Review Article

Incidence and predictors of acute coronary syndrome within a year following a negative stress test—a false sense of security: is routine screening any useful?

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Abstract: One of the major issues in management of the acute coronary syndrome (ACS) is classification of patients with atypical presentation who have low risk of having a coronary episode at presentation. There have been multiple studies on the stratification of high risk patients and medical management of such cases, however, there is a sub-class of patients who do not fit any category. In this paper, we have looked at the current literature on stratification of patients based on the study tools available and the risk of having a coronary episode during the following year. In our overview, we have found that the current methods in place namely, cardiac stress test and stress echocardiogram have a good prognostic factor in terms of mortality in the next one year and can safely stratify the patients at low risk when correlated with clinical presentation and laboratory studies. However, such data are limited for computerized tomography or magnetic resonant imaging and their application might be limited due to accessibility and cost of studies. Current guidelines for classification of high risk patient do an excellent job and we believe that proper application of stress tests together with other imaging modalities together with laboratory, clinical judgment, and proper use of medical management can help with safe discharge of patients from the emergency department (ED) and reduction of burden from healthcare.

Keywords: ST segment elevation myocardial infarction (STEMI); NSTEMI; stress testing; coronary artery disease (CAD)

Submitted Sep 05, 2017. Accepted for publication Nov 09, 2017.
doi: 10.21037/atm.2017.11.12
View this article at: http://dx.doi.org/10.21037/atm.2017.11.12

Introduction

Chest pain is one of the most frequent causes of presentation to the emergency department (ED) which has a substantial financial burden (between $10 to $12 billion per year) on the healthcare system, however, despite this significant cost, an acute coronary event is confirmed only in a minority of these patients. It is the low threshold for admission to prevent a cardiac event and possible litigation that are the major driving forces behind this high rate of admissions (1).

Thus, finding a proper method for risk stratification and screening would serve as a key stepping stone. There have been multiple methods of assessment of chest pain under investigation for facilitation of this process which include:

exercise treadmill test (ETT), exercise echocardiography, myocardial perfusion imaging nuclear scan, magnetic resonance imaging (MRI), and computer tomography angiography (2-5). Presently, patients presenting to the ED with acute chest pain undergo the protocol to rule out acute coronary syndrome (ACS) with electrocardiogram (ECG), cardiac enzymes and further testing. However, few patients are diagnosed with an ACS event. Primary percutaneous coronary intervention (PCI) is the standardized treatment of choice for ST segment elevation myocardial infarction (STEMI), non-STEMI and sometimes unstable angina; which allows for reperfusion of the myocardial tissue, hence, minimizing the damage, while chronic stable angina is managed medically as well for the same purpose of reducing damage to tissue as well as control of symptoms. Since these interventions heavily rely on coronary artery angiography (CAG), its use has exponentially grown over the recent years. Studies have shown that the use of the latter can be up to 36% in false-positive STEMI (6).

Finding the optimal way for screening patients and a proper method of risk stratification can help achieve a better standardized system that can both have a high specificity and sensitivity for ruling in and out acute myocardial ischemia while reducing the burden on the healthcare system. For this reason, we will take a look at each modality used in screening patients and their strength and weakness in predicting myocardial disease outcome in patients.

The role of exercise stress test

Several studies have investigated the use of exercise testing to rule out ACS in patients with low risk stratification, meaning, they had presented with chest pain but were clinically stable and ECG changes were normal or borderline and had nonspecific repolarization changes. During exercise testing, the criteria for a positive test for myocardial ischemia is the standard indicators of 1.0 mm horizontal or down sloping ST-segment shift; if such changes were present on the ECG, further testing or admission were carried out (7).

In the Rapid Rule-Out of Myocardial Ischemia Observation study which was the first prospective study looking at exercise testing using an accelerated diagnostic protocol for myocardial ischemia, 100 patients with chest pain were randomly assigned to a regular care group, and a chest pain center accelerated protocol group; which consisted of a 12-hour observation with ECG and cardiac enzymes. In the accelerated protocol group, exercise testing was performed which showed a 93% normal result and the 7% positive underwent a coronary angiography which showed negative results. Every patient with a negative test was discharged and followed up at 30 days which showed no coronary events. This resulted in a reduced length of hospital stay and reduction in cost per patient (8). In another study, authors studied the effectiveness of exercise stress testing as a modality for evaluation of coronary artery disease (CAD). Of 203 patients who were tested, 11 were found to have abnormal test results; of which 4 were found to have obstructive CAD. The calculated diagnostic yield for obstructive CAD was 2.5%. The authors concluded that the yield of routine use of noninvasive testing for CAD was minimal and an abnormal test has a low positive predictive value (PPV) (9), nevertheless, studies have shown that the negative predictive value of ETT has been high and can rule out myocardial ischemia with a high confidence (10).

This brings up the question that despite ETT being widely available, there are a significant portion of the patient population who may not be able to undergo this test modality, for example, the population that cannot achieve 85% of age-predicted maximal heart rat, poor mobility, or existing ECG abnormalities at rest such a left bundle branch block (4,7). While ETT has proven to have a great negative predictive value, there have been reports of it missing acute myocardial infarctions on rare occasions which can prove to be costly for the patient. In one instance, a 48-year-old man who presented with left sided chest pain underwent an ETT which was negative for myocardial ischemia, however, he presented 30 minutes later to the emergency department with acute substernal chest pain and was found to have acute antero-septal STEMI on ECG and underwent PCI (11). On another occasion, researchers report a 67-year-old man with acute myocardial infarction which took place 10 minutes after a negative ETT (12).

There have been several mechanisms proposed for the possible occurrence of the myocardial ischemia after a negative ETT. It has been speculated that it could be due to an atherosclerotic plaque rupture due to coronary artery spasms or that exercise itself can act as a trigger for platelet activation and thrombosis or atherosclerotic plaque ruptures inducing intraluminal thrombus formation (13-15). Thus, ETT has proven so far to be the most economical and relatively available myocardial test that can be performed in patients for checking the risk of myocardial disease in the hospital setting admission and as a follow up tool. It has a relatively good sensitivity and good PPV to rule in myocardial disease. Nevertheless, it has some negative sides

which can be outweighed by using it in conjunction with some of the following tools described.

The role of stress echocardiography

Stress echocardiography has become a strong tool in the diagnosis and risk stratification of patients who have CAD or are suspected of having the disease. The hallmark of myocardial ischemia during stress echocardiography is the occurrence of reduced systolic wall thickening due to the increased myocardial oxygen demand and supply-demand mismatch. This regional systolic wall thickening is specific for CAD. The use of microbubbles has made echocardiography reliable and the results reproducible (16). Echocardiography has been utilized with ETT in order to detect CAD and it has showed good sensitivity 93% and specificity 71%. It has an important diagnostic value in patient with chest pain. When combined with ETT, echocardiography has the ability to help in reclassification of cases where ECG is not diagnostic as an ACS event (2). Echocardiography has demonstrated utility in diagnosis and risk stratification in the emergency department and its addition to ECG and clinical findings provides valuable prognostic information with a negative predictive value of 98%. In terms of diagnostic and prognostic accuracy, it is similar to stress testing by using more expensive and advanced imaging modalities (17). Echocardiography can provide structural and functional data about the heart which are not possible to attain by ETT alone, in addition, it can be done at the bedside in a few minutes. It is also possible to attain information about flow abnormalities by using doppler and study wall motion abnormalities (18).

Another recent development in the field of echocardiography is 'continuous echocardiography' which allows for continuous wall motion imaging for the evaluation of NSTEMI in acute chest pain syndromes in the settings of indeterminate ECG findings and equivocal cardiac biomarkers. This method of continuous monitoring allows for regional wall motion abnormalities and transient left ventricular wall motion abnormalities. This method of echocardiography for CAD has a sensitivity, specificity and accuracy of 88%, 100% and 91% respectively, while these measurements in ECG for detection of CAD are 31%, 100% and 52% respectively (3). This shows that echocardiography can not only be an invaluable addition to ECG in ETT, but can also detect the abnormalities that are possibly missed by ECG alone.

One of the hallmarks of echocardiography is its ability to add incremental and independent information to the results of the ETT (19-21). In a study by Marwick *et al.* [2001] exercise echocardiography was used to collect data on 5,375 patients and this population of patients were followed up for 6 years. The patients who had a normal echocardiography had a mortality of 1% per year (19). Since CAD process is always undergoing worsening of stenotic lesions in patients, the increase in mortality after 6 years is not surprising and can be attributed to that disease process. In the study by McCully *et al.* [1998] exercise echocardiography was done on a total of 1,325 patients. The median length of follow-up was 23 months. There were 33 cardiac events in 26 patients and three patients died of cardiac causes which were 14, 19 and 20 months after the exercise echocardiogram. Ten patients had nonfatal myocardial infarctions and 20 underwent catheterization. The survival rates free of cardiac death or nonfatal myocardial infarction at 1, 2 and 3 years were 99.5%, 98.8% and 98.6%. The calculated cardiac death and nonfatal myocardial infarction rate per person-year was 0.5% and the cardiac event rate per person was 0.9%. As mentioned earlier, echocardiography can be vital in the risk stratification of the population of individuals who are at intermediate level of risk based on the Duke score and a non-diagnostic ETT.

The role of computer tomography coronary angiography (CTCA)

CTCA is another tool used to assess patients presenting to the hospital with chest pain that cannot undergo ETT. As previously mentioned, some of the reasons for ETT not being diagnostic can be poor mobility of the patients or fatigue. CT studies the primary outcome of the patient by using the coronary artery calcium scoring and CT coronary angiographic features to serve as variables in predictability. These are features such as plaque size and vessel wall involvement. High risk calcium score calculated by Agatston units were related to worse outcome where for every 100 Agatston unit increase in calcium score there was an increased risk of adverse outcome and higher scores of more than were associated with worse outcomes (4).

Presence of more than three segments with non-calcified plaques predicted adverse events, and the presence of coronary artery stenosis was the only significant predictor of adverse outcome directly related to the severity of the stenosis as it would be expected (4). It is also important to mention the ability of CTCA to possess a good prognostic value in identification of non-obstructive CAD and by

combining it with the cases of more than 400 Agatston units it can correctly identify patients at higher risk of MI and the score based on CT can help distinguish among patients with non-obstructive CAD and those at higher risk (22). In addition, one study showed that CTCA has the ability to reclassify approximately 2/3 of the patients regarding their risk of developing symptomatic CAD and reclassify 75% of intermediate risk and 59% of high risk patients as at a low cardiovascular risk (23). At the same time, it has been established that absence of any abnormalities on CTCA is associated with excellent negative predictive values (24). Another important benefit of CTCA in studying coronary anatomy is the decreased likelihood of causation of inadvertent harm to the patient by doing an ETT and provocation of a thrombus or plaque rupture. CTCA is proving to be a good alternative in cases where ETT is not feasible or it can be used in addition to ETT for achieving a more accurate diagnosis.

CTCA has displayed an excellent diagnostic accuracy with sensitivity that ranges from 87–99% and specificity 93–96%. ACCURACY trial found that CTCA is a highly sensitive and moderately specific test to predict significant coronary artery stenosis with sensitivity, specificity, PPV), and negative predictive value (NPV) of 94%, 83%, 48% and 99% for more than 70% stenosis (25). The CORE 64 trial enrolled patients with a <600 calcium score demonstrated the per-patient sensitivity, specificity, PPV, and NPV for detecting more than 50% stenosis of 85%, 90%, 91% and 83%, respectively (26). These findings are in line with the data obtained from the CONFIRM trial regarding CTCA being an effective tool for risk assessment for catheterization laboratory (22).

On CT, checking adverse plaque characteristics, will help in classification which include positive remodeling, low attenuation plaque which is suggestive of large necrotic core, napkin ring sign and spotty calcification. Positive remodeling is defined as a plaque extending eccentrically from the vessel wall and 'napkin ring sign' refers to a plaque core with low attenuation (27). The association of these high risk features with ACS has been established with the high risk plaques having positive remodeling and low attenuation necrotic cores (28). ACS has been reported of being up to 10 times more common in patient with high risk plaques. It is this strong predictive value of the CTCA that has made it the corner stone in cardiac analysis in coronary syndromes and an invaluable tool for risk stratification of this patient population.

The role of MRI

Stress cardiac imaging with MRI is an imaging technique that is used for obtaining cardiac function and detailed imaging of the heart during stress. The test is performed by doing a perfusion imaging following an intravenous infusion of gadolinium contrast or by obtaining wall motion imagining. Pharmacologic agents' dobutamine, dipyridamole or adenosine is used to induce stress. The images are used to assess ventricular dimensions, viability and the cardiac mass. According to the study by Nandalur *et al.* [2007], perfusion imaging showed a pooled sensitivity of 0.91 (95% CI: 0.88–0.94) and a specificity of 0.81 (95% CI: 0.77–0.85) when analyzed on a patient level and stress induced wall motion abnormalities imaging showed a pooled sensitivity of 0.83 (95% CI: 0.79–0.88) and specificity of 0.86 (95% CI: 0.81–0.91) on a patient level (29). When the studies after the Nandalur research findings were combined with the ones published after, researchers obtained a pooled sensitivity and specificity for stress wall motion cardiac MRI of 0.81 (95% CI: 0.77–0.84) and 0.85 (95% CI: 0.81–0.89) (30). MRI allows for assessment of the regional and global function of the ventricles and calculation of the ejection fraction and assesses wall motion. In terms of sensitivity, it is estimated to be between 90% and 100% while it has negative predictive value of 99%, which makes an excellent resource for excluding ACS and discharge of the patient. MRI based assessment has its own limitations as well (18). One limitation is the low sensitivity of magnetic perfusion imaging (MPI) in detecting small infarcts.

On the other hand, MPI has the benefit of being able to detect ischemia and infarct, taking less time to detect an ischemic or infarct compared to cardiac enzymes which take several hours to rise, and identify risk areas in the absence of ECG changes. However, one major drawback of MPI is the requirement for expensive machinery for the study to take place (5). MPI as a tool for assessment of stable patients can provide vital information in terms of the functioning of the heart and be able to classify the cardiac infarct or ischemia in a greater extent, however, its application has a more pronounced use in the patient population who are chronically ill and cannot undergo a ETT test or not stable enough for an ETT. Using contrast enhancement in MRI, researchers have been able to show the viability of the cardiac muscle before revascularization and its correlation with recovery from acute insult versus a nonviable damage to the myocardium. Hyper-enhancement or the lack of hyper-enhancement is the main features present in the

myocardium that correlate with the area of cellular damage. It has been shown that the lack of hyper-enhancement has been clinically proven to correlate with improvement in contractility after revascularization (31). Late gadolinium enhancement (LGE) which is a feature on MRI in patients with previous infarcts has been successfully used to correlate Q wave location and the extent of the infarct (32). Due to the concern for contrast induced nephrogenic systemic fibrosis in patients with kidney dysfunction, the use of native non-contrast mapping with T1 weighted imaging has been studied in which the T1 relaxation times are measured to look for myocardial edema and fibrosis. It was shown recently by Liu *et al.* [2017] that native T1 images are good at picking up both acute myocardial infarct and chronic myocardial infarct areas, however, they cannot differentiate between the two (33). However, this study presents another method for imaging in patients who cannot undergo other modalities to find the site of infarct.

Other tools

Another method for establishing functional ischemic vessels is by measuring the quantitative functional coronary flow reserve (CFR) through noninvasive assessment of the hyperemic reactivity of myocardium to vasodilator agents. Quantitative CFR measurement by positron emission tomography has shown to be able to effectively reclassify the risk of future cardiovascular events (34). Therefore, non-contrast phase contrast (PC) cine magnetic resonance imaging of the coronary sinus has emerged as a noninvasive method for quantifying global left ventricular myocardial blood flow (35). CFR can be calculated as the myocardial blood flow during the vasodilator infusion divided by the myocardial blood flow at rest by the PC cine MRI of the coronary sinus. Kato *et al.* [2017] analyzed the prognostic value of CFR by PC cine MRI for patients with known or suspected CAD and studied the predictive power of cardiac MRI for major adverse cardiac events (MACE). Their research showed that impairment of CFR was a significant independent predictor for MACE in patients with known and suspected CAD. It was also shown that the predictive values of CFR and stress perfusion cardiac MRI for the occurrence of MACE were comparable in patient with known CAD and in the ones with suspected CAD, CFR showed a higher hazard ratio and area under the curve compared to stress perfusion cardiac MRI (36). These all pointed to the usefulness of CFR for risk stratification and its superior ability to detect ischemia. These finding are in line with several other studies that have shown the superior prognostic value of stress perfusion in cardiac MRI with patient with known or suspected CAD (37,38).

Future directions

In recent times, there has been substantial development in the management of the cardiac ischemic condition and their diagnosis and categorization. To perform a risk assessment of patients, there are multiple resources that are widely used. The most widely used method is the ETT. This method is one of the most widely used methods of assessment of the patient for ischemic changes which can rule out ischemia with a good level of confidence. This test is still a primary method of assessment and can reliably categorize patients in their risk assessment for cardiac events with a very low risk of adverse events in the year following the test. Recent studies have shown that low-risk ETT patients have an excellent prognosis at 40 months despite a common prevalence of non-obstructive and obstructive CAD (39).

Exercise echocardiography is another variation on the ETT whereby it can help diagnose the falsely negative tests of the ETT as having a higher risk for cardiac events but examining their wall motion abnormalities during the test. It is a test that can be utilized on a case by case basis for the patient populations that have a higher risk. Research has shown that the ability to achieve a 9-minute-high exercise capacity (≥10 metabolic equivalents, METS) is a predictor of favorable prognosis and conferred an overall MACE of 0.4% per year (40). CTCA has also proven to be beneficial in assessment of cardiac patients. CTCA has also become more widespread in order to help stratify patients with intermediate risk assessment after ETT (39). Its use is limited to patients with severe atherosclerotic disease and patients with high risk plaque formation. More recently CT Perfusion and CTCA have been used in combination in order to assess coronary artery blood flow and the level of perfusion abnormality and the combination has proven to have a sensitivity of 86% and a specificity of 92% (41). MRI tests have proven to have good negative predictive value for diagnosing ACS and are being used more widely. Cardiac MRI has shown its significant predictive value for CFR in cardiac MRI stress perfusion for MACE in patients with known CAD (36). One of the main drawbacks of cardiac MRI is its cost and expertise required for interpretation.

Conclusions

How can we decide between these tests is a question that continues to be debated among the scientific community? It should be remembered that the use of the systems developed are not a rigid framework for assessment of patients. For patients who present to the emergency department after all the work up for an ACS is negative, the follow up assessment depends on a case by case basis. The fact is that a large majority of the patients will undergo an exercise test after the presentation when they are stabilized. In a case of a negative stress test, the etiology of the disease of the patient is assumed not to be due to cardiac causes. However, since there are cases that can be missed with ETT, the clinician can choose to use one of the other methods of testing in addition to the ETT based on the availability and clinical suspicion.

The occurrence of cardiac adverse effects is related to the patient characteristics, with more elderly populations with chronic diseases being at increased risk while the younger population at a lower risk. Overall, a negative ETT test result can have a good prognostic factor for ruling out myocardial ischemia and outpatient follow up with repetition of the test can provide adequate screening. In cases that are more complicated and in individuals who have more comorbid conditions, addition of the other screening modalities is preferable. Recently, there have been occurrences where individuals who have undergone revascularization did undergo ETT and dobutamine stress echo which was able to diagnose up to 4.3% of the individuals having re-stenosis of the vessel (42). It is therefore the diagnostic and prognostic value of the ETT in its different forms that makes it a vital tool in diagnosis of cardiac disease.

Acknowledgements

The authors would like to thank Samuel Latham for his contribution in provision of study materials or patients.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Pour-Ghaz I, Bob-Manuel T, Marella HK, Kelly J, Nanda A, Skelton WP 4th, Khouzam RN. Incidence and predictors of acute coronary syndrome within a year following a negative stress test—a false sense of security: is routine screening any useful? Ann Transl Med 2018;6(1):13. doi: 10.21037/atm.2017.11.12

