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Research Article

An Investigation of Myocardial Ischaemia risk factors of Maltese Patients Presenting for Myocardial Perfusion Scintigraphy

Karen Borg Grima[1*], Paul Bezzina[1], Louise Rainford[2]

[1]University of Malta, Faculty of Health Sciences, Department of Radiography, Msida, Malta

[2]Radiography and Diagnostic Imaging, School of Medicine, University College Dublin, Ireland

[*]**Corresponding author:** Karen Borg Grima, Faculty of Health Sciences, Department of Radiography, Msida, Malta. Tel: +35623401812; Email: karen.borg-grima@um.edu.mt

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Abstract

Objectives: This study identified the risk factors recorded in patient records for a sample of Maltese patients undergoing myocardial perfusion stress testing with the aim of reviewing the association between these factors and the results of the Electrocardiogram (ECG) and the Myocardial Perfusion Scintigraphy (MPS) findings.

Methods: Ethical approval was obtained from local research committees to review 252 patient medical histories.Non-traditional risk factors were investigated together with criteria unique to the Maltese population for the presence of myocardial ischaemia. The electrocardiogram and myocardial perfusion scintigraphy results were collated for each patient and compared to the Summed Stress score and risk factors present.

Results: The results obtained were analysed through regression analysis and chi-square tests with the use of IBM SPSS (version 24). The majority ofreviewed cases (46.8%) involved patients that had performed some type of unskilled manual job during the course of their life. Diabetes ($p = 0.012$), smoking ($p = 0.003$) and a past history of myocardial infarction ($p < 0.001$) showed a strong statistical correlation to the presence of myocardial ischaemia within the Maltese cohort. Results revealed that an arthritic inflammatory condition was present in 36% of patients presenting for myocardial scintigraphy.

Conclusion: The triage of patients into low, intermediate and high-risk subgroups cannot be solely based upon the traditional myocardial ischaemiarisk factors established within the literature. Population based risk factors may require reconsideration.

Keywords: Cardiac Risk Stratification; Ischaemic Heart Disease Risk Factors;Myocardial Ischaemia Risks; Myocardial Perfusion Scintigraphy; Myocardial Stress Testing

Introduction

According to the 'Global Burden of Disease Study' conducted by the World Health Organization (WHO) in 2010 the largest cause of death globally (13•3%) amongst all other causes was due toIschaemic Heart Disease (IHD)[1]. WHO also concluded that by 2020, IHD would occupy the number 1 leading cause of death worldwide? This fact may have already become a reality in certain developed and developing countries, when considering that this pathology together with stroke accounted for an estimated 12•9 million deaths in 2010, compared to the previous figure of one in five deaths 20 years earlier[1].Throughout the Mediterranean region, a mean of 10.4 Disability Adjusted Life Years (DALYs) per 1000 population are lost due to heart disease; in Malta, this figure was estimated to be 9 DALYs for IHD[2].The Maltese annual mortality report of 2013, published in 2015, indicated that IHD together with other heart diseases (including heart failure) and cerebrovascular diseases were the leading causes of death in Malta. Although an overall decreasing trend in mortality due to IHD was seen in Maltese males and females, as in the rest of the European countries, yet EU mortality rates for this pathology are consistently lower in both genders when compared to the Maltese figures (21.8% of deaths due to IHD in 2013) [3].

In a situation where IHD is estimated to cost EU economy 49 billion euro a year, 2.6 % of the total healthcare expenditure,

it is vital to identify 'Gatekeepers' or strategies to try and detect the patients presentingwith this pathology and to stratify them into various risk groups [1,4]. Improved risk stratification of patients together with early intervention can ensure a better clinical outcome for this disease [5].By assessing the potential benefits and harm the physician and the patient can make an informed choice amongst the various treatment options available [6].

Several risks have been mentioned in literature to be indicative of IHD. In April of 2010 the Maltese Ministry for Health published 'A Strategy for the Prevention and Control of Non-communicable Disease in Malta' [2]. As part of the WHO CINDI (Countrywide Integrated NonCommunicableDiseaseIntervention) programme, this document emphasizes the fact that Malta needs to tackle contemporarily a set of risk factors common to all No Communicable Diseases (NCD) such as cardiovascular disease, cancer and diabetes [2].There is strong evidencethat NCD are linked to several lifestyle-related key risk factors such as, an unhealthy diet, obesity, physical inactivity, hypertension, diabetes, raised serum lipids, tobacco use and alcohol abuse [2].

CINDI debates that smoking, physical inactivity and poor dietary habits are the top three risk factors that should be targeted in order to reduce IHD[2]. In countries that have followed this approach, a major reduction in IHD mortality was observed. Finland obtained an 80% reduction in IHD mortality (from 1972 till 1992) whilst Ireland obtained a 48.1 % reduction between the years 1985 and 2000, after following the CINDI proposals [2]. It is clear from the literature reviewed that many risk factors may be indicative of IHD, and that race and genetic make-up together with daily diet intake and cultural habits all combine to increase the complexity of diagnosing this condition at an early stage [7-9].

The correlation between traditional risk factors, clinical presentation and prognosis of IHD may vary across ethnic groups [10]. To date no research was found investigating the association and impact of coronary risk factors, including also non-traditional ones such as the type of occupation, on the presence of IHD in Maltese patients undergoing a myocardial perfusion stress test. The aim of this study was to investigate the association between several IHD risk factors, based on a literature search, and the results of the Electrocardiogram (ECG) and the Myocardial Perfusion Scintigraphy (MPS) findings taken from a Maltese patient cohort. The Sum Stress Score (SSS) generated for each patient post MPS examination was used as the main predictor of the presence of IHD and was in turn statistically evaluated diagnostic patient ECGfindings.

Methods

Based on the 2010 report of the American College of Cardiology Foundation/American Heart Association guidelines [11], for the assessment of cardiovascular risk in asymptomatic adults, and on the literature review performed, the researchers opted to include 15risk criteria in the self-designed data tool. The risk factors included wereAge group ; Gender ; District in Malta where the patient lived ; Family history of premature (< 60 years of age) IHDin any one of the parents ; presence of hypercholesterolemia or on cholesterol-lowering therapy ;presence of diabetes; smoking history; history of past myocardial infarctions prior to the Scintigraphy stress test ;past history of revascularisation procedures (PTCA or CABG) ; presence of chronic kidney disease ; presence of severe inflammatory conditions such as rheumatoid arthritis ; chest pain symptoms classified following the 3 categories of Diamond: typical angina, atypical angina and non-angina chest pain [12]; history of known hypertension (patients being on antihypertensive therapy) ;Body Mass Index (BMI) based on weight (kilograms) and height (metres) measurements ; type of occupation-classified using a 6 point scale (professional, intermediate, skilled non-manual, skilled manual, partly skilled and unskilled), based on the Black report [13].The researchers also included stress ECG results, denoting whether pharmacological or exercise stress testing was performed and the MPS results with the SSS for each patient. Based on the 20-segment model used locally within the clinical setting and on the Cedars-Sinai scoring system, a SSS of more than 13was taken to indicate a high-risk stress Sestamibi scan, an intermediate risk scan would have an SSS of 4 - 13, while a low risk scan would have an SSS less than 4 [14,15]. Inclusion and exclusion criteria were also set in order to limit possible sources of errors. In this context, patients who performed their stress test on treatment were excluded from this study to decrease bias across the chosen patient cohort.The researchers obtained a random sample of 252 numbers by using the programme Random.Orgout of a maximum of 2165 myocardial scintigraphy cases performed within 2 years in the local Nuclear Medicine unit of the state general hospital. The patients had all undergone a myocardial perfusion stress test between the years 2014 and 2015, giving ample time for the researchers to have results on follow-up examinations if required. All participants underwent the myocardial perfusion scintigraphy stress test following a referral from their cardiologist or medical specialist, in order to establish the presence of ischaemia or any ischaemic changes. Ethical permission was obtained to carry out this study from the hospital's data protection officer and management, and from the local University's Research Ethics Committee (UREC). Initially the Excel spreadsheet was used to enter the data being collected. At the end of the data collection period, the results were then tabulated into the SPSS package (version 24). Chi square tests and regression analyses were conducted and a p-value <0.05 was taken to be statistically significant for all results obtained.

Results

The distributions of the data were initially tested for normality to determine the use of parametric or non-parametric tests. Univariate, regression analysis models were used to study any associations between the ischaemic risk factors identified in the data tool above, with the SSS as the dependent variable. The SSS was

calculated for each patient following the myocardial scintigraphy stress scan, and was taken to be indicative of the severity of IHD.

63.9% (n=161/252) of the participants were males, with the majority (n=137/252) of the cases ranging from 60 to 75 years (Figure 1).

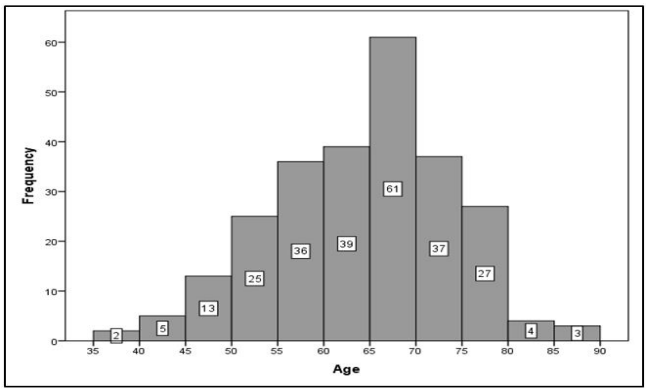

Figure 1: Age distribution of the cases.

Irrespective of the age group of the participants, 67.5% (n = 170/252) of cases showed no evidence of myocardial ischaemia, with only 14.7% (n = 37/252) having mild to moderate evidence of this pathology and the remainder demonstrating severe cardiac pathology. The majority of the participants falling within the 61-70 years age group (n = 68/106) had negative results on the MPS scan, despite the literature identifying this age category as the highest risk category for this pathology [16].The incidence of positive MPS findingswedone statistical significance (p = 0.438) between the Northern harbour district and the Southern harbour district, having 30/82 and 20/57 positive cases respectively. The majority ofthe cases (63.4%, n = 52/82) that showed no evidence of pathology lived in the Northern harbour district at the time of the study. Based on the last Malta standards authority - Food consumption survey of 2010, adults from the Northern harbour district consume considerably more yogurt and cheese during their morning snacks and lunch, while higher proportions of adults from the southern districts tended to be obese when compared to the northern regions [17].

According to a local newspaper article the high rate of obesity in Malta will cost the government approximately 35 million euro by 2020 due to all the associated pathologies such as heart disease and high blood pressure [18]. In contrast to this aspect the results indicated no statistical link between the BMI of the participants and the MPS scan findings (p = 0.256). Results also revealed (Table 1) that 46.8 % (n = 118/252) of the participants were unskilled workers, with the main occupations in this group being either housewife or labourer.

		Frequency	Percentage %
Occupation	Professional	16	6.3
	Intermediate	38	15.1
	Skilled non-manual	49	19.4
	Skilled manual	24	9.5
	Partly skilled	7	2.8
	Unskilled	118	46.8

Table 1: Occupational status of participants.

Analysis of occupational responses found no statistically significant (p = 0.363) findings in relation to participant MPSscan outcomes. The occupational category returning the highest number of referrals arose from unskilled workers (n=118/252) however of these only 32 had positive findings regarding myocardial ischaemia or infarction.

Family history of IHD (p = 0.456); hypercholesterolemia (p = 0.769); chronic kidney disease (p = 0.153); the presence of Rheumatoid arthritis, Osteoarthritis or inflammatory pathologies (p = 0.284); and hypertension (p = 0.609), were all noted as being not statistically significant when compared through chi-square tests to the presence or absence of myocardial ischaemia. Furthermore, the data collected indicated that 67.5% of the participants who had parents with a history of IHD (n = 85/126), showed no evidence of myocardial ischaemia on the scintigraphy stress test.

In contrastthe presence of diabetes (p = 0.012);cigarette smoking (p = 0.003); a history of past myocardial infarction (< 0.001); the presence of a previous PTCA or CABG procedure (< 0.001);and having prior chest pain symptoms (p = 0.031) were the main statistically significant factors that showed a substantial relationship with the presence of myocardial perfusion defects. These findings conform tothose of similar studies[16,19]. Both the SSS and the area (cm2) of the defect outlined on the MPS scan results (Table 2), were found to be accurate predictors of the presence or absence of myocardial ischaemia (p< 0.001). The results of the SSS revealed that 85% of the participants that had a normal (0-3) SSS (n = 130/153) demonstrated no evidence of myocardial ischaemia on the scintigraphy stress test, while 58.3% of the patients with an SSS of more than 13 (n = 14/24), had past episodes of myocardial infarction (Table2).

		Defect cm^2 STRESS		
MPS Results	0-10 Small Perfusion Defect	11-20 Mild to Moderate Perfusion defects	21 Onwards - Severe Perfusion Defect	Total

No Evidence of Myocardial Ischaemia	155	12	3	170
	79.50%	42.90%	10.30%	67.50%
Mild to Moderate Evidence of Myocardial Ischaemia	30	7	0	37
	79.50%	42.90%	10.30%	67.50%
Extensive Evidence of Myocardial Ischaemia	4	1	3	8
	2.10%	3.60%	10.30%	10.30%
Presence of Myocardial Infarction Alone	4	4	17	25
	2.10%	14.30%	58.60%	9.90%

Presence of Both Myocardial Infarction and Ischaemia	2	4	6	12
	1.00%	14.30%	20.70%	4.80%
Total	195	28	29	252
	100.00%	100.00%	100.00%	100.00%
p< 0.001				

Table 2: Defect area (cm^2) as indicated on MPS results.

The stress ECG results in this study, did not correlate (p = 0.283) with the MPS results (Table 3). Table 3 indicates that 73 patients (29%) had a sub maximal ECG stress test or an inconclusive test while 84 patients (33%), although being categorised as reaching the maximal stage using the Bruce protocol, had in fact only achieved stage 1 or 2 during their treadmill stress test.

		MPSResults				
Stress Ecg Results	No Evidence of Myocardial Ischaemia	Mild to Moderate Evidence of Myocardial Ischaemia	Extensive Evidence of Myocardial Ischaemia	Presence of Myocardial Infarction Alone	Presenceof Both Myocardial Infarctionand Ischaemia	Total
Max Bruce Protocol-Stage 1 Or 2	58	15	1	5	5	84
	69.00%	17.90%	1.20%	6.00%	6.00%	100.00%
Max Bruce Protocol Stage 3 Or 4	66	7	4	9	4	90
	73.30%	7.80%	4.40%	10.00%	4.40%	100.00%
SubMax Bruce Protocol - Stage 1 Or 2	24	7	3	8	3	45
	53.30%	15.60%	6.70%	17.80%	6.70%	100.00%
SubmaxBruce Protocol - Stage 3 Or 4	18	7	0	3	0	28
	64.30%	25.00%	0.00%	10.70%	0.00%	100.00%
Pharmacological Stress Test	4	1	0	0	0	5
	80.00%	20.00%	0.00%	0.00%	0.00%	100.00%
Total	170	37	8	25	12	252
	67.50%	14.70%	3.20%	9.90%	4.80%	100.00%
p = 0.283						

Table 3: Summary of Stress ECG results versus MPS results.

Discussion

After the Second World Warthe World Health Organisation (WHO) proceeded to define health as a 'State of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. This definition promoted several countries to adopt measures that encouraged physical fitness and good diet [16], whilst also leading to more research on the association between myocardial ischaemia, gender, diet and the genetic make-up.

Recent studies have shown that although IHD is one of the leading causes of death in women worldwide, reductions in mortality due to this pathology are lower in this gender than in men [20]. The disease tends to be underestimated in women leading to late diagnosis of IHD. Myocardial ischaemia without obstruction of the major coronary arteries, often having atypical and misleading symptoms, may result in a late diagnosis in females. Furthermore, the harmful effects of oestrogen deficiency that occur usually 5 years following menopause, have been strongly linked to the increased risk of IHD in women [20]. In this study the number of male participants was nearly twice that of the females, and 80.2% of the 91 female participants still indicated having no signs of myocardial ischaemia on the MPS studies.

The process of atherosclerosis starts early in life and its outcome is difficult to assess accurately since most atherosclerotic plaques are asymptomatic [9,21]. An individual may only become symptomatic with advancing age and in some cases the first indication of atherosclerosis is sudden cardiac death [9,21]. There-

fore, the incidence of IHD increases with age, with the highest risk group being that over 65 years [16]. This is in agreement with the largest number of participants in this study falling within the 65-70 years age range. Added to this, the age of the surgical population appears to be also increasing, due to more modern equipment and techniques leading to an increase in sophisticated surgery being performed on older higher risk patients. Patients 85 years or older may now be at a higher risk of cardiac morbidities and IHD following major operations [16].

Genetic predisposition for atherosclerosis also plays a role, providing an increased risk for developing IHD at an early age [8]. With Familial Hypercholesterolemia, an inherited mutant gene causes the absence of low density lipoprotein (LDL) receptors, resulting in high circulating blood LDL levels and a decrease in the removal of this type of cholesterol.

In a research carried out in London, amongst young patients, positive family history of premature IHD was found in 39% of participants. Children born of parents with a history of early onset of IHD, tended to have higher lipid abnormalities in the blood, to be insulin resistant, and obese, leading to a possible genetic linkage [10]. Certain ethnic groups, such as Asian Indians, tend to suffer from Myocardial Infarction (MI) at a younger age [10]. In contrast to this, the results of this study indicated no statistical association between a parental history of IHD and the presence of myocardial ischaemia, with only 22.2% (n = 28/126) of the participants showing signs of ischaemia, having parents suffering from IHD.

The BMI of the participants was another factor that was evaluated in this research and found not to be linked to the MPS results. The literature discusses the new term 'Metabolically Healthy' obese individuals, forming about 1/3 of all obese adults [22]. This category of obese individuals, though having a higher BMI than normal, are still considered at low risk of IHD and do not show any signs of hypertension, lipid disorders or insulin resistance. Different phenotypes of obesity may need to be redefined beyond the BMI, highlighting the importance of clinical diagnostic tests within this context [22]. The 'Metabolically Healthy' (MH) obese category tends to include more males, who have in general a lower exercise capacity than the non-obese individuals [22]. This may provide an insight into the number of inconclusive ECG treadmill stress tests in this patient cohort, which did not seem to correlate with the MPS results. The results of the online survey [23] revealed that different trends in practice exist between Nuclear Medicine departments when performing cardiac stress tests. Although more than half of the United Kingdom (UK) and European participants indicated that written procedures for cardiac stress testing do exist in their department, yet a number of participants in all the 3 regions (UK, Other European countries and Australasia) pointed out that they did not know or were unsure if such written procedures existed. In order to create standardisation of procedures across borders and to optimise the service given to patients there may be a need within the clinical setting to devise a system or common procedure that may aid to triage patients prior to their myocardial stress test [23]. Such a triaging protocol or system of work if possible, would permit the ideal stress test, whether exercise or pharmacological, to be performed on the patient category that would mostly benefit from it. The results of the current study appear to further re-enforce the requirement for a population based triage tool that takes into consideration also the life-style factors affecting a particular patient cohort.

Both the Framingham risk study and the TEKHARF study indicated other life-style factors that may affect the early onsetofIHD, such as high levels of alcohol consumption, physical inactivity and smoking habits [24]. All these risk factors together play a part in the speed with which atherosclerosis develops and the likelihood of a subsequent ischaemic event arising later on in life [24].

Yet results of other studies have further indicated that various life-style factors [16] such as employment grade [13,21] can be linked to the risk of developing IHD. According to literature [21] the differences in the psychosocial work environment, together with additional IHD risk factors, mostly smoking, may all contribute to the development of this pathology? The odds ratios for newly reported IHD reduced from 1•5 to 0•95 in men, and from 1•47 to 1•07 in women performing some type of clerical work when the above-mentioned risk factors were accounted for in the study by De Vogli, et al. (2007) [25]. Occupation has been found to be the principal indicator of determining social class, mostly because it provides a convenient measure for statistical analysis and because it does not only delineate the type of work but also has the potential to identify how strenuous and unhealthy it is[13]. Using the same occupational categories based on the British Registrar General's division.

The following occupational categories have been identified in this research [13]:

1. Professional, such as accountant, doctor and lawyer.
2. Intermediate, such as manager, nurse and schoolteacher.
3. Skilled non-manual, such as clerical worker, secretary and shop assistant.
4. Skilled manual, such as bus-driver, butcher and carpenter.
5. Partly skilled, such as agricultural worker, postman and bus conductor.
6. Unskilled such as cleaner, dock worker and labourer.

Hypertension, diabetes and the presence of the metabolic syndrome will further increase the chances of this IHD developing[8]. The current research indicated no statistical relationship between the presence of hypertension ($p = 0.609$) and evidence of myocardial ischaemia on the MPS scans, but this result may have been

due to the participants being on prescribed medicine, required to regulate their blood pressure. In contrast to this diabetes, was found to be a high predictor ($p = 0.012$) of the possibility of developing signs of myocardial ischaemia within the chosen Maltese cohort. The results of the current study also indicated that cigarette smoking ($p = 0.003$) was significantly associated with the presence of myocardial ischaemia in the Maltese patient cohort.Smoking is the most common risk factor contributing towards IHD [26], accounting for about 9% of the smoking young adults and adolescent population within the UK. Smoking appears to be more common amongst females, limiting the protection usually offered by hormones such as oestrogens towards IHD within this category [26].The current research also revealed that 189 participants out of252patients had chest pain symptoms prior to their MPS scans, revealing again a high significance of the presence of this symptom and its importance when screening patients for myocardial ischaemia [26].

Rheumatoid arthritis is another risk factor that appears to have been independently associated with an increased risk of cardiovascular disease [27], increasing at times the risk of IHD twofold similarly to that of diabetes mellitus. Systemic lupus e7ythematosus and other chronic inflammatory diseases have also been linked to the presence of IHD in patients [27]. Patients suffering from Ankylosing Spondylitis (AS) or other spondyloarthropathies have been found to have excess cardiovascular mortality of 20 to 40% when compared to other patients not suffering from such conditions. In contrast to these findings the results of this research indicated that the presence of inflammatory conditions was not related to the presence of myocardial ischaemia ($p = 0.284$). This result may have been affected by the intake of non-steroidal anti-inflammatory drugs in all the 90 participants suffering from inflammatory pathologies[27].Further research is indicated locally to explore the possible relevance of these arthritic conditions towards the onset of IHD, in larger patient cohorts.

Limitations

All the data that was collected was retrospective in nature, so queries that arose as the study was ongoing could not be solved by directly asking the patient or his/her physician. The patient's clinicalnotes were seen to disagree at times over a period of months. In such cases the staffs collecting the data was told to verify the clinical notes with the blood test results or results of other examinations present in the patient's history. A larger data set, with a more varied age range, may have provided the researchers with a more detailed epidemiological picture of the population being examined. A prospective study is recommended as further research; this will facilitate the recording of all relevant data at the time of examination and add to the cohort sample findings.

Conclusion

The results of this research highlighted the major risk factors that may be promoting the presence of ischaemic heart disease within the Maltese population. These risk factors should be kept in mind when assessing Maltese patients for this pathology and also prior to referring them for diagnostic imaging examinations, such as myocardial perfusion Scintigraphy stress scans. The authors further concluded that the identified risk factors could be incorporated into a triage tool that may aid to improve the stratification of Maltese patients into risk categories, whilst helping clinicians to direct each patient to the required clinical test. In Nuclear Medicine such a triage tool could aid the staff to direct each patient to the stress test (exercise or pharmacological) that would provide the required diagnostic results, possibly decreasing the number of inconclusive exercise stress tests in departments where this method of stressing patients is preferred over the pharmacological component.

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Disclosure of Interest

The authors declare that they have no conflicts of interest concerning this article.

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