A publishable article submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

Title: Electrocardiogram abnormalities in patients with heart failure with reduced ejection fraction at the Charlotte Maxeke Johannesburg Academic Hospital heart failure clinic.

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DECLARATION

I, Max Rath, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine, at the University of the Witwatersrand, Johannesburg. It has not been submitted before, for any degree or examination at this or any other university.

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Signed 5th day of March 2022

DEDICATION

This research paper is dedicated to my wife, Carolyn Rath, whose love, understanding and unwavering support has been key to the completion of this research.

ACKNOWLEDGEMENTS

I would like to use this opportunity to extend my utmost gratitude to Professor Eric Klug and Dr Thomas Kalk for their constant support and guidance through the process of this research submission. Their tireless efforts in helping shape my development in scientific research will stand for many years to come.

Thank you for the many drafts reviewed and understanding throughout this journey.

Abstract

Background:
The 12-lead electrocardiogram (ECG) is a low-cost tool used in the workup of all patients with heart failure with reduced ejection fraction (HFrEF). There is a paucity of evidence on the prognostic utility of the ECG in the African population with HFrEF.

Aim:
To describe the ECG abnormalities seen in patients with HFrEF and their predictive and prognostic utility during follow up at the Charlotte Maxeke Johannesburg Academic Hospital heart failure clinic.

Methods:
Data was collected retrospectively from heart failure clinic files at Charlotte Maxeke Johannesburg Academic Hospital. All new patients referred to this clinic between 01 January 2015 and 31 December 2016 with left ventricular ejection fraction less than 50% were included.

Results:
This study included 107 patients with HFrEF (median age 49 years). Of these, 43% (n=46) were male and 57% (n=61) were female. Most patients in the study were of African ethnicity (76.6%). The median follow up was 44.4 months. The most common ECG abnormalities were inverted T waves (67.3%), fragmented QRS (fQRS) (25.2%) and prolonged QTc interval (25.2%). Pathological Q waves were less common (16.8%). fQRS in lateral ECG leads was more common in patients with ischaemic heart disease (18.2%, p=0.033). QRS duration > 100ms was associated with cardiovascular events (47% of patients, p=0.022). LV non-recovery was associated with PR interval (median 176ms, p<0.001), fQRS (30.6% vs. 5.0%, p=0.026), and inferior inverted T waves (52.8% vs 20.0%, p=0.017).

Conclusion:
We demonstrate that some ECG abnormalities in HFrEF have different prevalence in South African patients to what has been described in more developed nations. Our findings show fQRS may be a useful marker of myocardial scar or prior myocardial infarction in our population.

Table of Contents

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List of abbreviations

AHA	American Heart Association
AF	Atrial fibrillation
ACE-I	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor–blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
AV	Aortic valve
BMI	Body Mass Index (kg/m^2)
bpm	Beats per minute
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
CMO	Cardiomyopathy
CRT	Cardiac resynchronization therapy
DCM	Dilated cardiomyopathy
DOAC	Direct oral anticoagulants
ECG	Electrocardiogram
ESC	European Society of Cardiology
GDMT	Guideline-directed medical therapy
HFrEF	Heart failure with reduced ejection fraction
HFimpEF	Heart failure with improved ejection fraction
HHD	Hypertensive heart disease
HR	Hazard ratio
ICD	Implantable cardiac defibrillator
IHD	Ischaemic heart disease
LBBB	Left bundle branch block
LMIC	Low-middle income class
LV	Left ventricle
LVEDD	LV external end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	LV external end-systolic diameter
LVH	Left ventricular hypertrophy
LVRR	Left ventricle reverse remodelling
MI	Myocardial infarction
MRA	Mineralocorticoid Receptor Antagonist
MRI	Magnetic resonance imaging
NICM	Non-ischaemic cardiomyopathy
NT-proBNP	N-terminal-pro hormone Brain Natriuretic Peptide
NSVT	Non-sustained ventricular tachycardia
NYHA FC	New York Heart Association functional classification of dyspnoea (I-IV)
PROTECT	ProBNP Outpatient Tailored Chronic HF Therapy
PVC	Premature ventricular contraction
RAAS	Renin-Angiotensin-Aldosterone System
RCT	Randomized control trial
RHD	Rheumatic heart disease
SGLT-2	Serum-glucose co-transporter-2
SSA	Sub-Saharan Africa
SCD	Sudden cardiac death
SHIFT	Systolic Heart Failure Treatment with the IF Inhibitor Ivabradine Trial
SR	Sinus rhythm

Chapter 1: Extended literature review and protocol

1.1 Extended literature review

1.1.1 Introduction

Heart failure with reduced ejection fraction (HFrEF) is poised to dominate cardiovascular medicine in the next 50 years. [1]

The burden of cardiovascular disease is increasing in Sub-Saharan Africa (SSA). Heart failure is the most common cardiac cause for hospitalization and mortality rates are significantly higher than the global average. [2, 3]

For decades, the electrocardiogram (ECG) has been a core investigative tool in cardiology. Much of the evidence on the diagnostic and prognostic utility of the ECG comes from research in developed nations. Adapting the research of developed countries to those of developing countries plays an important role in research as well as clinical medicine. Part of this process, however, requires evidence from patients in other countries.

1.1.2 Heart failure with reduced ejection fraction

The European Society of Cardiology (ESC) defines heart failure as a clinical syndrome with symptoms and signs resulting from a structural and/or functional cardiac abnormality. Evidence of pulmonary and/or systemic congestion or elevated natriuretic peptide levels (e.g., NT-proBNP) supports the diagnosis of heart failure.[4]

HFrEF is defined by the ESC as a left ventricular ejection fraction (LVEF) < 40% on transthoracic echocardiography. Heart failure with mildly reduced ejection fraction (HFmrEF) is defined as a LVEF of 41% to 49% and heart failure with preserved ejection fraction (HFpEF) is defined as LVEF > 50%. HFrEF carries the worst prognosis of these three classifications.[5]

Heart failure in the United States currently affects 5.7 million people. This is estimated to increase by 46% (8 million) by 2030. This increase observed in the developed world is largely due to the improved survival of patients with ischaemic heart disease (IHD). The absolute burden of cardiovascular disease in SSA has increased since 1990.[6]

In a 2017 meta-analysis of heart failure in SSA, hypertensive heart disease (HHD) was the most common aetiology, causing 39.2% of heart failure cases.[7] Cardiomyopathy (CMO) and RHD were the next most common aetiologies, at 22.7% and 13.8% respectively. In contrast to the developed world, IHD caused only 7.2% cases of heart failure in SSA. Importantly, this meta-analysis showed the considerable variation in the prevalence of aetiologies between each region in SSA (North, West, East, and South). There were only

two studies specific to Southern Africa. CMO was the most common in Southern Africa, causing 40.2% of cases of heart failure. Common causes of CMO in this region are HIV-associated CMO and peripartum CMO (ppCMO). In Southern Africa HHD, RHD and IHD accounted for 19.2%, 15.4% and 2.9% of cases respectively. [7]

The typical symptoms of HFrEF include dyspnoea or angina [graded as New York Heart Association functional class (NYHA FC) I-IV], fatigue, palpitations and ankle swelling. Initially, the body's physiological response may compensate, and the patient may remain asymptomatic during this adaptive process. Over time these neuro-hormonal compensatory mechanisms promote pathological remodelling of the myocardium. The remodelling process is pivotal in the progression of HFrEF. The result is thinning and dilatation in the affected LV segments, and hypertrophy and fibrosis in unaffected areas of the LV, resulting ultimately in a dilated and dysfunctional LV. [5, 8]

Treatment goals in HFrEF are aimed at improving patient symptoms, ability to function, and quality of life. Treatment goals are also aimed at preventing and reducing hospital admissions from heart failure as well as reducing overall cardiovascular mortality. Drugs that intervene in this neuro-hormonal activation, namely beta-blockers, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor–blockers (ARBs), angiotensin-neprilysin inhibitor (ARNI) and mineralocorticoid receptor antagonists (MRAs) have shown mortality benefit in HFrEF. The PARADIGM-HF trial, a large RCT published in 2014, showed significant benefit of the ARNI LCZ696 compared with enalapril for the treatment of HFrEF. [9]

More recently, the serum-glucose co-transporter-2 (SGLT2) inhibitors Dapagliflozin and Empagliflozin have been shown to reduce hospitalization and all-cause and cardiovascular mortality in patients with HFrEF with or without diabetes. A 2020 meta-analysis including both trials (DAPA-HF) for Dapagliflozin and EMPEROR-Reduced for Empagliflozin) showed SGLT-2 inhibition resulted in a 13% reduction in all-cause mortality (95% CI 0.77–0.98; p=0.018) and 14% reduction in cardiovascular mortality (0.86, 0.76–0.98; p=0.027).[10] SGLT-2 inhibitors are now recommended for all patients with HFrEF NYHA FC II-IV to reduce the risk of hospitalizations and cardiovascular death.[5]

Cardiac resynchronisation therapy (CRT) improves cardiac function in select patients with HFrEF and reduces morbidity and mortality. A significant cause of mortality in HFrEF is sudden death, and implantable cardiac defibrillators promote survival in this group.[5]

With guideline directed medical therapy (GDMT), some patients may have a recovery in their LVEF. Improved (or recovered) HFrEF (HFimpEF) is defined as initial LVEF $\leq$ 40% on echocardiogram, a $\geq$ 10-point increase from baseline LVEF and a second measurement of LVEF > 40%.[4] Patients with HFimpEF have improved quality of life, lower hospitalisation rates and lower mortality. Despite this, these patients still have higher morbidity and mortality than the normal population. Furthermore, many patients with HFimpEF develop recurrent heart failure with LV dysfunction, especially if GDMT is

stopped. As outlined in the 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure, there are gaps in research on the incidence, prevalence, and treatment of HFimpEF.[5, 11]

The prognosis of patients with HFrEF has improved over the last few decades. Data from Europe and North America show the one-year and five-year mortality rates for HF to be 20% and 53% respectively. One-year HF mortality rates in SSA are significantly higher than the rest of the world, ranging from 29% to 58%. According to the INTER-CHF study, the one-year HF mortality rate in Africa is the highest globally at 34%, twice the world average of 16.5%.[3, 5]

1.1.3 The electrocardiogram

The "discovery of the mechanism of the electrocardiogram" in 1895 won Willem Einthoven the Nobel Prize in Physiology and Medicine in 1924. In 1901, Einthoven described the first prototypes of his string galvanometer, which showed the first tracings of the electrical activity of the heart. In 1938, the American Heart Association (AHA) and Cardiac Society of Great Britain published their recommendation for using unipolar leads to record the horizontal plane of the heart with six chest leads (V1-V6). In 1942, Dr Emmanuel Goldberger connected unipolar leads to the left and right arms and left leg (the limb leads). This allowed a more detailed recording of the frontal plane of the heart in 30-degree increments (leads I, II, III, aVL, aVR and aVF). In 1954, the AHA published their recommendation for the standardization of the 12-lead ECG.[12]

Since then, the 12-lead ECG has become the most frequently performed cardiovascular test and part of a minimum workup, not only for patients with heart failure but for all patients presenting to general medicine. [13, 14]

The ECG is low-cost in contrast to other tools in cardiology. The ECG is an accurate and objective measure of cardiac electrophysiology and does not require a specialist cardiology service for basic interpretation. The interpretation of the 12-lead ECG requires visual assessment of several different waveforms and segments, namely P wave, PR segment, QRS segment, ST segment and T wave. In the last decade, the use of algorithms to produce automated ECG interpretation has become ubiquitous. Many of the modern ECG machines now provide this basic interpretation which assists with screening. [14]

Advancements in biomedical signal processing and computing has opened opportunity for new options for ECG analysis. In initial studies, several novel ECG markers have shown potential for their use in the diagnosis, prognostication, and response to treatment of cardiac pathologies. Furthermore, assistance from artificial intelligence algorithms, some of these markers have shown association with risk of cardiovascular morbidity and mortality in the asymptomatic population. [13]

1.1.4 The electrocardiogram in heart failure with reduced ejection fraction

For the diagnosis of HFrEF the 12-lead surface ECG has high sensitivity (89%) but low specificity. The ECG's utility in HFrEF is therefore mainly to rule out HFrEF i.e., if the ECG is normal then HFrEF is unlikely. Abnormalities on the ECG such as a widened QRS complex, AF, Q waves and LVH all increase the suspicion of HF but are not diagnostic. The ECG may also provide evidence for underlying aetiology or precipitating factor, for example atrial fibrillation or myocardial infarction.[5, 15]

Abnormalities on ECG are common in patients with HFrEF. In an analysis of ECG data from the Heart of Soweto study (2008), of 756 patients with confirmed HF (EF < 45%), 97% had abnormal ECGs. Data from studies in SSA suggest ECG abnormalities may differ by aetiology of HF and ethnicity. In the Heart of Soweto study, ECG changes associated with HF [axis deviation, left ventricular hypertrophy (LVH) and bundle branch block] were only seen in 48% of patients. Interestingly, left bundle branch block (LBBB) was 66% less prevalent than comparable studies in the developed world. This could be explained by the greater prevalence of ischaemic CMO in the developed world compared to that of South Africa.[16]

Investigating for aetiology is important as part of the management of HFrEF. Abnormalities on ECG may increase the suspicion of certain aetiologies. For example, Q waves on ECG increase the suspicion of IHD and left ventricular hypertrophy (LVH) on ECG is consistent with HHD.[15]

Over the past decade there has been growing evidence supporting the prognostic utility of the ECG for morbidity and mortality. Known ECG markers of worse prognosis in HF in international studies HF are elevated resting heart rate, the presence of atrial fibrillation (AF), a wide QRS complex and LVH. The THESUS-HF study looked at the prognostic significance of the ECG in patients presenting with acute HF in Sub-Saharan Africa. In this study heart rate was associated with higher rates of readmission at 60 days in patients with acute heart failure. Heart rate > 119 bpm was associated with the highest mortality risk. Sinus rhythm had the strongest association with survival.[15, 17]

Heart rate

Raised resting heart rate [in sinus rhythm (SR)] is a risk factor for worse cardiovascular outcomes and mortality. A higher resting heart rate becomes especially important in the setting of coronary artery disease. The Coronary Artery Surgery Study of 24 913 patients in Canada with suspected or proven CAD provided data on the prognostic value of resting HR in CAD. Over a median follow up of 14.7 years, a resting HR $\geq$ 83 bpm in patients with CAD (with or without HFrEF) was associated with significantly higher cardiovascular mortality [hazard ratio (HR)=1.31, CI 1.15–1.48,P<0.0001) and all-cause mortality (HR= 1.32, CI 1.19–1.47,P<0.0001).[18]

Sinus bradycardia (heart rate < 60 bpm) may complicate heart failure and may worsen symptoms through a reduction in cardiac output. Severe sinus bradycardia may be a cause of sudden cardiac death (SCD) in patients with HFrEF.[5]

The SHIFT trial was a randomised control trial (RCT) on the effects of the heart rate lowering drug Ivabradine, an If- channel inhibitor, on outcomes in chronic HFrEF when added to background GDMT. Endpoints in the trial were all-cause admission to hospital, admission for worsening heart failure, any cardiovascular admission or death, death from heart failure and all-cause mortality. The trial found reductions in the Ivabradine arm, admissions for worsening HF (672 [21%] placebo vs 514 [16%] ivabradine; HR 0.74, 0.66–0.83; p<0.0001) and deaths due to HF (151 [5%] vs 113 [3%]; HR 0.74, 0.58–0.94, p=0.014). Ivabradine has since been incorporated into the 2021 ESC HF guidelines to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite GDMT (Class IIa recommendation).[5]

Rhythm

Arrythmias and conduction disturbances are common in HFrEF and contribute to significant morbidity and mortality. AF is the most common supraventricular arrhythmia in HF. AF is characterized by disorganised electrical impulses originating from the atria. This leads to an irregular atrioventricular (AV) node response and subsequent irregular ventricular rhythm. AF has been shown to be both a complication as well as an aetiology of HFrEF. AF can also precipitate decompensation of pre-existing HF.

Complex structural and neurohormonal mechanisms propagate the development of AF as a complication of HFrEF. Structural changes to the atrium, including those caused by functional mitral regurgitation, predispose to the development and maintenance of AF in the setting of HFrEF. Activation of the renin-angiotensin-aldosterone system (RAAS) in HFrEF constitutes the main neurohormonal change driving the remodelling and fibrosis of the atria that also precipitate AF.[19] In DAPA-HF, an RCT comparing the efficacy of the SGLT-2 inhibitor Dapagliflozin to placebo for HFrEF, the prevalence of AF and HFrEF was 24%. This relationship seen between HFrEF and AF is in part because of shared risk factors. In addition, growing evidence shows closely related pathophysiology underlying HFrEF and AF.[20]
HFrEF complicated by AF is associated with a worse prognosis and is a major contributor to cardiovascular morbidity and mortality. AF predisposes to thrombus formation in the left atrial appendage which may lead to stroke or other cardio-embolic complications. AF doubles the risk of all-cause and cardiovascular mortality.[21]

In contrast, HFrEF caused by AF has a favourable prognosis. HFrEF may improve or resolve with treatment of the underlying arrhythmia for example through electrical cardioversion or more invasive radiofrequency ablation of AF.[5]

PR interval

The PR interval on the ECG represents the time from beginning of atrial depolarization (P wave) to beginning of ventricular depolarization. The normal PR interval duration is 120ms to 200ms. First-degree heart block is defined as a prolonged PR interval >200ms. First-degree heart block is seen in around 21% of patients with HFrEF, versus 9% of patients without HF. [17] PR prolongation has also been shown to predict worse LV systolic function in patients with HF.[22]

In a study of 3200 patients with heart failure from the Korean Heart Failure registry, a PR interval > 200ms was independently associated with higher mortality as well as higher rates of rehospitalization ($p<0.1$). A reason for this association may be that PR prolongation can reduce cardiac output and increase left atrial filling pressures thereby worsening HF. Data from the Framingham Heart Study show first-degree heart block is also associated with the development of AF (multivariable-adjusted HR=2.06, $p<0.001$) and as a consequence a higher morbidity and mortality.[23] Another reason may be that first-degree heart block is commonly associated with bradycardia. This limits the use of beta-blocker therapy which could lead to worse outcomes in patients with HFrEF.[24]

Q waves

Pathological Q waves are defined as (1) any Q-wave in leads V2–V3 ≥ 20ms or QS complex in leads V2 and V3, or (2) Q-wave ≥ 30ms and > 0.1mV deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping, or (3) R wave ≥ 40ms in V1–V2 and R/S ratio ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.[25] Their presence on ECG is specific for a prior transmural MI. However, pathological Q waves have poor sensitivity for prior MI. Between 25% to 63% of Q waves may regress or disappear over time. In one study of ECG findings in the normal South African population, Q waves were seen in up to 13% of patients without myocardial ischaemia. This was especially common in males. This suggests the presence of Q waves may be less applicable in the African population. [26-28]

QRS complex

The QRS complex reflects ventricular depolarization in the heart. Normal electrical activation of the ventricles of the heart occurs through impulses down the specialized His-Purkinje system and both left and right bundle branches. This results in synchronous activation of the septum from left to right and of both ventricles. Abnormalities of the QRS are common in HFrEF and have long been associated with poorer outcomes.

Prolongation of the QRS reflects intraventricular conduction delay. A QRS duration of greater than 100ms indicates a high likelihood that LVEF <45% (83% specificity, $p<0.001$). A QRS >120ms is 99.3% specific for a LVEF <45% ($p<0.001$). The sensitivity of prolonged QRS >100ms is poor (43.8%, $p<0.0001$). At >120ms the sensitivity drops to 13.8%

(p<0.0001). Furthermore, increases in QRS duration reflect worsening LVEF and are associated with a progressive increase in all-cause mortality. In one study five-year survival in HF patients with QRS ≥120ms was 47% compared to 84% in patients with QRS <120ms.[29]

Left bundle branch block (LBBB) occurs more commonly in HF with LVEF <45% than RBBB (25%-36% vs 4%-6%). LBBB predicts adverse LV remodelling and is associated with worse prognosis in HFrEF. In LBBB, instead of normal activation of the left ventricle through the left bundle branch, activation occurs via the right bundle branch. This causes right to left activation of the septum and activation of the LV free wall via myocardium which is much slower than the specialized Purkinje fibres. Evidence of a complete LBBB on the ECG is a widened QRS(≥120ms), absence of a Q wave in lead V6, small R wave in V1, deep S wave in V1 and positive QRS complex in V6. The result of this is uncoordinated LV contraction causing a significant increase in LV workload which over time leads to the remodelling seen with LBBB. [30-32]

Research at Duke University Hospital looked at race and sex differences in QRS duration and associated outcomes in patients with HFrEF. In this study LBBB was more common in white than black patients (20.8% vs 12.3%, p=0.012) and twice as common in women than in men of the same race (p=0.012). Furthermore, modest QRS prolongation was associated with an increase in mortality in only black HFrEF patients (16% for each 10ms increase up to QRS < 112ms, p=0.06). [33]

One of the novel markers on ECG is fragmented QRS (fQRS) complex. fQRS is the presence of additional spikes within the QRS complex, with or without bundle branch block morphology. fQRS is defined as additional R' waves or a notch in the R or S wave (fragmentation) in two contiguous leads corresponding to a coronary territory. Fragmented wide QRS (f-wQRS) is the presence of additional notches in the QRS complex in the presence of bundle branch block (QRS > 120ms).[34]

Studies on the pathophysiology behind fQRS show the marker is associated with myocardial scar. In patients post-MI, fQRS has been shown to be more sensitive for myocardial scar than Q wave (85.6% vs 36.3%) and has a higher negative predictive value (92.7% vs 70.8%). [34]

fQRS is associated with increased mortality in both coronary artery disease and NICM. Several studies in the last decade demonstrated poor prognostic outcome in HFrEF patients with their baseline ECG positive for fQRS. A 2018 meta-analysis on fQRS and prognosis in HFrEF shows association with increased all-cause mortality with LVEF <35% (risk ratio [RR] 1.63, 95% CI 1.22–2.19, p < 0.0001). Importantly, the meta-analysis only included Caucasian and Asian cohorts. In patients that did not receive ICD, fQRS significantly increased all-cause mortality compared to HFrEF patients that received ICD (RR = 2.46 with 95% CI 1.56–3.89 and 1.36 with 95% CI 1.08–1.71, respectively).[26, 35] fQRS thus provides valuable information about the condition of the heart and is easily

obtained from the surface ECG, making it an important novel ECG marker highly relevant to clinical practice.

HHD is an important aetiology of HFrEF because of the high prevalence of hypertension in the population. A large proportion of patients with HFrEF have a history of hypertension however there are differences in prevalence of LVH across race and gender. A study on ECG changes in African patients in the Seychelle's showed a higher average Sokolow-Lyon voltage. A large population-based study on elderly patients in the US in 2020 showed African-Americans had the highest incidence of LVH.[36, 37]

LVH may be diagnosed using surface 12-lead ECG using the Sokolow–Lyon criteria by adding the S wave amplitude in V1 and the R wave amplitude in V5 or V6. LVH is diagnosed when this value is ≥ 35mm. LVH may also be diagnosed using the Cornell voltage criteria for LVH on ECG or using echocardiographic measurement of LV mass.[38] LVH in response to hypertension is initially adaptive. Systolic dysfunction and HFrEF represents end-stage HHD. LVH is a marker of worse prognosis in HF. A recent population-based study from Finland showed LVH increased risk of hospitalization for HF in women compared to men (RR 1.9, CI 1.5 − 2.3, p<0.001).[37]

Ventricular ectopy, or premature ventricular contraction (PVC), is common in HFrEF. Up to 50% of HFrEF patients have PVCs on their ECG. PVCs may complicate, precipitate or be a cause of heart failure. A PVC burden of more than 10% of beats is considered significant as a cause of heart failure (termed PVC-induced cardiomyopathy). The key mechanism here is thought to be ventricular dyssynchrony. Important risk factors for development of PVC-induced cardiomyopathy include PVC burden and duration of exposure to PVCs.[39] Treatment of PVCs with either RFA or amiodarone has been shown to improve LV systolic function. Furthermore, a reduction in PVC burden has been associated with reduced hospitalizations and cardiovascular mortaility.[5, 39] Conversely, the presence of at least 1 PVC on a 12-lead ECG or > 30 PVCs per hour on Holter is associated with increased cardiovascular risk and increased mortality. [40]

QTc interval

The corrected QT interval (QTc) on the ECG represents the time from onset of ventricular depolarization to the end of ventricular repolarization and represents the period of ventricular systole. Prolonged QTc is known to increase risk of ventricular tachycardia and SCD in patients with CAD. Recent research shows that reduction in QTc prolongation correlates with LVEF recovery in heart failure with improved ejection fraction [(HFimpEF), follow-up LVEF ≥40% and ≥ 10% improvement from baseline]. [41]

Prolonged QTc interval is also associated with onset of new AF in the setting of HFrEF. In an analysis of 1505 individuals, incident AF was associated with a longer ST segment (HR=1.27; 95% Confidence Interval [CI]: 1.14–1.41], p<0.001) and prolonged T wave onset to T wave peak (HR=1.13; 95% CI: 1.07–1.20, p<0.001). [42]

T wave

The T wave on ECG represents ventricular repolarization. Inverted T waves on ECG are non-specific but may suggest aetiology of heart failure in patients, for example ischaemic heart disease or hypertension.

Frontal QRS-T plane angle

Another novel ECG marker is frontal QRS-T angle. This angle is defined as the difference between the direction of ventricular depolarization (frontal QRS axis) and repolarization (T wave axis), measured in degrees. This difference, easy calculated from the ECG, represents cardiac structural and electrical abnormalities. [43]

The frontal QRS-T plane angle is associated with reduced LV systolic function. It predicts arrhythmia, cardiac-related hospitalization, and all-cause mortality in patients with HFrEF. Consensus has not yet been reached on what is considered the normal frontal QRS-T angle range. In most studies on the predictive utility of this measurement, an angle of more than 90 to 100 degrees was associated with increased risk of the primary endpoint (cardiac mortality or total mortality).[44] In a study of 1140 patients with acute decompensated heart failure, the frontal QRS-T plane angle was an independent predictor of 2-year mortality. For every 20° increase in QRS-T angle there was a 4% increase in 2-year mortality (p=0.02).[43, 45]

1.1.5 SCD in heart failure with reduced ejection fraction

SCD accounts for a large proportion of deaths in HFrEF. SCD is most commonly due to electrical disturbances such as ventricular tachycardia, bradycardia, or asystole. This risk is greatest in patients with IHD. Predictors of SCD in HF patients have grown in importance since the advent of the ICD.[28]

An ICD is recommended to reduce SCD and all-cause mortality in patients with NHYA FC II-III dyspnoea in IHD with an LVEF $\leq$ 35% despite more than 3 months of GDMT (Class Ia). Evidence from the DANISH study showed no benefit of ICD implantation as a primary prevention strategy for all-cause mortality in patients with non-ischaemic cardiomyopathy (NICM).[5]

Up to 40% of patients with NICM undergo left ventricle reverse remodelling (LVRR). This involves a reduction in left ventricle volumes and improved systolic function with therapy and is associated with a better prognosis. Researchers have proposed the integration of multiple predictive markers to assess for likelihood of LVRR and SCD. This tailored arrhythmic risk stratification includes ECG, echocardiographic, cardiac magnetic resonance imaging (MRI) and genetic markers. There is limited access to cardiac MRI and genetic testing in the current South African setting. ECG markers that have strong

evidence for their role as a predictive tool for SCD are fQRS, non-sustained ventricular tachycardia (NSVT) on Holter, frequent premature ventricular contractions (PVC) and prolonged QRS. Furthermore, the presence of AF, LBBB, heart block and prolonged QRS make LVRR significantly less likely.[46]

Insights from the SCD in heart failure trial (SCD-HeFT) showed that African Americans when compared to Caucasians had more non-ischaemic causes of heart failure, worse NYHA FC, lower ejection fractions, lower prevalence of QRS $\geq$ 120ms (27% vs 44%, $p<0.05$) but higher prevalence of non-sustained ventricular tachycardia (31% vs 22%, $p<0.05$). [47]

1.1.6 The electrocardiogram in heart failure in South Africa

Available research on the ECG in the HFrEF population originates largely from studies in developed nations on predominantly Caucasian populations. Furthermore, much of the local evidence on ECG findings in Africans originates from studies that included only disease-free patients. One such study from 2013 of 387 patients showed ECG abnormalities were present in 51% of disease-free Africans. Importantly, the authors note that ECG findings such as T wave inversion, early repolarization, tall R waves and voltage criteria for LVH may be normal variants in the disease-free African population.[28] A similar study from 2016 reproduced similar findings in South African patients of African descent and showed that these findings on ECG were not associated with reduced LVEF.[48]

A small study of the diagnostic and prognostic utility of the ECG in follow up HF patients in Egypt showed correlation between QRS voltage and LV external end-diastolic diameter (LVEDD) and LV external end-systolic diameter (LVESD). QRS voltage was also inversely correlated with peripheral oedema.[49]

Evidence from THESUS-HF yielded insights into the prognostic significance of the ECG in acute heart failure patients in SSA. In the study, 97.7% of participants with the clinical diagnosis of HF had abnormal ECGs. Mean age was 52 years with median follow up of 180 days. A total of 77 deaths (Kaplan-Meier 17.5%) were observed within the follow up period, with 63 readmissions or deaths within 60 days. In THESUS-HF, increasing heart rate, lack of sinus rhythm and Q waves were the ECG markers associated with readmission within 60 days or death within 180 days.[17]

To date there exists a paucity of research on ECG changes in chronic HFrEF patients in SSA. While the sensitivity of the ECG for the diagnosis of HF is well-validated, the predictive and prognostic utility of ECG markers, old and new, remain understudied in patients with chronic HFrEF on the African continent.

1.2 Aim

To describe the electrocardiogram abnormalities in patients with heart failure with reduced ejection fraction and their predictive and prognostic utility over 5 years of follow up at the Charlotte Maxeke Johannesburg Academic Hospital heart failure clinic.

1.3 Objectives

1. Describe the prevalence of the following electrocardiogram markers in this population at first consultation and at follow up:

1.1. Ventricular rate
1.2. Rhythm
1.3. PR interval
1.4. Pathological Q waves
1.5. QRS
    1.5.1. Duration
    1.5.2. Bundle-branch pattern
    1.5.3. Frontal QRS Axis
    1.5.4. Fragmented QRS
    1.5.5. Left ventricular hypertrophy,
    1.5.6. R wave transition in anterior chest leads
1.6. Number of leads with T wave inversion
1.7. Upright R wave in lead aVR
1.8. Frontal QRS-T plane angle
1.9. QTc interval (using Bazett's formula)

2. Compare the prevalence of the above electrocardiogram markers with:
    2.1. Ethnicity
    2.2. Gender
    2.3. Comorbidities

3. Describe the association of the above electrocardiogram markers with:
    3.1. Change in ejection fraction with GDMT
    3.2. Hospitalisation due to heart failure
    3.3. Need for electrical cardioversion
    3.4. Cardiovascular events (TIA, CVA, other cardio-embolic events, ADHF, ACS)

1.4 Methodology

Study design
This will be a retrospective folder review of out-patient department records of all consecutive patients who attended the HFrEF Clinic in area 557 at Charlotte Maxeke

Johannesburg Academic Hospital, Gauteng, South Africa between 1 January 2015 and 31 December 2016.

Characteristics of the study population

Patients will be included in this study if they meet the following criteria:

1. Documented heart failure with reduced and moderately reduced ejection fraction (LVEF < 50%)
2. Have attended the heart failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital.

Patients will be excluded if clinical notes are insufficient to support data analysis.

Recruitment and enrolment

All heart failure patient records are documented and kept at the HFrEF Clinic in area 557 at Charlotte Maxeke Johannesburg Academic Hospital. Patients will be included if they meet the eligibility criteria. All new patients referred to the HFrEF Clinic in area 557 at Charlotte Maxeke Johannesburg Academic Hospital between 1 January 2015 and 31 December 2016 will be included in this study. This period was chosen for the following reasons:

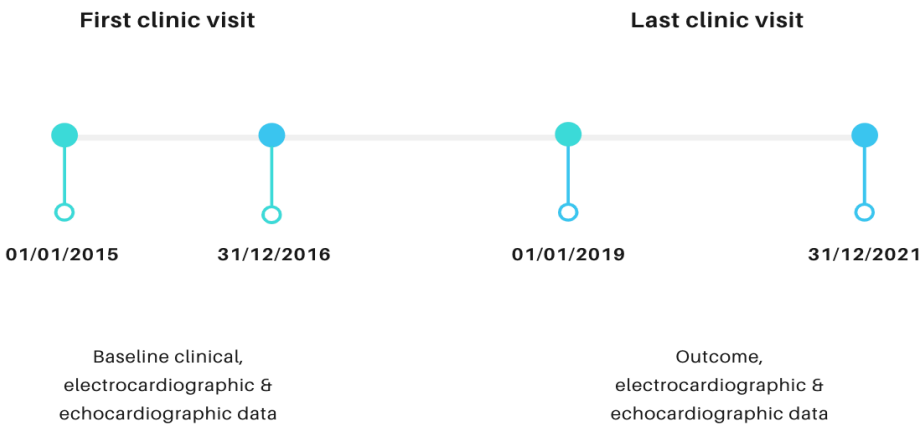
1. Availability of records during this time
2. To allow for adequate time between first and last clinic visit: data collection to occur between 2020 and 2021 therefore allowing approx. 5 years between first and last clinic visits.

Since this is a retrospective folder review, it will not be feasible to obtain consent from these patients to be included in this study. However, all collected names and data will remain confidential, as only the study investigators will have access to data. Prior to statistical analysis, all data will be anonymized to further protect patients' identity and information.

Data collection

Data to be collected is outlined in appendix 1.

As seen in the timeline below, baseline clinical, electrocardiographic, and echocardiographic data will be collected at the first clinic visit and then at the last clinic visit within the five-year time period:



Data will be collected retrospectively from the following sources:
CMJAH Heart failure Clinic folders

Sample size
As this is a descriptive study, all new patients referred to the HFrEF Clinic in area 557 at Charlotte Maxeke Johannesburg Academic Hospital between 1 January 2015 and 31 December 2016 will be included in this study. We anticipate the total number including between 150 and 300 patients. This is derived from the following calculation:

1. ~5-10 new HFrEF patients per week x ~50 weeks x 1 year = 250 to 500 new patients in 2015.

Data safety and monitoring
A paper-based data collection sheet (appendix 2) will be used for collecting data. The data collection sheets will be transcribed to RedCap, from where it will be exported to STATA for statistical analysis.

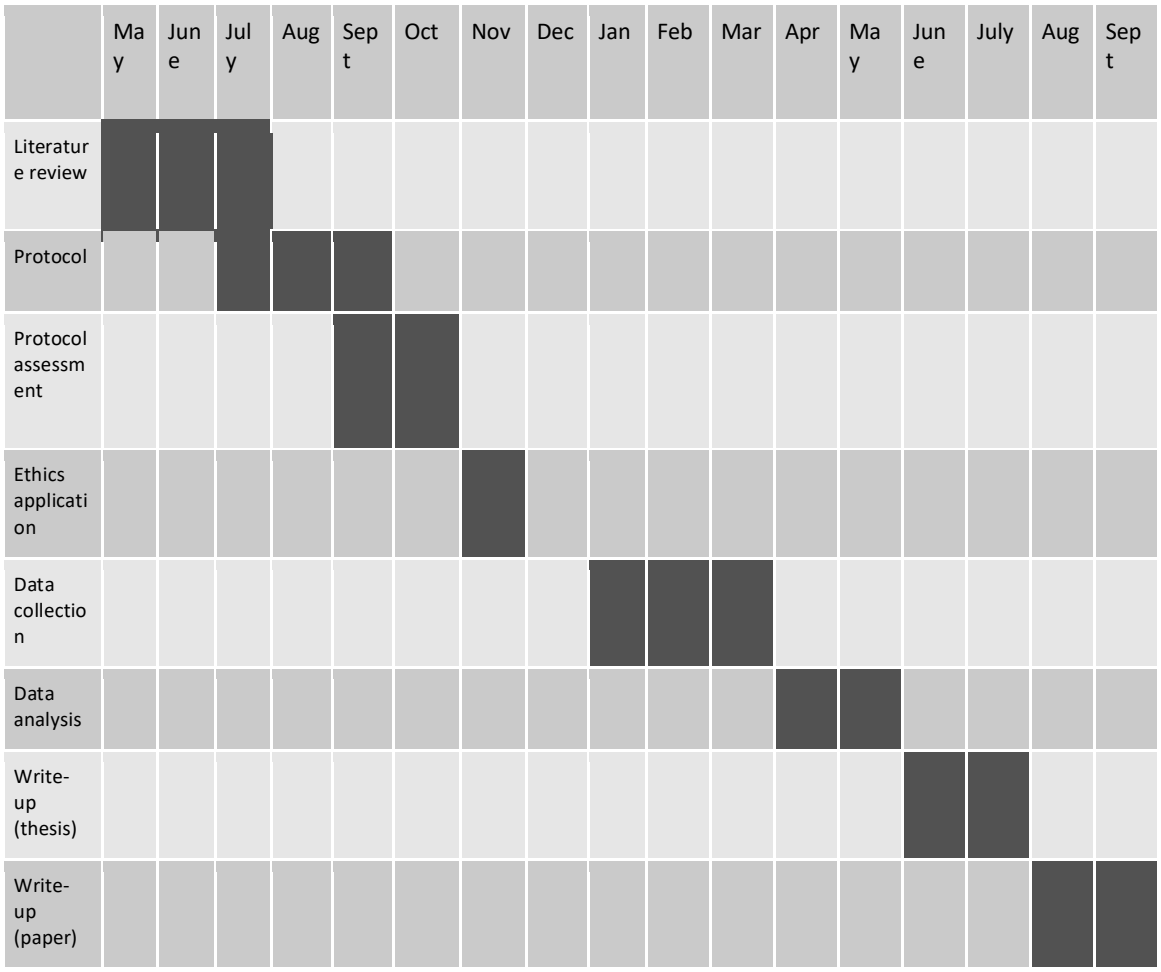
To protect patient confidentiality the paper-based data collection sheets will be locked in the cardiac clinic. Access to RedCap will be password protected and accessible only provided to investigators. Extracted data on RedCap will be anonymized prior to statistical analysis.

Data analysis
All analyses will be performed with Stata, version 14 (StataCorp, College Station, Texas). Descriptive statistics will be used to characterize the sample. Continuous variables will be expressed as mean (with standard deviation) or median (with interquartile range). Categorical data will be presented as frequencies and percentages. Continuous variables will be compared using either student t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed data). Depending on the distribution of data, either Chi-square or Fisher's exact test will be applied to compare categorical data.

1.5 Budget

None required

1.6 Timeline



1.7 Benefits of study

The benefits of this study are to

- Provide local data on prevalence, co-morbidities, and outcomes.
- Review current practices.
- Improve treatment approaches in the local context.
- Describe the predictive and prognostic utility of ECG markers in the local population.

1.8 Ethical consideration

- Risk: this is a low-risk study as it is a retrospective folder review which has no influence on patient management.

- Privacy and confidentiality: patient confidentiality will always be maintained.
- Patient data will be anonymized in an electronic database.
- Reimbursement for participation: no reimbursement for participants in this study.

References

1. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? Eur Heart J. 2015;36(46):3250-7.
2. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. The Lancet. 2009;374(9693):934-47.
3. Ajayi AA, Sofowora GG, Ladipo GO. Explaining Heart Failure Hyper-mortality in Sub Saharan Africa: Global Genomic and Environmental Contribution Review. J Natl Med Assoc. 2020;112(2):141-57.
4. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021;23(3):352-80.
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
6. Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, McMurray J, et al. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. Circulation. 2008;118(23):2360-7.
7. Agbor VN, Essouma M, Ntusi NAB, Nyaga UF, Bigna JJ, Noubiap JJ. Heart failure in sub-Saharan Africa: A contemporaneous systematic review and meta-analysis. Int J Cardiol. 2018;257:207-15.
8. Muslin AJ. The Pathophysiology of Heart Failure. Muscle2012. p. 523-35.
9. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
10. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. The Lancet. 2020;396(10254):819-29.
11. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart Failure With Recovered Left Ventricular Ejection Fraction: JACC Scientific Expert Panel. J Am Coll Cardiol. 2020;76(6):719-34.
12. AlGhatrif M, Lindsay J. A brief review: history to understand fundamentals of electrocardiography. J Community Hosp Intern Med Perspect. 2012;2(1).
13. Reichlin T, Abacherli R, Twerenbold R, Kuhne M, Schaer B, Muller C, et al. Advanced ECG in 2016: is there more than just a tracing? Swiss Med Wkly. 2016;146:w14303.
14. de Luna AB. Willem Einthoven and the ECG. Eur Heart J. 2019;40(41):3381-3.
15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the

European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
16. Lee G, Sliwa K, Carrington M, Stewart S. The Use of the Electrocardiogram in Heart Failure Patients in the Heart of Soweto Study. Heart, Lung and Circulation. 2008;17.
17. Dzudie A, Milo O, Edwards C, Cotter G, Davison BA, Damasceno A, et al. Prognostic significance of ECG abnormalities for mortality risk in acute heart failure: insight from the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF). J Card Fail. 2014;20(1):45-52.
18. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J. 2005;26(10):967-74.
19. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. The American Journal of Cardiology. 2003;91(6):2-8.
20. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail. 2019;21(11):1402-11.
21. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomstrom-Lundqvist C, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2020;41(5):655-720.
22. Salden F, Kutyifa V, Stockburger M, Prinzen FW, Vernooy K. Atrioventricular dromotropathy: evidence for a distinctive entity in heart failure with prolonged PR interval? Europace. 2018;20(7):1067-77.
23. <Cheng-2009-Long-term-outcomes-in-individuals-w.pdf>.
24. Park SJ, On YK, Byeon K, Kim JS, Choi JO, Choi DJ, et al. Short- and long-term outcomes depending on electrical dyssynchrony markers in patients presenting with acute heart failure: clinical implication of the first-degree atrioventricular block and QRS prolongation from the Korean Heart Failure registry. Am Heart J. 2013;165(1):57-64 e2.
25. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64.
26. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation. 2006;113(21):2495-501.
27. J J, A F, D K, S H, D L, J L. Electrocardiography. 20e ed: McGraw-Hill; 2020.
28. Sliwa K, Lee GA, Carrington MJ, Obel P, Okreglicki A, Stewart S. Redefining the ECG in urban South Africans: electrocardiographic findings in heart disease-free Africans. Int J Cardiol. 2013;167(5):2204-9.
29. Kalra PR, Sharma R, Shamim W, Doehner W, Wensel R, Bolger AP, et al. Clinical characteristics and survival of patients with chronic heart failure and prolonged QRS duration. Int J Cardiol. 2002;86(2-3):225-31.

30. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol. 2005;46(12):2183-92.
31. Smiseth OA, Aalen JM. Mechanism of harm from left bundle branch block. Trends Cardiovasc Med. 2019;29(6):335-42.
32. Aimo A, Gaggin HK, Barison A, Emdin M, Januzzi JL, Jr. Imaging, Biomarker, and Clinical Predictors of Cardiac Remodeling in Heart Failure With Reduced Ejection Fraction. JACC Heart Fail. 2019;7(9):782-94.
33. Randolph TC, Broderick S, Shaw LK, Chiswell K, Mentz RJ, Kutyifa V, et al. Race and Sex Differences in QRS Interval and Associated Outcome Among Patients with Left Ventricular Systolic Dysfunction. J Am Heart Assoc. 2017;6(3).
34. Supreeth RN, Francis J. Fragmented QRS - Its significance. Indian Pacing Electrophysiol J. 2020;20(1):27-32.
35. Kanitsoraphan C, Rattanawong P, Mekraksakit P, Chongsathidkiet P, Riangwiwat T, Kanjanahattakij N, et al. Baseline fragmented QRS is associated with increased all-cause mortality in heart failure with reduced ejection fraction: A systematic review and meta-analysis. Annals of Noninvasive Electrocardiology. 2019;24(2):e12597.
36. Zerkiebel N, Perret F, Bovet P, Abel M, Jaggy C, Paccaud F, et al. Electrocardiographic findings in a middle-aged African population in the Seychelles Islands. Journal of Electrocardiology. 2000;33(1).
37. Friedman A, Chudow J, Merritt Z, Shulman E, Fisher JD, Ferrick KJ, et al. Electrocardiogram abnormalities in older individuals by race and ethnicity. Journal of Electrocardiology. 2020.
38. Peguero JG, Lo Presti S, Perez J, Issa O, Brenes JC, Tolentino A. Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy. J Am Coll Cardiol. 2017;69(13):1694-703.
39. Latchamsetty R, Bogun F. Premature Ventricular Complex-Induced Cardiomyopathy. JACC Clin Electrophysiol. 2019;5(5):537-50.
40. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018;138(13):e272-e391.
41. Prenner SB, Swat SA, Ng J, Baldridge A, Wilcox JE. Parameters of repolarization heterogeneity are associated with myocardial recovery in acute heart failure. Int J Cardiol. 2020;301:147-51.
42. Roberts JD, Soliman EZ, Alonso A, Vittinghoff E, Chen LY, Loehr L, et al. Electrocardiographic intervals associated with incident atrial fibrillation: Dissecting the QT interval. Heart Rhythm. 2017;14(5):654-60.
43. Gotsman I, Keren A, Hellman Y, Banker J, Lotan C, Zwas DR. Usefulness of electrocardiographic frontal QRS-T angle to predict increased morbidity and mortality in patients with chronic heart failure. Am J Cardiol. 2013;111(10):1452-9.
44. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T angle: a review. Ann Noninvasive Electrocardiol. 2014;19(6):534-42.

45. Sweda R, Sabti Z, Strebel I, Kozhuharov N, Wussler D, Shrestha S, et al. Diagnostic and prognostic values of the QRS-T angle in patients with suspected acute decompensated heart failure. ESC Heart Fail. 2020;7(4):1817-29.
46. Cannata A, De Angelis G, Boscutti A, Normand C, Artico J, Gentile P, et al. Arrhythmic risk stratification in non-ischaemic dilated cardiomyopathy beyond ejection fraction. Heart. 2020;106(9):656-64.
47. Mitchell JE, Hellkamp AS, Mark DB, Anderson J, Poole JE, Lee KL, et al. Outcome in African Americans and other minorities in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Am Heart J. 2008;155(3):501-6.
48. Lohrmann GM, Peters F, Srivathsan K, Essop MR, Mookadam F. Electrocardiographic Abnormalities in Disease-Free Black South Africans and Correlations With Echocardiographic Indexes and Early Repolarization. Am J Cardiol. 2016;118(5):765-70.
49. Sadaka M, Aboelela A, Arab S, Nawar M. Electrocardiogram as prognostic and diagnostic parameter in follow up of patients with heart failure. Alexandria Journal of Medicine. 2013;49(2):145-52.

Appendix 1: Data to be collected

Data collection will include the following parameters:

Demographics:

i. Age and date of birth
ii. Gender
iii. Ethnicity

Comorbidities and risk factors:

iv. Former or current smoker
v. Hypertension
vi. Diabetes
vii. Dyslipidaemia
viii. Ischaemic heart disease
ix. Valvular heart disease: rheumatic/non-rheumatic
x. Cardiomyopathy
xi. Thyroid disease
xii. Prior stroke / TIA
xiii. Congenital heart disease

Clinical presentation (at first and last follow up visits)

b. Symptoms
    i. NYHA FC
c. Medications
    i. Beta-blocker
    ii. ACE-I or ARB
    iii. MRA
    iv. Furosemide
    v. Digoxin
d. Aetiology of HF (if known)

ECG characteristics at first consult and last follow up within 5 years

i. Heart rate
ii. Rhythm
iii. PR interval
iv. Pathological Q waves
v. QRS Duration
vi. Bundle-branch block
vii. QRS Axis
viii. Fragmented QRS
ix. Left ventricular hypertrophy,
x. Poor R wave progression
xi. Number of T waves inverted
xii. Upright R wave in lead aVR
xiii. QTc interval

Echo at first consult and last follow up within 5 years

xiv. LVEF
xv. LVEDD

Outcomes during the follow up period:

xvi. Hospitalisation from heart failure
xvii. Change in ejection fraction on GDMT
xviii. Need for electrical cardioversion
xix. Cardiovascular events

Appendix 2: Data collection sheet

Surname			**Folder no.**				
First Name			**Date of birth**				
Gender			**Ethnicity**				
Co-mobids	HPT	DM	Dyslipid	IHD	VHD	CMO	Hyperthyroid
	Prev cardioversion		CongenHD	CCF	CVA / TIA	ETOH	OSA
Risk factors	Smoking	PYH:	Obesity				
Aetiology of HF (if known)							
Clinic visit	**First:**		**Within 5-year f/u**		**Last:**		
Symptoms	NYHA:				NYHA:		
Vitals	HR:	BP:			HR:	BP:	
Meds	BB/ACE/ARB/MRA/OAC				BB/ACE/ARB/MRA/OAC		
ECG							
a.Heart rate							
a.Ryhthm							
a.PR interval							
a.Heart rate variability							
a.Pathological Q waves							
a.QRS							
i.Width							
i.Bundle-branch bl							
i.Axis							
i.Fragmented QRS							
i.,							
i.Poor R wave prog							
a.Number of T waves inve							
a.Upright R wave in lead A							
a.QT interval							
a.Heart rate							
Echo	LVEDD:	LVEF:			LVEDD:	LVEF:	
Cardioversion	Y	N	Y	N	Y	N	
Hospitalisation	Y, number:	N	Y, number:	N	Y, number:	N	
	Date:		Date:		Date:		
Complications	Date:		Date:		Date:		
	CVA / TIA		CVA / TIA		CVA / TIA		
	Other TE event:		Other TE event:		Other TE event:		
	ACS		ACS		ACS		
	Heart block:		Heart block:		Heart block:		
	Other:		Other:		Other:		
Other compl.							
Date completed:							
Investigator:							
Signature:							

Chapter 2: Submissible article

Title: Electrocardiogram abnormalities in patients with heart failure with reduced ejection fraction at the Charlotte Maxeke Johannesburg Academic Hospital heart failure clinic.

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Corresponding Author: Max Rath (drmaxrath@gmail.com)
Authors' Contributions: Dr Max Rath was the principal investigator and primary author of this research manuscript and protocol. Dr Thomas Kalk and Prof Eric Klug assisted with the design of the study, provided guidance with reporting on the data obtained and final editing of the manuscript.
Disclosures: No conflicts of interest to report.

Abstract

Aim: To describe the ECG abnormalities seen in patients with HFrEF and their predictive and prognostic utility during follow up at the Charlotte Maxeke Johannesburg Academic Hospital heart failure clinic.
Methods: Data was collected retrospectively from heart failure clinic files at Charlotte Maxeke Johannesburg Academic Hospital. All new patients referred to this clinic between 01 January 2015 and 31 December 2016 with left ventricular ejection fraction less than 50% were included.
Results: This study included 107 patients with HFrEF (median age 49 years). Of these, 43% (n=46) were male and 57% (n=61) were female. Most patients in the study were of African ethnicity (76.6%). The median follow up was 44.4 months. The most common ECG abnormalities were inverted T waves (67.3%), fragmented QRS (fQRS) (25.2%) and prolonged QTc interval (25.2%). Pathological Q waves were less common (16.8%). fQRS in lateral ECG leads was more common in patients with ischaemic heart disease (18.2%, p=0.033). QRS duration > 100ms was associated with cardiovascular events (47% of patients, p=0.022). LV non-recovery was associated with PR interval (median 176ms, p<0.001), fQRS (30.6% vs. 5.0%, p=0.026), and inferior inverted T waves (52.8% vs 20.0%, p=0.017).
Conclusion:
We demonstrate that some ECG abnormalities in HFrEF have different prevalence in South African patients to what has been described in more developed nations. Our findings show fQRS may be a useful marker of myocardial scar or prior myocardial infarction in our population.

Introduction

Heart failure is poised to dominate cardiovascular medicine in the next 50 years. Heart failure is the most common cardiac cause for hospitalisation in Sub-Saharan Africa, where mortality from heart failure is one of the highest in the world.[1]

Heart failure with reduced ejection fraction (HFrEF) is defined as a left ventricular ejection fraction (LVEF) < 40%. HFrEF carries a worse prognosis compared to other classifications of heart failure, namely mildly reduced ejection fraction (HFmrEF, LVEF between 40%-50%) and preserved ejection fraction (HFpEF, LVEF $\geq$ 50%).[2] Improved HFrEF (HFimpEF) is defined as initial LVEF $\leq$ 40% on echocardiogram, a $\geq$ 10-point increase from baseline LVEF and a second measurement of LVEF > 40%.[2] HFimpEF describes reverse LV remodelling. Patients with HFimpEF have improved quality of life, lower hospitalisation rates and lower mortality. For this reason, there is increasing research on this recently described entity in heart failure.[3]

The 12-lead electrocardiogram (ECG) is low-cost and widely available in South Africa. It is recommended as part of the workup for all patients with heart failure. ECG abnormalities in heart failure may vary by aetiology, precipitant, and ethnicity.[4] There are few studies describing ECG abnormalities in patients with chronic HFrEF in Sub-Saharan Africa. Furthermore, the predictive and prognostic significance of ECG markers in this population is not well described.[5]

There is growing evidence supporting the utility of novel ECG markers in heart failure. Fragmented QRS (fQRS) describes additional deflections within the QRS complex on ECG. This ECG abnormality indicates myocardial scar and in recent studies has been associated with increased all-cause mortality in patients with HFrEF.[6] Frontal QRS-T plane angle is the difference between QRS depolarization and repolarization. This ECG marker represents cardiac electrical heterogeneity and has been shown to predict hospitalization and all-cause mortality in patients with HFrEF.[7, 8]

This article describes the prevalence and prognostic utility of ECG abnormalities in patients with chronic HFrEF attending the Charlotte Maxeke Johannesburg Academic Hospital heart failure clinic in Johannesburg, South Africa.

Methods

Study design

A single centre retrospective review of out-patient files obtained from the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) heart failure clinic was conducted. The study population comprised all new patients referred to CMJAH heart failure clinic between 01 January 2015 and 31 December 2016.

Patients were referred from secondary or tertiary care facilities within Gauteng Province. Patients were also referred from other departments within CMJAH. Patients were then assessed by the heart failure clinic team, comprising heart failure specialists, consultant cardiologists and medical registrars.

Permission for data extraction was obtained from the CMJAH hospital executive committee as well as the University of the Witwatersrand Human Research Ethics Committee (medical) with the certificate number M201142.

Patients were included in the study if LVEF < 50% on transthoracic echocardiogram at first presentation at the heart failure clinic. Patients were excluded if (1) LVEF ≥ 50% on transthoracic echocardiogram at first presentation or if (2) data within the heart failure clinic records were insufficient to support data analysis.

Data from the first and last heart failure clinic visits was collected retrospectively into a data sheet. This included reading of the first and last visit ECGs. The last visit clinic was taken as the last time the patient was seen in clinic within the 5-year follow up period. The ECG from this visit was used as the last ECG reading during follow up. Discharge summaries for the patients included in the study were obtained from the CMJAH Department of Cardiology if ever admitted between date of referral and 5 years thereafter. These were used to compliment and cross-check data obtained from heart failure clinic files.

Variables

Data collected from heart failure files included patient demographics (age, gender, ethnicity), comorbidities, smoker status, aetiology of heart failure, New York Heart Association (NYHA) Functional class at both visits (i.e., first, and last visits), heart failure medications at both visits, 12-lead ECG readings from both visits and transthoracic echocardiogram readings from both visits. Records were reviewed during patient follow up for complications, namely any cardiovascular complication, cardioversion, or hospitalisation.

Aetiology of heart failure

Data on aetiology of heart failure aetiology was collected from the heart failure clinic files. Where possible, the assessment of aetiology of heart failure was complemented by data from the Department of Cardiology discharge summaries, coronary angiogram reports and/or Holter ECG reports. Importantly, patients with valvular heart disease and congenital heart disease attend a different specialist cardiac clinic at CMJAH and thus were not represented in the data.

12 lead ECG

All patients attending the heart failure clinic have a resting 12-lead ECG performed at every visit. ECG data collected and analysis included the following variables: heart rate (HR), rhythm, PR interval, corrected QT interval, QRS axis and duration, pathological Q waves, bundle-branch blocks, fragmented QRS, left ventricular hypertrophy, poor R wave progression, dominant R wave in AVR, T wave axis, frontal QRS-T plane angle, upright T wave in AVR and inverted T waves. Inferior leads are defined as II, III and AVF; Anterior leads as V3 and V4; Septal leads as V1 and V2; Lateral leads as V5, V6, I and AVL.

Sinus tachycardia was defined has HR > 100bpm in sinus rhythm on ECG. The PR interval was prolonged if ≥ 200ms in duration. Pathological Q waves were defined as (1) any Q-wave in leads V2–V3 ≥ 20ms or QS complex in leads V2 and V3, or (2) Q-wave ≥ 30ms and > 0.1mV deep or QS complex in leads I, II, aVL,

aVF, or V4–V6 in any two leads of a contiguous lead grouping, or (3) R wave ≥ 40ms in V1–V2 and R/S ratio ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.[9]

Right bundle branch block (RBBB) was defined as QRS duration ≥ 120ms with typical RBBB morphology. Similarly, left bundle branch block (LBBB) was defined as QRS duration ≥ 120ms with typical LBBB morphology.[10] Fragmented QRS was defined as additional additional spikes or deflections within the QRS complex, without bundle branch block morphology, present in two or more contiguous ECG leads.[11] The Sokolow–Lyon criteria were used to define left ventricular hypertrophy (LVH).[12] Poor R wave progression was defined as R wave in V3 ≤ 3mm and R wave in V2 ≤ R wave in V3.[13]

The absolute QT interval was corrected for HR using Bazett's formula. A corrected QT (QTc) interval of > 460ms (in females) and > 440ms (in males) was regarded as prolonged. The frontal QRS-T plane angle (measured in degrees) was defined as the difference between the direction of ventricular depolarization (QRS axis) and repolarization (T wave axis). If this angle exceeds 180 degrees, then the angle is calculated as 360 degrees minus the absolute difference between QRS axis and T axis. Wide frontal QRS-T angle has been defined in most studies as either >90 degrees or >100 degrees.[7, 14]

Echocardiography

Echocardiography readings were recorded at date of first clinic visit. For patients that had subsequent echocardiography assessment(s), the most recent echocardiogram within the last 5 years was recorded and date noted. The timing of the last echocardiogram measurement was taken as the most recent measurement within the five years follow up. It was not a requirement that the last ECG reading, and last echocardiogram measurement occurred at the same time.

Outcome

Hospitalizations, cardiac complications, and cardioversions were recorded from heart failure clinic files as well as CMJAH Department of Cardiology discharge summaries.

Recovered HFrEF was defined as initial LVEF $\leq$ 40% on echocardiogram, a $\geq$ 10-point increase from baseline LVEF and a second measurement of LVEF > 40%. Conversely, LV non-recovery was defined as initial LVEF $\leq$ 40% on echocardiogram, LVEF < 40% at last measurement or a less than 10% improvement from baseline LVEF.[2]

For all patients lost to follow up telephonic contact was attempted and reason for loss to follow up (death, defaulted, relocation) obtained if contact was made. A distress protocol for telephonic contact was approved by the University of the Witwatersrand Human Research Ethics Committee.

Statistical analysis

All analyses were performed with Stata, version 14 (StataCorp, College Station, Texas). Descriptive statistics will be used to characterize the sample. Continuous variables will be expressed as mean (with standard deviation) or median (with interquartile range). Categorical data will be presented as frequencies and percentages. Continuous variables will be compared using either student t-test (for

normally distributed data) or Wilcoxon rank-sum test (for skewed data). Depending on the distribution of data, either Chi- square or Fisher's exact test will be applied to compare categorical data.

Data were collected on Research Electronic Data Capture (REDCap Version 11.4.1), a secure electronic database hosted by the University of Witwatersrand. Data was then exported to Stata Version 14.2 (StataCorp, College Station, TX, USA) for statistical analysis. Descriptive statistics were used to summarise data. Continuous variables will be expressed as mean (with standard deviation) or median (with interquartile range). Categorical data will be presented as frequencies and percentages. Continuous variables will be compared using either student t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed data). Depending on the distribution of data, either Chi- square or Fisher's exact test will be applied to compare categorical data.

Where appropriate, the Kruskal–Wallis or Wilcoxon rank-sum test (for continuous variables) and chi-squared or Fisher's exact test (for categorical variables) were used to compare outcome measures at follow-up. Univariable and multivariable logistic regression analyses were done on all ECG variables that showed statistical significance, where p value is < 0.05.

Results

A total of 107 patients referred to the CMJAH heart failure clinic between 01 January 2015 and 31 December 2016 were identified meeting inclusion criteria. Eighteen patients were excluded because of either incomplete records (n=11) or LVEF > 50% at first visit (n=7). Baseline characteristics are summarized in Table 1. The median age of patients was 49 years old [interquartile range (IQR) 38-58 years]. Of these, 43% (n=46) were male and 57% (n=61) were female. Most patients in the study were African (n=82, 76.6%). More than half of patients (54%, n=58) had hypertension, 18.7% (n=20) had diabetes and 11.2% (n=12) had dyslipidaemia. Almost a third of patients (31.4%) were smokers.

The most common aetiology of heart failure seen at the heart failure clinic was cardiomyopathy (50.5%). In this group, chemotherapy-induced cardiomyopathy accounted for 35.2% (n=19), peripartum 22.2% (n=12), idiopathic 20.4% (n=11), post-infectious 11.1% (n=6) and tachycardia-induced cardiomyopathy7.4% (n=4). Other aetiologies of heart failure were hypertensive heart disease (28.9%) and ischaemic heart disease (20.6%).

At time of first heart failure clinic visit, 23.9% had NYHA functional class III or IV dyspnoea. Guideline-directed heart failure medications prescribed from time of first visit were beta-blocker (99.1%), angiotensin converting enzyme (ACE)-inhibitor or angiotensin receptor blocker (ARB) (96.5%), and mineralocorticoid-receptor antagonist (MRA) (80.5%). Most patients were on a loop diuretic (92.9%) and only 9.7% of patients were on Digoxin.

The median duration of follow up was 44.4 months (IQR 28.3-55.7 months). A large proportion of patients (30.8%) were hospitalized during this time between first and last clinic visit. The most common reason for hospitalization was acute decompensated heart failure (79.5%). Other causes of hospitalization were acute coronary syndrome (13.9%) and stroke (2.8%). A third of patients (33.6%) developed at least one cardiovascular event (acute decompensated heart failure, acute coronary

syndrome, CVA or other cardio-embolic event) between their first and last clinic visits. A small proportion (4.7%) of patients received cardioversion at clinic or during hospital admissions between their first and last clinic visits.

There was large loss to follow up (28%, n=30). Of the patients where telephonic contact was made (46.7%, n=14), six patients had demised, four had changed follow up site and four had defaulted follow up. The most common reason given for defaulting follow up was concerns around COVID-19.

Electrocardiographic features of the study population

Table 1 shows the ECG features of the study population at first clinic visit (n=107). For comparison, Table 2 shows the demographic, ECG, and echocardiographic characteristics of the study population as last clinic visit (n=75). The prevalence of ECG abnormalities at follow up remained similar to those at first clinic visit.

At first clinic visit the median HR was 79 bpm [IQR 72-93]. A small proportion of patients (18.7%) had sinus tachycardia at first clinic presentation. Atrial fibrillation was present in 5.6% of patients. The median PR interval was 170ms [IQR 150-190], with 14.0% of patients presenting with a prolonged PR interval.

The median QRS duration was 92ms [IQR 80-107]. LBBB was present in 9.3% of patients. LVH was present in 22.4% of patients. fQRS was seen in a quarter of patient ECGs (25.2%) with the inferior ECG leads (II, III, AVF) being most involved (present in 17.8% of all patient ECGs). Pathological Q waves were only seen in 16.8% of patients. Inverted T waves were the most common ECG abnormality, seen in 67.3% of patients and most often in the inferior leads (41.1%). The median QTc interval was 450ms [IQR 409 – 476]. The QTc interval was prolonged in 25.2% of patients. Almost a quarter of patients (24.2%) had a frontal QRS-T angle > 100 degrees.

The median time between the first and last ECGs was 42.3 months (IQR 28.8-55.7). A proportion of patients were lost to follow up (28%) and therefore did not have a second ECG for analysis. The median HR at last clinic visit was 76 bpm [IQR 70-82]. Only one patient had sinus tachycardia at their last clinic visit, however atrial fibrillation was more common (7.8%).

The median QRS duration at last visit was 90ms [IQR 80-110]. LBBB was present in 13% of patients. LVH was present in 10.4% of patients. fQRS was still seen in almost a quarter of patient ECGs (23.4%). Pathological Q waves were only seen in 15.6% of patients. Inverted T waves were still the most common ECG abnormality, seen in 62.3% of patients. The median QTc interval was 441ms [IQR 415 – 460]. The median QTc interval in males was 451.49ms [IQR 428.95- 484.03] and in females was 448.47 [IQR 422.32-471.83]. The QTc interval was prolonged in 53.1% (n=17) of male patients and in 22.2% (n=10) of female patients.

Table 1: Baseline characteristics: demographic, clinical, therapeutic, electrocardiographic and echocardiographic.

		Total N=107			Total N=107
Age	Median (IQR)	49.0 (38.0-58.0)	Heart rate	Median (IQR)	79.0 (71.0-93.0)
Gender			Sinus tachycardia	N (%)	20 (18.7)
Male	N (%)	46 (43.0)	Sinus	N (%)	100 (93.5)
Female	N (%)	61 (57.0)	Atrial fibrillation	N (%)	6 (5.6)
Ethnicity			Atrial flutter	N (%)	1 (0.9)
African	N (%)	82 (76.6)	PR Interval	Median (IQR)	170.0 (150.0-190.0)
White	N (%)	17 (15.9)	PR > 200ms	N (%)	16 (15.0)
Indian/Asian	N (%)	5 (4.7)	QRS duration	Median (IQR)	92.0 (80.0-108.0)
Coloured	N (%)	3 (2.8)	LBBB	N (%)	10 (9.3)
Comorbidities			RBBB	N (%)	9 (8.4)
Hypertension	N (%)	58 (54.2)	Fragmented QRS	N (%)	27 (25.2)
Diabetes	N (%)	20 (18.7)	Inferior fQRS	N (%)	19 (17.8)
Dyslipidaemia	N (%)	12 (11.2)	Anterior fQRS	N (%)	3 (2.8)
HIV	N (%)	16 (15.0)	Septal fQRS	N (%)	3 (2.8)
Obesity	N (%)	11 (10.3)	Lateral fQRS	N (%)	7 (6.5)
Smoker	N (%)	34 (31.8)	QRS axis	Median (IQR)	77.0 (27.0-101.0)
NYHA fc			Pathological Q waves	N (%)	18 (16.8)
1	N (%)	37 (34.6)	Inferior pathological Q	N (%)	12 (11.2)
2	N (%)	45 (42.1)	Anterior pathological Q	N (%)	3 (2.8)
3	N (%)	24 (22.4)	Septal pathological Q	N (%)	1 (0.9)
4	N (%)	1 (0.9)	Lateral pathological Q	N (%)	3 (2.8)
Medication			Left ventricular hypertrophy	N (%)	24 (22.4)
Beta Blocker	N (%)	106 (99.1)	Poor R wave progression	N (%)	20 (18.7)
ACE-I/ARBs	N (%)	104 (97.2)	Inverted T waves	N (%)	72 (67.3)
MRA	N (%)	86 (80.4)	Inferior inverted T waves	N (%)	44 (41.1)
Loop diuretic	N (%)	100 (93.5)	Anterior inverted T waves	N (%)	14 (13.1)
Digoxin	N (%)	11 (9.7)	Septal inverted T waves	N (%)	9 (8.4)
Aetiology			Lateral inverted T waves	N (%)	54 (50.5)
IHD	N (%)	22 (20.5)	QTc by Bazett	Median (IQR)	429.2 (406.5-445.1)
HHD	N (%)	31 (29.0)	T wave axis	Median (IQR)	42.0 (-30.0-90.0)
CMO	N (%)	54 (50.5)	Frontal QRS-T angle	Median (IQR)	29.0 (-54.0-130.0)
chemo-induced	N (%)	19 (17.8)	Frontal QRS-T angle > 100°	N (%)	26 (24.2)
PPCM	N (%)	12 (11.2)	Echocardiography		
idiopathic	N (%)	11 (10.3)	LVEF at first visit	Median (IQR)	30.0 (23.0-38.0)
post-infectious	N (%)	6 (5.6)			

NYHA fc New York Heart Association functional class, ACE-i Angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blockers, MRA Mineralocorticoid receptor antagonist, IHD Ischaemic heart disease, HHD Hypertensive heart disease, CMO Cardiomyopathy, PPCM peripartum cardiomyopathy, HR heart rate, LBBB left bundle branch block, RBBB right bundle branch block, fQRS Fragmented QRS, LVEF left ventricular ejection fraction.

Table 2: Patient characteristics at last clinic visit: demographic, clinical, therapeutic, electrocardiographic and echocardiographic.

		Total N=75			Total N=75
Gender			Heart rate	Median (IQR)	75.0 (68.0-81.50)
Male	N (%)	30 (40.0)	Sinus	N (%)	67 (89.3)
Female	N (%)	45 (60.0)	Atrial fibrillation	N (%)	6 (8.0)
Ethnicity			Atrial flutter	N (%)	1 (1.3)
African	N (%)	59 (78.6)	PR Interval	Median (IQR)	168.0 (144.0-190.0)
White	N (%)	11 (14.7)	PR > 200ms	N (%)	9 (12.0)
Indian/Asian	N (%)	3 (4.0)	QRS duration	Median (IQR)	92.0 (81.0-109.0)
Coloured	N (%)	2 (2.7)	LBBB	N (%)	10 (13.3)
Comorbidities			RBBB	N (%)	4 (5.3)
Hypertension	N (%)	43 (57.3)	Fragmented QRS	N (%)	18 (24.0)
Diabetes	N (%)	15 (20.0)	Inferior fQRS	N (%)	16 (21.3)
Dyslipidaemia	N (%)	10 (13.3)	Anterior fQRS	N (%)	3 (4.0)
HIV	N (%)	9 (12.0)	Septal fQRS	N (%)	0 (2.8)
Obesity	N (%)	9 (12.0)	Lateral fQRS	N (%)	4 (5.3)
Smoker	N (%)	22 (29.3)	QRS axis	Median (IQR)	77.0 (27.0-101.0)
NYHA fc			Pathological Q waves	N (%)	12 (16.0)
1	N (%)	53 (70.7)	Inferior pathological Q	N (%)	7 (9.3)
2	N (%)	16 (21.3)	Anterior pathological Q	N (%)	4 (5.3)
3	N (%)	4 (5.3)	Septal pathological Q	N (%)	2 (2.6)
4	N (%)	2 (2.7)	Lateral pathological Q	N (%)	3 (4.0)
Medication			Left ventricular hypertrophy	N (%)	8 (10.6)
Beta Blocker	N (%)	74 (98.7)	Poor R wave progression	N (%)	12 (16.0)
ACE-I/ARBs	N (%)	73 (97.3)	Inverted T waves	N (%)	48 (64.0)
MRA	N (%)	64 (85.3)	Inferior inverted T waves	N (%)	27 (36.0)
Loop diuretic	N (%)	69 (92.0)	Anterior inverted T waves	N (%)	10 (13.3)
Digoxin	N (%)	3 (4.0)	Septal inverted T waves	N (%)	7 (9.3)
Aetiology			Lateral inverted T waves	N (%)	33 (44.0)
IHD	N (%)	13 (17.3)	QTc by Bazett	Median (IQR)	440.6 (413.3-459.5)
HHD	N (%)	22 (29.3)	T wave axis	Median (IQR)	42.0 (-30.0-90.0)
CMO	N (%)	37 (49.3)	Frontal QRS-T angle	Median (IQR)	6.0 (-194.0-150.8)
chemo-induced	N (%)	12 (16.0)	Frontal QRS-T angle > 100°	N (%)	17 (22.6)
PPCM	N (%)	9 (12.0)	Echocardiography		
idiopathic	N (%)	8 (10.7)	LVEF at last visit	Median (IQR)	46.0 (32.0-54.5)
post-infectious	N (%)	4 (5.3)			

NYHA fc New York Heart Association functional class, ACE-i Angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blockers, MRA Mineralocorticoid receptor antagonist, IHD Ischaemic heart disease, HHD Hypertensive heart disease, CMO Cardiomyopathy, PPCM peripartum cardiomyopathy, HR heart rate, LBBB left bundle branch block, RBBB right bundle branch block, fQRS Fragmented QRS, LVEF left ventricular ejection fraction

Electrocardiographic differences between ethnic groups

A few ECG abnormalities had different prevalence in patients of African ethnicity (n=82, 76.7%) than other ethnicities (Table 1). Importantly, patients with other ethnicity were too few to compare across groups. The most common ECG findings in African patients were inverted T waves (68.3%), QRS duration >100ms (31.7%), fQRS (26.8%) and frontal QRS-T angle >100 degrees (25.6%). The most common ECG findings in Caucasian patients were inverted T waves (64.7%, n=11).

Electrocardiographic differences between aetiologies of heart failure

As seen in Table 2, the median QRS duration differed between aetiologies. In ischaemic heart disease this was 102ms [IQR 92-136], in hypertensive heart disease 92ms [IQR 84-106] and in cardiomyopathy 85ms [IQR 76-98.0] (p=0.003). The prevalence of fQRS in lateral ECG leads was significantly higher in patients with ischaemic heart disease than in hypertensive heart disease or cardiomyopathy (18.2% vs 6.5% vs 1.9% respectively, p=0.033).

Electrocardiographic abnormalities associated with LVEF ≤ 35%

The median QRS duration in patients with LVEF ≤ 35% at first visit was 94ms [IQR 82-114], significantly different to the median QRS duration patients with LVEF > 35% at first visit (86ms [IQR 76-102], p=0.021). Inverted T waves were also different between these two groups, seen in 73.9% of patients with LVEF ≤ 35% versus 55.3% in patients with LVEF > 35% at first visit (p=0.049).

Table 2: Electrocardiographic differences between aetiologies of heart failure.

		Ischaemic heart disease N=22	Hypertensive heart disease N=31	Cardiomyopathy N=54	p-value
Heart rate	Median (IQR)	78.0 (70.0-98.0)	76.0 (67.0-103.0)	80.5 (73.0-92.0)	0.74
Sinus tachycardia	N (%)	5 (22.7)	9 (29.0)	6 (11.1)	0.11
PR Interval	Median (IQR)	172.0 (150.0-194.0)	176.0 (155.0-198.0)	162.0 (144.0-182.0)	0.20
QRS duration	Median (IQR)	102.0 (92.0-136.0)	92.0 (84.0-106.0)	85.0 (76.0-98.0)	0.003
LBBB	N (%)	3 (13.6)	2 (6.5)	5 (9.3)	0.73
Fragmented QRS	N (%)	6 (27.3)	10 (32.3)	11 (20.4)	0.46
Fragmented QRS lateral	N (%)	4 (18.2)	2 (6.5)	1 (1.9)	0.033
Pathological Q waves	N (%)	6 (27.3)	3 (9.7)	9 (16.7)	0.24
Left ventricular hypertrophy	N (%)	5 (22.7)	9 (29.0)	10 (18.5)	0.53
Poor R wave progression	N (%)	7 (31.8)	5 (16.1)	8 (14.8)	0.21
Inverted T waves	N (%)	16 (72.7)	21 (67.7)	35 (64.8)	0.80
Inferior inverted T waves	N (%)	11 (50.0)	15 (48.4)	18 (33.3)	0.25
Lateral inverted T waves	N (%)	10 (45.5)	18 (58.1)	26 (48.1)	0.59
QTc by Bazett	Median (IQR)	439.9 (415.8-451.6)	424.4 (405.6-446.3)	426.6 (406.6-443.0)	0.23

LBBB left bundle branch block

Electrocardiographic abnormalities in patients with cardiovascular events or hospitalization

The only ECG marker associated with hospitalization between first and last clinic visit was QRS duration (median 98ms[IQR 84-114], p=0.039). A QRS duration of >100ms was not significantly associated with hospitalization (p=0.061). QRS duration was associated with the development at least one cardiovascular event (median in event group 98ms [IQR 83.0-124.0], p=0.007). QRS duration > 100ms was significantly associated with cardiovascular events (47% of patients in event group vs. 24% in non-event group, p=0.022). There were no other statistically significant ECG markers/abnormalities seen in patients that were hospitalized or that developed at least one cardiovascular event.

Electrocardiographic abnormalities associated with LV non-recovery

Of the 75 patients where follow up data was available, 56 (74.7%) had a second echocardiogram measurement. The median time between echocardiograms (first and last) was 31 months [IQR 21.3-46.2]. As seen in Table 3, a similar proportion of patients with hypertensive heart disease and cardiomyopathy had LV recovery (35.3% and 40.6% respectively. The median PR interval was significantly longer in patients with LV non-recovery (176ms [IQR 152-204]) versus those with LV recovery (146.0 [IQR 138.0-164.0], p<0.001). The frequency of fQRS was also higher in patients with LV non-recovery (30.6% vs. 5% in patients with LV recovery, p=0.026). Inverted T waves in the inferior leads were seen in 52.8% of patients with LV non-recovery versus 20.0% of patients with LV recovery (p=0.017).

Table 3: Electrocardiographic differences between LV recovery and non-recovery.

		Total	LV recovery	LV non-recovery	p-value
		N=56	N=20	N=36	
Ischaemic heart disease	N (%)	7 (12.5)	1 (5.0)	6 (16.7)	
Hypertensive heart disease	N (%)	17 (30.4)	6 (30.0)	11 (30.6)	
Cardiomyopathy	N (%)	32 (57.1)	13 (65.0)	19 (52.8)	
Heart rate	Median (IQR)	80.0 (72.5-92.5)	78.5 (70.5-91.5)	80.0 (74.5-97.5)	0.48
Sinus tachycardia	N (%)	10 (17.9)	2 (10.0)	8 (22.2)	0.25
PR Interval	Median (IQR)	166.0 (146.0-198.0)	146.0 (138.0-164.0)	176.0 (152.0-204.0)	<0.001
QRS duration	Median (IQR)	89.0 (80.0-102.0)	86.0 (79.0-93.0)	92.0 (82.0-105.0)	0.14
QRS > 100ms	N (%)	16 (28.6)	4 (20.0)	12 (33.3)	0.29
LBBB	N (%)	4 (7.1)	0 (0.0)	4 (11.1)	0.45
Fragmented QRS	N (%)	12 (21.4)	1 (5.0)	11 (30.6)	0.026
Pathological Q waves	N (%)	10 (17.9)	3 (15.0)	7 (19.4)	0.68
Left ventricular hypertrophy	N (%)	10 (17.9)	6 (30.0)	4 (11.1)	0.077
Poor R wave progression	N (%)	12 (21.4)	3 (15.0)	9 (25.0)	0.38
Inverted T waves	N (%)	41 (73.2)	12 (60.0)	29 (80.6)	0.096
Inferior inverted T waves	N (%)	23 (41.1)	4 (20.0)	19 (52.8)	0.017
Lateral inverted T waves	N (%)	32 (57.1)	8 (40.0)	24 (66.7)	0.053
QTc by Bazett	Median (IQR)	428.7 (408.4-443.3)	427.2 (401.2-441.5)	428.7 (411.4-444.0)	0.61
Frontal QRS-T angle	Median (IQR)	26.5 (-56.5-122.0)	18.0 (-52.0-132.0)	28.0 (-58.0-111.0)	0.70
Frontal QRS-T angle > 100°	N (%)	26 (46.5)	9 (45.0)	17 (47.2)	0.24
T axis	Median (IQR)	38.0 (-30.0-99.0)	45.0 (24.0-99.0)	30.0 (-35.0-99.5)	0.27

Discussion

Few studies have described ECG abnormalities seen in patients with HFrEF in Sub-Saharan Africa. Existing local evidence predominantly looks at ECG abnormalities in patients presenting with acute heart failure and the predictive utility of these for complication or readmission between six months and one year.[5, 15] In this study we describe the prevalence of ECG abnormalities in patients with HFrEF referred to the CMJAH heart failure clinic. The ECGs from first and last clinic visits were analysed. We also investigated associations between these ECG abnormalities and hospitalisations, cardiac complications and change in ejection fraction. The patient demographics in this study were substantially different to those in similar studies from developed nations. As seen in Table 1, most patients in our study were African (76.6%). In further contrast to studies from developed nations, ischaemic heart disease was less common than hypertensive heart disease and cardiomyopathy in our study. It is important to note there was a large proportion (50.5%) of patients with cardiomyopathy (post-chemotherapy, peripartum, idiopathic and post-infective) in this study.

In our study ECG abnormalities were common in outpatients with HFrEF, seen in 97.2% of patients at first visit. This supports well-accepted evidence of the high sensitivity of the ECG for the diagnosis of HFrEF.[2] The predominant ECG abnormalities (Table 1) seen in this study were inverted T waves (67.3%), fQRS (25.2%), prolonged QTc interval (25.2%), wide frontal QRS-T angle (24.2%), and LVH (22.4%). Sinus tachycardia was less prevalent than in other studies as most patients in our study were already on heart failure treatment and not in acute heart failure at their first clinic visit. For these reasons, our study failed to replicate evidence showing association between HR and severe LV dysfunction.

Pathological Q waves were less common in this study (16.8%) than in patients with HFrEF in developed nations. This is in keeping with local evidence with a similar finding (17.2% of patients in the THESUS-HF study).[5] This may suggest ischaemic heart disease is still a less common aetiology of HFrEF in Sub-Saharan Africa than in the developed world.

The prevalence of fQRS in HFrEF patients in Sub-Saharan Africa has not been well studied. In one local study of 66 patients with ppCMO, fQRS was not associated with poor outcome.[16] Recent international studies show fQRS correlates with myocardial scar and represents intraventricular conduction delay. fQRS is associated with all-cause mortality in patients with LVEF <35% (risk ratio [RR] 1.63, 95% CI 1.22–2.19, $p < 0.001$).[6] Studies have also suggested fQRS has higher sensitivity for prior myocardial infarction (MI) compared to pathological Q waves on ECG (85.6% vs. 36.3%).[17] In our study, fQRS was one of the more prevalent ECG abnormalities in HFrEF. The prevalence of fQRS in African patients in this study was 26.8% (n=22). Importantly, in keeping with the current understanding of fQRS, our study shows fQRS in lateral ECG leads is significantly more prevalent in patients with ischaemic heart disease than in other aetiologies of HFrEF (18.2% vs. 6.5% vs. 1.9%, p=0.033).

QRS duration and the presence of inverted T waves (lateral leads) were both associated with LVEF ≤ 35% at first clinic visit. In our study, the median QRS duration in patients with LVEF ≤ 35% at first visit was 92ms [IQR 82-114, p=0.021]. This is congruent with evidence showing increases in QRS duration reflect worsening LVEF. A QRS duration of >120ms has been shown to be 99.3% specific for LVEF < 45%.[18, 19] Our

study however did not show an association between QRS duration of >100ms and LVEF ≤ 35% (p=0.29). This may have been a result of fewer patients with QRS >100ms in the study (n=38).

In our study QRS duration was associated with hospitalization and QRS duration > 100ms associated with cardiovascular events. This finding is consistent with findings in developed nations where increasing QRS duration was associated with worse survival (47% 5-year survival where QRS ≥ 120ms).[18, 19] There were no other ECG abnormalities associated with hospitalization or cardiovascular events in our study. This was likely a result of the low number of these events (n=33 and n=36 respectively) as well as a significant loss to follow up (n=30). Unlike other local and international studies, our study did not show association between QTc interval prolongation and LV recovery, hospitalization, or cardiovascular events.[16, 20]

A recent review by the European Society of Cardiology has found that a prolonged PR interval is associated with reduced LV systolic function in HF and worse outcomes. The review suggests that restoration of AV coupling in patients with prolonged PR interval by pacing may improve cardiac function.[21] Interestingly in our study, a longer (but not prolonged) PR interval was significantly associated with LV non-recovery (median 176ms [IQR 152-204], p<0.001). It is important to consider that this finding is confounded by the use of beta blockers in this patient population (99.1% of patients) which prolong the PR interval and make this finding less reliable. It is likely that there were too few patients with a prolonged PR interval (> 200ms) (n=16) to show statistical significance. This finding may still suggest a longer PR interval contributes to LV non-recovery.

T wave abnormalities reflect abnormal ventricular repolarization. In our study, T wave inversion was seen in significantly more patients with LVEF ≤ 35% than patients with LVEF > 35%, particularly in the lateral ECG leads (58% vs 37%, p=0.036). This replicates a similar finding in a recent local study investigating the prognostic significance of the 12-lead ECG in peripartum cardiomyopathy, where T wave inversion was associated with an LVEF ≤35% at presentation (p = 0.038).[16] We also found that T wave inversion was associated with LV non-recovery (Table 3).

Recent evidence has shown an association between depolarization/repolarization heterogeneity and poor outcome in patients with HFrEF. A representation of this heterogeneity, easily calculated from the 12-lead ECG, is the frontal QRS-T angle. This novel ECG marker represents cardiac structural and electrical abnormalities. It has been associated with reduced LV systolic function, hospitalisation and all-cause mortality.[7, 8] In our study however, this marker was not significantly associated with reduced LV systolic function, hospitalizations or cardiovascular events. Again, this may have been a result of the limited number of events (hospitalizations or cardiovascular events) in our study.

ECG predictors of LV non-recovery, if validated, could be especially important in South Africa, where cardiology service is a scarce resource. These could help the identification of difficult to treat patients and those with a worse prognosis, thus guiding referral and resource allocation.

Limitations

There are several limitations in the present study. First, the size of the study was smaller than what was anticipated, thus limiting the power of the study. The number of new referrals to the heart failure was

half of what we expected in the two-year period from 2015 to 2016. There was also a high loss to follow up (28%). The main reason for this was likely mortality out of hospital. These sample size limitations limit the precision of estimates, especially logistic regression analyses. Second, the risk of inter-observer variability in echocardiogram measurement as well as ECG analysis is significant. This risk has been shown to be higher for certain ECG markers, such as fQRS.[22]

Lastly, the likelihood of referral bias in our study is high. This was a single-centre study conducted at a tertiary hospital. Severe and rare cases are more likely at this heart failure clinic. Furthermore, certain departments within CMJAH had a higher frequency of patient referral to the HF clinic. This can be appreciated by the large proportion of patients with ppCMO and chemotherapy induced CMO in the study population. The study population is therefore likely to be less representative of out-patients with heart failure attending clinics at secondary or primary care level. This limits the generalizability of our results.

Conclusion

This study demonstrates that some ECG abnormalities in HFrEF may have different prevalence in South African patients compared to patients from developed nations. This may reflect the ethnic diversity and unique burden of disease in this population. Importantly however, the significance of these observations is limited by the small sample size of the study and the presence of referral bias.

We show that some novel ECG markers may have utility beyond the conventional use of the 12-lead ECG in HFrEF. fQRS may be a more useful marker of myocardial scar or prior MI in our population, compared to pathological Q waves. The application of these ECG markers should be further studied in larger cohorts for their predictive and prognostic utility in HFrEF.

References

1. Ajayi AA, Sofowora GG, Ladipo GO. Explaining Heart Failure Hyper-mortality in Sub Saharan Africa: Global Genomic and Environmental Contribution Review. J Natl Med Assoc. 2020;112(2):141-57.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
3. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart Failure With Recovered Left Ventricular Ejection Fraction: JACC Scientific Expert Panel. J Am Coll Cardiol. 2020;76(6):719-34.
4. Mason JW, Ramseth DJ, Chanter DO, Moon TE, Goodman DB, Mendzelevski B. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. J Electrocardiol. 2007;40(3):228-34.
5. Dzudie A, Milo O, Edwards C, Cotter G, Davison BA, Damasceno A, et al. Prognostic significance of ECG abnormalities for mortality risk in acute heart failure: insight from the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF). J Card Fail. 2014;20(1):45-52.
6. Kanitsoraphan C, Rattanawong P, Mekraksakit P, Chongsathidkiet P, Riangwiwat T, Kanjanahattakij N, et al. Baseline fragmented QRS is associated with increased all-cause mortality in heart failure with reduced ejection fraction: A systematic review and meta-analysis. Annals of Noninvasive Electrocardiology. 2019;24(2):e12597.
7. Gotsman I, Keren A, Hellman Y, Banker J, Lotan C, Zwas DR. Usefulness of electrocardiographic frontal QRS-T angle to predict increased morbidity and mortality in patients with chronic heart failure. Am J Cardiol. 2013;111(10):1452-9.
8. Sweda R, Sabti Z, Strebel I, Kozhuharov N, Wussler D, Shrestha S, et al. Diagnostic and prognostic values of the QRS-T angle in patients with suspected acute decompensated heart failure. ESC Heart Fail. 2020;7(4):1817-29.
9. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64.
10. Smiseth OA, Aalen JM. Mechanism of harm from left bundle branch block. Trends Cardiovasc Med. 2019;29(6):335-42.
11. Supreeth RN, Francis J. Fragmented QRS - Its significance. Indian Pacing Electrophysiol J. 2020;20(1):27-32.
12. Peguero JG, Lo Presti S, Perez J, Issa O, Brenes JC, Tolentino A. Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy. J Am Coll Cardiol. 2017;69(13):1694-703.
13. <Anttila-2013-Relation-of-poor-r-wave-progression.pdf>.
14. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T angle: a review. Ann Noninvasive Electrocardiol. 2014;19(6):534-42.
15. Lee G, Sliwa K, Carrington M, Stewart S. The Use of the Electrocardiogram in Heart Failure Patients in the Heart of Soweto Study. Heart, Lung and Circulation. 2008;17.
16. Hoevelmann J, Viljoen CA, Manning K, Baard J, Hahnle L, Ntsekhe M, et al. The prognostic significance of the 12-lead ECG in peripartum cardiomyopathy. Int J Cardiol. 2019;276:177-84.
17. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation. 2006;113(21):2495-501.

18. Kalra PR, Sharma R, Shamim W, Doehner W, Wensel R, Bolger AP, et al. Clinical characteristics and survival of patients with chronic heart failure and prolonged QRS duration. Int J Cardiol. 2002;86(2-3):225-31.
19. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol. 2005;46(12):2183-92.
20. Prenner SB, Swat SA, Ng J, Baldridge A, Wilcox JE. Parameters of repolarization heterogeneity are associated with myocardial recovery in acute heart failure. Int J Cardiol. 2020;301:147-51.
21. Salden F, Kutyifa V, Stockburger M, Prinzen FW, Vernooy K. Atrioventricular dromotropathy: evidence for a distinctive entity in heart failure with prolonged PR interval? Europace. 2018;20(7):1067-77.
22. Vandenberk B, Robyns T, Goovaerts G, Claeys M, Helsen F, Van Soest S, et al. Inter- and intra-observer variability of visual fragmented QRS scoring in ischemic and non-ischemic cardiomyopathy. J Electrocardiol. 2018;51(3):549-54.

Appendix 1: Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr M Rath

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201142

NAME: (Principal Investigator)	Dr M Rath
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	*Electrocardiogram abnormalities in patients with heart failure with reduced ejection fraction at the Charlotte Maxeke Johannesburg Academic Hospital heart failure clinic*
DATE CONSIDERED:	2020/11/27
DECISION:	Approved unconditionally
CONDITIONS:	Approval now includes (1) data collection up to 2016/12/31, (2) access to CMJAH Cardiology Dept discharge summaries and (3) telephonic follow-up with disengaged patients, subject to a distress protocol
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr T Kalk
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/08/24

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

25/08/2021
Date

Appendix 2: Turnitin originality report

Electrocardiogram abnormalities in HFrEF final-1.docx

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