2	55 ± 2	65 ± 3	78 ± 6	
Female	24 ± 3	35 ± 3	46 ± 2	55 ± 3	65 ± 3	78 ± 4	
SEX: Male;Female	47;60	25;47	19;50	19;37	22;17	17;15	
SBP (mmHg)							
All	117 ± 10	122 ± 11	128 ± 9	129 ± 9	131 ± 10	128 ± 16	0.001
Male	120 ± 8	124 ± 9	130 ± 7	124 ± 8	130 ± 9	129 ± 15	0.001
Female	115 ± 11	121 ± 12	126 ± 9	130 ± 8	131 ± 10	126 ± 17	0.001
DBP (mmHg)							
All	74 ± 7	76 ± 8	78 ± 7	80 ± 5	81 ± 7	80 ± 10	0.001
Male	75 ± 5	77 ± 5	77 ± 5	79 ± 4	80 ± 7	80 ± 10	0.005
Female	72 ± 7	74 ± 8	78 ± 7	81 ± 5	81 ± 7	78 ± 11	0.001
Height (metres)							
All	1.7 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	
Male	1.7 ± 0.6	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	
Female	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	
Weight (kg)							
All	61.6 ± 10.2	67 ± 14.5	74.4 ± 14.6	72.6 ± 12.1	69.1 ± 14.4	61.4 ± 11.7	
Male	62 ± 8	70.5 ± 16.2	68.4 ± 12.5	73 ± 11	70.4 ± 9.2	63.4 ± 9.9	
Female	61 ± 11	65.7 ± 13.7	75.8 ± 14.8	72.4 ± 12.8	67.6 ± 18.6	51.6 ± 8.3	
BMI							
All	22.8 ± 3.8	25.4 ± 5.1	28.9 ± 6.4	28.3 ± 5.4	26.6 ± 5.6	22.8 ± 3.9	0.001
Male	21.7 ± 2.5	23.9 ± 4.4	23.6 ± 4.4	25.5 ± 3.7	25.3 ± 3.8	23.5 ± 4	0.001
Female	23.5 ± 4.3	26.0 ± 5.2	30.2 ± 6.2	29.6 ± 5.6	28.1 ± 7	21.4 ± 3.5	0.003

*P value for comparison of mean across age groups for gender

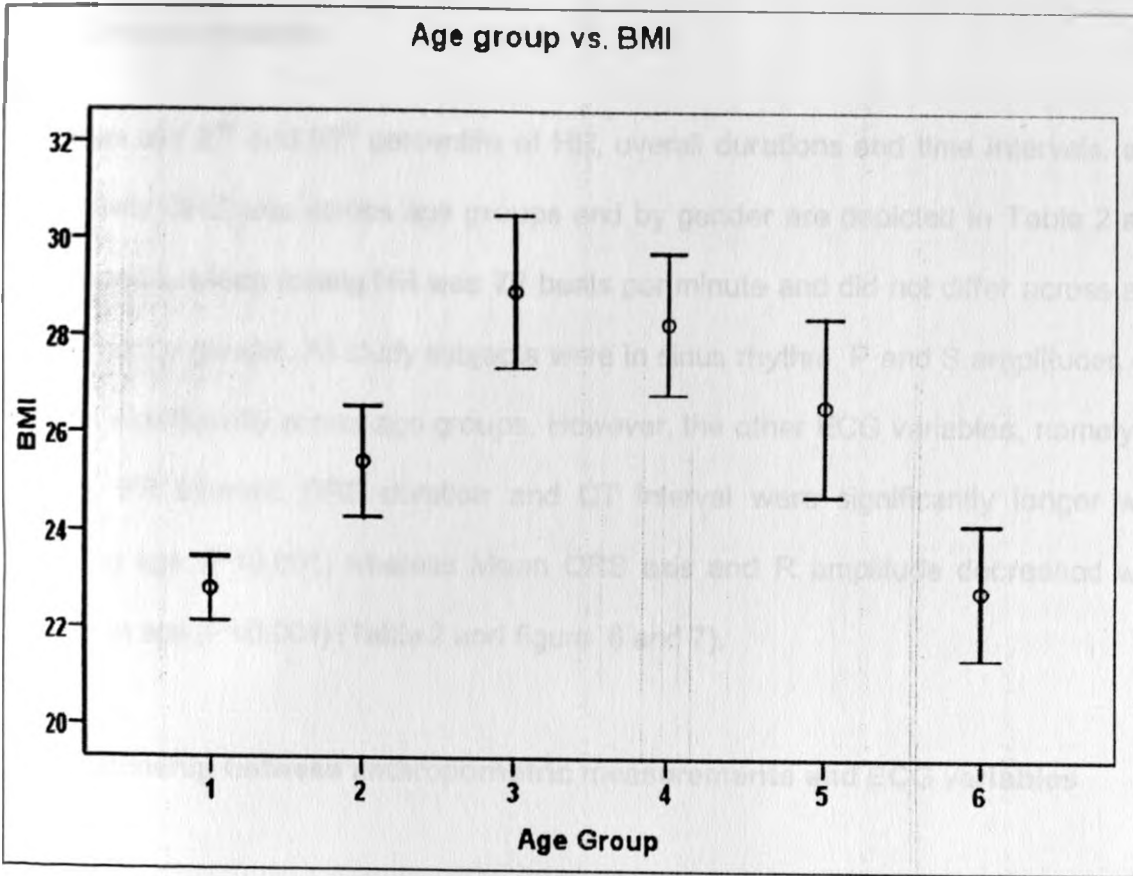


Figure 4: Error bar show age group trend for mean BMI and standard Deviation

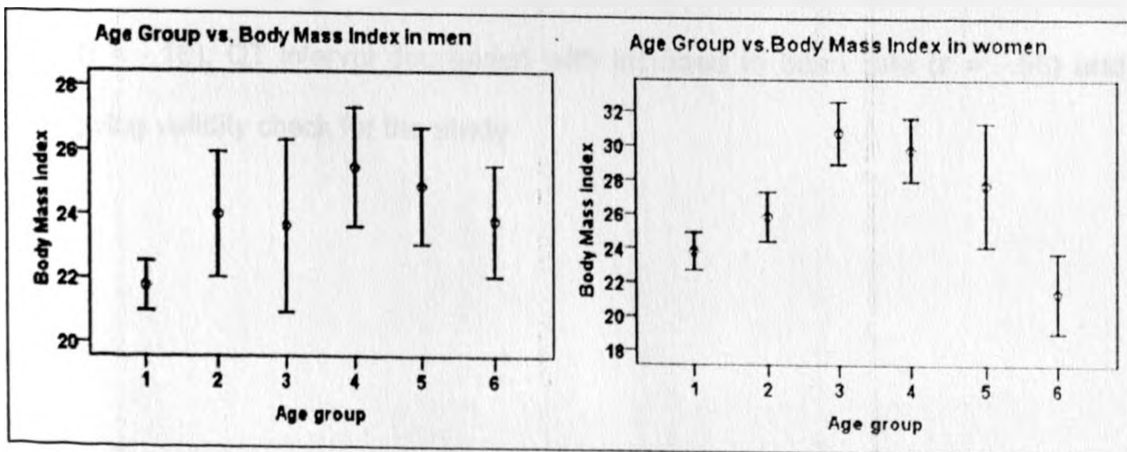


Figure 5: Error bars show comparison between men and women in Age groups, ECG variables and BMI

3.2 ECG measurements

The Mean and 2nd and 98th percentile of HR, overall durations and time intervals, and frontal-plane QRS axis across age groups and by gender are depicted in Table 2 and figure 6 and 8. Mean resting HR was 72 beats per minute and did not differ across age groups nor by gender. All study subjects were in sinus rhythm. P and S amplitudes did not differ significantly across age groups. However, the other ECG variables, namely; P duration, PR interval, QRS duration and QT interval were significantly longer with increasing age ($P < 0.001$) whereas Mean QRS axis and R amplitude decreased with increase in age ($P < 0.001$) (Table 2 and figure 6 and 7).

3.3 Relationship between anthropometric measurements and ECG variables

The correlation between ECG variables and weight, BMI and heart rate are shown in Figure 8. It depicts that P-wave duration increased with increase in weight as atrial activity increased with age ($r = .13$) while the Mean QRS axis decreased with increase in weight ($r = -.18$). QT interval decreased with increase in heart rate ($r = -.56$) and therefore giving validity check for the study.

Table 2: ECG parameters based on gender: Median (2nd percentile, 98th percentile)

ECG variable	Sex	Group 1 (18-30 years)	Group 2 (31-40 years)	Group 3 (41-50 years)	Group 4 (51-60 years)	Group 5 (61-70 years)	Group 6 (>70 years)	□P Values
HR (bpm)	ALL	75(50,101)	70(46,94)	75(52,102)	74(51,101)	71(59,102)	71(50,90)	0.093
	M	70(49,99)	62(45,86)	71(49,94)	66(51,98)	69(58,101)	68(49,89)	0.309
	F	76(47,101)**	72(50,98)***	73(52,97)*	74(53,104)***	70(61,96)	74(57,81)**	0.198
PDur (ms)	ALL	110(81,136)	117(91,142)	119(89,144)	123(100,140)	125(105,146)	132(115,148)	0.001
	M	110(78,136)	118(90,136)	114(96,136)	122(104,140)	125(105,145)	134(126,145)	0.001
	F	109(77,143)	116(87,149)*	120(86,143)***	123(97,144)	124(105,144)*	129(122,147)***	0.001
PR int (ms)	ALL	169(134,213)	181(138,227)	178(145,215)	186(160,227)	194(148,249)	219(189,252)	0.001
	M	172(125,213)	187(135,247)	170(142,211)	191(162,220)	199(149,216)	220(188,241)	0.001
	F	167(123,223)**	177(144,217)***	179(145,259)***	182(160,230)***	192(148,248)***	218(188,251)***	0.001
QRS int (ms)	ALL	65(41,93)	65(48,89)	64(39,93)	67(48,95)	76(45,105)	93(42,117)	0.001
	M	82(72,94)	65(51,109)	67(41,93)	67(48,87)	79(45,106)	98(65,117)	0.001
	F	67(53,94)***	67(51,90)*	65(49,102)**	68(48,102)	86(53,103)***	90(76,104)***	0.001
QTcB int (ms)	ALL	405(346,461)	411(336,466)	410(356,483)	427(376,506)	436(398,510)	477(400,542)	0.001
	M	391(318,455)	392(336,423)	401(347,490)	404(376,505)	442(400,509)	465(426,512)	0.001
	F	410(340,483)**	416(350,486)***	421(363,499)**	431(395,538)***	448(406,512)**	486(414,542)***	0.001

bpm, beats per minute; BMI, body mass index; F, female; HR, heart rate; int, interval; M, male; ms, milliseconds; Mv, millivolts.

* P<0.05, **P<0.01, *** P<0.001, P value stands for comparison within group and between gender.

□P value stands for comparison across age groups for specific gender

Mann-Whitney U test for sex differences, Cuzick's test for age trend. Numbers in brackets: median(Median (2nd percentile, 98th percentile))

Table 2: ECG parameters based on gender: Median (2nd percentile, 98th percentile) (Cont'd)

ECG variable	Sex	Group 1 (18-30 years)	Group 2 (31-40 years)	Group 3 (41-50 years)	Group 4 (51-60 years)	Group 5 (61-70 years)	Group 6 (>70 years)	□P Values
Ramp (Mv)	ALL	1.3(0.3,2.42)	1.1(0.3,2.0)	0.8(0.4,2.3)	1.2(0.4,1.8)	0.8(0.1,1.4)	0.7(0.3,1.4)	0.001
	M	1.5(0.4, 2.4)	1.2(0.6, 2)	0.7(0.4, 1.9)	1.3(0.6, 2.6)	0.6(0.1, 1.4)	0.8(0.2, 1.4)	0.022
	F	1.2(0.3, 2.4)*	1.1(0.3, 2)	0.9(0.4, 2.3)*	1.1(0.4, 1.8)	1.1(0.3, 1.3)**	0.7(0.3, 1.4)	0.001
Samp (Mv)	ALL	0.1(0.0,0.7)	0.0(0.0,0.4)	0.1(0.0,0.3)	0.0(0.0,0.3)	0.0(0.0,0.9)	0.1(0.0,0.9)	0.001
	M	0.1(0.0, 1.1)	0.1(0.0,0.4)	0.1(0.0, 0.3)	0.1(0.0, 0.6)	0.1(0.0, 0.9)	0.2(0.0, 0.9)	0.730
	F	0.0(0.0, 0.3)	0.0(0.0,0.4)	0.1(0.0, 0.3)	0.0(0.0, 0.3)	0.0(0.0, 0.5)	0.0(0.0, 0.7)*	0.169
QTcF int (ms)	ALL	387(334,437)	394(333,445)	403(333,448)	407(374,472)	420(376,482)	460(391,512)	0.001
	M	386(325,437)	388(333,432)	391(358,454)	393(376,477)	417(379,486)	452(425,487)	0.001
	F	395(346,454)***	398(344,455)**	406(360,455)**	421(380,496)***	423(392,485)**	471(427,517)**	0.001
QT int (ms)	ALL	361(308,430)	374(330,458)	378(287,423)	393(332,431)	402(341,470)	445(377,470)	0.001
	M	326(320,429)	373(322,456)	379(314,411)	389(319,430)	397(340,442)	439(393,458)	0.001
	F	362(364,458)***	374(332,471)	386(319,428)**	394(319,461)*	403(342,469)**	451(399,470)**	0.001
QRS axis (°)	ALL	60(-22,87)	50(-14,84)	30(-19,82)	30(-38,81)	20(-35,89)	12(-72,83)	0.001
	M	62(-72,108)	52(-14,81)	30(-7,82)	42(-48,73)	11(-35,89)	5(-72,58)	0.001
	F	59(-13,110)*	48(-15,85)	23(-23,120)*	23(-38,82)**	44(-26,82)**	41(-33,83)	0.001

bpm, beats per minute; BMI, body mass index; F, female; HR, heart rate; int, interval; M, male; ms, milliseconds; Mv, millivolts.

* P<0.05, **P<0.01, *** P<0.001, P value stands for comparison within group and between gender.

□P value stands for comparison across age groups for specific gender

Mann-Whitney U test for sex differences, Cuzick's test for age trend. Numbers in brackets: median(Median (2nd percentile, 98th percentile))

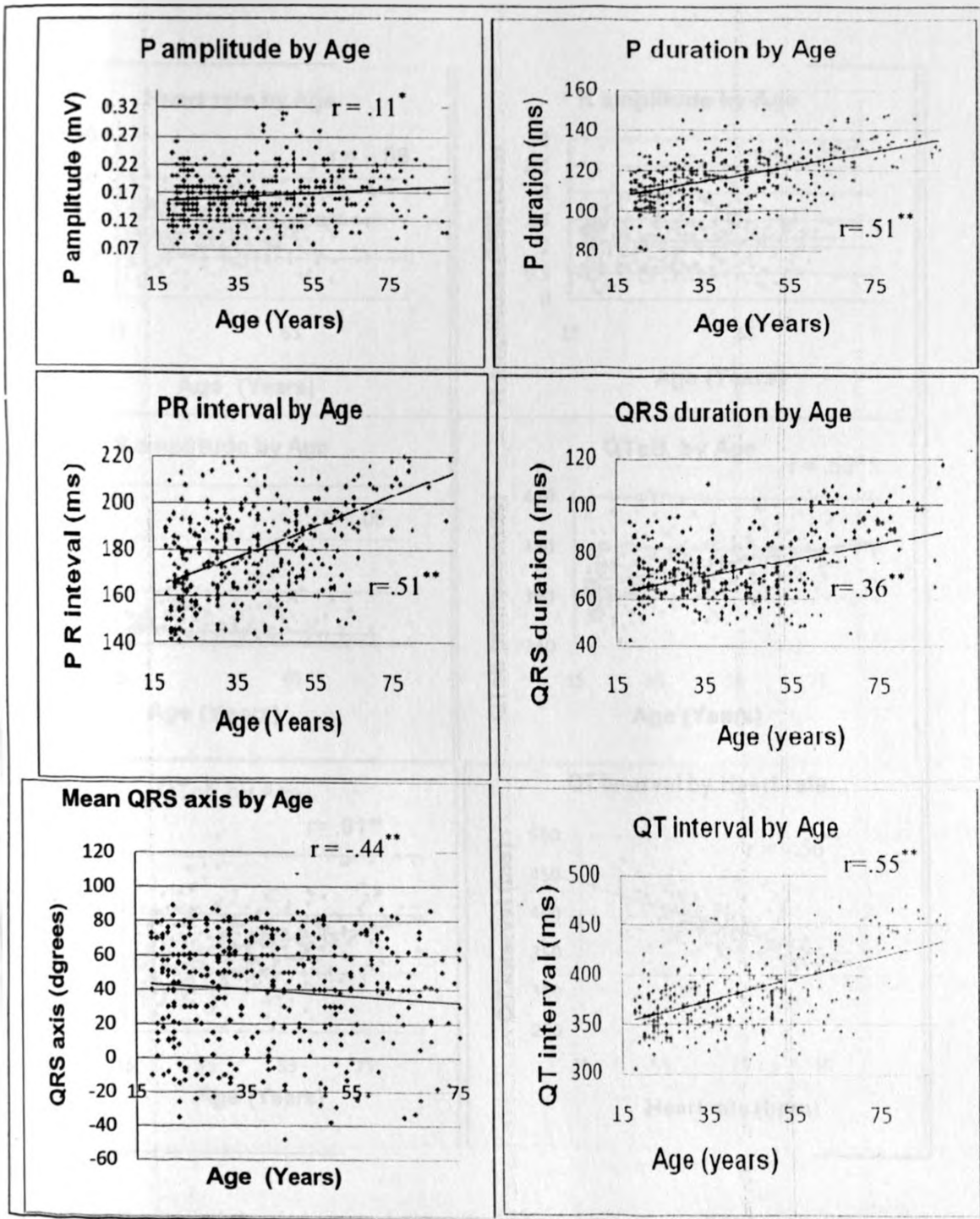


Figure 6: Scatter plots show correlations between Age versus ECG variables

r, stands for pearson correlatons; * $P < 0.05$, ** $P < 0.001$

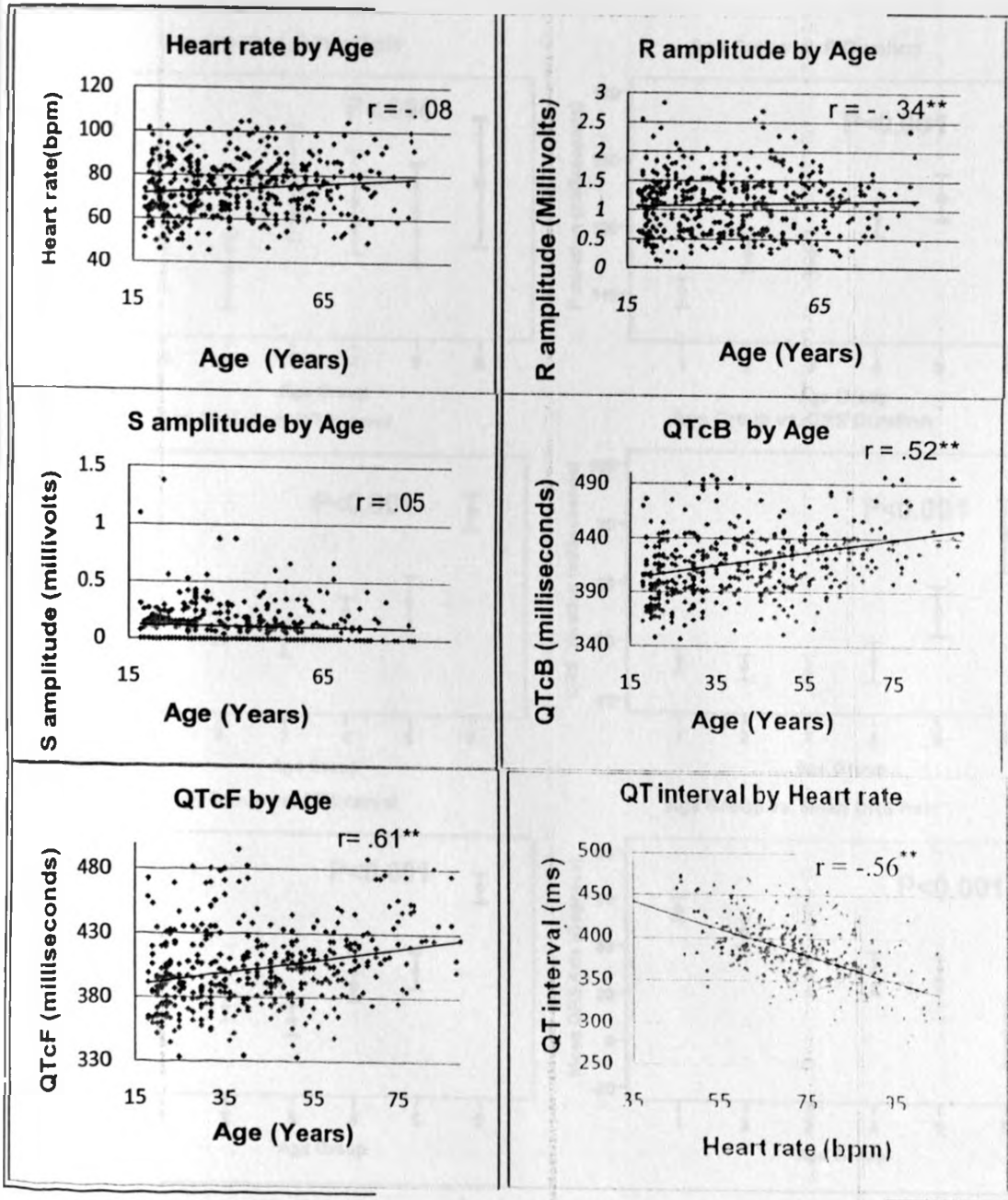


Figure 6: Scatter plots show correlations between Age versus ECG variables

r. stands for pearson correlatons; *P<0.05, **P<0.001(Cont'd)

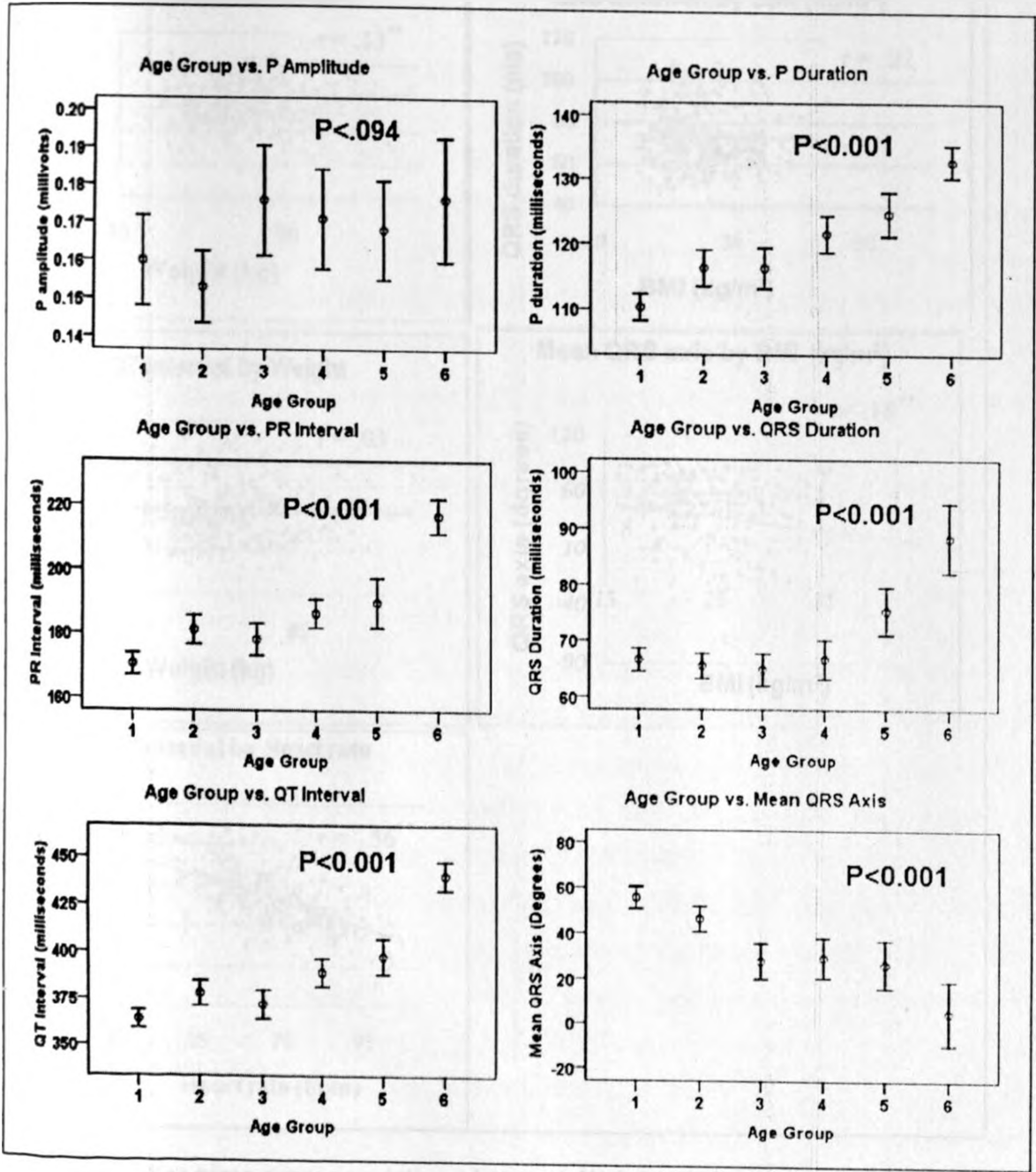


Figure 7: Error bars show relationship between Age groups and ECG variables

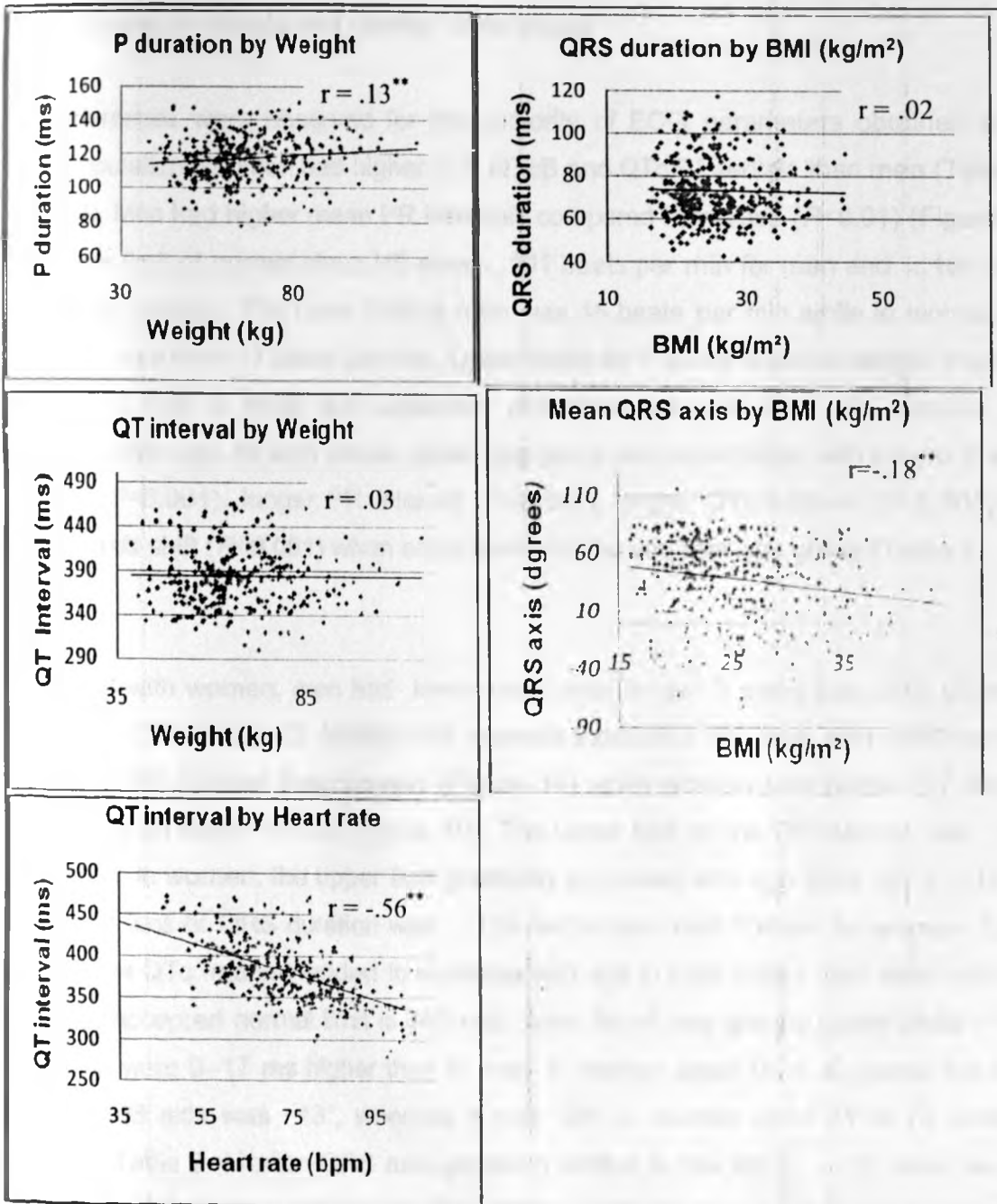


Figure 8: Scatter plots show correlations between Weight, BMI and heart rate versus ECG variables. r , stands for pearson correlatons; * $P < 0.05$, ** $P < 0.001$

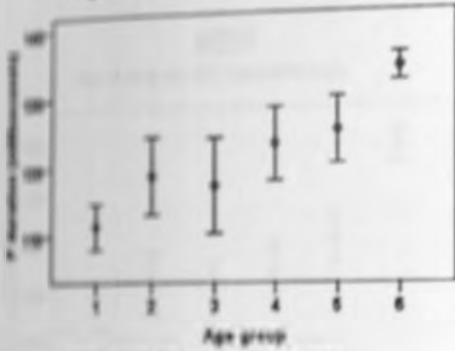
3.4 ECG measurements and gender differences

Sex differences were observed for the majority of ECG parameters obtained in the study population. Women had higher QT, QTcB and QTcF intervals than men (Table 2), (figure 9). Men had higher mean PR intervals compared to women ($P<0.01$) (Figure 11). The upper limit of normal sinus HR was ~ 101 beats per min for men and ~ 104 beats per min for women. The lower limit in men was 45 beats per min while in women, the lower limit was from 47 beats per min. Upper limits for P-wave duration ranged from 136 to 149 ms, with a small but consistent difference between men and women, and increased with age. In both sexes, older age group was associated with longer P wave duration ($P<0.001$), longer PR interval ($P<0.001$), longer QTc interval ($P<0.001$) and leftward axis shift ($P<0.001$) when compared with the younger age group (Table 2).

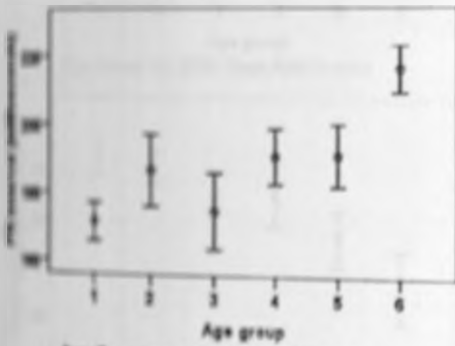
Compared with women, men had lower heart rate, longer P wave and QRS durations but shorter QTc (Table 2). Median PR intervals increased with age, with men having 8 ms longer PR interval than women (Figure 11) while women had higher QT interval compared with men ($P<0.05$) (Figure 10). The upper limit of the PR interval was ~ 247 ms in men; in women, the upper limit gradually increased with age from 167 to 218 ms. The upper limit of QRS duration was ~ 109 ms for men and 104 ms for women. Upper limits of the QTc interval tended to increase with age in both sexes, and were >454 ms in QTcB (accepted normal limit is 440 ms). Also, for all age groups upper limits of QTc in women were 9–17 ms higher than in men. In women aged 18 to 30 years, the lower limit of QRS axis was -13° , whereas it was -26° in women aged 61 to 70 years as shown in Table 2. Median QRS axis gradually shifted to the left by $\sim 15^\circ$ over the total age range, both in men and women. The BMI was higher age in the middle-aged years between 40 and 65 years and was significantly higher in women than in men with 18% of women being obese according to the definition ($\text{BMI}>30\text{kg/m}^2$) (Table 1 and Figure 4 and 5).

MEN

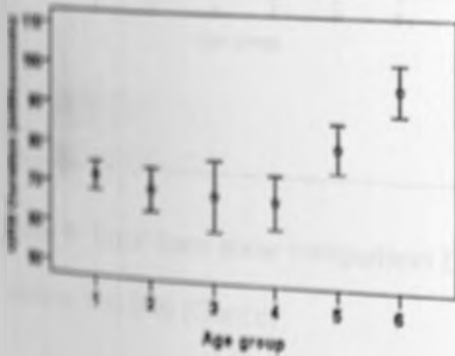
Age Group vs. P duration in men



Age Group vs. PR Interval in men

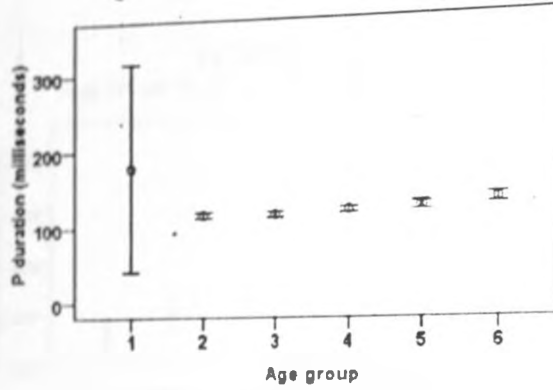


Age Group vs. QRS Duration in men

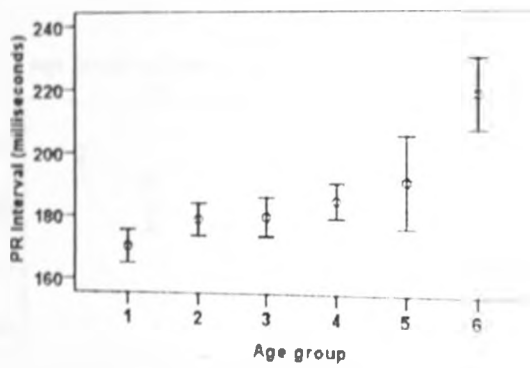


WOMEN

Age Group vs. P duration In women



Age Group vs. PR Interval in women



Age Group vs. QRS Duration in women

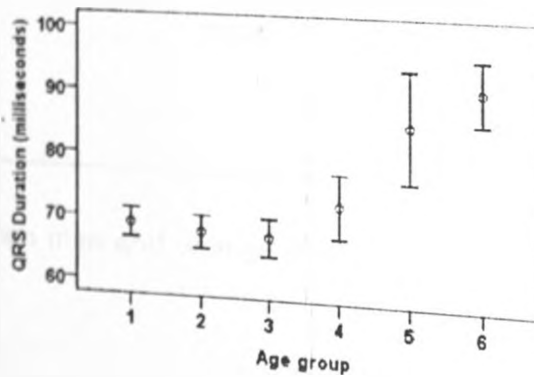


Figure 3: Error bars show comparison between men and women in Age groups and ECG variables

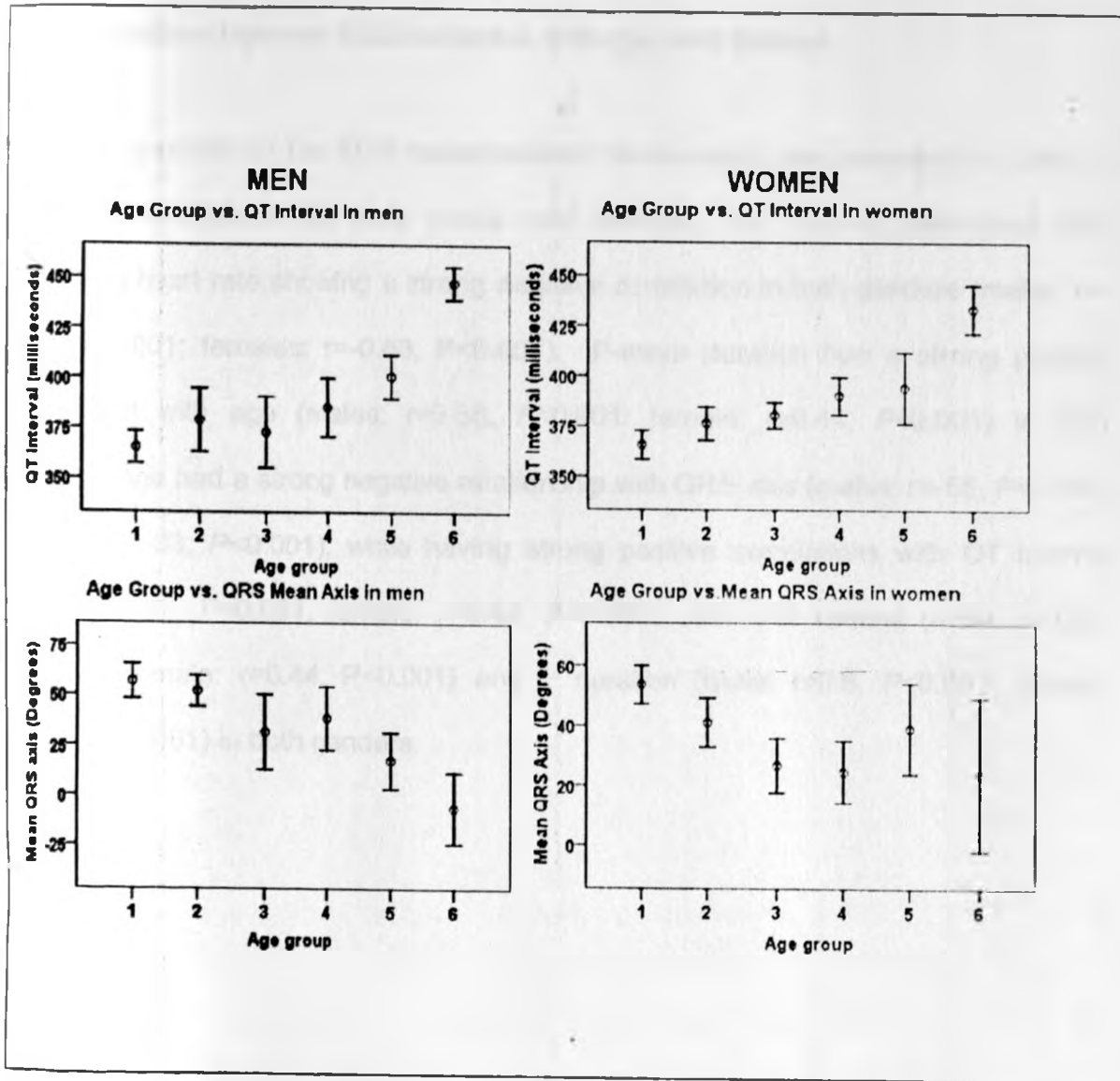


Figure 9: Error bars show comparison between men and women in Age groups, ECG variables and BMI (Cont'd)

3.5 Correlations between ECG variables with Age and Gender

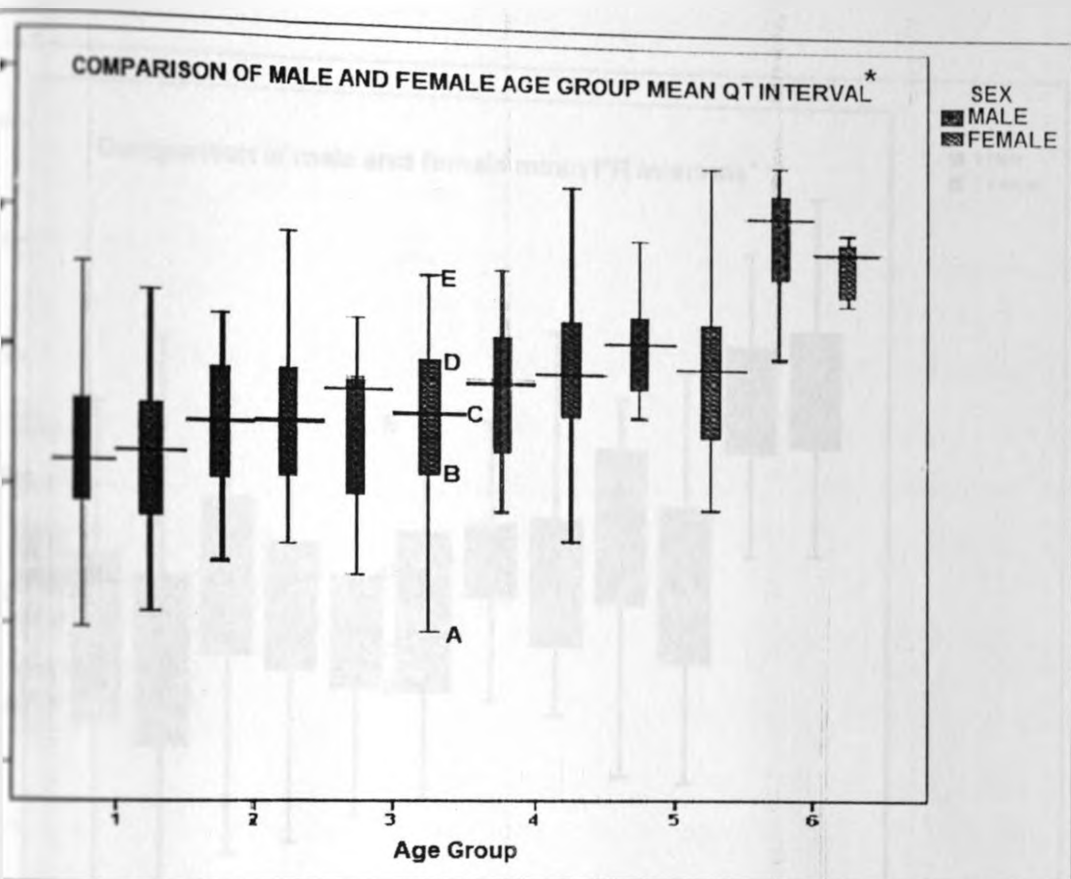
Bivariate analyses of the ECG measurements in the study are presented in Table 3, depicting correlations for both males and females. QT interval decreased with increasing heart rate showing a strong negative correlation in both genders (males: $r=-0.43$, $p<0.001$; females: $r=-0.63$, $P<0.001$). P-wave duration had a strong positive association with age (males: $r=0.58$, $P<0.001$; female: $r=0.44$, $P<0.001$) in both genders. Age had a strong negative relationship with QRS axis (males: $r=-.55$, $P<0.001$; females: $r=-.33$, $P<0.001$), while having strong positive correlations with QT interval (male: $r=0.67$, $P<0.001$, female: $r=0.43$, $P<0.001$), with PR interval (male: $r=0.58$, $P<0.001$; female: $r=0.44$, $P<0.001$) and P duration (male: $r=0.6$, $P<0.001$; female: $r=0.44$, $P<0.001$) in both genders.

Table 3: Pearson correlations between general characteristics and ECG variables by gender

Characteristics	Sex	HR	Pamp	Pdur	PR	Ramp	QRS	Samp	QRS axis	QT
Age	All	-.079	.11*	.51**	.51**	-.34**	.36**	.05	-.44**	.55**
	Male	.018	.09	.58**	.57**	.089	.44**	-.02	-.57**	.66**
	Female	-.09	.09	-.04	.44**	-.21**	.41**	.03	-.30**	.48**
Height	All	-.25**	-.03	.06	.07	.11*	.07	.23**	.05	.07
	Male	-.17*	-.19*	.06	.09	.09	-.08	.16	.05	.01
	Female	-.13	-.05	.04	-.09	.09	-.08	-.04	.10	-.06
Weight	All	-.07	-.09	.13**	.06	-.02	.05	-.09	-.16**	.03
	Male	.09	-.12	.23**	.23**	.04	-.01	-.17*	-.06**	.04
	Female	-.16*	-.06	.12	-.08	-.05	-.01	-.05	-.2**	-.02
DBP	All	.05	.05	.16**	.16**	-.03	.06	.05	-.22**	.13**
	Male	.02	.00	.23**	.28**	.00	.08	-.04	-.12	.23**
	Female	.05	.05	-.05	.13	-.04	.12	.1	-.27**	.12
SBP	All	-.02	.03	.24**	.152*	-.06	.13*	.04	-.26**	.19**
	Male	-.00	-.07	.20	.13	-.13	.12	-.01	-.2*	.28**
	Female	-.06	.04	.07	.16*	-.05	.16*	.05	-.27**	.21**
BMI	All	.05	-.06	.1	.016	-.07	.016	-.18**	-.18**	-.00
	Male	.20*	-.04	.22**	.21*	.00	.05	-.23**	-.12	.05
	Female	-.09	-.05	.1	-.06	-.05	.01	-.05	-.22**	-.02

BMI, body mass index; DBP, Diastolic blood pressure; HR, heart rate; ms, milliseconds; P Dur, P-wave duration; SBP, systolic blood pressure.

** $P < 0.001$; * $P < 0.05$ (P values are comparisons between a particular general characteristic and an ECG variable on Y and X axes)



10: Box plots comparing the mean QT interval between males and females. A, minimum value; B, 25th percentile value; C, median value; D, 75th percentile value; E shows the maximum value of PR intervals, respectively.

01

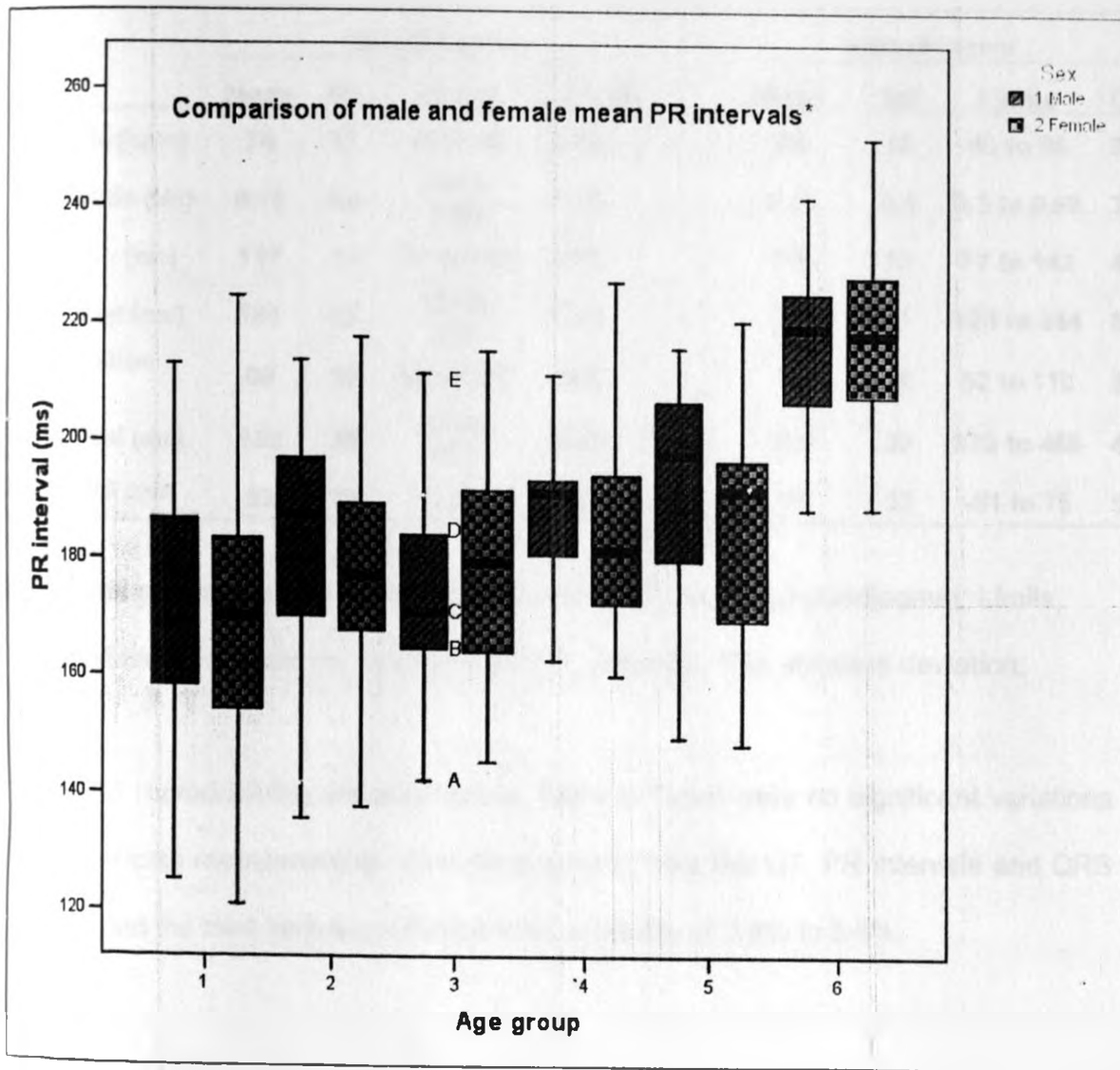


Figure 11: Box plots comparing the mean PR interval between males and females. A, minimum value; B, 25th percentile value; C, median value; D, 75th percentile value, while E shows the maximum value of PR intervals, respectively.

* $P < 0.01$

Table 4: Reproducibility of measurement of ECG parameters

Variable	Interobserver				Intraobserver			
	Mean	SD	Limits	CV (%)	Mean	SD	Limits	CV (%)
Heart rate (bpm)	74	13	45 to 99	2.5%	74	12	45 to 98	3.4%
P amplitude (Mv)	0.16	0.6	0.5 to 0.69	4.1%	0.17	0.4	0.5 to 0.69	3.6%
P duration (ms)	117	13	77 to 142	3.8%	116	13	77 to 142	4.7%
PR interval (ms)	181	23	121 to 259	5.3%	183	21	123 to 264	5.8%
QRS duration (ms)	68	13	52 to 107	4.6%	70	12	52 to 110	3.8%
QT interval (ms)	380	35	278 to 471	3.3%	379	32	272 to 466	4.1%
Mean QRS axis	32	33	- 52 to 82	4.2%	28	32	-61 to 75	5.1%

bpm, beats per minute; CV, coefficient of variation; ECG, Electrocardiogram; Limits, 95% confidence interval; ms, milliseconds; Mv, millivolts; SD, standard deviation;

Results for reproducibility are tabulated in Table 4. There were no significant variations in the duplicate measurements. All measurements from the QT, PR intervals and QRS duration had the best intra-and interobserver variability of 2.5% to 5.8%.

CHAPTER FOUR

DISCUSSION

4.1

In the present study Electrocardiographic variables (intervals and durations) differed in older age groups when compared to younger age groups and a leftward shift of the Mean QRS frontal plane axis with increasing age. The major Electrocardiogram (ECG) parameters commonly obtained in healthy adults and used for clinical diagnostic purposes increases with age as is discussed in the subsequent paragraphs. The present study also noted significant differences in the ECG parameters obtained between males and females. The potential mechanism of the gender differences is from acute direct effects of sex hormones, such as estrogen, progesterone or testosterone on cardiac repolarization although very little data exist concerning the direct electrophysiologic effects of sex hormones on cardiac tissue (Burke et al, 1997).

Electrocardiogram is an indispensable record of electrical activity of the heart, With the general objective of ECG being definition of the electrophysiological state of the heart in medically useful terms. The resting ECG permits to suspect or diagnose a large number of cardiac disorders like, cardiac arrhythmias, myocardial ischaemia (MI), and left ventricular hypertrophy (LVH). As a noninvasive, inexpensive, risk-free and simple technique, ECG may have higher utility in developing countries where resources are limited and cardiovascular diseases are rapidly emerging as a major health problem. ECG measurements (intervals, amplitudes, HR, and QRS axis) are known to differ with age, sex and race, yet most available data have been obtained in Caucasian populations.

The cardiovascular system exhibits a number of morphological, functional and clinical features associated with advancing age. Alterations in shape, size and weight of the heart, alterations of coronary arteries, valves and aorta are accompanied by typical changes in several haemodynamic variables. Thus, knowledge of the basics of interpretation ECG changes with normal ageing is helpful in differentiating normal from abnormal findings. These basics include familiarity with the age-related normal findings in heart rate, intervals, axis, and waveform morphologies.

The strength of the current study is the apparent health status of the study participants and of the fact that there is paucity of data on normal ECG parameters in black Africans. The prevalence of ECG changes with normal ageing in the general population, both in the present study and in previous studies, appears to be primarily due to cardiovascular changes with ageing. However, racial differences exist and it is uncertain whether these reflect physiologic differences such as genetic make-up between black Africans and other races or is simply the result of environmental and socio-economic factors such as poverty, nutritional status and physical activities. Results of the present study are in keeping with previously reported ECG changes with normal ageing (Mason et al, 2007; Wu et al, 2003 and Macfarlane and Lawrie, 1989). In the present study, the sample was restricted to apparently healthy individuals so that ECG findings are not confounded with pathology. One of the major and novel findings of this study is the association of BMI and the mean QRS axis: both are numerically similar in the middle-age period between 40 and 65 years. These findings may be attributed to fact that increase in BMI

is thought to be associated with increased intraabdominal fat thus, an upward shift of the diaphragm and a more horizontal anatomical position of the heart which causes a leftward axis shift of the heart (Wu et al, 2003).

The present study also found a positive correlation between P duration and increase in weight, a finding that has previously not been reported. This observation may be attributed to increased time of impulse transmission through the atria as a result of increased muscle mass and increased afterload (resistance against which the ventricles must pump to eject blood) due to increase in body weight and Obesity is often associated with LVH leading to increase BP in the body. Derivation of the commonly used ECG parameters for healthy adults as normal is obscure. Typical ECG parameters in current use for adults are 60 to 100 for resting heart rate, 140 to 210 milliseconds for PR interval, 70 to 110 milliseconds for QRS duration, -30° to 110° for QRS axis, and 460 milliseconds for the upper limit of QTc, as stated in *Marriott's Practical Electrocardiography* (Wagner, 2001). Electrocardiographers typically apply these ranges across most or all adult age groups, usually without regard to age and sex. These ranges are not consistent with published age- and sex-specific norms (Mason et al, 2007; Wu et al, 2003; Macfarlane and Lawrie, 1989); rather, they have been handed down from teachers to students of electrocardiography over many decades as easily remembered, although imprecise, estimates of normal. Unfortunately, their use results in incorrect categorization as normal or abnormal of a substantial proportion of subjects.

In the following paragraphs, the study discusses several established ECG criteria that may need adjustment when applied to a black African population. The study also makes limited comparisons of ECG differences between an African population and other racial groups, although such a comparison has its difficulties. Not only do the available studies use different statistics to report the various normal ECG parameters, but they also used digital computer-based software packages for measurements of ECG parameters, vary in their definition of age groups and often report varied set of parameters. They also differ in sample selection- random, population-based samples versus samples of apparently healthy individuals. To the best knowledge of the researcher, the only recent comprehensive report on normal ECG changes based on an apparently healthy population are studies by Mason et al (2007), Wu et al, (2003) and Macfarlane and Lawrie (1989), in Caucasian and Chinese men and women. Therefore, the present study only made limited comparisons of racial ECG differences, and suggest that the paucity of data on normal changes with ageing in racial groups other than the Caucasian and Chinese warrants further investigation and documentation. ECGs are frequently assigned an abnormal overall assessment in normal, healthy individuals because the meaning of "normal" to most Electrocardiographers is not based upon age, sex and racial differences but, rather, upon easily remembered, generally accepted ECG measurements, such as heart rate between 60 and 100 beats per min. The study subjects included both healthy volunteers and subjects with no cardiac disease.

Heart rate

Resting heart rate was slightly lower in men than women and in young men than older men though not statistically significant in this study population. The relation of heart rate to age may be explained by a higher level of physical activity by young men than older men, thus a better cardiovascular conditioning. The lower heart rate in men compared with women may be explained by the same phenomenon (Zerkiebel et al, 2000). Normal limits of sinus heart rate have mostly been set at 60 and 100 beats per min, although normal limits of 50 and 90 beats per min have also been suggested (Chou, 1996). The present study shows that the upper limit of normal heart rate for the study subjects is 104 beats per min. The lower limit of heart rate in this study was 45 beats per min for men, not dependent on age, whereas women showed a decreasing trend with age from 57 to 51 beats per min. This suggests that traditional criteria of sinus tachycardia and especially bradycardia need adjustment when applied to an African population.

P duration

The upper limit of P-wave duration has traditionally been defined as 120 ms (Macfarlane and Lawrie, 1989) and a value based on single-lead measurement and allowing easy testing (120 ms equals 3 mm at standard 25 mm/s paper speed). Upper limits in the present study ranged from 125 to 149 ms, with men having slightly higher values than women, and increasing with age. These findings suggest that the established criterion for left atrial abnormality may be adjusted in African subjects after further research with large sample sizes. This increase may be attributed to the increased atrial muscle mass

and stiffness coupled with increased ventricular hypertrophy due to increase in blood pressure with ageing and probably due to ageing process itself.

P amplitude

The median and upper limit of P amplitude gradually increase with age according to the current study findings although all are within the normal range for the general population where the upper limit is about 0.25 mV (Meek and Morris, 2002).

PR Interval

It has been previously reported that blacks have a prolonged PR interval compared to whites and Chinese (Rautaharju et al, 1994; Wu et al, 2003). The mean PR interval in the present study was about 12 ms longer than that reported by Mason (2007) in Caucasian individuals. The median and upper limit of PR interval gradually increases with age, particularly in women. Generally, PR interval increases with decreasing heart rate. In this study, women showed slower heart rates with increasing age, concomitant with progression of the PR interval. The longer atrio-ventricular conduction time observed in a general population of African black individuals might be, for instance, mediated by a race-dependent increase in vagal tone (Zerkiebel et al 2000). Independent of its exact mechanisms, this observation stresses the need to establish different norms for African populations.

QRS duration

Typical reference range for QRS duration is 70 to 110 milliseconds (Wagner, 2001). Previous studies observed a longer mean QRS duration in men than in women (Macfarlane and Lawrie, 1989; Mason et al, 2007), but Macfarlane and Lawrie (1989) reported a progressive decrease in mean QRS duration with increase in age, whereas Mason et al (2007) observed stability of the mean with increasing age.

In the present study, men had a longer QRS duration than women by about 6 ms in all age groups. This is probably explained by the larger cardiac dimensions in men (Okim et al, 1995); a hypothesis supported by the independent relationship observed between QRS duration and left ventricular mass (Zerkiebel et al, 2000). Similar gender differences have been reported in other studies (Levy et al 1987; Okim et al, 1995 and Macfarlane and Lawrie, 1989). Slightly higher values, but with similar sex differences, have been reported for a white population (Mason et al, 2007) and a Chinese population (Wu et al, 2003). The study results proved to be quite stable over the age groups, and imply that criteria involving QRS duration should be age and sex-specific when applied to an African population.

QTc interval

Although a number of other, and perhaps better, formulas than that of Bazett have been proposed, it remains the most widely applied clinical norm. The generally accepted upper normal limit of QTc interval is 440 ms (Bazett, 1920). In the present study data, the prevalence of QTc >440 ms was 14.4% in women and 8.3% in men. Upper limits in

both sexes tend to increase with age, and were mostly >440 ms. Also, women had consistently longer QTc intervals than men, up to 490 ms at an age ≥ 60 years. Thus, a uniform normal value of 440 ms regardless of sex and age may not seem appropriate in an African population although larger sample sizes are needed to make stronger conclusions. It is noteworthy that the study's upper limits are 8–16 ms higher than those previously reported in a white population (Macfarlane and Lawrie, 1989) and Chinese population (Wu et al, 2003).

Part of the gender differences in ECG parameters might be simply because of longer depolarisation time in men than in women as a result of increased ventricular mass in men than in women. This makes men inherently more likely to meet the criteria for any kind of ventricular conduction defect (Zerkiebel et al, 2000). Sex hormones have been proposed to be responsible for the differences in cardiac repolarization between men and women. Experimental and clinical data suggest an important role of testosterone in modulating cardiac repolarization. In fact Hara et al (1998), has shown that testosterone decreases action potential duration in endocardial cells at 30% and 90% of full repolarization in oophorectomized rabbits. The identification of receptors for gonadal hormones in the heart provided a rationale for investigating direct hormonal modulation of repolarization (Bidoggia et al, 2000).

Electrical axis

Both age and BMI were independently associated with a leftward shift of the Mean QRS frontal plane axis. Increasing BMI is thought to be associated with an upward shift of the

diaphragm and a more horizontal anatomical position of the heart (Wu et al, 2003). Rautaharju et al (1994), reported identical associations of age and obesity with the QRS axis. In addition, these studies found a substantial racial difference in the QRS axis between white and black Americans. Compared with values reported by Rautaharju, the mean QRS axis recorded in Africans was 8° less than American blacks and approximately 15° less than in American whites, suggesting an even more pronounced difference in Africans than in black Americans. This observation may imply that Left anterior fascicular block (LAFB) is over-diagnosed in African persons when applying the classical QRS axis cut off point of -30° . In our data, we found a leftward shift of 19° – 25° with increasing age.

The greatest effect of use of these study findings may include; more accurate diagnosis of bradycardia (which is overdiagnosed with current reference ranges); reduction in overdiagnosis of first-degree atrioventricular block; a more accurate recognition of the effect of age and obesity upon QRS axis; more accurate diagnosis of QT prolongation according to age and sex; and a generally better understanding of differences between men and women and among age and age/sex in the general populations.

4.2 Study limitations

1. The sampling technique used was Convenience non-probability sampling which has potential to introduce a degree of bias concerning the significance of observations made from them.

2. Among the study subjects, men were fewer than women, while the elderly population (above 60 years) was less than the younger population. This is probably due to the fact that most of the study subjects were from low socio-economic areas of the city hence a majority of men were working or looking for jobs on the days data were being collected. The study area being a city, a majority of the population are young people looking for employment, working or in colleges, while most of the elderly live in rural areas

4.3 CONCLUSIONS

The present study provides a systematic description of major ECG measurements in a healthy population of black African individuals. Similarly, to Caucasians and Chinese, significant trends over age and gender have previously been demonstrated for several variables, which stress the need to interpret ECG findings in view of such parameters. Several findings in this African population differ from those in Caucasian and Chinese populations. This suggests that generalization of the currently defined norms for the various ECG criteria (derived from Caucasian populations) may be unsuitable for black African population. The study findings have important clinical implications. It is recommended that existing reference ranges for the black African population be re-examined afresh and replaced by age and sex-specific values derived from large, diverse samples and that these norms be incorporated into ECG computer analysis algorithms and teaching curricula. The paucity of data on normal limits in racial groups other than the Caucasian and Chinese warrants further investigation and documentation.

4.4 Recommendations

- 1) From the study findings, ECG interpretations need to be based on age, sex and race of the subjects.
- 2) ECG variables for black African Kenyans may be interpreted based on the results of the present study until other results are available
- 3) Larger and diverse samples need to be studied

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APPENDIX 1

ELEMENTS OF INFORMED CONSENT

In seeking informed consent, the following shall be provided to each subject who will participate in the study:

1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the patient.
3. A description of any benefits to the patient or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures, if any, that might be advantageous to the patient.
5. A statement describing the extent, if any to which confidentiality of records identifying the subject will be maintained and note the possibility that a member of KNH staff may inspect the records.
6. For research involving more than minimal risks, an explanation as to whether any compensation and an explanation as to whether any medical treatment are

available if injury occurs, and if so what they consist of or where further information may be obtained.

7. An explanation of whom to contact for answers to pertinent questions about the subject's research rights, and whom to contact in the event of a research injury to the subject.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

APPENDIX 2

CONSENT FORM

Name

Age

Sex

Study No.

Date

I have been explained to in detail the purpose of the study and the investigative procedure/s that I will be subjected to. I agree to participate and comply with all the instructions during the entire period of the study in accordance with the above declaration.

Sign/ thumb print

Witness

NOTE: For the subjects who do not understand English language (both written and spoken), the elements of informed consent and consent form will be translated into Kiswahili and the subject's mother-tongue where necessary.

APPENDIX 3

IDENTIFICATION Date

Subject number Age

Sex Height

Occupation Weight.....

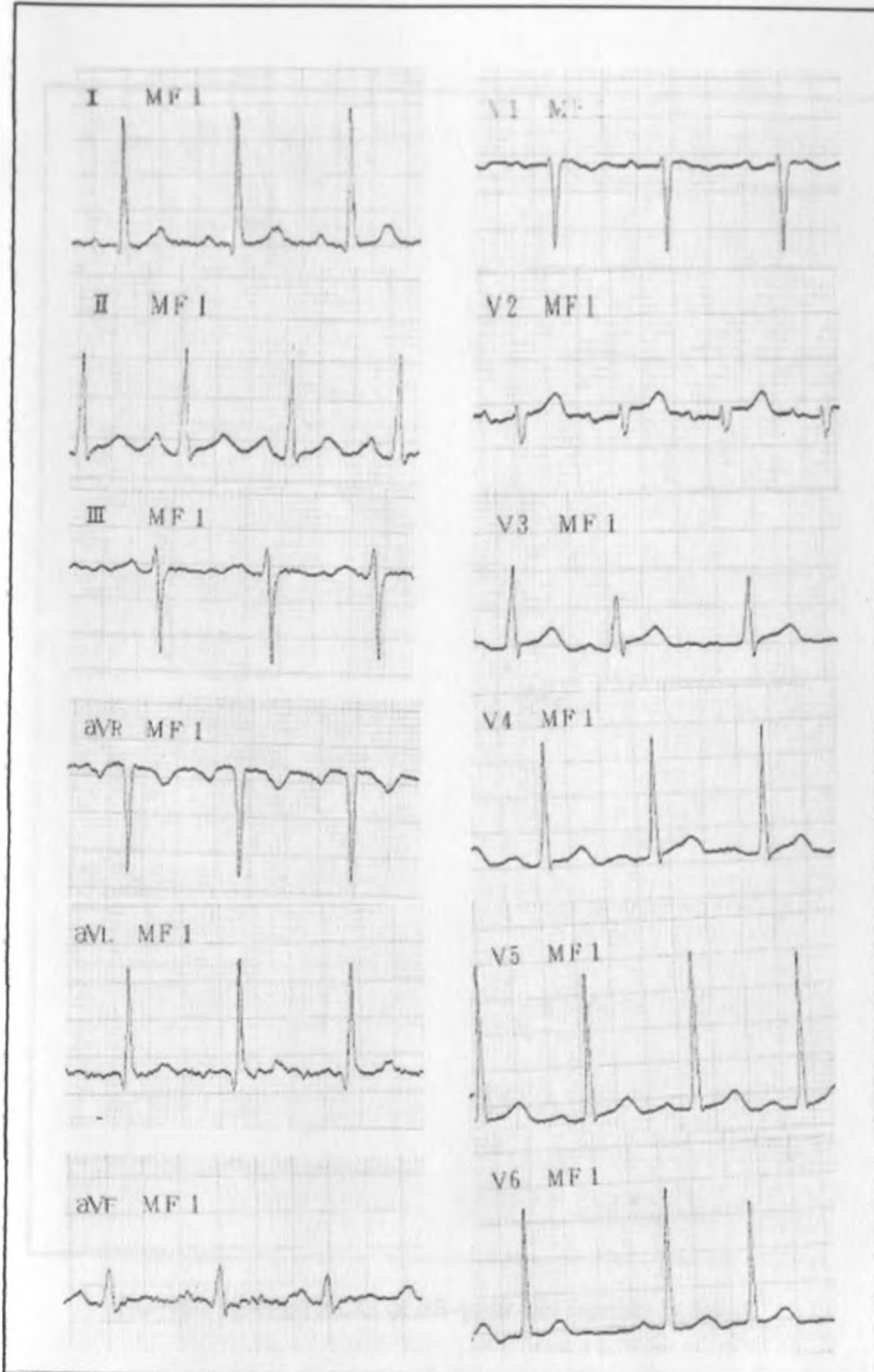
HISTORY	Yes	No
1. Present medical history (explain):		
2. Past medical history (explain):		
3. History of smoking:		
Age started smoking.....		
4. History of alcohol consumption How many litres per day? (Estimate).....		
5. Dietary history (explained to the subject)		
a). Excess fat consumption in the diet.....		
b). Eating of fatty foods as major meals.....		
c). Type of cooking fat used in the home.....		
d). Use of fruits and vegetables.....		
6. Family history of:		
a). Hypertension.....		
b). Stroke.....		
c). Coronary artery disease.....		
d). Congestive heart failure.....		
e). Any other, specify.....		
7. Last menstrual period (LMP).....		
8. use of any drugs, specify.....		
9. Use of Miraa.....		

APPENDIX 4

PHYSICAL EXAMINATION

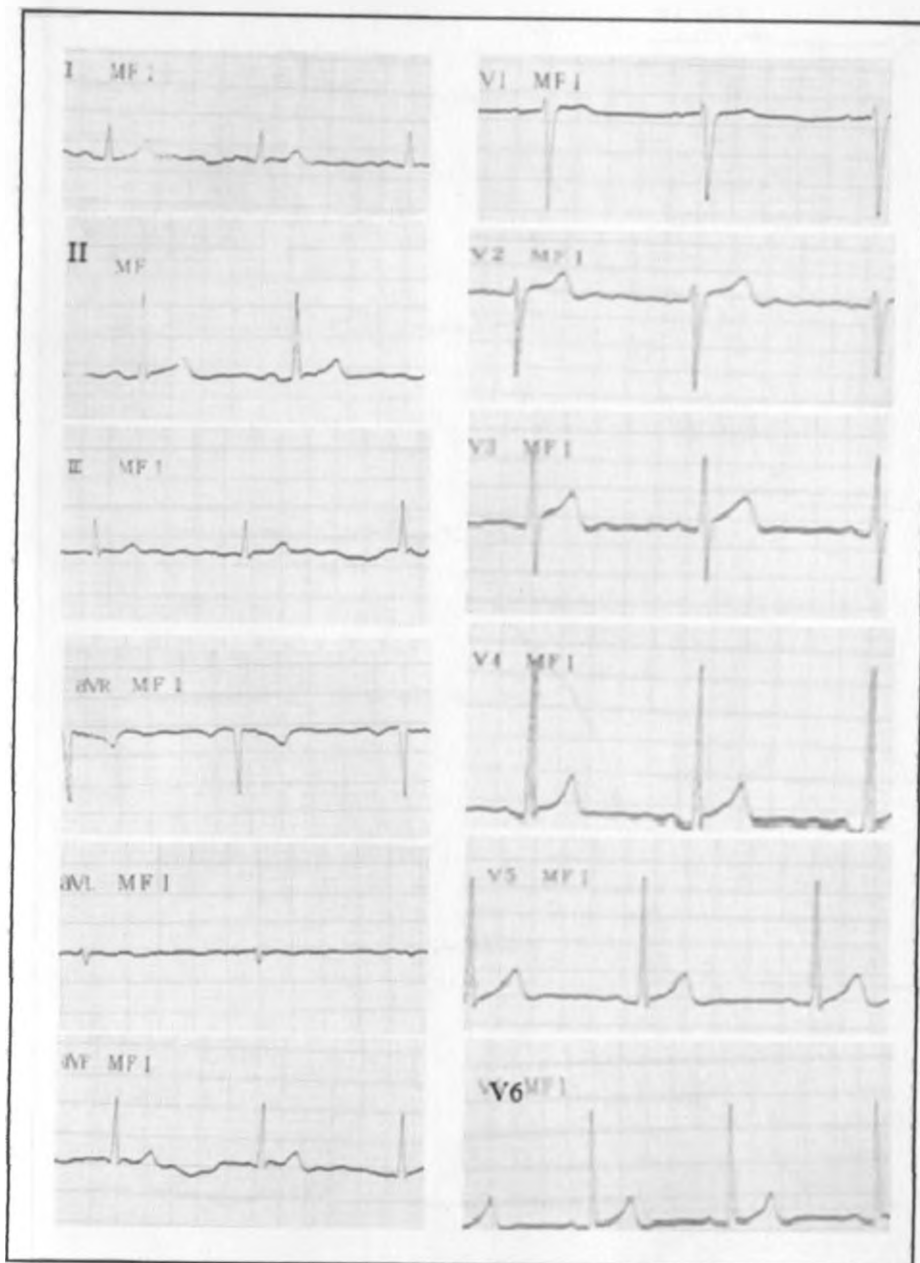
	Yes	No
1. General examination (describe).....		
2. Cardiovascular system		
a). Heart rate.....		
b). pulse pressure.....		
c). Blood pressure: standing.....		
Lying.....		
d). Auscultation (presence of heart sounds).....		
3. Central nervous system:		
a). Oriented?.....		
b). Mentally stable?.....		
c). Comment.....		
4. Respiratory system:		
a) Respiratory rate.....		
b) Lung sounds.....		
c) Any respiratory problems? Comment.....		
5. Per abdomen:		
a) Tenderness and guarding.....		
b) Any organ enlargement? Comment.....		

Appendix 5.1



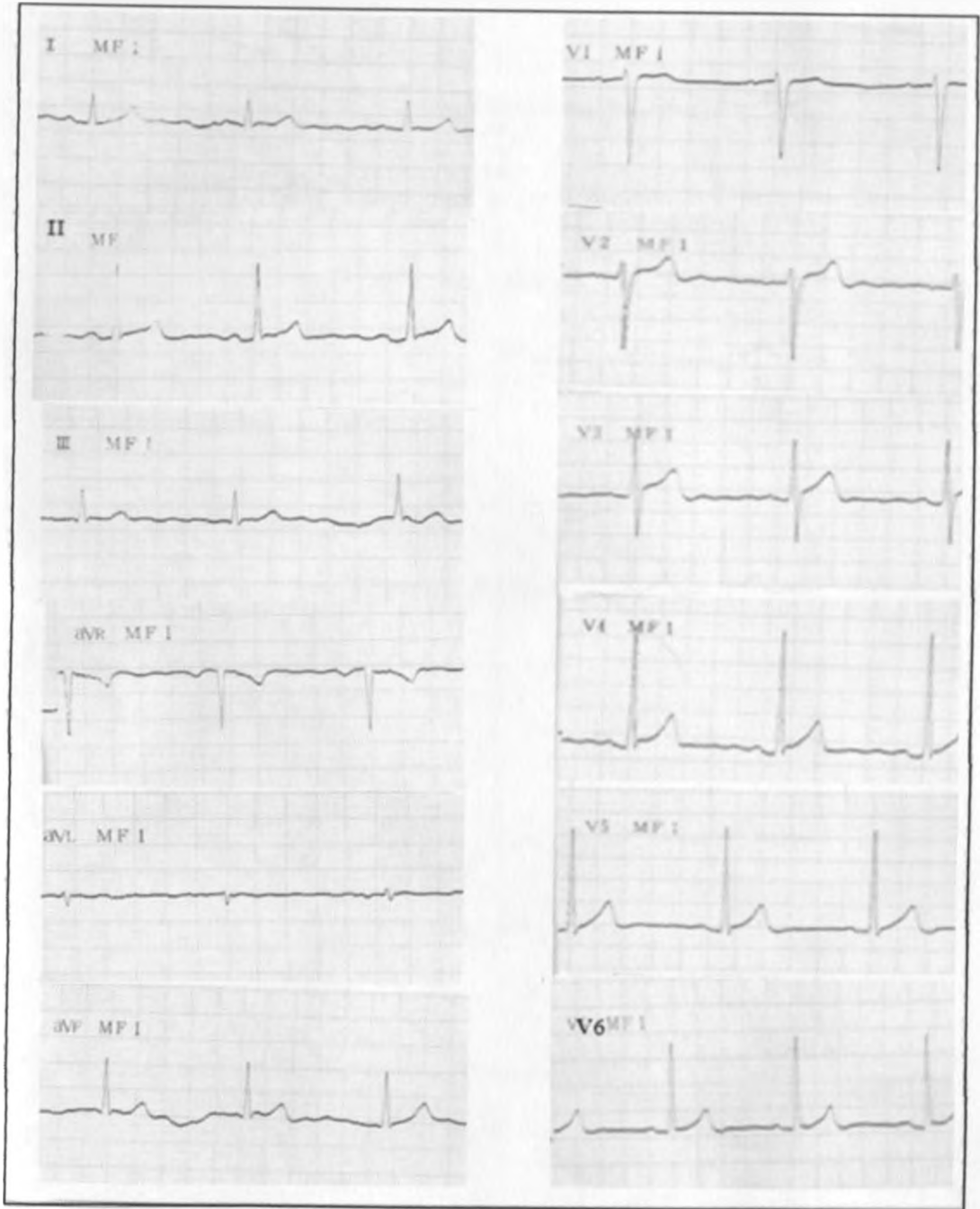
Normal 12-lead ECG of 34-year-old female subject.

Appendix 5.2



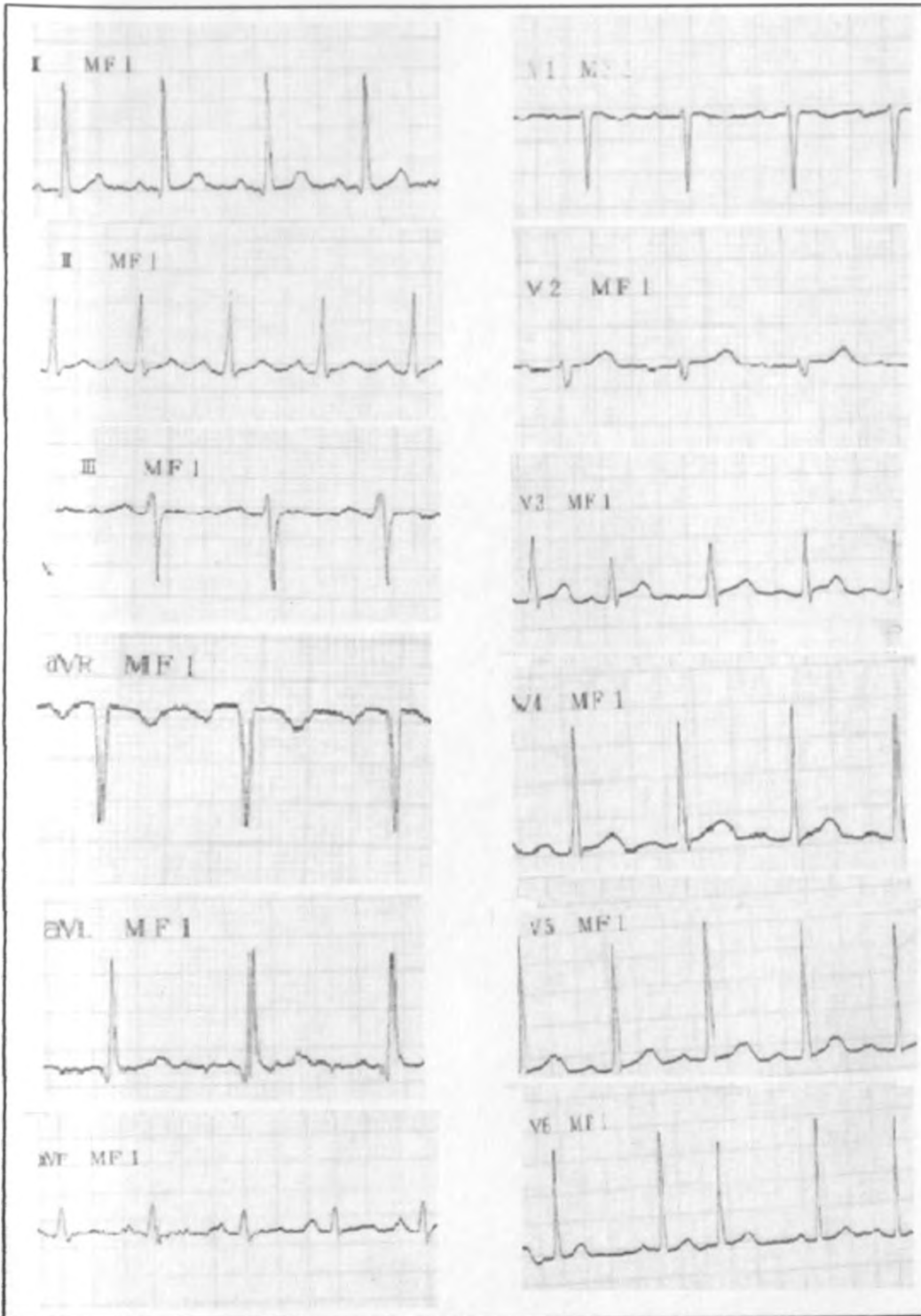
Normal 12-lead ECG of 68-year-old female subject

APPENDIX 5.3



Normal 12-lead ECG of 27-year-old male subject.

APPENDIX 5.4



Normal 12-lead ECG of 75-year-old male subject