Indonesian Journal of Cardiology
Indonesian J Cardiol 2022:43:30-36
pISSN: 0126-3773 / eISSN: 2620-4762
doi: 10.30701/ijc.1197

Case Reports

When Positive Ischemic Response on Treadmill Test Implies Otherwise: One Overlooked Pitfall on TMT

Dmitri Muhammad Rifanda[1], M. A. L. Parama[1],
Teuku Muhammad Haykal Putra[2], Wishnu Aditya Widodo[2]

Abstract

Background: Particular ischemic process that are portrayed in Electrocardiogram (ECG) changes bear similar depiction to different conditions, one of them is hypokalemia. On the other hand, Treadmill Test (TMT) has been used for decades for risk stratifying and diagnosing coronary artery disease (CAD) as a non-invasive, safe, and affordable screening test. However, using ECG changes as interpretation, TMT could have incidence of false-positive results reported in various conditions, one of which is hypokalemia. The aim is to report a case of positive ischemic response resemblance in TMT of a patient with severe hypokalemia.

Case Illustration: A-43-years-old female with history of unstable angina pectoris (UAP) with risk factors of diabetes mellitus and hypertension underwent several examinations. Computed Tomography Coronary Angiography (CTCA) showed a 60% stenosis lesion in Left Anterior Descending (LAD) coronary artery. Within 3 minutes of TMT the ECG showed ST-segment depression in lead II, III, aVF, V1-V6 and prominent elevation in lead aVR. Fear of left main coronary artery occlusion, the test was terminated and the patient was immediately planned for urgent Percutaneous Coronary Intervention (PCI). The result indicated non-significant coronary lesion. Potassium concentration of 1.87 mmol per liter and troponin levels were normal. Unbeknownst before, the patient had multiple episodes of vomiting for a whole day and felt dehydrated prior to the TMT. The patient was then treated for potassium implementation and discharged uneventfully.

Conclusion: Hypokalemia could induce widespread ST-Segment depression or ST-Segment elevation in right limb lead. Peculiarly in the context of stress testing or accompanied with chest pain, it is difficult to differentiate ECG changes in hypokalemia from true myocardial ischemia. Hypokalemia should be considered when the TMT result is not in concordance with true myocardial ischemia.

(Indonesian J Cardiol. 2022;43:30-36)

Keywords: Treadmill Test; Hypokalemia; Coronary artery disease.

[1] General Practitioner, Jakarta Heart Center, Jakarta, Indonesia.
[2] Cardiologist, Jakarta Heart Center, Jakarta, Indonesia.

Correspondence:
Dmitri Muhammad Rifanda,
General Practitioner, Jakarta Heart Centre, Indonesia.
Email: demethree.dr@gmail.com

Introduction

Exercise testing is a form of testing that elicits the presence or absence of cardiovascular disease which may be concealed at rest. It is usually performed by a treadmill. It is conducted under various indications such as recent acute coronary syndrome, incomplete revascularization, patients with suggestive symptoms of myocardial ischemia, and patients with risk factors of CAD. TMT can determine a patient's functional capacity, assess the probability and extent of CAD as well as assess risks, prognosis, and effects of therapy. It is a sensitive, non-invasive, affordable, and useful tool in detecting coronary artery disease, playing a sentry role for angiography.[1, 2]

Several factors could afflict specificity of the test leading to false-positive results. These conditions are in patients with some metabolic conditions (anemia, glucose load, hyperventilation, and hypokalemia), structural heart diseases (severe aortic stenosis, mitral valve prolapsed, severe aortic or mitral regurgitation, cardiomyopathies, and left ventricular hypertrophy), marked resting ST-segment depression, intraventricular conduction disturbances, pre-excitation syndromes, severe hypertension, severe hypoxia, sudden excessive exercise, supra-ventricular arrhythmias or digitalis therapy.[1,2]

Case Illustrations

A 43 years old woman came to our hospital with a complaint of recurrent anginal chest pain. She has a history of diabetes and hypertension. CTCA examination is planned for the patient after careful consideration of the patient's risk profile. The results showed 50-60% stenotic lesion in the proximal part of LAD. We decided to treat the patient medically. However, the patient complained that the symptoms persist despite optimal anti-ischemic medical therapy in multiple outpatient visits. We prescribed TMT for the patient to investigate ischemic response. Within 3 minutes of TMT, the ECG showed ST-segment depression in lead II, III, aVF, V1-V6 and prominent elevation in lead aVR measured at 2 mV (**figure 1 and 2**).

Unbeknownst to us before, the patient vomited multiple times in the morning before taking the first TMT. She had multiple episodes of vomiting and felt dehydrated underway to the test. She did not disclose this information during our routine screening prior to the TMT. We found out later on that the patient did not alarm us this information because she was afraid that the test might have been postponed. Potassium concentration of 1.87 mmol per liter and troponin levels were normal. The patient was treated for intravenous

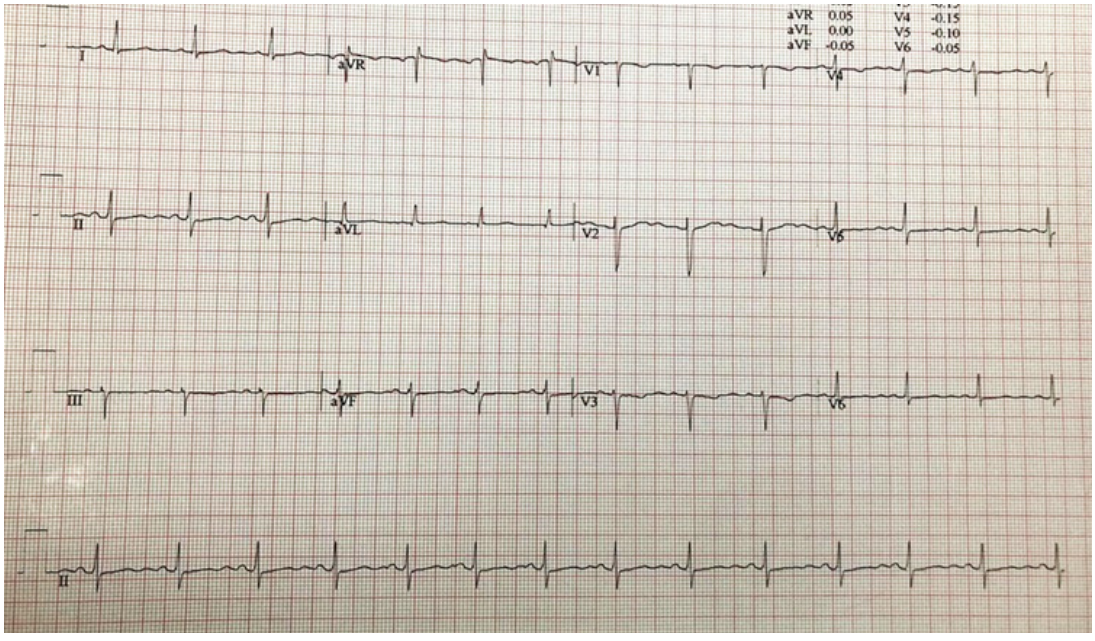

Figure 1. Baseline ECG.

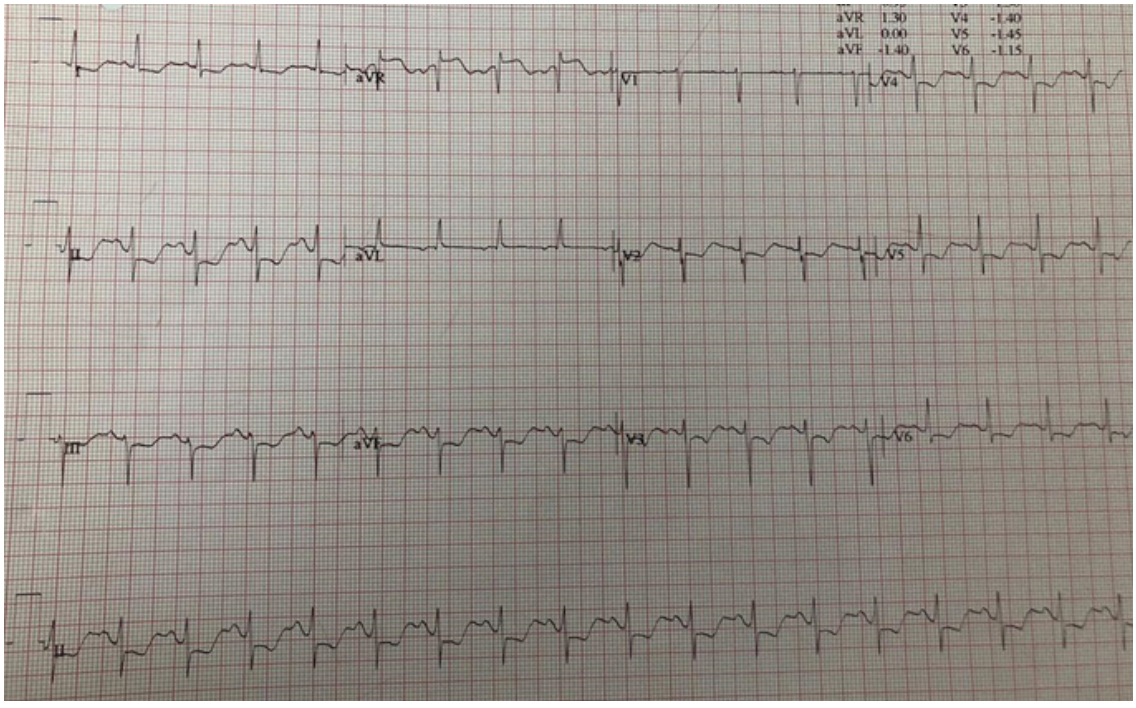

Figure 2. Treadmill Test ECG at peak exercise (01.30) showed ST segment elevation in AVR and widespread ST segment depression.

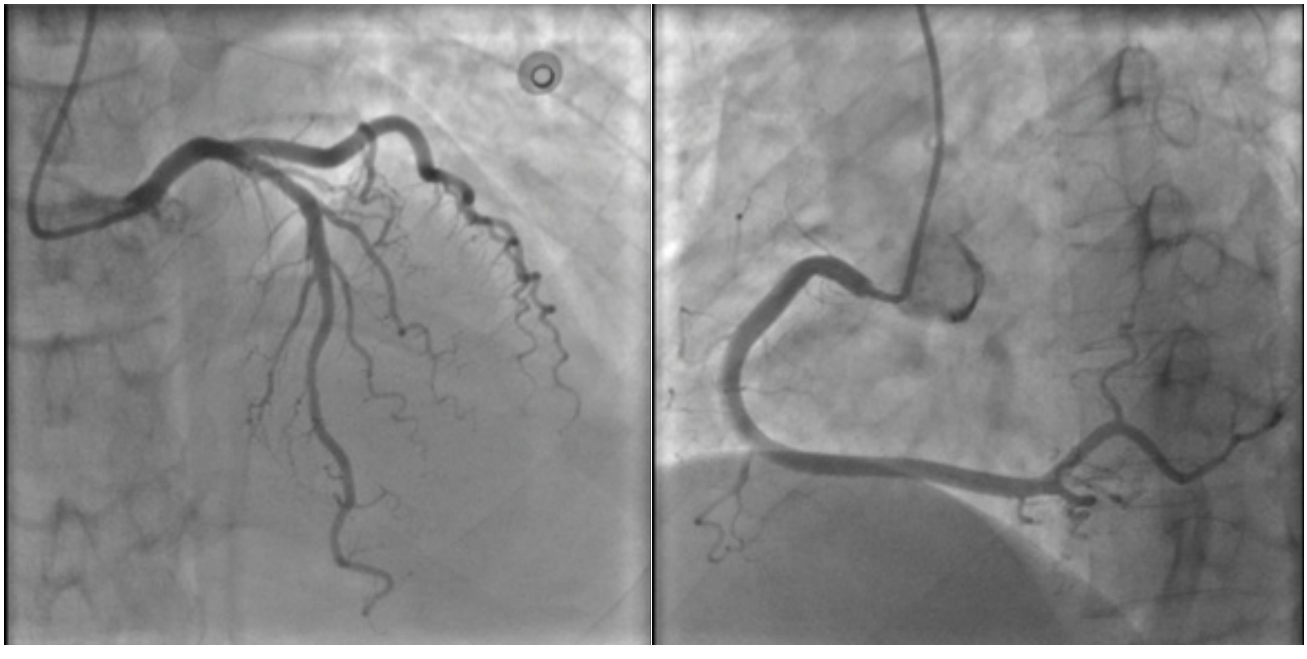

Figure 3. Coronary angiography shows non-significant lesion.

potassium replacement without being given any antithrombotic medication. The potassium level was restored to a normal level. There was no more episode of vomiting during hospitalization. The patient was then discharged uneventfully.

During the follow-up period in outpatient clinic, the patient was scheduled for another TMT to confirm the previous false-positive result of TMT. The second TMT examination showed a negative ischemic response without any ST changes. (**Figure 4**).

Discussions

Assessing the probability of CAD is to acquire the simplest input. It is important to obtain a thorough history, assess risk factors, and perform focused physical examinations. Particular history important for CAD diagnosis includes age, sex, and characteristics of the symptom. Chest pain should be classified as typical angina, atypical angina, noncardiac chest pain, or angina equivalent. It is imperative to emphasize other characteristics of the symptom such as induced by exertion, emotional stress, cold, or postprandial and relieved by rest. Risk factors that are important to point out are smoking, hypertension, diabetes, hyperlipidemia, and a family history of MI before age 60 years. Apart from resting Electrocardiography (ECG), CTCA or TMT would be the go-to non-invasive testing. Selecting which examination to be performed depends on risk stratification or pre-test probability of CAD which is based on patients' sex, age and symptoms.[3] Our patient presented with typical chest pain. According to the pre-test probability of obstructive coronary artery disease, this patient could be categorized as an intermediate risk of such disease.[3] Her risk of obstructive coronary artery disease is 10%. Considering her diabetic condition, we chose to conduct an additional examination. CTCA was preferred for her due to her risk of obstructive CAD around 10-15%.

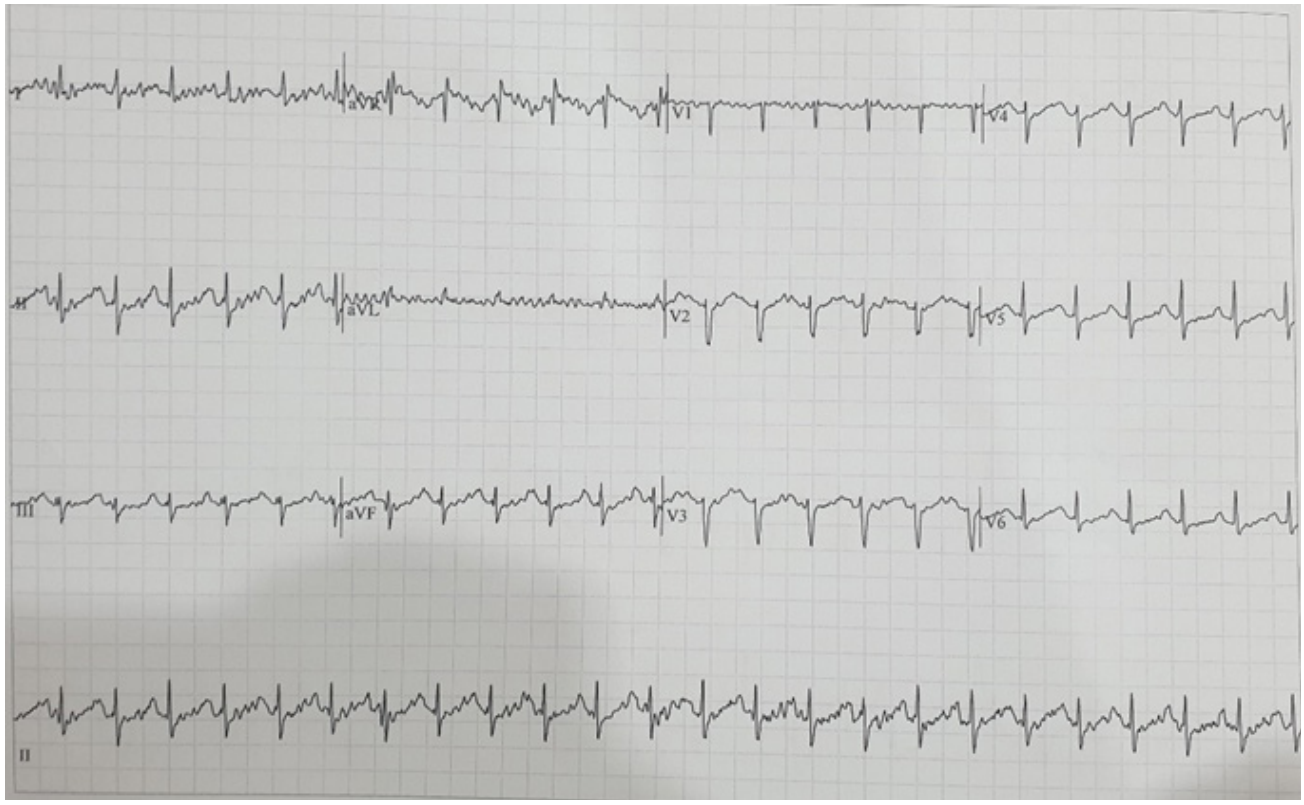

Figure 4. Second Treadmill Test ECG at peak exercise (04.30) showed non-significant ST-segment change.

CTCA has 97% to 99% negative predictive value which means it can effectively and safely rule out CAD. Whereas stress test is an effective risk stratification tool for prognosis. When imaging test came out with dubious conclusion to revascularize stenotic lesions in a coronary artery, stress test could help give additional data to decide revascularization procedure. Combining each information provides the highest non-invasive diagnostic and prognostic accuracies in CAD evaluation available so far.[2] The findings of 50-60% stenotic lesion in the proximal part of LAD based on CTCA urges the clinician to treat the patient medically. If the symptoms resided, there would be no need to perform further intervention. However, the symptoms persist despite optimal anti-ischemic medication. Based on this clinical situation, TMT was prescribed because her proximal stenotic lesion in LAD might benefit from a revascularization program. This is in line with ESC guideline regarding myocardial revascularization in which it was stated that such patient might get benefit from revascularization when there is a stenotic lesion over 50% in proximal part of LAD.[4] Specifically in our case, TMT was performed to confirm how significant the hindrance to coronary flow since an obstructive stenosis lesion was found from the CTCA result.[2,5]

When TMT is performed on a carefully selected group of patients, it possesses a prognostic value with 85% specificity. It is a helpful diagnostic tool to assess the risks and prognosis of CAD in the patients to determine whether further invasive approach is necessary. Exercise testing will either be positive, negative, equivocal, or uninterpretable if there is a limiting factor. Duke Treadmill Score (DTS) provides accurate diagnostic and prognostic information to determine if patients are at a low, intermediate, or high risk for ischemic heart disease, predicting 5-year survival. Our patient is at intermediate risk. The DTS uses three exercise parameters: exercise time, ST-segment deviation (depression or elevation), and exertional angina. Positive TMT test for ischemia is concluded when there is a ≥1.5 mm or more upsloping ST depression, or a ≥1 mm horizontal/downsloping ST depression. ST-elevation ≥1 mm in leads without q wave has ominous prognosis and it is a strong indication to stop the test immediately. In our patient, ST-segment elevation appeared in aVR lead suggesting left main coronary artery occlusion. The most appropriate approach at that time is to revascularize soon.[2,6]

Appropriate patient selection should be obliged as the following predisposing factors ensue false-positive results. Causes for a false positive test include metabolic conditions (anemia, glucose ingestion before the test, and hypokalaemia) and structural heart diseases (severe aortic stenosis, mitral valve prolapsed, severe aortic or mitral regurgitation, cardiomyopathies, and left ventricular hypertrophy). Digitalis therapy could also cause exercise-induced ST depression in 25% to 40% of normal subjects.[1,6,7] In our case, hypokalaemia played a significant role as a confounding factor. Non-significant stenosis in angiogram was identified despite shocking TMT result. Hence a false-positive result.

Hypokalaemia is one of the most common electrolyte disturbances and it can increase the risk of life-threatening arrhythmias. ECG characteristics associated with hypokalaemia include dynamic changes in T-wave morphology, ST-segment depression, prominent U waves, and prolongation of PR interval.[8] There have been rare case reports of hypokalemia causing widespread ST-segment depression and ST elevation in vector mimicking cardiac ischemia.[9] When serum potassium levels decline it affects an elevation in the resting membrane potential and prolongs action potential in cell membrane, specifically in phase 3 during action potential (repolarization and refractory period). It is correlated to a decrease of T wave amplitude, ST segment depression, and T wave inversion subsequently as Potassium levels decline.[10] Yet it is to be noticed that some patients with severe hypokalaemia do not have ECG changes although the risk of ECG changes and arrhythmias increases as serum potassium concentration decreases.[11] That might explain why our patient's resting ECG was found to be normal. ECG by itself is not a reliable tool to spot electrolyte problems, in this case, hypokalaemia. It is said that the presence of at least one of the four hypokalaemia ECG signs had a positive predictive value of merely 65.8%. The ability to predict specific electrolytes for clinicians is even inferior with positive predictive value of merely 41%. Thus, it is understandable if hypokalaemia does not always appear in ECG.[12]

In one study there are 15% TMT result with positive ischemic response belong to the hypokalaemic group. The same study explains the effects of exercise and catecholamines on extracellular concentration which has the greatest stimulus on the electrical stability of

the heart.[13] For that reason, this explanation illuminates why exercise triggers an ischemic response, as in our case it appeared in ECG during TMT and why it was concealed in resting state.

There are aforementioned factors that can cause false-positive TMT results apart from hypokalaemia as in this case as the main culprit. We thoroughly exclude other factors like thrombus. Coronary angiography (CAG) to the patient was performed in a matter of hours after we received the TMT result. The result exhibited neither thrombus nor spasm. In regards to artery spasm, we also gave nitrates as therapy. Other metabolic causes other than hypokalaemia were excluded due to normal laboratory findings. Structural heart diseases causes were also ruled out as echocardiography findings happened to be normal.

Hypokalaemia is one of the commonly encountered electrolyte disturbances and has the potential to increase the risk of arrhythmia. Hypokalaemia is defined as a potassium level <3.5 mmol/L. It can be classified as moderate hypokalaemia when potassium level <3.0 mmol/L and severe hypokalaemia when potassium level reaches <2.5 mmol/L. Hypokalemia can be resulted from renal loss, gastrointestinal loss, extracellular to internal cellular shifts, inadequacy of potassium intake, diarrhea, vomiting, and diuretic therapy. The level of serum potassium is vital for regulating depolarization and repolarization of the myocardium. Hypokalaemia can alter the cardiac action potential and result in abnormities of cardiac conduction.[8] In our case hypokalaemia derived from vomiting and dehydration prior to the test. It is easily treated with intravenous potassium supplementation with favorable outcome.[8]

Hypokalaemia-induced ST-segment depression may mimic myocardial ischemia. Determining the correct diagnostic might be difficult especially in cases when ST changes are accompanied by chest discomfort.[14] Therefore, it is very important to know the patient's history of possible hypokalemia prior to the TMT examination. Hypokalaemia is a medical emergency and if it is not resolved quickly decrease in cardiac output and peripheral perfusion may manifest in dysrhythmias and hypotension and it can lead to cardiac and respiratory arrest. Given the fact that untreated hypokalemia is associated with high morbidity and mortality, it is critical to recognize and treat that disorder promptly.[14] Clinicians must be careful and decisive to make a diagnosis so that appropriate therapy can be given.

Conclusion

TMT is advantageous in many aspects as a key examination for CAD, emphatically in patients with high-risk profile. Only in a handful of situations, its result could be mistakenly interpreted as false positive. One of the reasons is hypokalemia which tends to be much overlooked and undersense. Clinicians need to be much aware of hypokalemia while performing TMT because it might mimic myocardial infarct.

References

1. Attar, A., Mehrzadeh, A., Foulad, M., Aldavood, D., Fallahzadeh, M. A., Assadian Rad, M., & Khosropanah, S. (2017). Accuracy of exercise tolerance test in the diagnosis of coronary artery disease in patients with left dominant coronary circulation. Indian Heart Journal, 69(5): 624-627.
2. Vilcant V, Zeltser R. Treadmill Stress Testing. 2021 Jul 26. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing;* 2021 Jan–. PMID: 29763078.
3. Knuuti, J., Wijns, W. and Saraste, A., 2019. Corrigendum to: 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal*, 41(44), pp.4242-4242.
4. Neumann, F., Sousa-Uva, M., Ahlsson, A., 2018. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal*, 40(2), pp.87-165.
5. Weaver, W. and Burchell, H., 1960. Serum Potassium and the Electrocardiogram in Hypokalemia. *Circulation*, 21(4), pp.505-521.
6. Wrenn, K., Slovis, B. and Slovis, C., 1990. The ability of physicians to predict electrolyte deficiency from the ECG. *Annals of Emergency Medicine*, 19(5), pp.580-583.
7. Bittencourt, M. S., Hulten, E., Polonsky, T. S., Hoffman, U., Nasir, K., Abbara, S., di Carli, M., & Blankstein, R. (2016). European Society of Cardiology–Recommended Coronary Artery Disease Consortium Pretest Probability Scores More Accurately Predict Obstructive Coronary Disease and Cardiovascular Events Than the Diamond and Forrester Score. *Circulation*, 134(3): 201-211.
8. Kharabsheh, S. M., Al-Sugair, A., Al-Buraiki, J.,

& Farhan, J. (2006). Overview of Exercise Stress Testing. *Annals of Saudi Medicine*, 26(1):1-6.
9. Fitzgerald, B. T., Scalia, W. M., & Scalia, G. M. (2019). Female False Positive Exercise Stress ECG Testing – Fact Versus Fiction. *Heart, Lung and Circulation*, 28(5):735-741.
10. Wang X, Han D, Li G. Electrocardiographic manifestations in severe hypokalemia. *Journal of International Medical Research*. 2018;48(1):030006051881105.
11. Chua, C. E., Choi, E., & Khoo, E. Y. H. (2018). ECG changes of severe hypokalemia. QJM: *An International Journal of Medicine*, 111(8):581-582
12. Diercks, D. B., Shumaik, G. M., Harrigan, R. A., Brady, W. J., & Chan, T. C. (2004). Electrocardiographic manifestations: electrolyte abnormalities. *The Journal of Emergency Medicine*, 27(2):153-160
13. Modesto, K., Møller, J. and Freeman, W., 2006. Safety of Exercise Stress Testing in Patients With Abnormal Concentrations of Serum Potassium††Portions of this manuscript were published in abstract form in Circulation 2002;106(suppl):II-437 (used with permission). *The American Journal of Cardiology*, 97(8), pp.1247-1249.
14. Petrov, D., Sardovski, S., & Milanova, M. (2012). Severe Hypokalemia Masquerading Myocardial Ischemia. *Cardiology Research*, 3(5):236-238.