Adult Cardiology

Nitroglycerin Test and Troponin T in Predicting Coronary Artery Disease in Patients Presenting with Chest Pain at the Emergency Room

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Background --- Chest pain is one of the cardinal manifestations that bring a patient to the emergency room or to a cardiologist's clinic. However, such pain may originate not only in the heart but also from a variety of non-cardiac causes. Evaluation of a patient with chest pain in the emergency room is time consuming and expensive and can often result in an unclear diagnosis. This study was undertaken to assess the value of a simple bedside test, the NTG test in the evaluation of patients who presents in the emergency room for initial episode of chest pain.

Methods --- This is a prospective cross sectional study that includes all patients who would come in at the ER for the first time presenting with chest pain described as heaviness or squeezing, for more than six hours. Excluded are those who are previously diagnosed to have coronary artery disease or who have prior intake of nitroglycerin or sildenafil. Clinical data from the ER, ECG, result of Troponin T and lipid profile were noted. The initial step would involve identifying patients with headache and patients with non headache after being given nitroglycerin 400mcg, sublingual. If the patient complains of headache, this were labeled negative nitroglycerin test. Blood sample for Troponin T were extracted. Patients with positive or negative nitroglycerin test were then be referred for coronary angiogram to determine the severity of the coronary artery disease.

Results --- The study was able to include thirty-five patients for the analysis. The mean age is 49 and majority were males. There were 18 who were positive for the NTG test while the rest were negative. The prevalence of headache was 51%. There were 25 hypertensive patients, 13 smokers, 6 with family history of coronary artery disease, 30 with abnormal ECG readings, 11 with high total cholesterol, 10 with high LDL levels, and 12 patients with low HDL levels. Troponin T was positive in 2 subjects. Sixteen patients showed insignificant/significant coronary artery disease.

Conclusion --- Nitroglycerin test is a simple bedside procedure but a reliable predictor of coronary artery disease. The validity measures of NTG test, with coronary angiography as the gold standard in determining coronary artery disease, showed a sensitivity of 100% and a specificity of 89.5% with a positive predictive value of 88.9% and a negative predictive value of 100% , p=0.000. ***Phil Heart Center J 2012;16:32-38.***

Chest pain is one of the cardinal manifestations that bring a patient to the emergency room or to a cardiologist's clinic. However, such pain may originate not only in the heart but also from a variety of non-cardiac causes.

The number of individuals with undiagnosed Coronary Artery Disease is increasing; one could blame environmental factors or genetics. They often seek consult once chest pain sets in and it is up to the physician to determine whether it is from a cardiac or non-cardiac origin. Evaluation of a patient with chest pain in the emergency room is time consuming and expensive and can often result in an unclear diagnosis. This study was undertaken to assess the value of a simple bedside test, the NTG test in the evaluation of patients who presents in the emergency room for initial episodes of chest pain.

Medical decision making is challenging in this modern era. It is characterized by imperfect information and complex problems that vary in presentation and response to treatment.[1] It is further complicated by variation in disease, uncertainty of medical information and scarcity of resources especially for medical allocations like invasive diagnostic procedure. Before ordering a diagnostic test, the physician must consider

the probability of the test's correctly identifying people with and without the disease. Sensitivity refers to the proportion of people with disease correctly identified by the diagnostic test. Specificity refers to the proportion of those without the disease correctly identified by the diagnostic test as non disease.[1]

Angina Pectoris was first described as a distinct clinical entity by William Heberden in the latter half of the 18th century. In the second half of the 19th century, amyl nitrite was found out to provide transient relief of angina. In 1846, Sobrero synthesized the drug and observed that the small quantity of this oily substance placed under the tongue elicited severe headache. It was not until the introduction of nitroglycerin in 1879 that effective relief of acute episodes of angina became possible.[2]

The most commonly used organic nitrates, nitroglycerin (NTG), isosorbide dinitrate (ISDN), and isosorbide mononitrate (ISDN), are available in a variety of formulations with different routes of administration.[3-4] The nitrates are rapidly absorbed from the gastrointestinal tract, skin, and mucous membranes. Among these agents, ISDN and NTG undergo extensive first-pass hepatic metabolism when given orally.[2]

The pharmacodynamic actions of nitrates, which is manifested in hemodynamic and antianginal effects, are mediated through vasodilatation of capacitance veins and conductive arteries; dilatation of capacitance veins, which reduces ventricular volume and preload, lowers myocardial oxygen demand and improves subendocardial blood flow; dilatation of systemic conductive arteries in combination with the reduction of left ventricular volume, which both lowers afterload, reduces myocardial oxygen consumption; and dilatation of epicardial coronary arteries, including stenotic segments, can improve blood flow to areas of ischemia.[4]

Literature states that NTG, which has a plasma half-life of approximately one to four minute, undergoes hepatic and intravascular metabolism, yielding biologically active dinitrate metabolites that have a half-life of approximately 40 minutes.

This biotransformation, which involves denitration of the nitrate and subsequent liberation of nitric oxide that leads to stimulation of guanylyl cyclase, leading to the conversion of guanosine triphosphate to cyclic guanosine monophosphate, initiates the chain of events leading to vasodilation. The exact mechanism by which this process happens remains controversial; although it was originally proposed that reduced sulfhydryl groups were an essential substrate for bioconversion, they are probably required only as cofactors.[4]

Nitric oxide, which is also known as endothelium-derived relaxing factor (EDRF), is also involved in endothelial function and vascular growth as well as myocardial contractility. In addition to its vasodilatory effects, it causes reduction of platelet adhesion and aggregation.[4] Nitroglycerin test[5] is a simple diagnostic modality that is noninvasive, easy to perform, readily available and is basically a bedside procedure to predict the possibility of coronary artery disease in patients presenting with acute chest pain for the first time at the emergency room. Nitroglycerin test[6] is a nitroglycerin induced headache test. Headache is caused by the vasodilatory action of this drug in the cerebral vessels. It has been reported that the response to the endothelium dependent stimuli that dilates human arteries have been found to be markedly dysfunctional in patient with both early and advanced atherosclerosis and that they have the tendency to vasoconstrict inappropriately.[5-6]

Endothelial function is most often assessed as a vasodilator response to pharmacological or mechanical stimuli like nitroglycerin. It was reported that endothelial vasodilator dysfunction has been observed in patients with traditional coronary risk factors, even in the absence of evidence for atherosclerotic lesions.[7] This would not only predict coronary disease progression and cardiovascular event rates, "but the assessment of endothelial vasodilator function would emerge as an important diagnostic and prognostic tool in patients with coronary heart disease and with the vasodilatory response of a certain vessel made

dysfunctional by the presence of atherosclerosis."[7]

The headache response, a manifestation of arteriolar and venous dilatation, would be less likely to occur among advanced form of atherosclerosis where plaque and smooth muscle proliferation has already taken place.[7-8] At the emergency room, ECG can be done, however, the sensitivity may be as low as 50%, and up to 40% of patients with angina, and patients with evolving MI are sent home inappropriately.[9] "An ECG fails to provide conclusive diagnostic information, cardiac specific contractile proteins are widely used for decision making and are valid predictors of adverse events in patients with acute coronary syndromes."[9] In the FRISC-II substudy, they state that the troponins are sensitive biomarkers for myocardial necrosis, which might occur as a result of persistent or transient thrombotic vessel occlusion at the site of plaque rupture or erosion. Moreover, "small areas of myocardial necrosis caused by microembolizations from the thrombus, occluding arterioles and capillaries downstream, might be an alternative or contributory cause of minor elevations of troponin in unstable CAD."[10]

"Normally, cardiac troponin T and cardiac troponin I are not detectable in the blood of healthy persons. Release of these troponins can occur when myocytes are damaged by a variety of conditions such as trauma, exposure to toxins, inflammation, and necrosis due to occlusion of a portion of the coronary vasculature."[11] The majority of cardiac troponin T and cardiac troponin I is bound to myofilaments, and the remainder is free in the cytosol. When there is damage to these myocytes, the first to be released is from the cytosolic pool, followed by a more protracted release from stores bound to deteriorating myofilaments.[11]

Microinfarction can produce elevations of cardiac troponin T and cardiac troponin I in the peripheral blood that are not associated with elevations of the MB fraction of creatine kinase (CK-MB). Given the nearly absolute specificity of cardiac troponins for myocardial tissue and their high sensitivity for even microscopic zones of myocardial necrosis, and since, Cardiac-specific troponins are useful not only because they come close to fulfilling many of the criteria for an ideal biologic marker, but also because they convey prognostic information. The American College of Cardiology and European Society of Cardiology subsequently declared them to be the preferred biologic markers for diagnosing myocardial infarction.[10,12-14]

Coronary angiography remains to be the gold standard for identifying the presence or absence of arterial narrowing related to atherosclerotic coronary artery disease; it also provides the most reliable anatomical information. It is performed by directly injecting radiopaque contrast material into the coronary arteries and will record radiographic images on a cinefilm or digital recording. This information can provide the physician more precise characterization of the coronary arteries.[1]

The significance of the study is that nitroglycerin test would serve as an initial diagnostic procedure, which could be predictive of coronary artery disease, in determining/validating patients, if they really have coronary artery disease, who present with acute chest pain for the first time for more than 6 hours in the emergency room. This study is undertaken to determine the reliability of nitroglycerin test as an evaluating tool in predicting the presence of coronary artery disease in patients presenting with chest pain for more than six hours who came in the emergency room of our institution for the first time.

METHODOLOGY

This is a prospective cross-sectional study that includes all patients seen for the first time at the ER PHC, presenting with an acute chest pain described as heaviness, squeezing, for more than six hours, from 01 December 2007 to 30 November 2008. Excluded were those with previous diagnosis of coronary artery disease, previous in-

take of nitroglycerin, those with blood pressure be less than 80mmHg and those taking sildenafil drug.

Clinical data from the ER including age, sex, past medical history, family history, personal and social history, physical exam, result of cardiac enzyme (troponin T) and lipid profile were noted. Interpretation of ECG was recorded.

The initial step would involve identifying the patients with headache and patients with non headache. Patients who would come in the emergency room complaining of chest pain for the first time for more than six hours were given one dose of nitroglycerin 400mcg sublingual. The headache response was observed for the first minute up to an hour. If the patient complains of headache or of a throbbing sensation of the head sufficient enough to cause discomfort, this was labeled as negative nitroglycerin test. Baseline patient's characteristics were noted and compared both in patients who have positive or negative Nitroglycerin test.

Once the patients with positive or negative nitroglycerin test had been identified, blood sample for Troponin T was extracted to determine the prognosis of coronary artery disease for patient with positive Nitroglycerin test and to determine the predictive value of negative Nitroglycerin test. Troponin T was requested as a validating parameter. Patients with positive or negative nitroglycerin test were then referred to the invasive laboratory for coronary angiogram to determine the severity of the coronary artery disease.

Statistical analysis. Data were described as frequency and percentages. Association of different factors with occurrence of headache was determined using chi square test. Validity measures, such as specificity, sensitivity and predictive value were determined to know whether nitroglycerin can be a predictor of coronary artery disease.

Sample size was computed to be 35 based on an Alpha of 95%, relative error of 20% at assumed sensitivity of 90%, based on a previous study.[5]

RESULTS

The study was able to include 35 patients for the analysis. Patients belonged to the NTG test positive or negative successfully underwent coronary angiography which is the gold standard confirmatory test in this study.

Table 1 shows the clinico-demographic characteristics of the included subjects. The NTG test showed 18 positive NTG test and 17 negative NTG test, wherein the prevalence of headache after administration of sublingual Nitroglycerin tablet was 51%.

The mean age of all subjects is 49 with the oldest age of 71 and the youngest was 26. About 66% were males. Demographic and clinical characteristics of the patients showed 25 hypertensive patients; 14 belonged to the positive NTG test and 11 to the negative NTG test. Thirteen patients were smokers; 9 belonged to the positive NTG test and 4 to the negative NTG test. Six patients had a family history of coronary artery disease; 3 belonged to the positive NTG test and 3 to the negative NTG test.

Thirty had abnormal ECG readings, of which, 17 belonged to the positive NTG and 13 to the negative NTG test. Of the 5 normal ECG readings, 1 belonged to the positive NTG and 4 to the negative NTG test.

Cholesterol levels were also noted. Eleven patients showed high total cholesterol levels, of which 4 belonged to the positive NTG test and 7 to the negative NTG test. Seventeen had normal total cholesterol levels, 10 belonged to the positive NTG test and 7 to the ne-gative NTG test. Ten patients had high LDL levels, 4 belonged to the positive NTG test and 6 to the negative NTG test. Sixteen had normal LDL levels, 10 belonged to the positive NTG test and 6 to the negative NTG test. As of the HDL levels, 14 patients showed normal levels, 7 belonged to the positive NTG test and 7 to the nega-tive NTG test. Twelve patients had low HDL levels, 7 belonged to the positive NTG test and 5 to the negative NTG test.

Table 1. Clinico-demographic characteristic of subjects included in the study, according to the result of the NTG test (PHC, 2009)

Characteristic	(+) NTG Test n=18	(-) NTG Test n = 17	p-value
Age			0.815
20-40 y/o	1	3	
41-50 y/o	8	9	
51-60 y/o	6	5	
61-70 y/o	3	0	
Male	11	12	0.815
HPN	14	11	0.470
Smoker	9	4	0.204
DM	6	1	0.088
FHx of CAD	3	3	1.000
Abnormal ECG	17	13	0.234
High Cholesterol	4/14	7/14	0.439
High Serum LDL	4/14	6/12	0.422
Low Serum HDL	7/14	5/12	0.422

Table 2. Comparison of negative or positive CAD based on coronary angiography results with positive and negative troponin T results (PHC, 2009)

	CAD (+)	CAD (-)	Total
Troponin (+)	2	0	2
Troponin (-)	14	19	33
TOTAL	16	19	35
Sn=	12.5% (CI : 2.2, 39.6)	Sp	100% (CI: 79.1,100.0)
PPV	100% (CI: 19.8, 100.0)	NPV	57.6% (CI:39.4, 74.0)
Kappa	0.134+ 0.085	P=value	0.056

Table 3. Comparison of negative or positive CAD based on coronary angiography results with positive and negative NTG Test (PHC, 2009)

	CAD (+)	CAD (-)	Total
NTG (+)	16	2	18
NTG (-)	0	17	17
TOTAL	16	19	35
Sn=	100% (CI :75.9,100.0)	Sp	89.5% (CI: 65.6, 98.2)
PPV	88.9% (CI: 63.9, 98.1)	NPV	100% (CI:77.1, 100.0)
Kappa	0.88+ 0.168	P=value	0.000

All the thirty-five patients came in at the emergency room with chest pain. Troponin T was   positive in 2 patients and negative in 33 patients. (Table 2). The two patients who had positive troponin T had positive NTG test. Among those with negative troponin T, 14 belonged to the positive NTG and 19 to the negative NTG test.

All of the thirty-five patients consented to undergo coronary angiography. Sixteen patients showed insignificant/ significant coronary artery disease basing on the result of the confirmatory test while 19 had normal results. These 16 patients who had coronary artery disease were symptom negative, but had positive NTG test. Among the 19 patients who had normal coronary angiography results, 2 were symptom negative (positive NTG) and 17 were symptom positive (negative NTG).

DISCUSSION

This study is about nitroglycerin test, otherwise called the JACOBA'S SIGN[5] in honor of a person who originally thought about the possibility of the body's vasodilator response that will serve as a predictor for coronary artery disease.

The Investigator chose nitroglycerin tablet, taken sublingually aside from its low cost, it is readily available and easy to administer. Its effect could also be immediately observed at the bedside.

It was previously discussed that NTG which is converted to nitric oxide upon entering the vascular smooth muscle would be used as a test for vasodilatory capacity of the vascular bed, including the cerebral and coronary vessels[6,7]

The response to the endothelium dependent stimuli that dilates human arteries have been found to be markedly dysfunctional in patient with both early and advanced atherosclerosis and that they have the tendency to vasoconstrict inappropriately.[7] The headache response, a manifestation of arteriolar and venous dilatation would be less likely to occur among advanced form of atherosclerosis where plaque and smooth muscle proliferation has already taken place; thus, the basis of this study.

The validity measures of the Nitroglycerin test was done based on different clinical and diagnostic setting. Coronary angiogram, which is the gold standard for predicting coronary artery disease, was also done to verify the NTG result.

The headache response was noted in 17 patients, and 18 patients showed otherwise. About 10 patients were excluded in the study due to previous intake of nitrates.

The association of demographic and clinical characteristics of patients with NTG results was also noted. There was no significant difference between the 2 groups according to the NTG result. Although, some of the patients included in the study were not able to undergo lipid profile due to technical problems.

The association between Troponin T and the NTG test in all the patients included in this study, who all presented with chest pain did not show a significant result. The sensitivity showed 12.5%, with a confidence interval of 2.2 and 39.6; specificity at 100% with a confidence interval of 79.1 and 100.0; positive predictive value of 100% with a confidence interval of 19.8 and 100.0; negative predictive value of 57.6% with a confidence interval of 39.4 and 74.0; Kappa coefficient of 0.134+ 0.085 and a P value of 0.056,chi square analysis showed a non significant result.

The association between the coronary angiogram results with the results of the NTG test showed significant results with a sensitivity of 100%, confidence interval of 75.9 and 100; specificity of 89.5%, confidence interval of 65.6 and 98.2; positive predictive value is 88.9% with a confidence interval of 63.9 and 98.1; negative predictive value is 100%, confidence interval of 77.1 and 100.0; Kappa coefficient is 0.88 ± 0.168 and p of 0.000, wherein chi square analysis showed a significant result.

In this study, patients who tested with NTG sublingual and who presented with positive NTG results, showed positive coronary artery disease regardless of the degree of the stenosis of the coronary artery. Patients who tested with NTG sublingual and who presented with negative NTG results showed normal coronaries or mild luminal irregularities after coronary angiography. In this study, NTG test performed better than Troponin T in patients who came in the emergency room complaining of chest pain. Troponin T did not show significant results because as previously stated Troponin T is a sensitive marker for myocardial necrosis and the patients who came in did not have myocardial necrosis yet or is not suffering from acute myocardial infarction.

The limitation of the NTG Test is that patient who had previously taken NTG were disqualified from the study; these are the subset of patients which would probably have shown positive NTG test, thus, a probable positive Coronary Artery Disease.

We recommend that another follow up study with more patients and it would be prudent to follow up patients included in the study, to see if these patients develop coronary artery disease over time.

CONCLUSION

Nitroglycerin (NTG) test is a simple bedside procedure but a reliable predictor of coronary artery disease. The validity measures of NTG test, with Coronary angiography as the gold standard in determining coronary artery disease, showed a sensitivity of 100% and a specificity of 89.5% with a positive predictive value of 88.9% and a negative predictive value of 100%, p=0.000.

There is a highly significant correlation between a positive Nitroglycerin test and the presence of a coronary artery disease as shown in this study. The NTG test would be a valuable tool in assessing patients with chest pain.

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