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Prediction of MINOCA in Men Using ECG and Clinical History

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ABSTRACT: *Recently, cases of myocardial infarction with non-obstructive coronary arteries lesions "which are closer to be normal sometimes" have been noticed to increase during cardiac coronary catheterization. This phenomenon has re-highlighted the psychological and physiological factors causing infarction, and studied thoroughly pathological mechanisms that take place at the vascular endothelial level and in the muscle cellular matrix in general, in an attempt to detect factors responsible for this exacerbating phenomenon. In this study, we divided patients with myocardial infarction into two groups; one including 20 male patients who have myocardial infarction with non-obstructive coronary arteries (target group), and the other including 180 male patients who have myocardial infarction with obstructive coronary arteries (control group). In our research, we tried to study many clinical factors and electrocardiographic markers, and link them with cases of infarction with normal arteries. Then, we compared those with their conventional counterparts who have infarction with obstructive arteries. We also included the psychological distress factor as an independent indicator, and tried to find its connection with this disorder. At the end of the study, we found that there are important statistical characteristics that largely deny normal arteries and outweigh obstructive injury such as diabetes, age group, and electrocardiographic changes on limb lead II, while we did not notice any statistical significance of smoking or hereditary story for prediction in the two groups.*

Keywords *- Coronary Spasm, Endothelial Dysfunction, Microvascular Dysfunction, Myocarditis, Myocardial Infarction with Non-Obstructive Coronary Arteries.*

I. INTRODUCTION

Myocardial infarction in the absence of obstructive coronary artery disease is found in 10% of all patients with acute infarction who are referred for coronary angiography. The interest and awareness of myocardial infarction with non-obstructive coronary arteries "MINOCA" have increased recently due to the frequent use of coronary angiography. There are a variety of causes that can result in this clinical condition. MIONCA are still unknown but endothelial dysfunction has been suggested as a possible cause. As such, it is important that patients are appropriately diagnosed and an evaluation to uncover the correct cause is performed so that, when possible, specific therapies to treat the underlying cause can be prescribed. This research tries to provide a clinically useful keys and electrocardiographic parameters for the diagnostic evaluation of patients with myocardial infarction in the absence of obstructive coronary artery disease.

II. HEADINGS

1. Introduction

Pathological mechanism of acute myocardial infarction AMI involves many non-atherosclerotic causes, including but not limited to: spontaneous arterial thrombosis, coronary vasospasm, endothelial dissection, vasculitis, microvascular emboli, etc.

1.3 Coronary Embolism:

Coronary embolization sources that cause cardiac damage are various, and the most common of which is infective endocarditis. Less common causes include prosthetic valve embolus, neoplasms, air embolus during cardiac surgery and calcium deposits during surgical intervention on degenerative valvular diseases.

2.3 Spontaneous Coronary Artery Dissection:

Spontaneous coronary artery dissection has long been considered one of the rare causes of myocardial infarction. This concept has changed completely following the tremendous advances in coronary endothelial radiography and imaging particularly after using IVUS and OCT. Spontaneous coronary artery dissection is currently thought to be responsible for 10% to 30% of cases of acute myocardial infarction in women under 50 years of age. Dissection flap is often visible during coronary imaging with cardiac coronary catheterization, and a clot may be observed next to, or embedded within, the flap. But, sometimes, radiographic diagnosis may be confused, and dissection is not as obvious as usual, but rather appears in the form of a spasm in the coronary vessel wall, or even as an ulcerous coronary atherosclerosis, in which case special and specific imaging techniques of coronal endothelium should be used to detect dissection. Therapeutic steps for spontaneous coronary dissection fall under the same general treatment plan for management of obstructive coronary lesions, where transcutaneous intervention or surgical correction of narrowing lesions is recommended, knowing that transcutaneous intervention carries greater risks and challenges than regular narrowing lesions, whereas conservative treatment is sufficient in cases where coronary flow remain in good condition [1].

3.3 Coronary Arteritis:

Although rare, they remain among the reasons given for diagnosis of non-atherosclerotic myocardial infarction. Types of vasculitis vary according to the pathological anatomy of the vascular wall, and the pathogenesis, including:

1.3.1 Syphilitic aortic inflammation which usually infects the ostium of coronary arteries.

2.3.1 Takayasu arteritis, which also extends to the structure of medium and large arteries and has several distinct anatomical forms.

3.3.1 Poly-arteritis Nodosa, which is characterized by presence of multi-nodular lesions along the artery.

4.3.1 Kawasaki arteritis, which affects infants in particular and is characterized by specific mucosal changes within the tissue structure of coronary artery walls.

5.3.1 Necrotizing Arteritis and Giant Cell Arteritis, which can affect whole body of the vessle.

4.1 Radiation:

Exposure of the mediastinum to therapeutic doses of radiation may cause irreversible damage in the coronary endothelium, which predisposes to ischemia in the cardiac muscle without explicit atherosclerotic presence [2].

5.1 Infiltrative Diseases:

Infiltrative metabolic diseases (such as Amyloidosis) may have some cardiac manifestations resulting from accompanying arterial injuries. Of these manifestations is a myocardial infarction with normal coronary lumens, but their walls have defects where their layers are invaded by pathogenic infiltrators.

6.1 Hypercoagulopathy:

Hypercoagulopathy cases are considered to be among the causes of myocardial infarction resulting from non-atherosclerotic origin. Arterial lumen is temporarily occluded by a thrombus, which quickly dissolves as a result of anti-coagulation cascade activation. It was noticed that the risk of infarction was higher in people with high serum concentration of fibrinogen and plasminogen inhibitors in comparison with general population [3]. In contrast, there was no association between myocardial

infarction in general and the most common thrombotic abnormalities; i.e. disorders of Leiden, agent V [3], despite the latter being accused to be the reason behind myocardial infarction with non-obstructive coronary arteries MINOCA in a significant proportion of young men [4]. Recently, the significant role for elevated homocysteine as a predisposing risk factor for myocardial infarction has been the center of many talks, especially when other traditional risk factors are absent, where elevated homocysteine is thought to increase serum concentrations of both coagulation factors VII and thrombin [5]. The importance of diagnosing this disorder stems from the possibility of correcting and reversing its effect by giving vitamins [6].

2. Design

Our study adopts the Prospective approach in conducting research, where we insert samples within the research subject under study, then we apply the research rules to them. This study is based on Longitudinal Randomized ground, that is, we list the samples consecutively and without certain selectivity. Then we track the cases and analyze data through direct Cross-Sectional Analysis once groups are sorted out.

3. Method

The study begins once the case gets admission into the intensive coronary care unit at one of the two centers approved in the study, provided that acute myocardial infarction of both types (NSTEMI, STEMI) is the diagnostic reason for admission. Research is conducted on three successive stages, provided that interval between these stages is the fastest possible, taking into account the conditions and capacity available in both two research centers.

First stage starts at the time of admission, where the first part of research form is filled by the resident physician in charge of immediate management of cases in the intensive care unit. This part includes general data about the patient as well as a background on presence, or lack, of emotional stress before the chest pain episode. Second research phase includes a more in-depth approach to the case, especially after the critical period has passed. This stage involves conducting some blood tests related to the research, in addition to documentation of the electrocardiographic signs at the time of admission. Third research stage is conducted in the catheterization laboratory, where patients are classified into two research groups according to results of the diagnostic catheterization conducted:

1.3 Target Group: Patients with normal or slightly occluded coronary arteries (less than 50% of diameter of the coronary artery) (1).

2.3 Control Group: Includes patients with single or multiple obstructive lesions.

Patients from both groups were selected via randomly computerizing method from the total number of cases recorded as of the date of the research; October/2017, where the total number of 200 patients is achieved including 10% for the MINOCA percentage (which has been achieved in the majority of international researches in this context). Therefore, it includes 20 patients for the first group (target) and 180 patients for the second group (control).

In other words, we were keen on applying principle of intentional proportion in order to obtain statistical ratios and indicators that we can compare with the international researches in this regard, and which are almost based on the same rate applied in this study; 10% of studied samples. Eventually, we will process all existing data according to the appropriate statistical programs and then draw conclusions thereof.

4. Results

The number of male patients with ST elevation myocardial infarction was eight out of the total target group (MINOCA one), i.e. 40%, while the number of those with non-ST elevation myocardial infarction was twelve out of the total of this group, equivalent to 60%. In the control group (Obstructive one), infarction with ST elevation happened in 57 patients, approximately 31%, whereas non-ST

elevation infarction was found in 123 patients, equivalent to approximately 68%. We did not notice a significant statistical difference in rates of both types of infarction (STEMI, NSTEMI) between the two groups, where percentages showed close numbers between these two groups. This indicates absence of likelihood of either of the two types to outweigh the other in prediction of the pathogenesis under disease "MINOCA in men".

The average age in the target group was 45 years old, whereas it increased by around 11 years in the control group to be 56 years. This indicates, most importantly, a significance of the age factor as a predictive indicator of the pathogenesis under study. Smoking had no role in the likelihood of developing the disease between the two groups, as it did not show a significant statistical difference between them, similar to the emotional stress factor and the hereditary family history related to the first degree of kinship exclusively, where we did not find any statistical significance to them for prediction purposes. Diabetes mellitus, with its two types, showed clear odds in favor of the control group when present, as it existed in 107 patients by about 60%, while its proportion in patients from the target group did not exceed the 40% rate. These odds in expectation did not exist in patients with hypertension or with a history of a cerebrovascular case; the proportions were similar between patients in both groups. The incidence of explicit anginal attack for the first time during this hospitalization showed a distinct statistical difference between patients in the two groups; the incidence of angina occurring for the first time exceeded two thirds of the patients in the target group, while for their counterparts in the control group, it did not exceed half. "Table 1" "Fig.1".

Table 1. Clinical Characteristics for all Patients

Total Number	200		
Studied Sample	Target Group N=20 (10%)	Control Group N=180 (90%)	P-Value
STEMI	8 (40%)	57 (31.6%)	0.134
NSTEMI	12 (60%)	123 (68.3%)	0.197
Age Average	45±	56±	0.023
Smoke	6 (30%)	51 (28.3%)	0.239
Emotional Stress	5 (25%)	34 (18.8%)	0.098
Hereditary History	7 (35%)	62 (34.4%)	0.468
Diabetes Mellitus	8 (40%)	107 (59.4%)	0.044
Hypertension	11 (55%)	114 (63.3%)	0.221
Previous CVA	3 (15%)	25 (13.8%)	0.356
First Anginal Attack	13 (65%)	86 (47.7%)	0.038

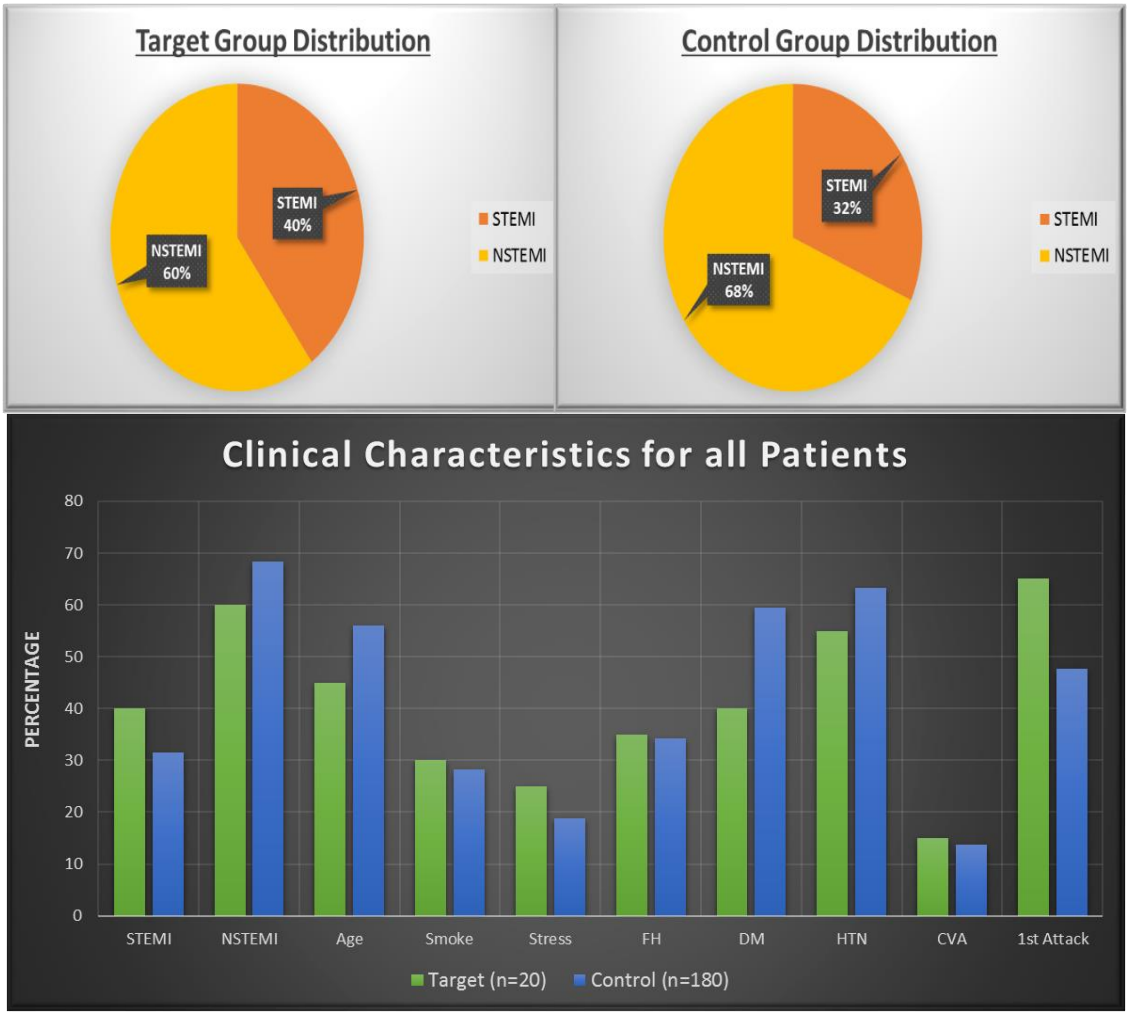

Figure 1. Clinical characteristics for all patients.

Looking at ST-elevation infarction in both groups, we found that: the following electrocardiographic changes had no statistical significance for one group over the other, i.e. these factors do not reflect even the lowest predictive value for the studied pathogenesis (ST-elevation on the anterior leads V1,2; ST elevation on septal leads V3,4; ST elevation on antero-lateral leads V5,6; ST elevation on absolute lateral leads I, AvL; T-wave inversion on one of the anterior leads; T-wave inversion on the inferior lead III; T-wave inversion on the inferior lead AvF; T-wave inversion on absolute lateral leads I, AvL).

In contrast, we observed significant statistical importance of the following factors in the negation of the studied pathogenesis (ST elevation on the inferior lead II; ST elevation on the inferior lead III; ST elevation on the inferior lead AvF; ST elevation on AvR lead; presence of pathologic Q-wave on one of the anterior leads; presence of pathologic Q-wave on the inferior lead II; the presence of the pathologic Q-wave on the inferior lead III; the presence of the pathologic Q-wave on the inferior lead AvF; the inversion of T-wave on the inferior lead II). “Table 2” “Fig.2”.

Table 2. Electrical Characteristics for STEMI Patients

Total Number	65		P-Value
Studied Sample	Target Group N=8 (12.3%)	Control Group N=57 (87.7%)	
Electrical Signs	Findings		
ST Elevation on Anterior Leads V1,2	2 (25%)	18 (31.5%)	0.113
ST Elevation on Septal Leads V3,4	5 (62.5%)	23 (40.3%)	0.087
ST Elevation on Antero-Lateral Leads V5,6	3 (37.5%)	17 (29.8%)	0.190
ST Elevation on Absolute Lateral Leads I, AvL	2 (25%)	12 (21%)	0.188
ST Elevation on Inferior Lead II	2 (25%)	27 (47.3%)	0.032
ST Elevation on Inferior Lead III	3 (37.5%)	34 (59.7%)	0.012
ST Elevation on Inferior Lead AvF	3 (37.5%)	34 (59.7%)	0.022
ST Elevation on AvR	0 (0%)	6 (10.5%)	0.001
Pathologic Q Wave on any Anterior Leads	1 (12.5%)	19 (33.3%)	0.022
Pathologic Q Wave on Inferior Lead II	0 (0%)	21 (36.8%)	0.001
Pathologic Q Wave on Inferior Lead III	0 (0%)	28 (49%)	0.001
Pathologic Q Wave on Inferior Lead AvF	1 (12.5%)	30 (52.6%)	0.003
T Wave Inversion on any Anterior Leads	5 (62.5%)	23 (40.3%)	0.086
T Wave Inversion on Inferior Lead II	2 (25%)	25 (43.8%)	0.023
T Wave Inversion on Inferior Lead III	3 (37.5%)	31 (54.3%)	0.065
T Wave Inversion on Inferior Lead AvF	3 (37.5%)	31 (54.3%)	0.065
T Wave Inversion on Absolute Lateral Lead I, AvL	3 (37.5%)	12 (21%)	0.097

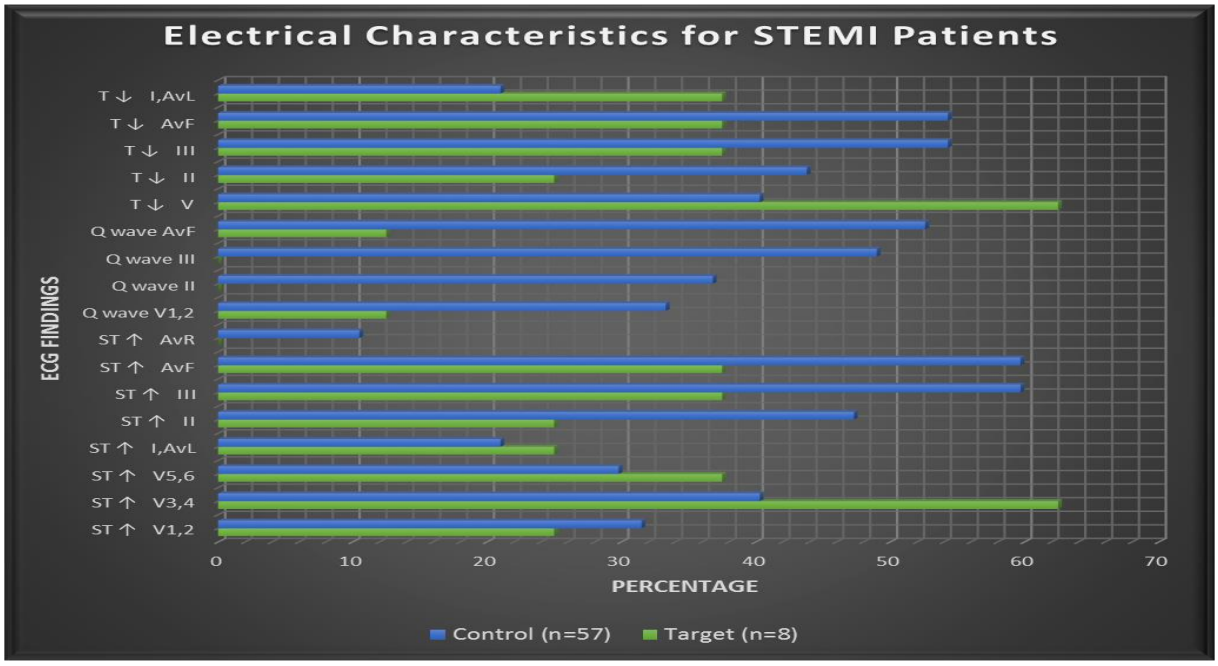

Figure 2. Electrical characteristics for STEMI patients

As for the mathematical data of non-ST elevation infarction male patients, the results were as follows: Many electrocardiographic signs cannot be adopted as predictive indicators due to their insignificant statistical values, namely: ST depression on anterior leads V1,2; ST depression on antero-septal Leads V3,4; ST depression on anterolateral leads V5,6; ST depression on inferior lead III; ST

depression on inferior lead AvF; ST depression on absolute lateral leads I, AvL; T wave inversion on any of the anterior leads; T-wave inversion on inferior lead III; T-wave inversion on inferior lead AvF; T-wave inversion on absolute lateral leads I, AvL.

While the following factors were statistically significant and denied the pathogenic injury under study, and they are: the ST depression on the inferior lead II; ST elevation on lead AvR; T-wave inversion on inferior lead II. "Table 3" "Fig.3".

Table 3. Electrical Characteristics for NSTEMI Patients

Total Number	135		P-Value
Studied Sample	Target Group N=12 (8.8%)	Control Group N=123 (91.2%)	
Electrical Signs	Findings		
ST Depression on Anterior Leads V1,2	5 (41.6%)	72 (58.5%)	0.115
ST Depression on Anteroseptal Leads V3,4	7 (58.36%)	83 (67.4%)	0.534
ST Depression on Anterolateral Leads V5,6	7 (58.3%)	79 (64.2%)	0.512
ST Depression on Inferior Lead II	1 (8.3%)	36 (29.2%)	0.040
ST Depression on Inferior Lead III	5 (41.6%)	40 (32.5%)	0.345
ST Depression on Inferior Lead AvF	5 (41.6%)	40 (32.5%)	0.345
ST Depression on Absolute Lateral Leads I, AvL	6 (50%)	76 (61.7%)	0.256
ST Elevation on AvR	0 (0%)	21 (17%)	0.001
T Wave Inversion on any Anterior Leads	9 (75%)	95 (77.2%)	0.453
T Wave Inversion on Inferior Lead II	1 (8.3%)	36 (29.2%)	0.040
T Wave Inversion on Inferior Lead III	5 (41.6%)	43 (35%)	0.334
T Wave Inversion on Inferior Lead AvF	5 (41.6%)	43 (35%)	0.334
T Wave Inversion on Absolute Lateral Leads I, AvL	6 (50%)	76 (61.7%)	0.256

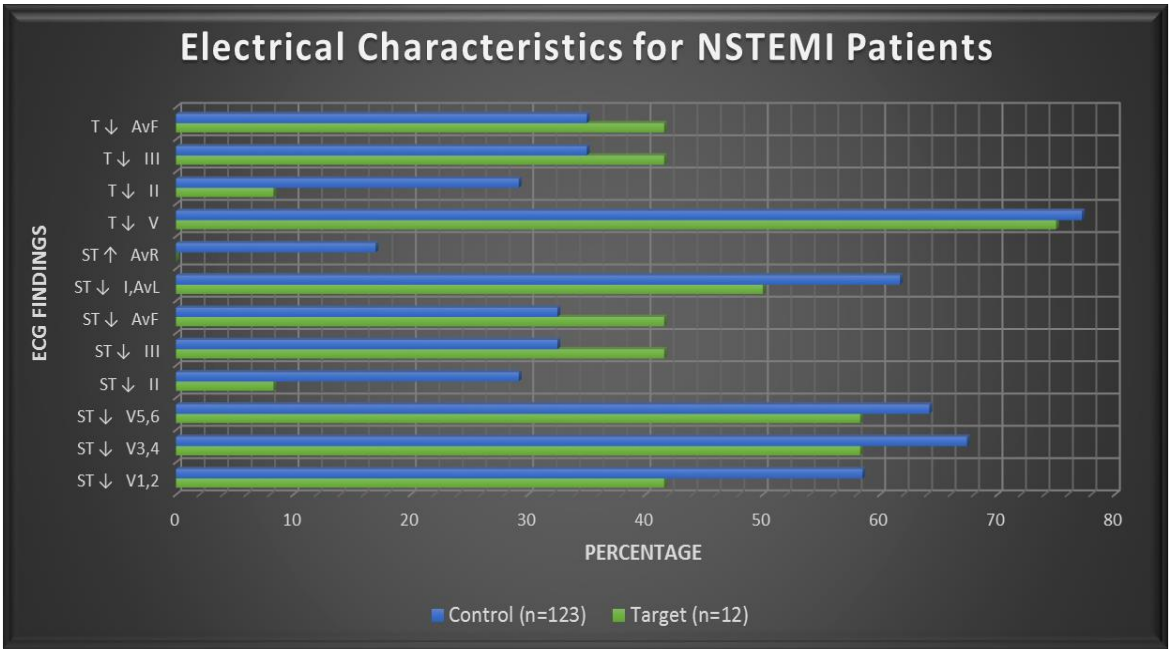

Figure 3. Electrical characteristics for NSTEMI patients.

5. Discussion

Although the size of studied sample is small, it still represents a standard model that meets all academic specifications for research. This sample includes a wide range of associated epidemiology, such as: diabetes mellitus, hypertension and cerebrovascular accidents with prevalence rates in the community that are consistent with the reality of epidemiological studies and pathological surveys conducted in our country, and also involves a wide variety of age groups. The hereditary aspect of the clinical questioning was not overlooked, just like the psychological factor accompanying hospitalization on the spot.

However, with regard to the statistical approach, we used many matrices with various electrocardiographic complications, with which we were able to achieve an ideal template and a coordinated research environment. Convergence in prevalence of the two types of infarction (NSTEMI, STEMI) between the two groups indicates correspondence of studied pathogenesis (non-obstructive) with its control counterpart (obstructive), in other words, we can give the term "preliminary similarity of pathogenesis" in terms of type of infarction between the two groups in women.

ST elevation infarction accounted for about one third of cases in both groups, while non-ST elevation infarction accounted for the remaining two thirds. Male patients aged around 45 years tend to have a myocardial infarction with normal coronary arteries, while those with conventional obstructive injuries, are about 56 years of age. Smoking, as an independent factor, was unlikely to make either of the two group prevail, as the pathological history which is related to endothelial and cytoplasmic dysfunction caused by nicotine may have a common ground between both types of infarction [7].

Presence of diabetes mellitus as a predictive factor explicitly demonstrated tendency towards the obstructive type, where patients with diabetes in the control group were about two thirds, while they did not reach half in their counterparts' target group. Diabetes role should not be ignored in the induction of many inflammatory factors at the cellular level, which ultimately lead to the formation of arterial atherosclerosis and making it fragile and tearable as a result of metabolic disorder caused by diabetes [8].

The only positive factor in prevalence of non-obstructive injury is the first anginal attack taking place at the moment of admission, as anginal attacks were recorded to be recurrent in more than half of the control group patients prior to the attack at the time of admission. On the other hand, frequency of anginal attacks was limited in the target group; as little as in less than one third. Perhaps the only explanation for this phenomenon is the presence of acute spastic factor in the pathogenic mechanism of non-obstructive infarction, thus confers a temporary and sudden event on the process, while arterial atherosclerosis attacks reoccur as an angina repeatedly before turning into an explicit infarction.

Given the findings inferred from electrocardiographic changes of ST elevation infarction in both groups, we find that traditional inferior infarction accompanied by ST elevation, or appearance of the pathogenic Q wave clearly indicates an obstructive injury, i.e. lesions of arteries responsible for perfusion of the lower segment of the heart (CX or RCA) are often explicit and obstructive, while the conventional anterior infarction accompanied by ST elevation on anterior leads shows no significant statistical differences, except for explicit and transient wall necrosis represented by Q wave which favours the obstructive injury. We can attribute this paradox to the wide margin in misdiagnosis of anterior infarction, or rather the common errors in approach to ST elevation on anterior leads as we often overlook pericarditis, prinzmetal angina, or even severe cardiac hypertrophy, most of which pretending to be non-descriptive ST elevations, so we include it _ inadvertently _ under anterior infarction, and then we are surprised that the coronary arteries are normal to a large extent. With regards to ST elevation on the limb lead AvR, its significant obstructive indications are not surprising, especially at the level of Left

Main Coronary Artery or proximal root arteries as apparent in many international studies, so its presence as a predictive factor for obstructive injury is not excluded.

As for the important statistical factors to predict the studied injury (infarction with normal arteries) in patients with non-ST elevation myocardial infarction, we found the following; Ischemic electrocardiographic changes on inferior lead II, which are represented by T-wave inversion, or ST depression, indicate a definite obstructive injury, but if the changes are limited to inferior leads III, Avf; they do not confirm the obstructive injury over the opposite one; therefore, the lead II and its electrocardiographic indicators play an important predictive role in denying non-obstructive injury. Like statistical measures in infarction with ST elevation, changes on inferior lead AvR; i.e. ST elevation in infarction patients as distinct from non-ST elevation infarction patients clearly demonstrated the likelihood of obstructive injury for the above mentioned reasons.

6. Inferences

1.6 Absence of likelihood of one type of infarction over the other (NSTEMI, STEMI) in predicting the type of injury (MINOCA or Obstructive).

2.6 A clear likelihood of predicting the pathogenesis of the studied case at the age around beginning of fifties.

3.6 Smoking is a common pathogenic factor in both mechanisms but cannot predict either type of injury.

4.6 Hereditary story (first degree kinship), or the associated hypertension does not help predict the type of injury.

5.6 Diabetes mellitus can be highly a predictive factor of obstructive infection.

6.6 With accompanying predictive factors, the first thoracic anginal attack makes non-obstructive causes outweigh.

7.6 In general, patients with absolute inferior infarction rarely have non-obstructive reasons for injury.

8.6 Anterior infarction does not absolutely indicate the type of injury (obstructive or not) and can only be predicted if accompanied by pathogenic electrocardiographic signs manifested by presence of Q wave at admission.

9.6 ST elevation on limb lead AvR always indicates an inevitable obstructive injury.

10.6 Changes on inferior lead II are more likely to be obstructive in non-ST elevation infarctions.

7. Obstacles

We were not able to include all cases of infarction admitted into the two units of coronary intensive care within the two accredited research centers, because of inability to continue to the third stage of research form (coronary catheterization) for a variety of reasons, the most important of which are: Old Age, Complicated Case (severe illness and presence of other diseases), Cardiogenic shock, and cardiac failure. We were unable to find a standard scale for what is known as Emotional Stress or psychological stress, and therefore the adoption of this factor was often arbitrary.

8. Recommendations

It is necessary to search and scrutinize as much as possible when admitting any male infarction case that does not have explicit ischemic precedents at the level of both clinical story and accompanying pathological factors. Translate ambulatory ECG attentively and pay attention to the precise details of distribution and location of changes on the electrocardiograph. Do not jump to conclusions while approaching any such disease, as no definitive factor was found for denial or confirmation of obstructive or non-obstructive injury. This subject is an issue that needs further supportive research to be able to absolutely recommend its findings.

III. CONCLUSION

From a concise clinical story and rapid patient questioning, we can obtain indicators that deny (mainly) non-obstructive injury, including: diabetes mellitus, recurrent attacks, and age group. In addition, there are important predictive signs obtained after examining the ECG at the time of admission, such as ST elevation on limb lead AvR and presence of ischemic changes on inferior lead II.

IV. ACKNOWLEDGMENT

This research does not include any written consent by studied samples because the study's methodology does not conflict with principles of research ethics. The study is conducted in the Intensive Coronary Care Unit and the Cath LAB in Aleppo University Hospital and Aleppo University Heart Hospital. All samples under study receive the treatment protocol followed in the two centers mentioned above, without any interference or modification to the diagnostic or therapeutic procedures in force.

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