M.W. Luong, MD, FRCPC, M. Ignaszewski, MD, C.M. Taylor, MD, FRCPC

Stress testing: A contribution from Dr Robert A. Bruce, father of exercise cardiology

The exercise treadmill test known as the Bruce protocol continues to play an important role in diagnosing coronary artery disease in intermediate-risk patients.

ABSTRACT: Recognizing the important physiological relationship between the heart and exercise, Dr Robert Arthur Bruce undertook research that revolutionized the way physicians approach cardiac disease. His contributions to exercise physiology and cardiology have shaped many concepts used today in clinical practice. He is best known for developing a protocol for the exercise treadmill test known as the Bruce protocol. Because of its universality, reproducibility, and practicality, the protocol remains one of the most widely used methods for diagnosing ischemic heart disease. Patients commonly start exercising on a treadmill set at 1.7 miles per hour and a 10% grade, and increase to a maximum speed of 6.0 miles per hour and a 22% grade. The aim of testing is to detect the presence of coronary artery disease by looking for electrocardiogram changes during times of stress. The sensitivity of exercise treadmill testing is estimated to be 70% and the specificity to be 80%. These values range broadly depending on multiple factors, including the definition of a positive test result. The strongest predictor of survival found on exercise treadmill testing is exercise capacity. Treadmill testing can also be combined with imaging modalities to further increase sensitivity and specificity, making it one of the first tests considered when coronary artery disease is suspected in a patient.

Dr Robert Arthur Bruce was born in Somerville, Massachusetts, on 20 November 1916. He graduated from Boston University with a bachelor of science degree and went on to finish his medical studies at the University of Rochester School of Medicine in 1943. In 1950, at the age of 34, Dr Bruce was appointed as the first chief of cardiology at the University of Washington School of Medicine, where he served as director for 21 years and co-director for another 10 years.[1,2]

During his time at the University of Washington, Dr Bruce contributed to the evolution of the exercise treadmill test (ETT) from a single-stage cardiac stress test to a multistage examination called the Bruce protocol, which involved increasing both speed and incline while monitoring a patient's cardiovascular response using electrodes. Before the development of the Bruce protocol, physicians had been using the Master two-

Dr Luong is a cardiology resident in the Division of Cardiology at the University of British Columbia. Dr Ignaszewski is a medical resident at the State University of New York Upstate Medical University. Dr Taylor is a staff cardiologist in the Division of Cardiology at the University of British Columbia.

This article has been peer reviewed.

step exercise test, which involves obtaining an electrocardiogram (ECG) after a patient has repeatedly climbed up onto and down from a small platform,[3,4] a test that can be too strenuous for some patients.

In 1963, when Dr Bruce described the stress test in print, he identified angina as the development of chest pain with exercise due to either underlying coronary artery disease (CAD), a previous myocardial infarction (MI), or a ventricular aneurysm.[5] The ETT remains a well-proven tool for diagnosing underlying CAD and for determining a patient's maximal functional aerobic capacity, a term that Dr Bruce himself coined.

Dr Bruce was also one of the founders of the Seattle Heart Watch program in 1971, which led to the development of a database including results from more than 10 000 individuals who completed his treadmill test over a 10-year span. Using ambulatory cardiac patients and healthy individuals as test subjects, the program proved that the Bruce protocol was both a reproducible and verifiable method for diagnosing underlying heart disease. It is with this very database that Dr Bruce created the standards we use when assessing today's patients.[1,4]

Publishing well over 300 articles, Dr Bruce was an innovator above all, and was one of the first physicians to contemplate the benefit of thrombolysis in acute coronary syndrome. Moreover, his merging of cardiology with technology inspired him to successfully measure QRS and ST segments during exercise.[1]

Dr Bruce is truly a giant of cardiovascular medicine, whose inquisitive nature led him to research that advanced the field. He held many leadership positions throughout his illustrious career, including founding and serving as the second president of the Association of University Cardiologists in 1969.[2,6]

As a believer in practising his own medicine, Dr Bruce enjoyed a healthy lifestyle and walked a mile along the waterfront with his wife almost daily until his passing. Every bit the gentleman, he donned a sport coat and tie at a celebration of his life and career with his closest family, friends, and colleagues on 11 February 2004 in Seattle, Washington.[2,6] He passed away the next day at age 87 after a 13-year battle with chronic lymphocytic leukemia. His discoveries in exercise physiology and cardiology have altered the way cardiology is practised. Dr Bruce's name will remain synonymous with one of the most extensively used screening and diagnostic tools for detecting signs of CAD, and he will forever be known as the father of exercise cardiology because of this.

Exercise treadmill testing

Exercise treadmill testing to identify CAD is now a widely available and relatively low-cost examination that has been used for more than 60 years.[7] The use of the ETT has expanded to include testing for functional capacity, chronotropic incompetence, cardiac rehabilitation, valvular heart disease, hypertrophic cardiomyopathy, arrhythmias, and pacemaker evaluation.[8-10] In addition, exercise testing has been combined with other modalities such as radionuclide imaging and echocardiography to elicit information that may be required in select patients.

The ETT can reveal cardiovascular abnormalities that are not seen at rest by taking measurements that unmask these during aerobic exercise, when the heart responds to the body's demand for more oxygen by increasing heart rate, stroke volume, and cardiac output. Much of this oxygen demand is from skeletal muscle, where oxygen extraction increases by up to threefold. As exercise intensity increases, the increase in cardiac output by up to sixfold is due mainly to an increased heart rate as stroke volume plateaus. In addition, total peripheral resistance and diastolic blood pressure (DBP) decreases, while systolic blood pressure (SBP) and pulse pressure increases.[10]

The heart rate increase during exercise is due to decreased vagal tone followed by increased sympathetic tone. As people age, beta-receptor responsiveness decreases, leading to a lower maximum heart rate and cardiac output in the elderly. A common and simplified method of estimating a person's maximum heart rate is 220 minus age. To take into account individual variability, it is common practice to conclude that patients reach their target heart rate at 85% of this calculated maximum value.[11] After exercise, the increased vagal tone will rapidly reduce the heart rate in the first 30 seconds, followed by a more gradual decline back to baseline.

Another value that can be obtained from an ETT is a patient's myocardial oxygen uptake. This value is estimated by the product of heart rate and SBP. This rate-pressure product is important since myocardial oxygen uptake and coronary perfusion are directly correlated. Since coronary flow can increase by up to fivefold above baseline with exercise, a patient who has obstructed coronary arteries cannot meet this increased demand and ischemia results. In general, a rate-pressure product 25 000 or higher indicates that a patient has achieved an adequate workload.[10] The rate-pressure product can also be used to estimate when ischemia occurs and is a better predictor of when ischemia will develop than the exercise testing stage.[12]

Maximal oxygen uptake (VO2 max) is an additional accurate representation of a person's cardiovascular fitness and exercise capacity, and is estimated from the peak workload achieved on an ETT. This is usually expressed in terms of a metabolic equivalent task (MET), where 1 MET is equal to 3.5 mL O_2 per kg per min. The VO2 max value is affected by age, gender, baseline exercise capacity and genetics.[10] Metabolic equivalent tasks (METs) can be estimated based on the protocol used for an ETT.

Table 1. Absolute contraindications for exercise testing.[10]

Acute myocardial infarction, within 2 days
Ongoing unstable angina
Uncontrolled cardiac arrhythmia with hemodynamic compromise
Active endocarditis
Symptomatic severe aortic stenosis
Decompensated heart failure
Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis
Acute myocarditis or pericarditis
Acute aortic dissection
Physical disability that precludes safe and adequate testing

Table 2. Relative contraindications for exercise testing.[10]

Known obstructive left main coronary artery stenosis
Moderate to severe aortic stenosis with uncertain relation to symptoms
Tachyarrhythmias with uncontrolled ventricular rates
Acquired advanced or complete heart block
Hypertrophic obstructive cardiomyopathy with severe resting gradient
Recent stroke or transient ischemic attack
Mental impairment with limited ability to cooperate
Resting hypertension with SBP > 200 mm Hg or DBP > 110 mm Hg
Uncorrected medical conditions, such as significant anemia, important electrolyte imbalance, and hyperthyroidism

Patient selection

Exercise stress testing to diagnose CAD is considered appropriate in an adult patient who is able to exercise and who has an intermediate pretest probability of CAD with an interpretable ECG. Patients with more than 1 mm of resting ST depression, left bundle branch block (LBBB), ventricular paced rhythm, or pre-excitation syndrome (e.g., Wolff-Parkinson-White syndrome) will not have an interpretable ECG and should not be referred for the purpose of diagnosing CAD. Additional absolute contraindications and relative contraindications for exercise testing are described in **Table 1** and **Table 2**.

Test preparation

Patients arriving for the test should be dressed comfortably in appropriate exercising attire. They should not have eaten in the preceding 3 hours, but may have taken regular medications with sips of water. When assessing for CAD, medications that may dampen a patient's heart rate and blood pressure response to exercise should be held the morning of the ETT. This applies especially to beta blockers.

Test protocols

There are several protocols that can be used for an ETT and these are based on patient abilities and the reason for examination. The most common protocol used is the Bruce protocol whereby patients start exercising at 1.7 miles per hour on a 10% grade. Every 3 minutes the speed and grade increase to a maximum of 6.0 miles per hour and 22% grade. The Bruce protocol is used commonly and is well described in many studies involving exercise testing.

When patients have ambulation difficulties, the large increments in workload between stages may lead to premature discontinuation of the ETT and an underestimation of the patient's true workload capacity. Modifications have been made to the Bruce protocol and other protocols to overcome these potential limitations.[10] The modified Bruce protocol starts off at the same speed as the Bruce protocol but with an initial grade of 0%. The Cornell, Naughton, and Balke protocols use a more gradual increase in workload and are reasonable options for patients who are unable to ambulate comfortably.[13] Ramp protocols also exist whereby patients start off with no incline and at a low speed. The incline and speed are then gradually and progressively increased according to the patient's functional abilities.[10]

After an appropriate protocol has been selected for a patient and the test is proceeding, it is important to recognize when stress testing should stop. The current recommendations for terminating an exercise test are listed in **Table 3** and **Table 4**.

Once the ETT has been completed, there is an obligatory cool-down period. Patients are typically moni-

tored for 6 to 8 minutes after test completion but may require additional monitoring of blood pressure, heart rate, or ST segments if they have not normalized or if they remain symptomatic. Additionally, ST segment deviation, a relatively poor prognostic factor, may only occur during the postexercise period.[10]

Monitoring

It is important to monitor patients for the development of symptoms during and after the test. Particular attention should be paid to the presence of angina and dyspnea. Exercise-limiting angina is especially important because it indicates a poorer prognosis according to the Duke treadmill score (DTS). The DTS is a validated tool that provides both prognostic and diagnostic information in evaluating patients with suspected CAD[14] (see more about this below). In addition, exercise-limiting dyspnea independent of angina has also been recognized as a worrisome ETT finding.[15]

Exercise capacity on an ETT has long been touted as a predictor of cardiovascular risk. In a meta-analysis by Kodama and colleagues, there was a decrease in cardiovascular events of approximately 15% with every 1-MET increase in aerobic exercise capacity. Kodama also found that subjects who were able to exercise to a level beyond 7.9 METs had a significantly better cardiovascular prognosis than those who did not.[16] A patient's predicted exercise ability can be estimated based on sex and age, making it important to note what patients are able to achieve as a percentage of their predicted abilities.[10]

Table 3. Absolute indications to terminate exercise test.[10]

ST elevation > 1 mm in leads without pre-exisiting Q waves because of prior MI (other than leads aVR, aVL, and V1)
Drop in SBP > 10 mm Hg, despite an increase in workload, when accompanied by other evidence of ischemia
Moderate-to-severe angina
Central nervous system symptoms (dizziness, near syncope, ataxia)
Signs of poor perfusion (cyanosis or pallor)
Sustained ventricular tachycardia or other arrhythmia that interferes with normal maintenance of cardiac output during exercise, such as second- or third-degree atrioventricular block
Technical difficulties in monitoring the electrocardiogram or SBP
Subject's desire to stop

Table 4. Relative indications to terminate exercise test.[10]

Marked ST segment depression > 2 mm measured 60 to 80 milliseconds after the J point in a patient with suspected ischemia
Drop in SBP > 10 mm Hg, despite an increase in workload, in the absence of other evidence of ischemia
Increasing chest pain
Fatigue, shortness of breath, wheezing, leg cramps, or claudication
Arrhythmias other than ventricular tachycardia that have the potential to become more complex or affect hemodynamic stability, such as multifocal ectopy, ventricular triplets, supraventricular tachycardia, or bradyarrhythmias
Development of bundle branch block that cannot be immediately distinguished from ventricular tachycardia
Exaggerated hypertensive response with SBP > 250 mm Hg or DBP > 115 mm Hg

ECG changes

The aim of exercise treadmill testing is to detect CAD by identifying ECG changes during times of stress, when there is an imbalance between myocardial oxygen supply and demand. At increasing levels of stress, production of adenosine triphosphate is decreased and production of lactate is increased, ultimately affecting the electrical properties of the myocardium, which can be detected subsequently on the surface ECG. A pattern of characteristic alterations known as the ischemic cascade develops with reduced left ventricular compliance followed by localized wall motion abnormalities, increased left ventricular end-diastolic pressure, ST segment changes, and lastly angina (**Figure 1**). It is these last two findings that can be assessed on a standard ETT.[10]

Close attention to ECG changes is needed to identify signs of ischemia.

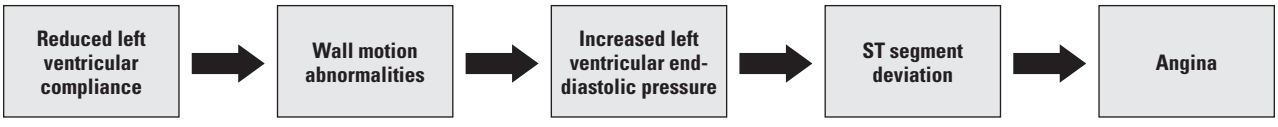
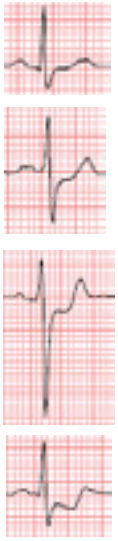


Figure 1. The ischemic cascade.

When looking for exercise-induced ischemia, the ST segment has long been the focus and is measured relative to the end of the PR segment. The baseline should be stable to determine any significant ST segment deviations, and three or more consecutive beats should be used to detect ST changes. The ST segment tangential direction should be measured at 60 to 80 milliseconds after the J point. A positive test for ischemia shows at least 1 mm ST depression that is either horizontal or downsloping (**Figure 2**). Upsloping ST depression, however, can be seen in up to 20% of the normal population and is therefore not diagnostic for ischemia. If more than 1 mm upsloping ST depression is identified, the test is deemed equivocal.[10] It is important to note that ST changes identified on ETT do not reliably predict the coronary artery affected. The main exception to this is in rare cases where ST elevation develops in leads without pre-existing Q waves.[10]

Some subjects may have resting ECG changes, such as T wave and ST segment deviations, that normalize with exercise due to elimination of electric forces that are directed against each other, a phenomenon termed ischemic counterpoise. Furthermore, ST changes in leads with existing Q waves may represent ongoing ischemia in the territory or wall motion abnormalities from prior infarcts.[10] In patients with underlying conduction abnormalities, interpretation of the ETT is more difficult. With underlying left bundle branch block the ETT cannot be interpreted, but this is not the case in patients with underlying right bundle branch block (RBBB). The ECG of a patient with underlying RBBB can still demonstrate ischemia in all leads other than V1 to V3. In RBBB, the anterior precordial leads will usually have baseline ST depression that worsens with exercise; these changes are not associated with underlying CAD.

ECG changes other than ST segment deviations have also been implicated as signs of ischemia, though they are less well studied and have not been duplicated. These possible signs of ischemia include increases in P wave duration, particularly in lead V1, increases in R wave amplitude at peak exercise, absent QRS shortening, increases in T wave amplitude, exercise-induced U wave inversions, and absent QT interval shortening.[10]



No ST depression	Negative stress test
Upsloping ST depression (>1mm)	Equivocal stress test
Horizontal ST depression (>1mm)	Positive stress test
Downsloping ST depression (>1mm)	

Figure 2. ST segment depression with exercise.

Arrhythmias

Exercise increases sympathetic tone and increases myocardial demand, which are both potential mechanisms for inducing supraventricular and ventricular arrhythmias. These arrhythmias are potentially dangerous in the postexercise period, when catecholamine levels are high while the patient is still vasodilated.[10]

Ectopic atrial arrhythmias may occur in subjects with underlying cardiac disease, such as rheumatic heart disease or Wolff-Parkinson-White syndrome, but may also be seen in subjects with no identified abnormalities. Atrial fibrillation and flutter may transiently occur in less than 1% of ETTs. Generally, these transient arrhythmias are not related to underlying ischemic heart disease. This is in contrast to ventricular arrhythmias, which are the most frequent arrhythmia seen during exercise. Premature ventricular beats are more concerning when accompanied by a family history of sudden cardiac death, previous myocardial ischemia, or existing cardiomyopathy. Studies have suggested that ventricular ectopy, particularly in the recovery period after an ETT, may be associated with an increased risk of death.[17]

The development of atrioventricular (AV) block is relatively uncommon during ETT, particularly since vagal tone is decreased during exercise. When AV block develops, it may be related to medications, CAD, or aortic stenosis.[10] Rate-related con-

duction abnormalities can develop in patients while exercising, but the development of LBBB or RBBB with exercise is not necessarily related to underlying CAD. However, LBBB during exercise may be an independent risk factor for death and major cardiac events.[18] Developing RBBB during exercise is less common than developing LBBB, but may occur more commonly in patients with underlying CAD than in patients with LBBB.[10]

Alternatives to ETT

When patients are physically unable to exercise on a treadmill, alternatives to the ETT are available. ECG changes can be recorded during pharmacological stress testing with adrenergic agents such as dobutamine or vasodilating agents such as adenosine. These agents are often used in conjunction with nuclear myocardial perfusion imaging with single-photon emission computed tomography (SPECT), which increases both the sensitivity and specificity of detecting CAD. Stress echocardiograms can also be performed to look for wall motion abnormalities, which are seen earlier than ST segment deviations as part of the ischemic cascade. Lastly, magnetic resonance imaging (MRI) and computed tomography (CT) scans are also being used increasingly to detect CAD.[10]

Sensitivity and specificity of ETT

The sensitivity of ETT is estimated to be 70% and the specificity is estimated to be 80%.[19] These values range broadly depending on multiple factors, including the definition of a positive ETT, prevalence of disease, underlying cardiomyopathies, and resting ECG abnormalities. For example, the sensitivity of a test increases with multivessel CAD, while the specificity can be lowered if an ETT is done on a subject with resting ECG abnormalities that are more likely to lead to false-positive results. Similarly, the predictive value of an ETT is influenced by the prevalence of CAD in the population, which can be predicted by the patient's underlying risk factors. As such, exercise testing to identify CAD is inappropriate for a low-risk, asymptomatic patient.[10]

Prognostic value of ETT

Looking at ETT results, the strongest predictor of survival is exercise capacity, which is how much exercise a patient can sustain. One caveat is that an ETT is often terminated when patients reach their target heart rate, so merely noting the time it takes for a patient to reach this stage does not indicate how much longer they would otherwise have been able to continue exercising. Furthermore, exercise capacity is best assessed by calculating a patient's workload in METs as opposed to simply indicating how many minutes the patient exercised. There are no simple numbers of METs one must reach to be considered to have high exercise capacity because this number varies with age and gender.[10]

Chronotropic incompetence is another prognostically important variable defined by the failure to reach 85% of the maximum predicted heart rate. Heart rate response is important during exertion because it is a measure of how well the patient's cardiac output matches metabolic demands, and an impaired response predicts cardiac events and overall mortality.

Abnormal heart rate response is also prognostically important, and is defined as a decline during recovery of less than 12 beats per minute after ETT termination while the patient is still upright. However, this value is affected by the type of protocol used, and universal agreement on the exact heart rate decline is lacking.[10]

Hypotension during exercise may indicate left ventricular outflow tract obstruction, severe left ventricular dysfunction, and significant CAD, and is a marker of an increased risk of cardiac events.[20] During exercise, it is abnormal to see the SBP dip below the resting value or drop 10 mm Hg or more after an initial increase. However, the most common reason for hypotension during exercise is the use of antihypertensive medications, making it important to review a patient's medication profile before testing. Blood pressure can also rise excessively during exercise and this too has been shown to predict mortality. A hypertensive response is defined by a rise of SBP to 210 mm Hg and beyond for men and to 190 mm Hg and beyond for women.[20] Furthermore, a rise in DBP of more than 10 mm Hg or a rise to an absolute value beyond 90 mm Hg may also be a sign of CAD.[21] These hypertensive responses may predict an increased risk of developing hypertension, left ventricular hypertrophy, and cardiac events.[20]

Perhaps the most popular prognostic risk score used for the ETT is the Duke treadmill score. The DTS is calculated by subtracting 5 times the ST depression (measured in mm) and 4 times the angina score (no angina = 0, non-limiting angina = 1, and test-limiting angina = 2) from the total exercise duration (measured in minutes) on the standard Bruce protocol. Subjects are considered low risk if they score 5 or above, intermediate risk if they score between 4 and −10, and high risk if they score −11 and below. Subjects with a high-risk DTS are much more likely to have triple-vessel or left main CAD, and have a reduced 5-year survival rate of 65%.[14]

Summary

Dr Bruce will forever be known as the father of exercise cardiology. The easy, relatively low-cost test he developed continues to play an important role in diagnosing CAD in intermediate-risk patients. The Bruce protocol allows patients to exercise on a treadmill according to their baseline functional status, and is used to determine a patient's exercise capacity, predict overall mortality, and stratify patient risk, irrespective of the presence of CAD.

Today exercise treadmill testing is also being combined with imaging modalities to increase sensitivity and specificity for CAD, making the ETT a flexible test that is often used first when CAD is suspected in a patient.

Competing interests

None declared.

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