Appropriate use of Exercise Electrocardiograms in an Academic Hospital in Johannesburg

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Student's contribution to article(s) and agreement of co-author(s) I, Nicholas Rich, student number 2528054, declare that this research report is my work and that I contributed adequately towards research findings published in the articles(s) stated below which are included in my research report.

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Article Title: Appropriate use of Exercise Electrocardiograms in an Academic Hospital in Johannesburg

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Dedication

Thank you to my Lord and my loving family.

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Author guidelines

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Research report

Abstract

Aims
Exercise electrocardiograms (ExECGs) are widely used in resource-limited settings to screen for patients with chest pain of unknown origin. Despite this, the appropriate use of the ExECG has never been determined. We aimed to evaluate whether ExECGs, to investigate patients with chest pain of unknown origin, were being done appropriately in Johannesburg.

Methods
We retrospectively evaluated 318 consecutive ExECGs done on patients between 1 January 2018 and 31 December 2019, at a single tertiary centre, the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This included ExECGs for patients selected in the Cardiology department and those referred from other hospitals and departments. Following the 2019 European Society of Cardiology (ESC) Guidelines for diagnosing and managing chronic coronary syndromes, solely those patients at intermediate pretest probability of occlusive CAD using the Diamond-Forester Classification were considered appropriate.

Results
Only 130 (40.9%) patients in our study sample had a documented pretest risk stratification to establish pretest probability, of which 75 patients (57.7%) were documented as having an intermediate pretest likelihood of CAD. The pretest risk stratification of the remaining 188 patients of the total study population could not be determined. When these patients without a pretest risk stratification are considered inappropriate then only 23.6% are at intermediate risk for CAD.

Conclusion
In our study, we found that only 23.6% of ExECGs performed at the CMJAH for the evaluation of chest pain of unknown origin were appropriate. (232 words)

Keywords
Exercise electrocardiogram (ExECG), inappropriate referral, coronary artery disease (CAD), risk stratification, and pretest probability.

Abbreviations

ANOVA		Analysis of variance
CAD		Coronary artery disease
CMJAH		Charlotte Maxeke Johannesburg Academic Hospital
ECG		Electrocardiogram
ESC		European Society of Cardiology
ExECG		Exercise electrocardiogram
LBBB		Left bundle branch block
LMIC		Low and middle-income Country
REDCAP		Research Electronic Data Capture
RBBB		Right bundle branch block
SPECT-MPI		Single photon emission computed tomography - myocardial perfusion imaging
STD		ST segment depression
STE		ST segment elevation

Lay summary

Exercise electrocardiograms are among the many tests to screen patients for coronary artery disease. We conducted this study to see if the use of exercise electrocardiograms at the Charlotte Maxeke Johannesburg Hospital was being done on patients at the correct risk profile, according to European Society of Cardiology guidelines. Of the 318 exercise electrocardiograms performed to assess chest pain of unknown cause, only 75 (23.6%) were documented to be at the correct risk profile. We conclude that too many inappropriate exercise electrocardiograms are being done.

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide (1). Three-quarters of global cardiovascular deaths occur in low-and-middle-income countries (LMICs) (2). Patients with chest pain of unknown origin need to be appropriately evaluated to rule out CAD (3). Currently, there are multiple non-invasive cardiac imaging modalities in use, ranging from the exercise electrocardiogram (ExECG) and stress echocardiography to newer modalities such as coronary computed tomography angiography, stress cardiac magnetic resonance and single photon emission computed tomography - myocardial perfusion imaging (SPECT-MPI) (3). The European Society of Cardiology (ESC) has revised their 2013 class 1C recommendation for ExECGs as the first-line investigation for all patients with chronic coronary syndrome (CCS) (4). The 2019 ESC guidelines for diagnosing and managing chronic coronary syndromes now recommends that the choice of investigation should be individualised for different patients and centres (3). They recommend considering individual patient characteristics, preferences, availability and local expertise (3). This was likely due to the 2019 meta-analysis by Knuuti and colleagues, which showed that ExECGs, in comparison to the aforementioned newer modalities, have limited diagnostic power to confirm or exclude CCS. However, access to these newer non-invasive cardiac imaging modalities is limited in many LMICs (5).

The ExECG is a vital screening tool for CAD. It is a safe, non-invasive, low-cost test that requires relatively minimal expertise for performance and interpretation (6). During exercise, increasing metabolic requirements from exercising muscles need to be matched by an increase in cardiac output. Neurohormonal adaptations are required for this to occur. In those with coronary artery disease, the expected increase in coronary flow is compromised, often by atherosclerotic plaque, with a failure of coronary dilation. An ExECG can detect compromise in coronary flow by revealing various ECG changes indicating ischemia (6).

Despite its wide regional use, there is a paucity of published data on the appropriate clinical use of ExECGs in sub-Saharan Africa. South Africa is a resource-limited country. Therefore, it is important to consider how to cost-effectively investigate patients with chest pain of unknown origin. Our aim was to determine the level of appropriate referral for ExECGs in patients with chest pain of unknown origin. Additionally, we sought to determine our local specificity and sensitivity data for ExECGs in predicting CAD.

Methods

Study design, setting and selection of study participants

We conducted a single-centre, retrospective, observational study at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a state-owned tertiary hospital in South Africa. At the CMJAH non-invasive cardiac laboratory, ExECGs are performed on patients at the request of both registrar and consultant cardiologists for patients reviewed in the cardiology department. Additionally, patients are referred for ExECGs by doctors of various levels of experience from other departments in the hospital and other affiliated secondary and primary health care centres. These referrals from outside the cardiology department are screened by registrar and consultant cardiologists. This results in many patients being considered for an ExECG. The department does a pretest risk stratification of patients with chest pain of unknown origin for CAD using the Diamond-Forrester classification. This classification considers age, sex, and type of chest pain (7). In line with ESC Chronic Coronary Syndrome guidelines, neither patients with a low nor a high pretest probability of CAD should have an ExECG (3). The ExECGs are performed by cardiology physiologists using the modified Bruce protocol. This entails monitoring patients with a twelve-lead electrocardiogram (ECG) and subjecting them to a specific exercise protocol on a treadmill, with increasing speeds and inclines. During an ExECG patients are evaluated for exercise capacity, ischemic symptoms, and haemodynamic and electrocardiographic changes (8, 9). The ‘metabolic equivalent’ (METs), a quantification of exercise capacity, is calculated to compare different patients and different protocols. Finally, the Duke treadmill score is calculated because of its established prognostic value (10). This score is calculated using the exercise time (min) - (5x ST deviation) - (4x treadmill angina index) (10). An adequate ExECG was defined as patients who achieved an age-predicted heart rate ((220-age(years) x 85%) and METs equal to or greater than 4. ExECG results are reviewed by registrar and consultant cardiologists and determined to be positive, negative or indeterminate. Positive ExECG results were defined by the presence of typical chest pain, ST-segment elevation or depression, or those with a Duke treadmill score less than -10. Negative ExECG results were defined by a Duke treadmill score of +5 or greater, the absence of chest pain, ECG elevation and depression in those meeting the requirement of an adequate ExECG. Indeterminate results were defined as a Duke treadmill score between -10 and +4 or an inadequate ExECG.

At the CMJAH, consultant cardiologists are free to use their clinical judgment for the choice of investigation and management of individual cases. However, the standard of practice for the CMJAH is for those with positive ExECGs to have coronary angiograms. In most cases, patients with a negative ExECG are referred for evaluation of non-cardiac causes of chest pain. Lastly, those with an indeterminate ExECG result are recommended to go for single photon emission tomography - myocardial perfusion imaging (SPECT-MPI).

The ExECG record book at the non-invasive cardiac laboratory was used to identify patients for inclusion in the study. We included all patients who underwent an ExECG between 1 January 2018 and 31 December 2019. After estimating the average number of ExECGs done per month, this period met a predefined sample size. Patients under 18 years of age, those known with CAD and patients with incomplete records were excluded **(Figure 1)**. We defined those with incomplete records as patients needing a documented name or an ExECG result. Those described with CAD were those with angiographically proven occlusive CAD. Only patients documented at intermediate pretest probability of CAD were considered appropriate.

We documented study variables from the ExECG record book, the non-invasive cardiac laboratory and cardiac clinic files. Furthermore, the cardiology department's online coronary angiogram report database and the nuclear medicine online SPECT-MPI report databases were used to add and confirm the results of coronary angiograms and SPECT-MPI, respectively. Baseline data captured included demographics (age, gender), comorbidities (human immunodeficiency virus (HIV) status, hypertension, diabetes, dyslipidaemia, smoking status, family history of CAD), medication (digoxin and beta blockers) and baseline ECG (normal, left bundle branch block (LBBB), right bundle branch block (RBBB), ST-segment elevation (STE), ST segment depression (STD)). The indications (see **Figure 1**) and contraindications for ExECGs, pretest probability for CAD (low, intermediate, high) and results obtained (Duke treadmill score, METs achieved, % heart rate, STE, STD, presence of chest pain, end prematurely, outcome (positive, negative or indeterminate), SPECT-MPI (not performed, normal or abnormal) and coronary angiography (not performed, normal, single vessel disease, double vessel disease, triple vessel disease) were captured. Of note is that we did not interpret ExECGs, SPECT-MPI, or coronary angiograms. Instead, we reported the reviewer's findings and final assessment. These variables were stored in a Research Electronic Data Capture (RedCap) database. Permission to conduct the study was obtained from the University of the Witwatersrand Medical Human Research Ethics Committee (Clearance certificate number: M210530) and relevant hospital authorities.

Statistical analysis
Statistical analysis was performed using STATA 16 software (version 16.1). Categorical variables were summarised as frequencies and percentages, and Pearson's Chi-square test was used to evaluate categorical variables for inter-group differences. We analysed variance (ANOVA) to compare normally distributed continuous variables in three or more groups of patients. The

median and interquartile ranges (IQR) were used for continuous variables with a non-normal distribution. We compared normally distributed continuous variables using the Student's t-test, and the Wilcoxon rank-sum (Mann-Whitney) test was used to compare medians for non-normal data. All statistical tests were two-sided, and a p-value of less than 0.05 was considered to represent statistical significance.

Results

The final study population comprised 318 patients. The mean age was 53.7 ± 14.0 years with 169 (53.1%) females. Hypertension was the most common comorbidity, reported in 172 (54.1%) patients. Only 13 (4.1%) patients were documented with HIV. The study population was noted to have 62 (19.5%) patients with dyslipidemia, 59 (18.5%) diabetics, 53 (16.7%) smokers and 49 (15.5%) patients with a family history of CAD. A documented baseline resting ECG was available in 66 (21.0%) patients. These revealed left bundle branch blocks in two (0.01%) patients and right bundle branch blocks in five (0.02%) patients.

Only 130 (40.9%) patients in our study population had a documented pretest risk stratification to establish pretest probability. Of those with a pretest risk stratification, 75 patients (57.7%) were at an intermediate risk for CAD. Of the remaining 55 patients with a documented inappropriate risk stratification, 43 (78.2%) patients had a low pretest probability of CAD. There were 3.6 times more patients at a low pretest probability of CAD than at a high pretest probability of CAD. The pretest risk stratification of the remaining 188 patients of the total study population could not be determined. When these patients, without a pretest risk stratification, are considered inappropriate, only 23.6% are at intermediate risk for CAD. Neither sex nor the identified risk factors for CAD were statistically significant risk factors for an appropriate referral (**Table 1**).

Figure 2 depicts the study populations' ExECG results and their subsequent investigations. There were fewer positive ExECGs than negative ExECGs. Of the 44 (13.9%) patients who had positive ExECGs, 24 (54.6%) had ST elevation, depression, or both, 22 (50.0%) had chest pain, and 17 (38.6%) had a Duke treadmill score of less than -10. Smoking was the only statistically significant associated risk factor associated with positive ExECGs (p-value 0.042). Looking closer at the 75 patients with an intermediate pretest probability for CAD, eight (10.7%) had a positive ExECG and 35 (46.7%) had a negative ExECG.

Indeterminate ExECG results were found in 119 (37%) patients. This is a result of 59 (49.6%) patients who had suboptimal target heart rates (<85% of maximum heart rate), 29 patients (24.2%) who had suboptimal METs (<4), and 76 patients (63.9%) who had moderate Duke treadmill scores.No further testing were done on the 85 (71.4%) patients with indeterminate results. Of the minority further investigated, 14 patients received a SPECT-MPI test in accordance with the department's recommended subsequent investigation. In comparison, 20 patients with indeterminate results received a coronary angiogram in the ensuing investigation. More patients had positive results from coronary angiography (11 patients) than SPECT-MPI (1 patient).

In our study population, 52 patients, regardless of risk stratification, underwent a coronary angiogram. Four patients with intermediate pretest probability of CAD were subsequently referred for coronary angiography, and none were found to have occlusive CAD. Excluding those with indeterminate ExECGs for sensitivity and specificity calculations reduced the number of angiograms to 32. Angiographically proven occlusive CAD was found in 22 of 26 patients who had positive ExECGs. Likewise, occlusive CAD was excluded in 5 of the 9 patients who had negative ExECGs. There was a positive association between meeting target heart rates and a negative coronary angiogram (p-value 0.012) but not METS <4 and a negative angiogram (p-value 0.199). A low Duke treadmill score was more discriminating in ruling out angiographically confirmed occlusive CAD (p-value 0.025) than a high Duke treadmill score compared to angiographically confirmed occlusive CAD (p-value 0.325). There were statistically significant associations between ST changes (p-value 0.005) and angiographically proven occlusive CAD and chest pain and angiographically proven occlusive CAD (p-value 0.003). Of the 32 patients with positive coronary angiography, 12 (37.5%) patients had single vessel disease, 9 (28.1%) patients had double vessel disease, and 11 (34.4%) patients had triple vessel disease.

Discussion

We retrospectively reviewed records of patients referred for ExECG over two years in a state-owned tertiary academic centre in Johannesburg, South Africa. Our study confirmed that only 23.6% of ExECGs performed at the CMJAH for the evaluation of chest pain of unknown origin were appropriate. Many patients with no documented risk stratification contribute to this low value.

Figure 1 shows a significant difference between the proportion of patients at intermediate pretest probability when only considering the 40.9% of patients with a documented pretest risk stratification. We could not confidently assert the pretest risk stratification when it was not reported. This was attributable to the records infrequently specifying whether patients' chest pain was typical, atypical or non-cardiac. The alternate value of 57.7% presumably

overestimates the study population. ExECGs requested within the Cardiology department are more likely to be correctly risk stratified than by other disciplines in other departments and hospitals. Other disciplines are probably unaware of the need to risk-stratify patients using the Diamond-Forester classification.
However, 23.6% underestimates the actual patient population, and some patients might have been correctly stratified but have yet to be documented. Regardless, too many inappropriate ExECGs were performed.

The consequences of doing inappropriate ExECGs need to be emphasised. ExECGs are a waste of resources when done inappropriately and result in delays of appropriate diagnostic testing, misdiagnosis and inappropriate treatment of patients (11). Regardless of the resources available, inappropriate ExECGs should not be done. In LMICs, however, improper resource utilisation has more significant detrimental impacts on health care systems. Instead, resources should be reallocated to where patients would benefit the most. The financial and time costs for patients to access health care for an unnecessary investigation should not be trivialised.

Numerous potential causes can be blamed for the low percentage of appropriate ExECGs. The safety, non-invasive nature and low cost of ExECGs likely result in an attitude of complacency where cardiology physiologists might perform ExECGs with the hope that cardiologists can usefully interpret them. Screening of ExECGs at the CMJAH is likely not prioritised above invasive and more expensive procedures because of the busyness of the cardiology department at the CMJAH. This might result in the lack of gatekeeping of outside referrals. A lack of understanding of the role of ExECGs is likely an important reason for inappropriate referrals.

Practical interventions should be implemented to prevent inappropriate ExECGs. We recommend that doctors be educated on the importance of risk stratification of patients with chest pain. A focus on education programmes preventing those at low pretest probability of CAD could result in a more significant decrease in inappropriate ExECGs since most inappropriate referrals involved young patients with a low pretest probability of CAD. Additionally, appropriate screening would be increased if ExECG referral forms had a mandatory risk stratification section. Moreover, a section on these referral forms insisting on characterising the type of chest pain would ensure more accurate risk stratification.

Our study's low rate of appropriate ExECGs is consistent with findings from Brazil (11), Iran (12) , and Pakistan (13) , where 22%, 60.7%, and 21% of referrals were appropriate, respectively. These studies are comparable in demographics and resource availability. They suggest that female sex and private health care systems are possible risk factors for inappropriate ExECGs (11, 14). Moreover, we concur with these authors, who recommend carefully using healthcare resources regardless of their cost or availability (11, 13).

Smoking was the only positive association found with a positive ExECG. This is unsurprising as smoking is a well-established risk factor for coronary artery disease. In keeping with this, independent from a positive ExECG, smoking was approaching statistical significance as a risk factor for an angiographically proven CAD in our population (p-value 0.052). It is debatable whether our finding that smoking was a risk factor for a positive ExECG should influence the decision to choose an ExECG as the initial investigation when more than one cardiac stress test is available. Indeed, it is still inappropriate to do an ExECG on a smoker who is at a low or high pretest probability of CAD.

An unexpected finding in our study was the large proportion of indeterminate ExECG results. The utility of ExECGs would be improved if more patients were appropriately stressed, achieving their target heart rates and METs. Healthcare workers should be appropriately trained to assist patients in meeting their target heart rate and METs. Having said this, the most significant determinant in our study of indeterminate ExECGs was a Duke treadmill score between -10 and +4. Interestingly, Khattar and colleagues found indeterminate ECGs or inability to exercise as a poor prognostic finding in their study of individuals with recent onset suspected cardiac chest pain. They had similar prognostic outcomes in terms of mortality and hospitalisation with ACS when compared with those with positive ExECGs (15). This is consistent with the high proportion of angiographically proven CAD in the small subset of patients who received angiograms after indeterminate ExECGs. Khattar and colleagues also found that the time to stress tomography was significantly longer than the time to coronary angiography (15). With this in mind, conducting a prospective study further investigating patients with indeterminate ExECGs would be interesting.

Furthermore, the many indeterminate and negative ExECGs highlight the need for a clear investigative pathway for these patients. **Figure 2** highlights many patients who did not go on to be assessed with coronary angiography or SPECT-MPI testing. The latest ESC guidelines focus on choosing between other non-invasive modalities because of their superior sensitivity and specificity (3). Because of their accessibility, clinicians in LMICs are still dependent on ExECGs to guide their decision-making. No clear recommendations are made when ExECGs are indeterminate or negative. We recommend a multidisciplinary approach involving gastroenterology and pulmonology subspecialists to investigate these patients best. This could be formalised with institutional protocols.

Our study had notable limitations mainly due to its retrospective nature. The study was limited because the investigators were not interpreting ExECGs but simply reporting the reviewer's interpretation of their findings and results. We could not derive meaningful sensitivity and specificity results from the data available at the CMJAH. Due to the retrospective nature of this study, which reviewed patients managed at the CMJAH, all patients we included had ExECGs, but not all patients had angiograms. A prospective study would be necessary where all patients underwent a coronary angiogram to determine sensitivity and specificity accurately. However, the ethics of such a study would be questionable because angiograms after a negative ExECG are not indicated and would subject participants to an unnecessary risk of complications. We expected a few patients to undergo coronary angiography after a negative ExECG. However, we were surprised to see fewer patients without coronary angiograms amongst those with a positive ExECG. This small number of patients resulted in a high percentage of positive angiograms after positive ExECGs. This positive correlation was much higher than the 50-68% sensitivity reported in the literature (16). Those who underwent angiograms were sub-selected by consultant cardiologists based on their clinical judgment.

The need for comprehensive note-taking in the available paper-based records should be noted. A contributory factor is the relatively quick and non-invasive nature of ExECGs. These are often performed as outpatient procedures in clinics with high patient burdens. In particular, comorbidities and baseline ECGs were poorly documented in the records available. This limited the possibility of finding associations with positive ExECGs. Similarly, it was rarely documented whether patients were taking beta-blockers at the time of the study, which may have contributed to the number of indeterminate results due to failure to meet target heart rates. We were unable to verify whether the medical history of the patient's chest pain was correctly classified as typical, atypical or non-cardiac and, therefore, correctly risk stratified. Lastly, the single-site design of the study limits the generalisability of the results.

Despite our study's limitations, essential conclusions can still be drawn. ExECGs are a cost-effective and readily available cardiac stress test that should be used appropriately. Our study highlights the necessity of implementing interventions to prevent inappropriate ExECGs and the need for further research to maximise their utility.

Conclusion

Our study found that, according to contemporary clinical practice guidelines, only 23.6% of ExECGs performed at the CMJAH between 2018 and 2019 to evaluate chest pain of unknown origin were appropriate referrals.

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Appendices

a) Figure 1

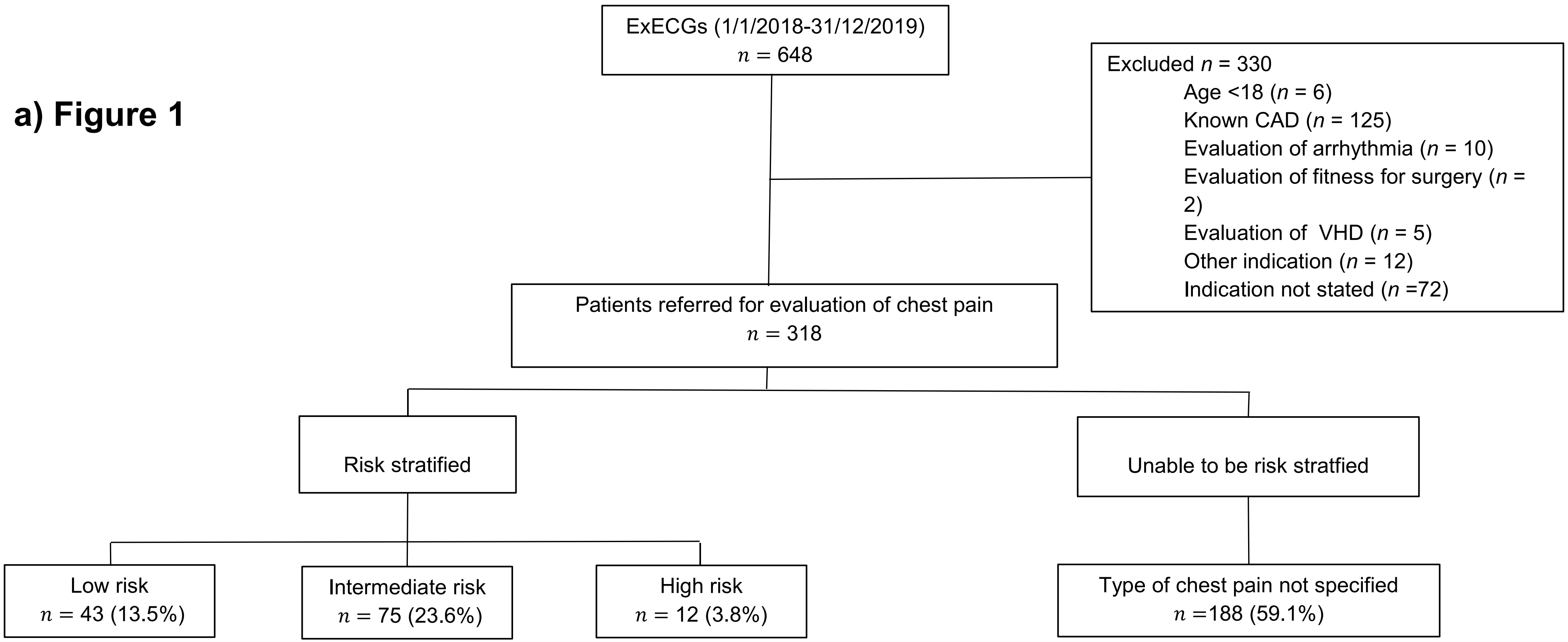

Figure 1. Number of ExECGs, exclusions and appropriate referrals. CAD, coronary artery disease, ExECG, exercise electrocardiogram, VHD, valvular heart disease

b) Figure 2

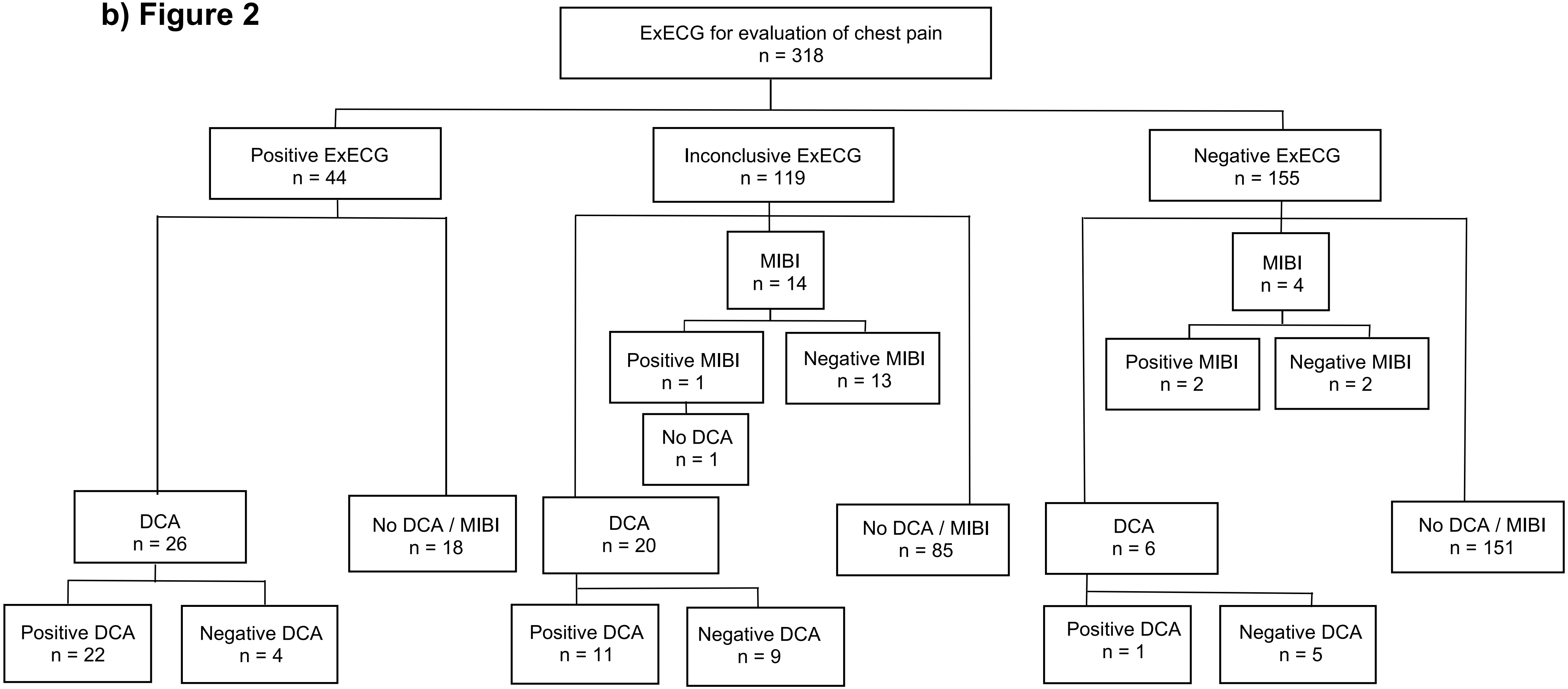

Figure 2 Patients ExECG results and their next investigations. DCA, diagnostic coronary angiogram, ExECG, exercise electrocardiogram, MIBI, Tc-99m sestamibi mycocardial perfusion scintigraphy.

c) Table 1

Table 1 Clinical characteristics of patients referred for evaluation of chest pain, stratified according to the appropriate use criteria.

Clinical parameter	Appropriate use criteria N=75 (23.6%)	Inappropriate referrals N=243 (76.4%)	p-value
Age, years	58.5 ± 10.4	52.2 ± 14.6	<0.001
Male	39 (52.0)	110 (45.3)	0.307
Risk Factors for CAD			
Hypertension	45 (60.0)	127 (52.3)	0.240
Diabetes mellitus	14 (18.7)	45 (18.5)	0.977
HIV	3 (4.1)	10 (4.1)	0.998
Dyslipidaemia	17 (22.7)	45 (18.5)	0.428
Family history of CAD	10 (13.3)	39 (16.1)	0.560
Smoking	14 (18.7)	39 (16.1)	0.595
Medication			
Beta-blocker	13 (17.3)	37 (15.2)	0.661
Digoxin	1 (1.3)	0 (0)	0.072

CAD, coronary artery disease, HIV, human immunodeficiency virus.

d) Protocol

MMED Proposal

Appropriate use of Exercise Electrocardiograms in an Academic Hospital in Johannesburg

Student and Principal Investigator: Dr Nicholas Rich, MBChB (UCT)

Student Number: 2528054

Primary Supervisor: Nqoba Tsabedze

Academic and Clinical Head: Division of Cardiology, Charlotte Maxeke Johannesburg Academic Hospital and the University of the Witwatersrand

Secondary Supervisor: Thomas Kalk

Senior Consultant, Division of Cardiology, Charlotte Maxeke Johannesburg Academic Hospital and the University of the Witwatersrand

CONTENTS

ABBREVIATIONS

ACC/AHA		American College of Cardiology/American Heart Association
CAD		Coronary artery disease
CMJAH		Charlotte Maxeke Johannesburg Academic Hospital
ECG		Electrocardiogram
ESC		European Society of Cardiology
EST		Exercise stress test
ExECG		Exercise electrocardiogram
MIBI scan		Sestamibi scan
PCI		Percutaneous coronary intervention
REDCAP		Research Electronic Data Capture

1. INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. (1) There is an increasingly large burden of CAD in low- and middle-income countries. (2) Patients with chest pain of unknown origin need to be appropriately evaluated to rule out CAD. (3) CAD can be categorised into acute and chronic coronary syndromes (CCS). (3) Despite the development of newer imaging modalities, exercise electrocardiograms (ExECG) remain an important form of exercise stress testing for patients with suspected and confirmed CCS. (4) An audit in Johannesburg of ExECGs would reveal if ExECGs are being done optimally and if patients are being referred appropriately. It would provide local use sensitivity and specificity data which would inform local patient management.

2. BACKGROUND AND LITERATURE REVIEW

2.1ExECGs

An ExECG is a type of exercise stress test. When individuals exercise, increasing metabolic requirements from exercising muscles need to be matched by an increase in cardiac output. (5) Neurohormonal adaptations are required for this to occur. (5) In those with coronary artery disease, the expected increase in coronary flow is compromised, often by atherosclerotic plaque, with a failure of coronary dilation. (5) An ExECG can detect this compromise in coronary flow by revealing various changes indicating ischemia. (5) During an ExECG a patient is subjected to a specific exercise protocol, often on a treadmill, with increasing speeds and inclines, while monitored with a twelve-lead electrocardiogram (ECG). The most common protocol used is the Bruce or modified Bruce protocol. During an ExECG patients are evaluated for exercise capacity, ischemic symptoms, haemodynamic and electrocardiographic changes. (4, 6) The unit ‘metabolic equivalent’ is a measure that allows the comparison of exercise capacity for different protocols. The Duke treadmill score can be calculated as it has been demonstrated to have a prognostic value. (7) The score consists of exercise time - (5x ST deviation) - (4x treadmill angina index). (7)

2.2 Indications and contraindications for ExECGs

ExECGs have been validated for diagnostic, prognostic and exercise capacity testing. (4, 7-9) ExECGs as a diagnostic test for the detection of CCS are only recommended for those with intermediate-risk of CAD. (3) The risk for CAD is determined by the Diamond Forester classification which considers age, gender, and character of chest pain (Appendix A). ExECGs are not recommended for those at high ischaemic risk because of the possibility of false negatives. (4) American College of Cardiology / American Heart Association (ACC/AHA) guidelines recommend ExECGs as the first-line investigation for CCS. This contrasts with the European Society of Cardiology (ESC) who had this recommendation in 2013 but moved to their latest recommendation in 2019 where no specific investigation is recommended. This was influenced by the findings of Knuuti and colleagues that claim ExECGs have limited diagnostic power in comparison to newer imaging modalities. (10) The European Society of Cardiology guidelines recommends that the choice of investigation needs to be individualised to different patients and centres with individual patient characteristics, preference, availability, and local expertise taken into consideration. (3) ExECGs are not recommended for those who have limitations preventing them from exercise, those who have resting ECG abnormalities and those taking digoxin. (3)

2.3 Advantages of ExECGs over other modalities

In comparison to newer imaging modalities, ExECGs are non-invasive, safe, inexpensive, require less expertise and are more readily accessible in South Africa. This is in contrast with newer investigations such as coronary computed tomography, stress cardiac magnetic resonance, positron emission tomography, single-photon emission computed tomography that have a greater ability to rule in or out CCS. (10)

2.4 Implications of ExECG results

Current guidelines emphasise the importance of risk stratification of patients to inform individual management. (3) An individual with a Duke Treadmill score equating to a >3% annual risk of mortality is assessed as being at high risk. (3)

Invasive angiography is recommended for those at high risk. (3) At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) those with positive findings of ExECGs often get invasive angiography with the possibility of percutaneous coronary intervention (angioplasty). Those with indeterminate results are followed up with nuclear medicine sestamibi (MIBI) scans. Studies in first world countries have shown ExECGs to have a sensitivity ranging from 50-68% and a specificity between 77-90% for detecting CAD. (4, 11) Comparing the outcomes of ExECGs to the findings of invasive angiography at CMJAH would provide local sensitivity and specificity data.

In conclusion, research into CAD is important because of the associated mortality and morbidity. It is unclear whether current guideline recommendations for ExECGs are being followed in Johannesburg. ExECGs are a validated form of exercise stress tests with many advantages but their diagnostic powers compared to newer modalities have been questioned. It is not known whether the reported sensitivity and specificities of ExECGs in first world countries are similar in a South African setting.

3. AIMS, OBJECTIVES AND METHODOLOGY

3.1 Study aim

- To evaluate the appropriate use of electrocardiogram (ECG) stress testing at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).
- To determine the local sensitivity and specificity of ExECGs at CMJAH.

3.2 Study objectives

Primary objectives

- To determine if patients undergoing ExECGs are in line with current guidelines recommendations and are referred for the correct indication.
- To compare ExECG findings with angiography findings at CMJAH.

Secondary objectives

- To describe the demographics and comorbidities of patients undergoing ExECGs at CMJAH.
- To describe the results of ExECGs at CMJAH in 2019.
- To determine any associations with positive ExECGs at CMJAH in 2019.
- To determine what subsequent management steps patients undergo.
- To determine the outcomes of patients undergoing ExECG.

3.3 METHODOLOGY

3.3.1Study design

- A retrospective review of all ExECGs at CMJAH between 1 January 2018 and 31 December 2019.

3.3.2 Study setting

- Charlotte Maxeke Academic Hospital, a public tertiary centre, is the single site of the study.

3.3.3 Study population and sample size

- All ExECGs done between 1 January 2018 and 31 December 2019 will be included in the study population. A sample size of 360 patients will result in the precision of 0.0516 and 0.0376 for sensitivity and specificity respectively. This is made using the standard formula for a proportion in descriptive studies:

$$\Delta = +/- z\sqrt{p*(1-p)/n}. \quad (12)$$

  where Δ is the proportion, z equates to a p-value of 0.05, p is an estimate that 50% of the sample has CAD and n is the sample size number.
- Inclusion criteria

  All patients who had undergone exercise stress tests in 2018 and 2019

  Patients over 18 years of age.
- Exclusion criteria

  Incomplete medical records.

3.3.4 Data collection

The principal investigator will review the electronic database at CMJAH department of Cardiology and Department of Nuclear Medicine for cases meeting the inclusion and exclusion criteria. Cases will be assigned a study number and transcribed to a REDCAP (Research Electronic Data Capture) database. The data elements to be abstracted can be seen in Appendix 2.

3.3.5 Data analysis

Baseline and demographic characteristics will be summarized by standard descriptive summaries. Categorical variables will be expressed as number and percentage with Chi-squared or Fisher exact test. Continuous variables will be expressed as mean with standard deviation or median with interquartile range and compared with Student t-test or Mann-Whitney test. Correlations will be tested with Pearson or Spearman's correlation coefficients. P values of <0.5 will be considered statistically significant.

3.4 Funding

Minimal costs are expected and will be incurred by the primary investigator. The University of Witwatersrand has provided a tuition bursary for the primary investigator.

3.5 Ethics

Due to the nature of the study, no ethical issues are anticipated. Ethical clearance will be obtained from the University of the Witwatersrand (WITS) Human Research Ethics Committee. Consent will be obtained from the Cardiology Department at Charlotte Maxeke Johannesburg Academic Hospital. Maintaining confidentiality of case identities will be prioritised with data only being shared amongst the primary investigator and supervisors on password-protected databases. Findings are intended to be published in an academic journal to enhance patient care.

3.6 Timing

	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Literature Review										
Preparing protocol										
Ethics application										
Protocol assessment										
Data collection										
Data analysis										
Write up										

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e) Data collection sheet

<u>Demographics</u>	
Age	
Sex	Male / Female
Race	African / Coloured / Indian / White / Other
<u>Comorbidities</u>	
HIV status	Positive / Negative / Unknown
CAD	Yes / No
HPT	Yes / No
DM	Yes / No
Smoker	Yes / No
Dyslipidaemia	Yes / No
<u>Medication</u>	
Beta Blocker	Yes / No
Digoxin	Yes / No
<u>Indication</u>	
Pre-test probability	Low / Intermediate / High risk

Contraindication	Yes / No
<u>Findings</u>	Positive / Negative
Specify	
Target heart rate achieved	Yes / No
Metabolic equivalents achieved	
ST changes	Nil / Anterior / Septal / Inferior / Lateral / Other (specify)

Time to return to baseline heart rate	
Reason for stopping ExECG	
Duke Treadmill Score	
<u>Subsequent Investigations</u>	
Coronary angiogram	Yes / No
Finding	Normal / Abnormal
Specify	Single / Dual / Triple vessel Disease
MIBI scan	Yes / No
Finding	Normal / Abnormal

Specify	Description / Location of ischemic burden

2

f) Ethics clearance certificate

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Dr N Rich

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210530

NAME: (Principal Investigator)	Dr N Rich
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine - Cardiology Medical School University
PROJECT TITLE:	*Appropriate use of exercise electrocardiograms in Johannesburg*
DATE CONSIDERED:	2021/05/28
DECISION:	Approived unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor N Tsabedze
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/09/15

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 **May** and therefore reports and re-certification will be due in the month of **May** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date

g) Turnitin similarity report

MMED Turnitin draft.docx

by Nicholas Rich

Submission date: 21-Oct-2024 07:19PM (UTC+0200)
Submission ID: 2492575097
File name: MMED_Turnitin_draft.docx (68.53K)
Word count: 3773
Character count: 21905

Abbreviations

ANOVA	Analysis of variance
CAD	Coronary artery disease
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ECG	Electrocardiogram
ESC	European Society of Cardiology
ExECG	Exercise electrocardiogram
LBBB	Left bundle branch block
LMIC	Low and middle-income Country
REDCAP	Research Electronic Data Capture
RBBB	Right bundle branch block
SPECT	Single photon emission computed tomography
STD	ST segment depression
STE	ST segment elevation

Abstract

Aims

Exercise electrocardiograms (ExECGs) are widely used in resource-limited settings to screen for patients with chest pain of unknown origin. Despite this, the appropriate use of the ExECG has never been determined. We aimed to evaluate whether ExECGs, to investigate patients with chest pain of unknown origin, were being done appropriately in Johannesburg.

Methods

We retrospectively evaluated 318 consecutive ExECGs done on patients between 1 January 2018 and 31 December 2019, at a single tertiary centre, the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This included ExECGs for patients selected in the Cardiology department and those referred from other hospitals and departments. Following the 2019 European Society of Cardiology (ESC) Guidelines for diagnosing and managing chronic coronary syndromes, solely those patients at intermediate pretest probability of occlusive CAD using the Diamond-Forester Classification were considered appropriate.

Results

Only 130 (40.9%) patients in our study sample had a documented pretest risk stratification to establish pretest probability, of which 75 patients (57.7%) were documented as having an intermediate pretest likelihood of CAD. The pretest risk stratification of the remaining 188 patients of the total study population could not be determined. When these patients without a pretest risk stratification are considered inappropriate then only 23.6% are at intermediate risk for CAD.

Conclusion

In our study, we found that only 23.6% of ExECGs performed at the CMJAH for the evaluation of chest pain of unknown origin were appropriate. (232 words)

Keywords

Exercise electrocardiogram (ExECG), inappropriate referral, coronary artery disease (CAD), risk stratification, and pretest probability.

Lay summary

Exercise electrocardiograms are among the many tests to screen patients for coronary artery disease. We conducted this study to see if the use of exercise electrocardiograms at the Charlotte Maxeke Johannesburg Hospital was being done on patients at the correct risk profile, according to European Society of Cardiology guidelines. Of the 318 exercise electrocardiograms performed to assess chest pain of unknown cause, only 75 (23.6%) were documented to be at the correct risk profile. We conclude that too many inappropriate exercise electrocardiograms are being done.

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide (1). Three-quarters of global cardiovascular deaths occur in low-and-middle-income countries (LMICs) (2). Patients with chest pain of unknown origin need to be appropriately evaluated to rule out CAD (3). Currently, there are multiple non-invasive cardiac imaging modalities in use, ranging from the exercise electrocardiogram (ExECG) and stress echocardiography to newer modalities such as coronary computed tomography angiography, stress cardiac magnetic resonance and single photon emission computed tomography (SPECT) (3). The European Society of Cardiology (ESC) has revised their 2013 class 1C recommendation for ExECGs as the first-line investigation for all patients with chronic coronary syndrome (CCS) (4). The 2019 ESC guidelines for diagnosing and managing chronic coronary syndromes now recommends that the choice of investigation should be individualised for different patients and centres (3). They recommend considering individual patient characteristics, preferences, availability and local expertise (3). This was likely due to the 2019 meta-analysis by Knuuti and colleagues, which showed that ExECGs, in comparison to the aforementioned newer modalities, have limited diagnostic power to confirm or exclude CCS. However, access to these newer non-invasive cardiac imaging modalities is limited in many LMICs (5).

The ExECG is a vital screening tool for CAD. It is a safe, non-invasive, low-cost test that requires relatively minimal expertise for performance and interpretation (6). During exercise, increasing metabolic requirements from exercising muscles need to be matched by an increase in cardiac output. Neurohormonal adaptations are required for this to occur. In those with coronary artery disease, the expected increase in coronary flow is compromised, often by atherosclerotic plaque, with a failure of coronary dilation. An ExECG can detect compromise in coronary flow by revealing various ECG changes indicating ischemia (6).

Despite its wide regional use, there is a paucity of published data on the appropriate clinical use of ExECGs in sub-Saharan Africa. South Africa is a resource-limited country. Therefore, it is important to consider how to cost-effectively investigate patients with chest pain of unknown origin. Our aim was to determine the level of appropriate referral for ExECGs in patients with chest pain of unknown origin. Additionally, we sought to determine our local specificity and sensitivity data for ExECGs in predicting CAD.

Methods

Study design, setting and selection of study participants

We conducted a single-centre, retrospective, observational study at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a state-owned tertiary hospital in South Africa. At the CMJAH non-invasive cardiac laboratory, ExECGs are performed on patients at the request of both registrar and consultant cardiologists for patients reviewed in the cardiology department. Additionally, patients are referred for ExECGs by doctors of various levels of experience from other departments in the hospital and other affiliated secondary and primary health care centres. These referrals from outside the cardiology department are screened by registrar and consultant cardiologists. This results in many patients being considered for an ExECG. The department risk stratifies patients with chest pain of unknown origin for CAD using the Diamond-Forrester classification. This classification considers age, sex, and type of chest pain (7). In line with ESC Chronic Coronary Syndrome guidelines, neither patients with a low nor a high pretest probability of CAD should have an ExECG (3). The ExECGs are performed by cardiology physiologists using the modified Bruce protocol. This entails monitoring patients with a twelve-lead electrocardiogram (ECG) and subjecting them to a specific exercise protocol on a treadmill, with increasing speeds and inclines. During an ExECG patients are evaluated for exercise capacity, ischemic symptoms, and haemodynamic and electrocardiographic changes (8, 9). The 'metabolic equivalent' (METs), a quantification of exercise capacity, is calculated to compare different patients and different protocols. Finally, the Duke treadmill score is calculated because of its established prognostic value (10). This score is calculated using the exercise time (min) - (5x ST deviation) - (4x treadmill angina index) (10). An adequate ExECG was defined as patients who achieved an age-predicted heart rate ((220-age(years) x 85%) and METs equal to or greater than 4. ExECG results are reviewed by registrar and consultant cardiologists and determined to be positive, negative or indeterminate. Positive ExECG results were defined by the presence of typical chest pain, ST-segment elevation or depression, or those with a Duke treadmill score less than -10. Negative ExECG results were defined by a Duke treadmill score of +5 or greater, the absence of chest pain, ECG elevation and depression in those meeting the requirement of an adequate ExECG. Indeterminate results were defined as a Duke treadmill score between -10 and +4 or an inadequate ExECG.

At the CMJAH, consultant cardiologists are free to use their clinical judgment for the management of individual cases. However, the standard of practice for the CMJAH is for those with positive ExECGs to have coronary angiograms. In most cases, patients with a negative ExECG are referred for evaluation of non-cardiac causes of chest pain. Lastly, those with an indeterminate ExECG result are recommended to go for a 'MIBI' i.e. a myocardial perfusion imaging with single photon emission tomography (SPECT).

The ExECG record book at the non-invasive cardiac laboratory was used to identify patients for inclusion in the study. We included all patients who underwent an ExECG between 1 January 2018 and 31 December 2019. This period met a predefined sample size after estimating the average number of ExECGs done per month. Patients under 18 years of age, those known with CAD and patients with incomplete records were excluded **(Figure 1)**. We defined those with incomplete records as patients without a documented name or an ExECG result. Those defined with CAD were those with angiographically proven occlusive CAD. Only patients documented at intermediate pretest probability of CAD were considered appropriate.

We documented study variables from the ExECG record book, the non-invasive cardiac laboratory and cardiac clinic files. Furthermore, the cardiology department's online coronary angiogram report database and the nuclear medicine online SPECT report databases were used to add and confirm the results of coronary angiograms and SPECT respectively. Baseline data captured included demographics (age, gender), comorbidities (human immunodeficiency virus (HIV) status, hypertension, diabetes, dyslipidaemia, smoking status, family history of CAD), medication (digoxin and beta blockers) and baseline ECG (normal, left bundle branch block (LBBB), right bundle branch block (RBBB), ST-segment elevation (STE), ST segment depression (STD)). The indications (see **Figure 1**) and contraindications for ExECGs, pretest probability for CAD (low, intermediate, high) and results obtained (Duke treadmill score, METs achieved, % heart rate, STE, STD, presence of chest pain, end prematurely, outcome (positive, negative or indeterminate), SPECT (not performed, normal or abnormal) and coronary angiography (not performed, normal, single vessel disease, double vessel disease, triple vessel disease) were captured. Of note, we did not interpret ExECGs, SPECT or coronary angiograms. Rather we reported the reviewer's findings and final assessment. These variables were stored in a Research Electronic Data Capture (RedCap) database. Permission to conduct the study was obtained from the University of the Witwatersrand Medical Human Research Ethics Committee (Clearance certificate number: M210530) and relevant hospital authorities.

Statistical analysis

Statistical analysis was performed using STATA 16 software (version 16.1). Categorical variables were summarised as frequencies and percentages, and Pearson's Chi-square test was used to evaluate categorical variables for inter-group differences. We analysed variance (ANOVA) to compare normally distributed continuous variables in three or more groups of patients. The median and interquartile ranges (IQR) were used for continuous variables with a non-normal distribution. We compared normally distributed continuous variables using the Student's t-test, and the Wilcoxon rank-sum (Mann-Whitney) test was used to compare medians for non-normal data. All statistical tests were two-sided and a p-value of less than 0.05 was considered to represent statistical significance.

Results

The final study population comprised 318 patients. The mean age was 53.7 ± 14.0 years with 169 (53.1%) females. Hypertension was the most common comorbidity, reported in 172 (54.1%) patients. Only 13 (4.1%) patients were documented with HIV. The study population was noted to have 62 (19.5%) patients with dyslipidemia, 59 (18.5%) diabetics, 53 (16.7%) smokers and 49 (15.5%) patients with a family history of CAD. A documented baseline resting ECG was available in 66 (21.0%) patients. These revealed left bundle branch blocks in two (0.01%) patients and right bundle branch blocks in five (0.02%) patients.

Only 130 (40.9%) patients in our study population had a documented pretest risk stratification to establish pretest probability. Of those that had a pretest risk stratification, 75 patients (57.7%) were at an intermediate risk for CAD. Of the remaining 55 patients with a documented inappropriate risk stratification, 43 (78.2%) patients were at a low pretest probability of CAD. There were 3.6 times more patients at a low pretest probability of CAD than at a high pretest probability of CAD. The pretest risk stratification of the remaining 188 patients of the total study population could not be determined. When these patients, without a pretest risk stratification, are considered inappropriate then only 23.6% are at intermediate risk for CAD. Neither sex nor the identified risk factors for CAD were statistically significant risk factors for an appropriate referral (**Table 1**).

Figure 2 depicts the study populations' ExECG results and their next investigations. There were fewer positive ExECGs than negative ExECGs. Of the 44 (13.9%) patients who had positive ExECGs, 24 (54.6%) had ST elevation, depression or both, 22 (50.0%) had chest pain, and 17 (38.6%) had a Duke treadmill score of less than -10. Smoking was the only statistically significant associated risk factor associated with positive ExECGs (p-value 0.042). Looking closer at the 75 patients with an intermediate pretest probability for CAD, eight (10.7%) had a positive ExECG and 35 (46.7%) had a negative ExECG. Indeterminate ExECG results were found in 119 (37%) patients. Of these patients, 59 (49.6%) had suboptimal target heart rates (<85% of maximum heart rate), 29 patients (24.2%) had suboptimal METs (<4) and 76 patients (63.9%) had moderate Duke treadmill scores.

No further testing was done on 85 (71.4%) patients who had indeterminate results. Of the minority further investigated, 14 patients received a SPECT test, in keeping with the department's recommended next investigation. In comparison, 20 of those with indeterminate results had a coronary angiogram as the next investigation. More patients had positive results from coronary angiography (11 patients) than SPECT (1 patient).

In our study population, 52 patients underwent a coronary angiogram. Four patients with intermediate pretest probability of CAD were subsequently referred for coronary angiography and none were found to have occlusive CAD. Excluding those with indeterminate ExECGs for sensitivity and specificity calculations reduced the number of angiograms to 32. Angiographically proven occlusive CAD was found in 22 of 26 patients who had positive ExECGs. Likewise, occlusive CAD was excluded in 5 of the 9 patients who had negative ExECGs.There was a positive association between meeting target heart rates and a negative coronary angiogram (p-value 0.012) but not METS <4 and a negative angiogram (p-value 0.199). A low Duke treadmill score was found to be more discriminating in ruling out angiographically confirmed occlusive CAD (p-value 0.025) than a high Duke treadmill score when compared to angiographically confirmed occlusive CAD (p-value 0.325). There were statistically significant associations between ST changes (p-value 0.005) and angiographically proven occlusive CAD and chest pain and angiographically proven occlusive CAD (p-value 0.003). Of the 32 patients with positive coronary angiography, 12 (37.5%) patients had single vessel disease, 9 (28.1%) patients had double vessel disease and 11 (34.4%) patients had triple vessel disease.

Discussion

We conducted a retrospective review of records of patients referred for ExECG over two years in a state-owned tertiary academic centre in Johannesburg, South Africa. In our study, we found that only 23.6% of ExECGs performed at the CMJAH for the evaluation of chest pain of unknown origin were appropriate. A large contributor to this low value is the number of patients with no documented risk stratification.

As seen in **Figure 1**, there is a significant difference between the proportion of patients at intermediate pretest probability when only considering the 40.9% of patients with a documented pretest risk stratification. We could not make any confident assertions about the pretest risk stratification when it was not documented. This was attributable to the records infrequently specifying whether patients' chest pain was typical, atypical or non-cardiac. The alternate value of 57.7% is presumably an overestimation of the study population. ExECGs requested within the Cardiology department are more likely to be correctly risk stratified than by other disciplines in other departments and hospitals. Other disciplines are probably unaware of the need to risk-stratify patients using the Diamond-Forester classification. However, the argument can be made that the 23.6% is an underestimation of the true patient population where some patients might have been correctly stratified but not documented. Regardless too many inappropriate ExECGs were done.

The consequences of doing inappropriate ExECGs need to be emphasised. ExECGs are a waste of resources when done inappropriately and result in delays of appropriate diagnostic testing, misdiagnosis and inappropriate treatment of patients (11). Regardless of the resources available, inappropriate ExECGs should not be done. In LMICs, however, improper resource utilisation has greater detrimental impacts on health care systems. Rather resources should be reallocated to where patients would benefit the most. The cost, both financial and in time, spent for patients on accessing health care for an unnecessary investigation should not be trivialised.

Numerous potential causes can be blamed for the low percentage of appropriate ExECGs. The safety, non-invasive nature and low cost of ExECGs likely result in an attitude of complacency where cardiology physiologists might perform ExECGs with the hope that they can still be usefully interpreted by cardiologists. Screening of ExECGs at the CMJAH is likely not prioritised above invasive and more expensive procedures because of the busyness of the cardiology department at the CMJAH. This might result in the lack of gatekeeping of outside referrals. A lack of understanding of the role of ExECGs is likely an important reason for inappropriate referrals.

Practical interventions should be implemented to prevent inappropriate ExECGs. We recommend that doctors be educated on the importance of risk stratification of patients with chest pain. A focus on education programmes preventing those at low pretest probability of CAD could result in a greater decrease in inappropriate ExECGs since the majority of inappropriate referrals involved young patients with a low pretest probability of CAD. Additionally, appropriate screening would be increased if ExECG referral forms had a mandatory risk stratification section. Moreover, a section on these referral forms insisting on characterising the type of chest pain would ensure more accurate risk stratification.

The low rate of appropriate ExECGs found in our study is consistent with findings from Brazil (11), Iran (12) and Pakistan (13) where 22%, 60.7% and 21% of referrals were appropriate, respectively. These studies are comparable in demographics and resource availability. They suggest female sex and private health care systems are possible risk factors for inappropriate ExECGs (11, 14). Moreover, we concur with these authors who recommend the careful use of healthcare resources regardless of their cost or availability (11, 13).

Smoking was the only positive association found with a positive ExECG. This is unsurprising as smoking is a well-established risk factor for coronary artery disease. In keeping with this, smoking independent from a positive ExECG, was approaching statistical significance as a risk factor for an angiographically proven CAD in our population (p-value 0.052). It is debatable whether our finding that smoking was a risk factor for a positive ExECG should influence the decision to choose an ExECG as the initial investigation when more than one cardiac stress test is available. Certainly, it is still inappropriate to do an ExECG on a smoker who is at a low or high pretest probability of CAD.

An unexpected finding in our study was the large proportion of indeterminate ExECG results. The utility of ExECGs would be improved if more patients were appropriately stressed meeting their target heart rates and METs. Healthcare workers should be appropriately trained to assist patients in meeting their target heart rate and METs. Having said this, the biggest determinant in our study of indeterminate ExECGs was a Duke treadmill score between -10 and +4. Interestingly Khattar and colleagues found indeterminate ECGs or inability to exercise as a poor prognostic finding in their study of individuals with recent onset suspected cardiac chest pain. They had similar prognostic outcomes in terms of mortality and hospitalisation with ACS when compared with those with positive ExECGs (15). This is consistent with the high proportion of angiographically proven CAD in the small subset of patients who received angiograms after indeterminate ExECGs. Khattar and colleagues also found that the time to stress tomography was significantly longer than the time to coronary angiography (15). With this in mind, it would be interesting to conduct a prospective study further investigating patients with indeterminate ExECGs.

Furthermore, the large number of both indeterminate and negative ExECGs highlights the lack of a clear investigative pathway for these patients. **Figure 2** highlights a large number of patients who did not go on to be assessed with coronary angiography or SPECT testing. The latest ESC guidelines focus on choosing between other non-invasive modalities because of their superior sensitivity and specificity (3). Because of their accessibility, clinicians in LMICs are still dependent on ExECGs to guide their decision-making. No clear recommendations are made when ExECGs are indeterminate or negative. We recommend a multidisciplinary approach involving gastroenterology and pulmonology subspecialists to best investigate our patients. This could be formalised with institutional protocols.

Our study had notable limitations largely due to its retrospective nature. The study was limited by the fact that the investigators were not interpreting ExECGs but simply reporting the reviewer's interpretation of their findings and final results. We were unable to derive meaningful sensitivity and specificity results from the data available at the CMJAH. Due to the retrospective nature of this study reviewing patients who were managed at the CMJAH, all patients we included had an ExECG but not all patients had angiograms. A prospective study would be necessary where all patients underwent a coronary angiogram to accurately determine sensitivity and specificity. However, the ethics of such a study would be questionable because angiograms after a negative ExECG are not indicated and would put patients at the unnecessary risk of complications. While it was expected that there would be few patients who underwent a coronary angiogram after a negative ExECG, it was surprising to see so few patients without angiograms who had a positive ExECG. The high percentage of positive angiograms after positive ExECGs is limited by the small number of patients. This positive correlation is much higher than the 50-68% sensitivity reported in the literature (16). Those who underwent angiograms were sub-selected by consultant cardiologists based on their clinical judgment. We cannot make conclusions about sensitivity and specificity based on the data available at the CMJAH.

The lack of comprehensive note-taking in the available paper-based records should be noted. A contributory factor is the relatively quick and non-invasive nature of ExECGs. These are often performed as an outpatient procedure in clinics with high patient burdens. In particular, comorbidities and baseline ECGs were poorly documented in the records available. This limited the possibility of finding associations with positive ExECGs. Similarly, it was rarely documented whether patients were taking beta-blockers at the time of the study, which may have contributed to the number of indeterminate results due to failure to meet target heart rates. We were unable to verify whether the medical history of patients' chest pain was correctly classified as typical, atypical or non-cardiac and therefore correctly risk stratified. The CMJAH Cardiology department can improve with better documentation and filing of patient information. The online coronary angiogram database is an example of the CMJAH cardiology department's effort to shift to online record keeping. Lastly, the single-site design of the study limits the generalisability of the results.

Despite the limitations of our study, important conclusions can still be drawn from our findings. ExECGs are a cost-effective and readily available cardiac stress test that should be used appropriately. Our study highlights the necessity of implementing interventions to prevent inappropriate ExECGs and the need for further research into maximizing their utility.

Conclusion

In our study, we found that only 23.6% of ExECGs performed at the CMJAH between 2018 and 2019 for the evaluation of chest pain of unknown origin were appropriate.

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