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Decreasing the Rate of False Negative Invasive Coronary Angiography by Determining Combined two Clinical Criteria in Patients with Presumped Chronic Stable Angina

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ABSTRACT:
BACKGROUND :decreasing the False Negative(F
rates of Invasive Coronary Angiography (ICA.)is of paramount importance in decreasing the wasted local resources which are already demanding.
OBJECTIVES: to find clinical criteria associated with low rates of FN.s results of ICA.in patients with Chronic Stable Angina(CSA
PATIENT AND METHOD: 120 patients with presumed Chronic Stable Angina(CSA.), referred to ICA.; divided according to the presence of HT, Diabetes(DM.) ; then to the presence of combined DM\Hypertension.
RESULTS: FN rates in subgroups of HT.;DM. ;and DM\HT. were as follows:35;9;4\60(of the total negative ICA. Results).
CONCLUSIONS: males , smoking ,and HT. were not associated with decreasing the FN. rates of ICA, ;while the presence of DM\HT. was more closely associated than the presence of DM. alone , in decreasing such a rate .
KEY WORDS: Chronic Stable Angina(CSA.), Refractory Chest Pain, Typical \ Atypical Angina, Framingham Risk Score(FRS.) , Exercise Tolerance Test (ETT.) Invasive Coronary Angiography (ICA.) ,False Negative Result(FN.),

TYPE OF STUDY: case controlled ; retrospective; analytic study; controlled to age, sex, smoking habit, and HT.

INTRODUCTION: Anginal symptoms are defined as stable if there are no substantial deterioration in symptoms(exertional chest pain) over several weeks.[(1).] For most patients, the clinical definition of Chronic Stable Angina (CSA.) (Ischemic Heart Disease, IHD.) closely correlates with the stability or quiescence of an atherosclerotic plaque(Coronary Artery Disease, CAD.)[(1)] The existence of risk factors of CAD. as Hypertension (HT.)\ Diabetes Mellitus(DM.)\ Smoking \Positive Family history\ hyperlipidemia\ advanced age, increase the likelihood that the chest pain is being caused by Myocardial Ischemia.[(1)] FRS(Framingham Risk Score)labeled as:"low risk `10% intermediate risk 10-20% high risk`20%".Risk assessment for estimating 10 year risk of having heart attack :is designed for adults aged 20 years and older, who do not have heart disease or DM.It include the following: age , total cholesterol(`240 mg\dl) HDL (`40 mg\dl), Smoking, Systolic blood pressure(`160mmgh) , [(2)]"Criteria of typical Angina Pectoris(AP.): substernal; heavy or squeezing feeling; precipitated by exertion or emotion; and promptly relieved by rest or Angesid".[(3).]"Criteria of Atypical AP.: located in left chest or arm in the absence of median chest pain; sharp ;repeated or very prolonged; unrelated to exertion; not relieved by rest or Angesid; relieved by Antacids; and characterized by palpitations with out chest pain".[(3)]

"Probability of CAD by age, gender, and symptoms (from ACC\AHA guidelines)"[(4 ,14)]

AGE (YEARS)	GENDER	TYPICAL AP.	ATYPICAL AP.	NON ANGINAL CHEST PAIN	ASYMPTOMATIC
30-39	MEN	INTERMEDIATE	INTERMEDIATE	LOW	VERY LOW
30-39	WOMEN	INTERMEDIATE	VERY LOW	VERY LOW	VERY LOW
40-49	MEN	HIGH	INTERMEDIATE	INTERMEDIATE	LOW

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40-49	WOMEN	INTERMEDIATE	LOW	VERY LOW	VERY LOW
50-59	MEN	HIGH	INTERMEDIATE	INTERMEDIATE	LOW
50-59	WOMEN	INTERMEDIATE	INTERMEDIATE	LOW	VERY LOW
60-69	MEN	HIGH	INTERMEDIATE	INTERMEDIATE	LOW
60-69	WOMEN	HIGH	INTERMEDIATE	INTERMEDIATE	LOW

The concept of exercise ECG. (Exercise Tolerance Test, ETT) arise from observation of ST segment depression caused by exercise –induced ischemia.[1] ETT. is used alone , and as a gateway to Nuclear or Echo Stress Tests .[1]"False *+ve result continue to be a* problem in many patients, and supplemental imaging techniques are often necessary to enhance the diagnostic performance of the test".[2]The related Sensitivity, and Specificity(Sn., Sp.) of the ETT. vary with the population being tested(Bays theorem)[1]"ETT. is best used to the evaluation of the patient at Intermediate risk with Atypical history , or patient at low risk with Typical history".[1]"The Positive Predictive Value (PPV.) of the ETT. (which is the measure of the likelihood that an abnormal test finding represent a True Positive),is highly dependant on pre-test probability(prevalence of the disease)in the population being tested".[1]The prognostic value of ST segment shift in females is less than in males."The Negative Predictive value of the Exercise ECG. response appear to be lower in males than in females,; whereas the Positive Predictive value of the ST. segment depression is higher in males than in females".[5,15]

The administration of B- blocker drugs lead to increase the prevalence of False Negative response of ETT.[5]

TP(True +ve)= Patient with CAD. ---To be treated.

TN (True _ve)= Patient with out CAD.---To be reassured.

FP (False +ve) =Patient incorrectly classified as having CAD.---He is needlessly treated.

FN(False _ve) =Patient incorrectly classified as not having CAD---He should be treated.[6]

FN rate is proportional to CAD. prevalence;

FP rate is inversely related to CAD. prevalence.[7]

INCLUSION CRITERIA:1.Patients with CSA. with high risk +ve ETT.

2.Suspected CSA.presenting with refractory chest pain.

EXLUSION CRITERIA:1.Patient above age 75 year , and below 40 years.

2.Patients with history of MI. \Post MI. angina.

3. Unstable Angina(UA.).

4.Strong +ve Family history of IHD.

PATIENT CRITERIA AND METHOD:120 patients had been consecutively studied for ICA. ,referred as suspected CSA. , presenting with refractory chest pain , or with formal ETT(high risk +ve , or Inconclusive ETT.) with normal ECG. and normal Echo study at rest. All had been requested for Invasive Coronary Angiography (ICA.),which was performed at AL –Sader Medical City \Al-Najaf \. AL-Sader teaching hospital. from 1\3\2015-1\9\2015; They were divided in 2 groups ; First group was composed of 60 patient in whom the ICA was positive; The second group was composed of another 60 patients in whom ICA. was negative; Each group was subdivided according to the presence of diabetes

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mellitus (DM.) in the first stage; then to the presence of combined DM. and hypertension (HT.) in each patient.

Total number of males in this study was 65;

Total number of females inthis study was 55 ; and as follows;

	Males	Females
+ve ICA	33	27
-ve ICA_	32	28

Mean age in females was 57 years(45-70 years);Mean age in males was 54 years (40- 72 years).

Regarding current smoking habit;both groups were reclassified as follows:

	Currently Smokers	Non _Smokers
+ve ICA	34	26
-ve ICA	32	28

Total number of smokers were 66; and those quitting or non_ smokers were 54.So they were matched to smoking.

Regarding HT.; both groups were matched as follows:

	HT	Non_-HT
+ve ICA	31	29
-ve ICA	35	25

Total number of patients with HT. were 67; and non_ HT. were 53.

All 120 patients have taking their related medications ,including Lipid lowering agents, with limited number of patient still had elevated Total serum cholesterol, or low levels of HDL.(Non confounding factor).All 120 patients in this study were referred requesting for ICA. for diagnosis of suspected Ischemic chest pain presumably presenting as Chronic stable angina (CSA.) ,documented with +ve Exercise tolerance test (ETT);or presented with refractory ischemic chest pain in patients with intermediate or high probability of Coronary artery disease (CAD.);ECG at rest were not helpful except to exclude Unstable angina(UA)(dynamic ST depression), and old Myocardial infarction(MI.)(pathological Q); otherwise ,ECGs were essentially normal at rest ; except some patients with Left Ventricular Hypertrophy(LVH.) ,without strain pattern.Echo finding were not significant at rest ,but indicated to all patients to assess LV. ejection fraction (LVEF.), and find out any Structural heart disease(SHD.)to be excluded from the study .Most ETT. results were inconclusive in _ve ICA. group ; they mainly were not reaching the target heart rate(HR.),due to limiting chest pain\ dyspnoea\ fatigue\ pre-syncope which led toearly termination of the test (collectively, labeled as impaired Functional Capacity,(FC.);The distribution of ETT . results was as follows: Regarding the distribution of the Inconclusive ETT results in the whole cohort, it was mainly related to the _ve ICA (but was not discriminating FP. from FN. results), as shown in the following table:

	INCONCLUSIVE ETT.	CONCLUSIVE ETT.	TOTAL
+ve ICA.	9	32	41
-VE ICA.	16	5	21

This means that only 62\120 patient were presented with formal ETT., including 25\62) with Inconclusive results.Those 120 patients had been studied consecutively in AL-Sader Medical city ,and were equally divided into groups.

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Group1 had +ve ICA , Group 2 had _ve ICA ;

"Definition of +ve ICA.: Critical stenosis (`75% of cross sectional area CSA.) of one or more of major epicardial Coronary Artery(CA.),or major branch";

Definition of _ve ICA:No critical , or Subcritical(`75%of CSA.)(Asymptomatic CAD.).Both groups were subdivided according to the presence of certain patient criteria to show their impact on the incidence of false _ve ICA.The first chosen criteria was the presence of DM.;and the results in both groups are shown in the table:

	DM	No DM	
+ve ICA	18	42	Total 60
-ve ICA	9	51	Total 60

The second chosen clinical criterion was the presence of combined DM. and HT. in the same patient of both groups; and the results in both groups are shown in the following table:

	DM.+HT	No DM. No HT	
+ve ICA	12	48	Total 60
_ve ICA	4	56	Total 60

STATISTICS:"Sensitivity(Sn.)=Probability of the screening positive if the disease is truly present" (the higher the Sn. ,the lower the false negatives)."Specificity(Sp.)=.Probability of the screening negative if the disease is truly absent".(the higher the Sp. ,the lower the false positives)PV_VE(Negative Predictive Value) =Probability of the testing truly negative out of all the negatives detected by the screening test.PV+VE(Positive Predictive Value)= Probability of the testing truly positive out of the positives detected by the screening test.

Sensitivity(Sn.) =a\a+c
Specificity(Sp.)= d\b+d

PV_VE=a\a+b

PV+VE= d\d+c

FN(False Negative)=1-Sn.

FP(False Positive)=1- Sp.
Statistical methods used were 2*2 table ,Chi square, and P value.

RESULTS:Sn1(in the DM. group)=0.666 Sn.2(in the DM. and HT. group)=0.75

Sp1=0.7 Sp2=0.54

FN rate1= 0.334 FN rate 2=0.25 FP rate1=0.3 FP rate 2=0.46

PV_VE 1=0.85 PV_VE2=0.933 PV+VE 1=0.3 PV+VE2=0.2

X2 of group Male gender=0.0653, P=0.798(not significant)

X2 of group Smoking = 0.1665 P=0.683(not significant)

X2 of group HT. =o.570 P=0.450(not significant)

X2 of DM. group =3.903 P=0 0482(significant)

X2 of DM.\ HT. group =4.647 P=0.031(more significant)

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X2 of DM.\HT. group after exclusion of two patients with Syndrome X =8.118 P=0.0044(most significant)

X2of Inconclusive ETT results in the cohort=17. 009 P= 3.72E-05(significant)(i.e.:significant correlation between InconclusiveETT. and _ve ICA.)

DISCUSSION: "We need better strategies for risk stratification , in order to increase the diagnostic yield of cardiac catheterization".[8]"A+ve ICA test result was recorded in 68.6% of all patients of one of cohort studied (397.954 patients)".[8]"Surprisingly enough, only a minority of patients (37.6%) had Obstructive CAD".[8]The low diagnostic yield of Coronary Angiography points to the flawed pathophysiology link between CAD and IHD(Ischemic(HD)[9].But Patel MR. "et al paper provides a strong evidence that Coronary risk factors , as assessed by Framingham risk score (FRS),have a clear relation with coronary artery atherosclerosis, but are not predictive of IHD".[10].Regarding all clinical criteria: the presence of DM. or not was the only isolated clinical criterion who had statistical significance in decreasing the incidence of false _ve IC A.(false –ve ICA=9\60);But when both groups are sub- classified according to the presence of combined DM. and HT. in the same patient ,the false _ve ICA results were further decreased (from 9\60 to 4\60).FN rate2 was lower than FN.rate1 (0.25 vs. 0.33), with unavoidable increase in FP rate(0.46 vs. 0.3)and PV _VE 2 was higher than PV_VE1(0.93 vs. 0.85).This difference was attributed to selection of higher risk patients.Furthermore, in two patients of those four , criteria of Syndrome X had been fulfilled (ischemic exertional chest pain + Normal ECG at rest + Normal Echo study at rest + high risk +ve ETT + -ve ICA, in Diabetic middle aged females)) .Thus, we had left only with two patients with false _ve ICA (2\60).

The third patient was presented with Inconclusive ETT. due to limiting dyspnoea and palpitation, retrospectively he had symptoms of Irritable Bowel Syndrome(IBS.), he was a middle aged male with DM. and HT., with Atypical AP., dyspnoea, non-exertional palpitation, who was wrongly labeled as Refractory AP.This points out to the vital role of pre-request clinical labeling of patients into Typical or Atypical AP,., and the necessisity of double clinical checking before ICA.

The fourth patient had Inconclusive ETT. due to limiting fatique\ dyspnoea , retrospectively he had exertional dyspnoea , dyspnoea during talking, exertional palpitation, with non- limiting Atypical mild chest pain.,he was also middle aged male with DM. and HT. with history of current smoking, with no Gastro –Intestinal (GI.) symptoms , with history of Mental disturbance can be labeled as Depressive Anxiety ;This clinical scenario has tempered the referring physician to rank his patient into CSA. by viewing his pre -test probability of CAD.(by gender ,and age) and his clinical criteria with high FRS.This point out further to the necessisity of pre-test double checking of the referred patient , aiming further elimination of possible FN. results of ICA."Patients with higher Framingham risk score ((FRS) were more likely to have obstructive CAD., but the result of non-invasive test(ETT) had a limited additive value for the presence of obstructive CAD".[8].But the limitation of FRS. don't include Diabetic patients (clinically labeled as IHD. Equivalent).The remaining five patients who had FN. results of ICA. in the first group (with chosen DM. as discriminating clinical criterion,), in Group 1,had the following criteria:

All those five patients were presented with Refractory chest pain, ,inconclusive ETT. (due to limiting dyspnoea\ palpitation), All had symptoms of IBS. with Anxiety Depression. ,They were three males and two females in middle age, ,with predominant palpitation and non- exertional dyspnoea(Atypical AP.)The ischemic chest pain was either with +ve ETT. , or presenting with refractory nature (not responding or partially or delayed response to sublingual Angesid tablets.Those point out to the vital impact to the prospective double clinical checking(before ICA),And point out to the inappropriate attitude of the clinician in referring their patients to ICA. on the basis of Inconclusive ETT. , so it is wise to advice their patients to repeat the test after stabilization of their non- cardiac symptoms ,whatever they were,in order to increase their Functional capacity , measured by attained MET., or trying Modified Bruce Protocol escalation of speed, with out change in the angle of inclination."The patient with angina and documented ischemia is classified as a patient with IHD. only when coronary stenosis can be documented"[8].

"Morphologic imaging technique consume large amount of resources ,yet their role , if any , appear to be in reclassifying patients at intermediate risk with traditional risk factor module".[9]

The most clear indication for non invasive CT. Coronary Angiography (CTCAng.)is to reliably exclude

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CAD. in patients in patients with a low to intermediate pretest likelihood of disease,such as patients whose findings in previous stress tests are inconclusive and those who present with atypical angina ,and thus avoid unnecessary ICA.. To do this, a test should have a minimal proportion of false _ve results and thus a relatively high sensitivity.(11)

"Clinicians often use diagnostic test as a package or strategy , thus one can use a single test ,but a diagnostic test or a strategy should begin by identifying the patient, diagnostic intervention strategy ,comparison (with other related tests) ,and outcome of interest".(12)

"Usually when clinicians think about diagnostic test, they focus on accuracy (Sensitivity ,Specificity);That is , how well a test classify patients correctly as having or not having a disease".(12) "False +ve results will result in adverse effect(unnecessary) and intervention, including the probability of follow up ICA. with out benefit; and the false _ve results will result in patients not receiving the benefits of available intervention that help to decrease the subsequent risk of coronary events".(12) "It is relatively certain that a minimum of false +ve and false _ve results will benefit the patients.(12). Furthermore , the complications of ICA. (MI., DEATH), although rare, are undoubtedly important".(12) Major uncertainty about the impact of false _ve test on patient important outcome would have lead to down-grading the quality of evidence from high to low .(12)

As the proportion of CAD. increase (≥20) ,FN rate become a great consideration(13)

This false _ve ICA results can be explained by :

1.False +ve ETT\ Inconclusive ETT.

2.Non ischemic chronic chest pain \Atypical chest pain in young aged people wrongly labeled as suffering from Ischemic Heart Disease(IHD.), even in the presence of combined DM. and HT., even if they were ranked in the intermediate or high probability of having IHD.

Inconclusive ETT. were 7\9 in patients with DM. with FN .results of ICA.

While they were 8\11 in the same group with FP. results of ICA.

"The impact of inconclusive test result is less clear, but they are clearly undesirable"(12).

Those who presented with +ve ETT. In this group were labeled as FN.\ FP. according to the presence of DM. in them(2\9 vs 3\11)

The rest of this group (40\60)were referred to ICA. due to their Refractory Chest Pain.

The incidence of +ve ETT. in _ve ICA. were as follows:

1. 2 +ve ETT. With FN. results due to SyndromeX
2. 3+ve ETT. With FP. results due to LVH.(Left Ventricular Hypertrophy in one of them, the second with pre-testST. Depression, and the third with middle aged Diabetic female).

"The application of the yielding approach requires a shift in the clinicians thinking to recognize that , whatever their accuracy, the diagnostic tests are of value only if they result in improved outcome of a patient".(12)The most appropriate testing strategy of the work up of symptomatic CAD. depend upon the pretest probability of the disease which can be estimated on the basis of clinical presentation(13).

CONCLUSIONS:1.DM. alone was the only patient criterion that have significant impact on decreasing the FN results ,if was compared with HT., Smoking habit, male gender, and age.

2.Combined DM. with HT. in the same patient was the most effective clinical criterion in decreasing the FN .results of ICA., if was compared with DM. alone.

3. No substitute for reviewing pre- test CAD. probability rank , and the presenting chest pain(Typical\ Atypical ischemic chest pain.), creating a thorough imaging strategy that have a positive impact ,for further decreasing the FN. results.

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RECOMMENDATIONS:1.Check the patient s who present with suspected CSA. and Inconclusive ETT. , for combined DM. and HT., before referring them to ICA. ;If positive ,thus their FN. results are in the lowest possible range.

2. Don't relay on Inconclusive ETT. in patients with suspected CSA. , for referring them to ICA. , try to repeat it later; otherwise ,it will increase the _ve results of ICA. (FN. and TN.. altogether)

3. Pre- test double checking (cross checking) , by another cardiologist , is vital to decrease FN. results further , especially viewing the presence of combined DM. and HT.

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تقليل نسبة السالب الكادب من نتائج قسطرة الشرايين التاجية لمرضى الدبحة الصدرية المستقرة بالنظر الى بعض الصفات السريرية لديهم

الملخص:
المقدمة:ان لتقليل نسبة السالب الكادب لقسطرة الشرايين التاجية اهمية قصوى في تقليل هدر الموارد المحلية ,وهي تحت ضغط الطلب المتنامي اصلا.

هدف البحث:ايجاد الصفات السريرية التي ترافق تقليل نسبة السالب الكادب للقسطرة.

المرضى والطريقة: 120 مريضا محالا لفحص قسطرة الشرايين ,للاشتباه بوجود دبحة صدرية مستقرة لديهم. قسموا حسب وجود السكر

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لديهم اولا:ثم قسموا حسب وجود السكر والضغط مجتمعين.

النتائج: نسبة السالب الكادب لمجاميع :الضغطو السكرو والسكر مع الضغط لديهم كما يلي: 4:9:35\60(من مجموع السالب للقسطرة).

الاستنتاجات: مجاميع الدكورية, والتدخين, والضغط غير مترافقين مع تقليل نسبة السالب الكادب. ومجموعة السكر\ الضغط كانوا مترافقين اكثر من مجموعة السكر فقط,في تقليل هده النسبة.