CHAPTER II
LITERATURE REVIEW

1. Anatomy of the coronary arteries and circulation

There are two anatomically separate vascular beds or circuits through which blood is driven. The left ventricular drives blood through the systemic circulation and the right ventricle drives it though the pulmonary circulation. In each case, vessels connecting the ventricle to capillaries of that circulation have to withstand more pressure and are thicker than the vessels leading from the capillaries to the atrium. The former vessels are called arteries and the latter veins. In the systemic circulation, arteries convey oxygenated blood from the left ventricle to the capillaries, whereas veins carry the deoxygenated blood from the capillaries to the heart. In the pulmonary circulation, the arteries are again by definition those vessels conveying blood from the right ventricle to the pulmonary capillaries. Because this blood has reached the right ventricle from the systemic vein and it deoxygenated, the blood in the pulmonary arteries is deoxygenated, in contrast to the blood in all the other arteries which is oxygenated. Similarly, blood leaving the pulmonary capillaries by the pulmonary veins to the heart is oxygenated, in contrast to blood in all the other veins, which is deoxygenated. This pattern varies from species to species and from individual to individual. In human, the coronary arteries have attracted popular attention because when partially or completely occluded by coronary atherosclerosis, the myocardial oxygen supply becomes inadequate and the myocardium starts to suffer from the effect of lack of oxygen.

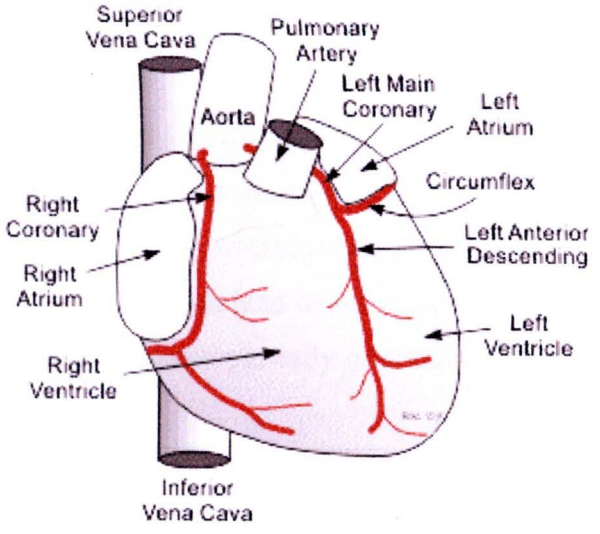

Figure 1 Structure of coronary artery

2. CAD

CAD is the commonest cause of heart disease and the most important major cause of death in the many developing countries in the world (Cook, 2006). Twice as many deaths from CAD now occur in developing countries as in developed. In the overwhelming majority of cases, disease of the coronary arteries is due to atherosclerosis.

2.1 Definition

CAD is a narrowing or blockage of the arteries and vessels that provide oxygen and nutrients to the heart. It is caused by atherosclerosis, an accumulation of fatty materials on the inner linings of arteries. The resulting blockage restricts blood flow to the heart. When the blood flow is completely cut off, the result is a heart attack.

2.2 Pathophysiology

CAD was characterized by changes in both structure and function of the blood vessels. Atherosclerotic processes cause an abnormal deposition of lipids in the vascular wall, leukocyte infiltration and vascular inflammation, plaque formation and thickening of the vascular wall. These changes lead to narrowing of the lumen

(i.e., stenosis), which restricts blood flow. There are also subtle, yet functionally important changes that can occur before overt changes in structure are observed. Early in the disease process, the endothelial cells that line the coronary arteries become dysfunctional. Because the endothelium produces important substances such as nitric oxide and prostacyclin that are required for normal coronary function, endothelial dysfunction can lead to coronary vasospasm, impaired relaxation and formation of blood clots that can partially or completely occlude the vessel.

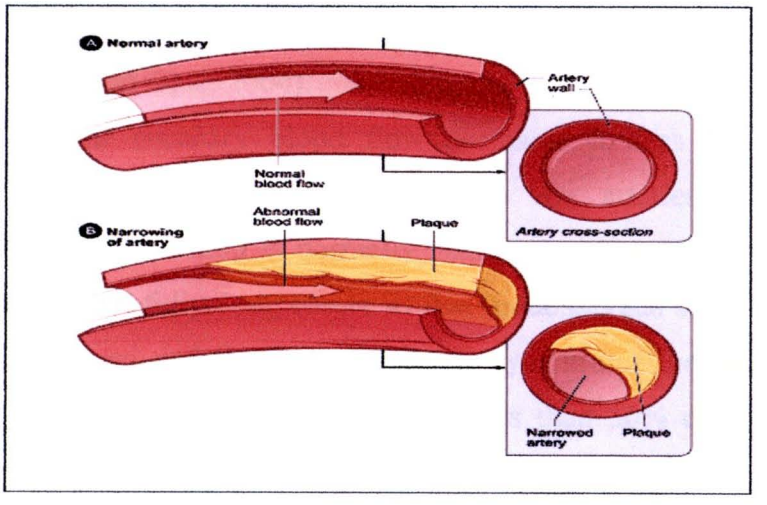

Figure 2 Plaque formation

The effects of CAD on the coronary arteries are highly variable, from diffuse damage to a localized narrow or stenosis. The direct hemodynamic effect of coronary stenosis is to decrease the coronary perfusion pressure in the distal segment of the diseased artery. Second, the indirect effect of tissue ischemia causes contractile failure, thereby increasing the left ventricular end-diastolic pressure, which in turn compresses subendocardial tissue and reduces coronary perfusion further to increase ischemia. Third, as discussed in the preceding section, ischemia has direct vasodilatory effects on the coronary circulation, acting by the formation of adenosine and NO, and opening of the vascular K_{ATP} channels. Fourth, because the vascular endothelium is damaged in CAD, such vasodilatory stimuli are usually overcome by a variety of vasoconstrictive forces including neurohumoral mechanisms (Zhang et al., 2003) and endothelin.

To reduce coronary blood flow by stenosis required a very large decrease in arterial lumen. The most important factor is the severity of the stenosis and the consequent increase in resistance to blood flow across the stenosis. The resistance increase by a power of 4 as the radius decrease (Poiseuille law), and reducing the internal diameter from 80% to 90% dramatically elevates the resistance. Resting flow is not affected until the stenosis is very severe and one estimate is that a 70% reduction in internal diameter with a 90% to 95% decrease in luminal area is required for basal coronary flow to decrease. When the internal diameter is reduced beyond 30%, the response to those stimuli normally increasing coronary flow starts to be impaired (Lionel and Opie, 2004).

As the coronary blood flow decreases to less than the limits of autoregulation, the extraction of oxygen from the arteries blood decreases. Nonetheless, because extraction is normally nearly complete (Parsons et al., 1993), this mechanism can not fully compensate so that tissue oxygen stores of hemoglobin and myoglobin decrease, and the respiratory chain cytochromes become less oxidized. When the myocardial blood flow decreases to less than 50% of control, tissue of oxygen stores decrease to minimum and any further flow reduction means that the respiratory chain becames even less oxidized. The result is the development of anaerobic metabolism.

The angina is the main symptom of CAD but it is not always present that is attributable not to an increase in myocardial oxygen demand, as it is in classic angina, but to the transient reduction coronary blood flow. The attacks are usually self-limiting, but the pain may be severe. Many people have no symptoms of CAD before having a heart attack; 63% of women and 48% of men who died suddenly of CAD had no previous symptoms of the disease.

2.3 Risk factors of CAD

Numerous factors or conditions are known to increase the probability that CVD will develop that involves the heart and/or blood vessels (Veryard, 2007).

Reversible risk factors

Some risks factors such as tobacco smoking, high blood pressure, high total cholesterol, obesity, physical inactivity, alcohol consumption, diabetes mellitus (DM), and dyslipidemia are modifiable and can be targeted in the order to improve CVD progression.

Tobacco smoking

Smoking is known to roughly double life-time risk of CVD (Doll and Hill., 1966), and is thought to increase cardiovascular risk by several different mechanisms including enhanced oxidative modification of LDL, decreased HDL levels, endothelial dysfunction, increased oxidative stress, increased platelet adhesion, inappropriate stimulating of the sympathetic nervous system by nicotine. Even minimal smoking increase the risk and the heaviest smokers are at the greatest danger of cardiovascular event. Studies indicate that low-tar and low-nicotine cigarettes do not significantly decrease the occurrence of myocardial infarction compared with regular cigarettes. Smokers are 2-4 times more likely than non-smokers to die of sudden heart attack (Panagiotakos et al., 2007).

Hypertension

Patients with hypertension face at least a 200% increase in risk of CAD. High BP is known to be one of risk factors of CVD, causing the heart to thicken and becoming stiffer (Weber, 1996). It is a leading cause of mortality and morbidity globally. It also increases risks of stroke, heart attack, kidney failure and congestive heart failure.

Obesity

An association of BMI, with CVD mortality have been shown significant positive (Barrett-Connor et al, 1984, Dyer et al., 2004; Garfinkel and Stellman, 1998; Jousilahti et al., 1996; Manson et al., 1995). Individuals who have excess body fat especially at waist have great strain on their hearts They are more likely to develop heart disease and stroke even if they have no other risk factors (Smith and Haslam, 2007; Thompson et al., 2007).

Physical inactivity

An inactive lifestyle is a risk factor for CVD (Ignarro et al., 2007). Physical inactivity promotes CVD via multiple mechanisms. Low fitness is associated with many CVD risk factors e.g. reduced plasma HDL, higher levels of blood pressure, insulin resistance and obesity. Exercise was demonstrated that it can help control blood cholesterol, diabetes and obesity as well as help lower blood pressure in some people (Ekelund et al., 2007; Lazarevic et al., 2006).

Alcohol consumption

Chronic drinking of alcohol can raise BP which contributes to heart failure and lead to stroke. It can also contribute to high TG, cancer and other diseases and produce irregular heartbeats (Stanciu and Campeanu, 1997). The risk of heart disease in people who drink moderate amounts of alcohol is lower than in nondrinkers.

DM

DM, the impaired glucose tolerance, is known to be a risk factor for CVD. It cause both macrovascular (such as retinopathy, and nephropathy), and microvascular disease (such as myocardial infraction, and stroke), leading to cardiovascular complications. The mechanism may relate in part to the non-enzymatic glycation of lipoproteins in diabetes patients (which may enhance uptake of cholesterol by scavenger macrophages, or to a prothrombotic tendency and anti-fibrinolytic state that may prevail in patients with this condition (Lilly, 2003). Pervious studies found that impaired glucouse tolerance is associated with central obesity, hypertension, and dyslipidemia.

Dyslipidemia

It has long been known that lipid abnormalities are major risk factors for premature CAD (Genest et al., 1991; Kinosian et al., 1994; Martin et al., 1986; Miller and Miller, 1975; Stamler et al., 1986). Observational studies have shown that compared with countries with traditionally low saturated fat intake and low serum cholesterol levels, the United State and other societies with higher consumption of saturated fat and cholesterol level have higher mortality rates due to coronary disease (Lilly, 2003).

Irreversible risk factors

Increasing age

Ageing is associated with vascular alterations that may lead to an increased susceptibility to CVD. CVD is the major cause of death in older men and women (Mazzeo et al., 1998). At older ages, women who have heart attacks are more likely than men to die from it within a few weeks.

Gender

Middle-aged women are much less likely than men to develop CVD. This difference progressively narrows after the menopause, and is mainly estrogen mediated (Kuller et al., 2000). Previous studied suggest that estrogen (the levels of which decline after menopause) may have atheroprotective properties. Physiologic estrogen levels in premenopausal women lower LDL and lipoprotein and raise HDL levels.

Heredity

Children of parents with heart disease are more likely to develop CAD. African Americans have more severe high blood pressure than Caucasians and a higher risk of heart disease. Heart disease risk is also higher among Mexican Americans, American Indians, native Hawaiians and some Asian Americans (Caillier, 2006; Manresa et al., 2006). This is partly due to higher rates of obesity and diabetes in these populations.

2.4 Test for diagnosis of CAD

In diagnosis a physician will take general examination and chest examination. Other diagnostic tests include EST, ECG, echocardiography, coronary angiography and radionuclide imaging.

EST measures how the heart and blood vessels respond to exertion when the patient is exercising on a treadmill or a stationary bicycle. This is an appropriate screening test for those with high risk factors.

ECG shows the heart's activity and may reveal a lack of oxygen (ischemia). However, the definite diagnosis can not be made from ECG. About 50% of patients with significant CAD have normal resting ECG.

Echocardiography can be used to detect enlarged hearts and abnormal cardiac movement, and to estimate the ejection fraction. An ultrasound pulse of 2.5 MHs is generated by a piezoelectric transmitter-receiver on the chest wall and is reflected back by internal structures. As sound travels through fluid at known velocity, the time taken between transmission and reception is a measure of distance. This allows a picture of internal structure to be built up.

Coronary angiography is by far the most commonly performed invasive cardiac investigation in western countries. It is used both to establish whether or not a patient has significant CAD and to determine their suitability for interventional treatment including percutaneous transluminal coronary angioplasty and coronary artery bypass surgery. Selective angiography is also the investigation of choice when re-examining patients who have recurrent symptoms following coronary artery bypass surgery.

Radionuclide imaging can be combined with exercise stress testing to overcome these limitations and to increase the sensitivity and specificity of the test. A radionuclide is injected intravenously at peak exercise and immediate imaging is performed. The radionuclide accumulates in proportion to the degree of perfusion of viable myocardial cells. Radionuclide exercise tests are 80-90% sensitive and 80-90% specific for the presence of clinically significant CAD.

2.5 Pathophysiology of CAD limiting exercise

Although mild CAD may be difficult to detect, simultaneous gas exchange measurements with ECG may improve the diagnostic capabilities of an EST. CAD will usually reduce the peak $\dot{V}O_{2,max}$. Patients with CAD may or may not experience chest pain. When the exercise-induced increase in myocardial oxygen requirement is not met by the myocardial oxygen supply, myocardial ischemia may result in ST segment and T wave changes in the ECG, and ventricular ectopic beats may develop with increasing frequency as the work rate is increased. Also, characteristic gas exchange abnormalities may develop during exercise when myocardial ischemia develops.

The $\Delta \dot{V}O_2/\Delta WR$ ratio is normal at low work rates of an incremental exercise test, but may abruptly decrease when myocardial ischemia. The ECG usually

becomes abnormal, whether or not angina develops, when $\Delta \dot{V}O_2/\Delta WR$ decreases (Belardinelli et al., 2003).

In normal persons, the O_2 pulse decrease immediately after exercise. However, a paradoxical increase in O_2 pulse commonly occurs in patients who develop myocardial ischemia or heart failure in response to exercise. This paradoxical increase in O_2 pulse may be due to an immediate increase in stroke volume in these patients because of the abrupt decrease in left ventricular afterload when exercise stop (Koike et al., 1990).

In patients with CAD, the breathing reserve is normal or high because the subject is forced to stop exercise from symptoms at a relatively low metabolic rate. The ventilatory equivalents are normal, manifesting relatively uniform ventilation-perfusion relationships in contrast to those observed in patients with chronic stable heart failure.

3. Aerobic capacity

Aerobic capacity is the highest amount of oxygen consumed ($\dot{V}O_{2,max}$) during maximal exercise in activities that use the large muscle groups in the legs or arms and legs combined (Gokoglu et al., 2007).

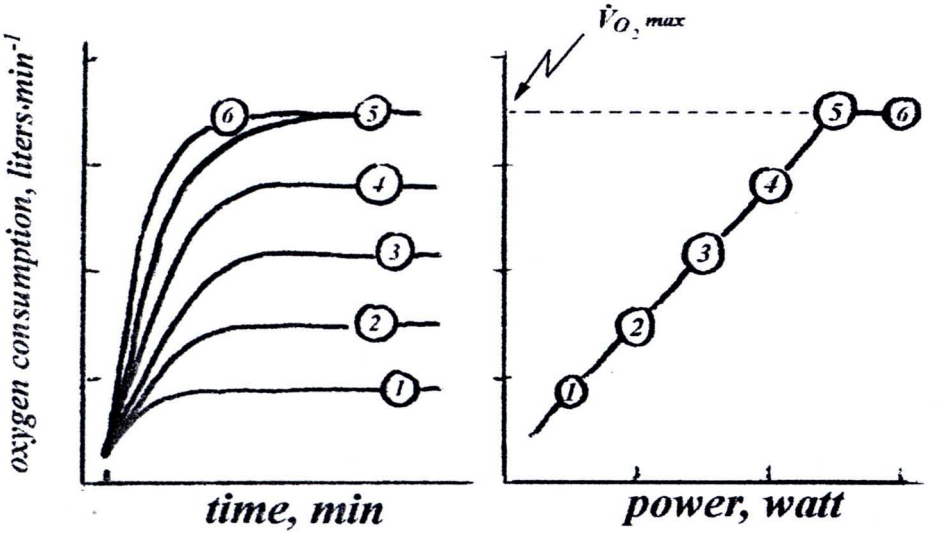

Figure 3 Relationship between oxygen consumption ($\dot{V}_{O2}$) and time and work rate

3.1 Maximum oxygen consumption ($\dot{V}O_{2,max}$)

$\dot{V}O_2$ is linearly related to the workload. As the exercise intensity increases, $\dot{V}O_2$ increases proportionally. However there comes a point at which the $\dot{V}O_2$ ceases to rise even though the exercise intensity continues to rise. This point is referred to as the $\dot{V}O_{2,max}$ and is considered to be the point of reference of maximal aerobic capacity.

$\dot{V}O_{2,max}$ is the most common and most importantt measurement derived from gas exchange data during excercise. That is an objective measurement of exercise capacity: it defines the upper limits of the cardiopulmonary system. It is determined by the capacity to increase HR , augment stroke volume and direct blood flow to the active muscles. It is often the most important variable measured, although this depends on the setting and the cortext of the particular patient being tested. $\dot{V}O_{2,max}$ should initially be considered in terms of what would be normal for a given individual if patients were healthy. However, the observation that $\dot{V}O_{2,max}$ falls within the normal range for a given gender and age makes a strong and multifactorial statement: the individual has no significant impairment in the cardiopulmonary system. Implicit in this statement, of coures, is that the patients has no major limitation to cardiac output, its redistribution, or skeletal muscle metabolism or function. Changes in $\dot{V}O_{2,max}$ following training or detraining or caused by disease closely parallel changes in cardiac size and maximal output (Blomqvist and Saltin, 1983; Ehsani et al., 1978; Saltin et al., 1968). Clearly, $\dot{V}O_{2,max}$ is directly related to the integrated function of several systems. The body clearly has an upper limit for oxygen utilization at a particular state of fitness or training. This is usually determined by the maximum cardiac output (Kitzman et al., 1991), the arterial oxygen content, the fractional distribution of the cardiac output to the exercising muscle, and the ability of the muscle to extract oxygen. The ventilatory capacity determines the upper limit of $\dot{V}O_2$ only when ventilation is insufficient to eliminate the carbon dioxide produced by aerobic metabolism and the bicarbonate buffering of lactic acid.

The best method to assess aerobic capacity is to measure $\dot{V}O_2$ directly in the laboratory while the subject maximally exercising. Various protocols can be

used which usually yield similar results. However treadmill tests generally give higher values than cycle protocols. This is probably due to the fact that most individuals are accustomed to walking or running but not to cycling. The accuracy of $\dot{V}O_{2,max}$ test can be maximized by achievement of several criteria: a plateau of $\dot{V}O_2$ with an increase in workload, an RER that exceeds 1.15, a plateau of HR and being within ±15 /min of the subject's predicted HR_{max}, and exhaustion of the subject. Thus, the results of each test should be evaluated to whether or not a true $\dot{V}O_{2,max}$ is achieved. While laboratory testing using indirect calorimetry is the most accurate method to determine maximal aerobic capacity, the procedure is expensive and time-consuming. Field tests were developed in order to test large numbers of subjects more quickly and easily and were based on their correlation with laboratory data. Cooper's 12-minute and 1.5-mile runs are two of the most widely known and used field tests. However, these tests also require a highly motivated subject exercising to voluntary exhaustion in order to maximize their predication ability. Not all individuals have the motivation to perform a maximal test and certain contraindications prohibit maximal testing of an individual. Consequently, tests to estimate $\dot{V}O_{2,max}$ were devised based on the HR response at a submaximal workload. These $\dot{V}O_{2,max}$ values and norms for Thai population show in Table 1 and Table 2 (Sport science institute, 2000).

Table 1 Level of aerobic capacity determined by $\dot{V}O_{2,max}$ values (ml/kg/min) in men

Level of aerobic capacity	**Men (years)**					
	17-19	**20-29**	**30-39**	**40-49**	**50-59**	**60-72**
Excellent	>55.5	>51.6	>43.3	>37.4	.>33.9	>30.7
Good	50.6-55.4	47.1-51.5	39.4-43.2	34.1-37.3	30.7-33.8	27.9-30.6
Fair	40.7-50.5	38.0-47.0	31.5-39.3	27.4-34.0	24.2-30.6	22.2-27.8
Poor	35.8-40.6	33.5-37.9	27.6-31.4	24.1-27.3	21.0-24.1	19.4-22.1
Very poor	<35.7	<33.4	<27.5	<24.0	<20.9	<19.3

Table 2 Level of aerobic capacity determined by $\dot{V}O_{2,max}$ values (ml/kg/min) in women

Level of aerobic capacity	Women (years)					
	17-19	**20-29**	**30-39**	**40-49**	**50-59**	**60-72**
Excellent	>48.0	>45.8	>40.2	>35.8	>30.9	>30.8
Good	43.9-47.9	41.9-45.7	36.9-40.1	32.4-35.7	28.3-30.8	27.8-30.7
Fair	35.6-43.8	34.0-41.8	28.7-36.8	25.5-32.3	23.0-28.2	21.7-27.7
Poor	31.5-35.5	30.1-33.9	24.9-28.6	22.1-25.4	20.4-22.9	18.7-21.6
Very poor	<31.4	<30.0	<24.8	<22.0	<20.3	<18.6

3.2 Estimation of $\dot{V}O_{2,max}$

$\dot{V}O_2$ and HR were shown to be measured by different protocols using steps, bicycle, and treadmill. As might be expected, the variability of $\dot{V}O_2$ expressed as liters per minute on the bicycle tests was least because of the constant external load and very small variability of efficiency among subjects. However, since bicycle testing is independent on body weight, a marked variability in $\dot{V}O_2$, expressed as milliliters per kilogram per minute was found. The treadmill, with its weight-dependent workload, shows a small variation in oxygen reported as liters per minute. There is no significant difference in the variability of the HR response. Bruce and coworkers have published oxygen data describing the milliliter per kilogram per minute for subjects using the Bruce protocol, which is excellent. When adjustment was made for the sex and physical activity of the subject, the $\dot{V}O_{2,max}$ was estimated with what appears to be acceptable accuracy (Bruce et al., 1973). Previous studied, reported the time on the protocol proposed by Bruce as an estimate of $\dot{V}O_2$ and found it to be unreliable (Froelicher et al, 1974). $\dot{V}O_{2,max}$ can also be accurately estimated without relying on direct measurement, which requires expensive laboratory equipment. When $\dot{V}O_{2,max}$ is estimated based on valid and reliable methods, there is a close statistical relationship between the estimated.

4. Energy expenditures

A MET is the resting metabolic rate. One MET is approximately equal to an oxygen consumption of 3.5 ml/kg/min. Activities that increase metabolism less than 6 METs are classified as low-intensity exercise, 6-8 METs are classified as moderate-intensity exercise. Vigorous exercise increases metabolic rate by more than 10 METs.

METs are only intended to be an approximation of exercise intensity. Skill, body weight, body fat and environment affect the accuracy of METs. As a practical matter, however, these limitations are disregarded. METs are a good way to express exercise intensity because the system is easy for people to remember and understand.

5 Heart rate recovery (HRR)

Recovery of the HR immediately after exercise is a function of vagal reactivation. Because a generalized decrease in vagal activity is known to be a risk factor for death. This period was considered the recovery period. The value for the recovery of HR was defined as the reduction in the HR from the rate at peak exercise to the rate one minute after the cessation of. HRR has also been described as a predictor of mortality in patients who have suspected CHD (Cole et al., 1999) and heart failure (Imai et al., 1994).

HRR is an independent marker of mortality in patients with known or suspected coronary disease and provides information additive to coronary severity and clinical and exercise parameters (Vivekananthan et al., 2003). Abnormal HRR was defined as a decrease of $\leq$12 beats from peak HR during exercise and one minute after the cessation of test (Shetler et al., 2001).

6. EST

The EST is the reasonable first choice for prognostic assessment. Because of its widespread utilization, any improvement in the predictive accuracy of the EST could have an enormous impact on the cost-effective delivery of cardiologic care (Froelicher et al., 1988). However, a storm of controversy also exists on whether positive EST findings truly represent myocardial ischemia or pseudonormalization in

patients with microvascular angina. Previous studied report that EST have a very low sensitivity in detecting myocardial ischemia in microvascular angina (Epstein et al., 1991); however, Camici and coworker reported that, although the sensitivity is high, the specificity is low (Camici et al., 1992).

Since and ECG obtained during or between episodes of chest discomfort may be normal, such tracing do not rule out the diagnosis of ischemic heart disease. For this reason, an EST (also termed exercise tolerance test) is a valuable diagnostic and prognostic aid. During this test, the patient exercise on treadmill or a stationary bicycle to progressively higher workloads. Patients are observed for chest discomfort or inordinate dyspnea. HR and ECG tracings are continuously recorded and BP is checked at regular intervals (Lilly, 2003).

6.1 Indications for the EST

Evaluation of the patient with chest pain

If the chest pain pattern is suspicious, the presence or absence of disease can often be confirmed by an exercise stress test. The reliability depends on the magnitude and time of onset of the ST changes, on the HR and BP response and very importantly, on the prevalence of disease in the population under study. Exercise testing remains one of the more practical approaches to diagnosis.

Determination of prognosis and severity of disease

Several studies have confirmed that severity of disease, which is a major factor in prognosis, can be estimated with considerable accuracy with exercise stress test (Dagenais et al., 1982; Goldschlager et al., 1976).

Evaluation of the effects of medical and surgical therapy

An exercise stress test should measure the patient's relative myocardial blood flow, onset of ST depression in terms of the work applied, and aerobic capacity before and after treatment. Numerous studies reported that exercise stress test has important value in predicting postoperative graft patency (Assad-Morell et al., 1975; Frick et al., 1983; Stuart et al., 1979).

Screening for latent coronary disease

It was once believed that significant coronary disease usually produces angina. When symptoms of typical angina are described by the patient, coronary

disease can be predicted with considerable reliability, but when no history of pain is present, there is still a strong possibility of significant narrowing in the coronary tree in patients with appropriate risk factors.

Early detection of labile hypertension

The response to exercise is an increase blood pressure. Several studies have demonstrated that an unusually high pressure in persons who are normotensive at rest suggests that they may become hypertensive in the future.

Evaluation of congestive heart failure

Previous studies have used exercise stress test to understand function changes, to establish mechanisms, and to measure response to therapy (Franciosa, 1984; Kramer et al., 1983).

Evaluation of arrhythmias

The presence of exercise-induced arrhythmias on the ability to predict future events in coronary patients. Previous studied have used the symptom-limited exercise test routinely to evaluate malignant arrhythmias (Young et al., 1984).

Evaluation of functional capacity

The most important physician decisions in the patient who has angina or who has had a myocardial infarction is how much exercise the patient can tolerate.

Evaluation of congenital heart disease

EST has been especially useful in congenital aortic stenosis (Bruce et al., 1973). That provides valuable guidelines.

Stimulus to motivate chance in lifestyle

One of the most serious problems in our sedentary population or in those with coronary disease is the need to motivate patients to stop smoking, to follow a diet, to exercise regularly and to make other necessary changes in their lifestyles. Because the results associated with such changes in their habit patterns are not readily apparent to them, a stimulus of some sort is often needed. The patient's performance on a stress test often serves just such a function. In our cardiac rehabilitation program, the stress test response is explained to the patient, and its meaning in regard to progress often motivates cooperation not otherwise forthcoming. This has been the experience of cardiac rehabilitation units across the country.

6.2 Contraindications for the EST

The most important safety factor in exercise stress test is a knowledgeable and experienced of physician in charge. This experience and knowledge are essential for the physician to undertake the risk of exercising cardiac patients.

Absolute contraindications

It is generally agreed that stress testing should not be done on the following patients:

1. Patients with an acute myocardial infarction.
2. Patients suffering from acute myocarditis or pericarditis.
3. Patients exhibiting signs of unstable progressive angina.
4. Patients with rapid ventricular or atrial arrhythmias at the time of the test.
5. Patients with second or third degree heart block.
6. Patients with known severe left main coronary stenosis disease.
7. Acutely ill patients.
8. Patients with locomotion problems.
9. Severe symptomatic aortic stenosis.

Relative contraindications (Relative contraindications can be superseded if benefits outweigh risks of exercise)

1. Aortic stenosis

Cardiac arrest from exercise stress test in patients with aortic stenosis resulted in a cautious approach in patients with this valvular lesion. In adults with moderate valvular disease, it can be a very useful procedure with an acceptable risk when used cautiously. In children EST has been found to be useful and safe.

2. Suspected left main coronary stenosis
3. Severe hypertension

If the patient has severe resting hypertension (240/130) requiring multiple medications, the test should be gave or used with extreme caution. If hypertension can be brought under control with medication, the exercise testing may be done with safety.

4. Idiopathic hypertrophic subaortic stenosis and asymmetrical septal hypertrophy

In conditions in which outflow obstruction may be severe, sudden death after exercise occurs even in young patients, regardless of the degree of obstruction (Frank and Braunwald, 1968).

5. Severe ST segment depression at rest

ST segment depression at rest should be viewed with caution because it may indicate severe subendocardial ischemia. If these patients with ST segment depression at rest are tested, it should be done with extreme caution.

6. Congestive heart failure

6.3 Parameter to be measured during EST

BP

SBP should show a progressive increase during exercise and a progressive decline after exercise. A decrease in SBP or a failure to increase SBP is abnormal and may indicate clinically significant myocardial ischemia, left ventricular dysfunction or chronotropic insufficiency. Examples where this may occur are valvular heart disease, such as severe aortic stenosis (James et al., 1982), cardiomyopathy (either hypertrophic without flow obstruction or dilated) arrhythmias, such as sinus node dysfunction, rate-dependent heart block and pacemaker dysfunction or ischemic heart disease. Patients with cardiac ischemia may have ischemic changes on ECG. Alternatively, patients with no cardiac or pulmonary abnormalities may have chest pain and shortness of breath as they approach peak exercise capacity. In this case, the use of metabolic testing will allow the determination that they have passed anaerobic threshold and are exercising at maximal capacity.

DBP should remain stable or decrease with exercise. An increase in DBP may indicate HT. Both SBP and DBP may decline during the recovery phase due to vasodilatation and pooling in the lower extremities.

BP response is important both to ensure the safety of the patient and to provide information on the strength of the cardiac contraction and the state of the peripheral resistant. It may also be of value in predicting hypertension in the future.

BP should be recorded before and with exercise at each work level as well as in recovery.

HR

HR is the best indicator of the magnitude of exertion. The person doing the test must know the approximate predicted maximum HR and be familiar with the average response to the protocol selected to the protocol selected for each of the various age groups.

Although it has been known that the HR gives a reasonably reliable measure of the cardiac output, the tendency to a lower HR under a standard exercise load has been frequently considered to be a matter of better conditioning. Indeed, the observable decrease in resting and exercise HR after physical fitness programs is regarded as a most desirable result and is carefully recorded. Previous study has found that a slow HR response on the treadmill is a reliable predictor of CAD (Wiens et al., 1984).

ECG

The wide recognition of the important recording at the lower end of the ECG frequency range has been a significant development in the instrumentation necessary for accurate stress test. The use of all 12 leads of the conventional systems has the advantage of wide familiarity. The ECG trace has three main components that are related to the amplitude and direction of the wave of depolarization at that moment. The normal ECG complex consists of the P wave, the PR interval, the QRS complex, the ST segment and the T wave. The P wave is a small deflection due to depolarization of the atria. This is followed by the QRS complex, which is general 0.08 s in duration and reflects ventricular depolarization. It is the largest deflection because of the large ventricular muscle mass. The relative size of the Q, R and S component varies between leads, and is dependent on the orientation of the heart. In lead II the Q wave is seen as a small downward deflection, correlating to the left to right depolarization of the interventricular septum. The R wave is a strong upward deflection, corresponding to depolarization of the main mass of the ventricles. The S wave is a small downward deflection in lead II, and relates to depolarization of the last part of the ventricles close of the base of the heart. The T wave corresponds to ventricular repolarization. The PR interval reflects the delay between atrial and

ventricular depolarization and is largely related to delay in the atrioventricular node. It is measured from the beginning of the P wave of the ECG to the beginning of Q wave and ranges from 0.12 to 0.20 s. It shortens as HR increases. The ST segment approximates to the plateau of the ventricular muscle action potential, and is 0.25 s. When the myocardium is injured, this can either depress or elevate the ECG baseline. It has been reported that in patients with a first myocardial infarction and without residual ischemia, exercise-induced ST segment elevation in Q leads is related to a more damaged coronary microcirculation and to less viable myocardium (Higgins and Higgins, 2007). Exercise-induced ST segment elevation is a rare phenomenon in patients without prior myocardial infarction. When occurring purely during exercise, coronary lesions are frequent and often severe, in the other hand ST segment elevation of the recovery phase is frequently associate with normal arteries or less severe lesion (Labbe et al., 1999). The QT interval is a simple and surprisingly interesting measure of cardiac function. QT interval is a function of ventricular repolarization time and is measured from the onset of the QRS complex to the end of the T wave. The length of this interval is inversely related to HR (James and Ron, 1985). Furthermore, it allows for the effects of exercise-induced changes in autonomic function on the QT interval. This is important as changes in the output of the different components of the autonomic nervous system have varying effects on the QT interval at different intensities of exercise and in differing disease states, actions that would be disguised by the pacing approach. Many interventions or diseases affect the autonomic nervous system and through this, the QT interval. If the effects of such interventions/diseases on the QT interval were to be measured in the absence of exercise-induced changes in the autonomic nervous system, then the effect of these interventions/diseases on the QT interval might be missed (Abildskov, 1976). Given the overwhelming importance of the autonomic nervous system in cardiovascular function, and as most cardiac diseases and many drugs affecting the QT interval are associated with changes in autonomic nervous system function, it is clearly important to incorporate the effects of the autonomic nervous system into the QT–HR data set, as the incremental exercise tests do.

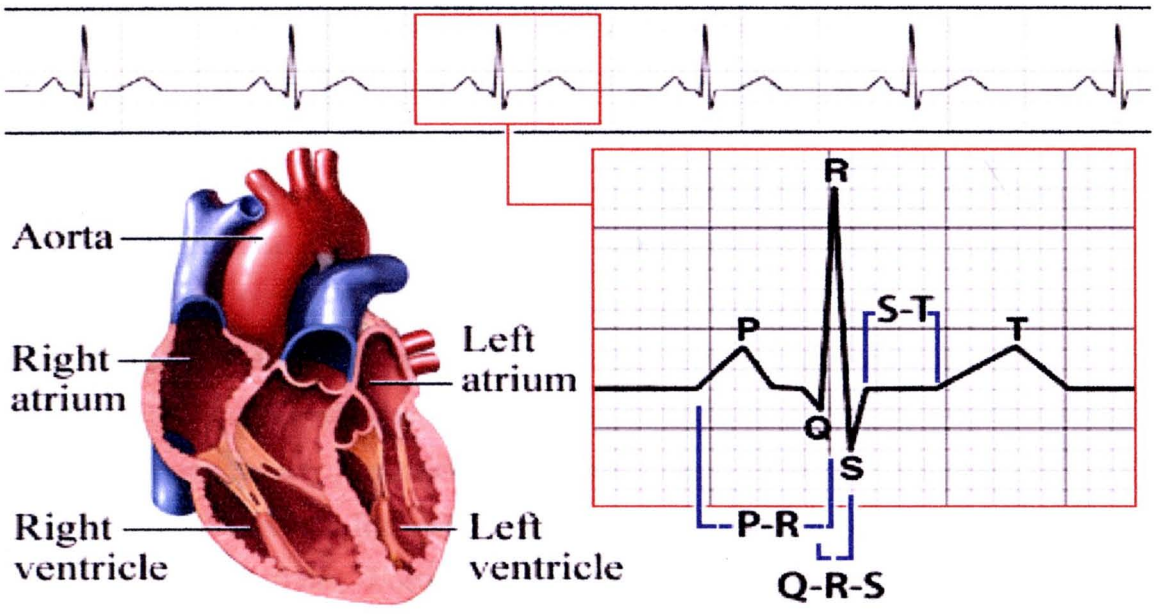

Figure 4 The normal ECG

6.4 Termination of the EST (Ellestad, 2003; Gibbons et al., 2002)

It's generally agreed by the physician that the test should be terminate when:

Absolute indications for termination of EST

1. Drop in SBP of greater than 10 mm Hg from baseline blood pressure, despite an increase in workload, when accompanied by other evidence of ischemia
2. Moderate to severe angina
3. Increasing nervous system symptoms (eg, ataxia, dizziness, near-syncope)
4. Signs of poor perfusion (cyanosis or pallor)
5. Technical difficulties in monitoring ECG tracings or SBP
6. Subject's desire to stop
7. Sustained ventricular tachycardia
8. ST elevation (>1 mm) in leads without diagnostic Q waves (other than V_1 or aVR)

Relative indications for termination of EST

(The following indications may be superseded if done so far good clinical reasons)

1. Drop in SBP greater than or equal to 10 mm Hg from baseline BP, despite an increase in workload, in the absence of other evidence of ischemia

2. ST or QRS changes such as excessive ST depression (>2 mm of horizontal or down-sloping ST segment depression) or marked axis shift.

3. Arrhythmias other than sustained ventricular tachycardia including multifocal premature ventricular contractions (PVCs), triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias

4. Fatigue, shortness of breath, wheezing, leg cramps or claudication

5. Development of bundle branch block or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia

6. Increasing chest pain

7. Hypertensive response

Patients should understand that they can stop voluntarily but are encouraged to try to reach or exceed maximum predicted HR.

6.5 Abnormal stress test response

There has been some confusion regarding the relative importance of the various stress test abnormalities in prediction morbidity and mortality. The low incidence of many cardiac events after an MI, especially death and recurrent infarction, necessitates a highly specific test to perform adequately as an accurate predictor. Most abnormalities with stress testing are of moderate specificity; therefore, only low-risk and high-risk groups can be identified. Despite these problems, certain trends and conclusion can be inferred that are clinically useful.

ST segment depression

The development of ST segment depression with exercise is probably the most reliable sign of myocardial ischemia and appears to be the most useful parameter of prognostic importance. Previous studies found that exercise induced ST segment depression of 1 mm or greater on a submaximal treadmill protocol was highly predictive of subsequent mortality during a one year period (Theroux et al.,

1979). Sami and coworkers found that an eightfold increased risk of cardiac arrest and recurrent infarction in patients with ST segment depression of 2 mm or greater on a modified symptom-limited treadmill test. There was a tendency toward increased risk with greater ST segment depression (Sami et al., 1979). The accuracy of exercise-induced ST segment depression in providing prognostic information can be influenced by several factors. Early termination of the stress test at a predetermined level of exercise may result in underestimation the incidence of ischemic ST chances. Resting ST segment abnormalities, digitalis effect, myocardial hypertrophy and conduction abnormalities make interpretation of exercise-induced ST segment changes difficult.

Angina

Few studies have investigated exercise-induced angina as an isolated prognostic factor, although it occurs in 5% to 40% pf patients undergoing post- MI exercise testing (Ericsson et al., 1973; Sami et al., 1979). Angina reflects the subjective status of patients and provides an incentive to intervene therapeutically.

Hemodynamic Response

Certain hemodynamic responses to predischarge treadmill stress testing are also important. Reduced exercise capacity roughly reflects impaired left ventricular function and may attribute its prognostic value to this association (Paine et al., 1978). Inadequate BP response (defined as an increase of 10 mm or less in SBP with systolic pressure from peak SBP) also appeared predictive of coronary events and seemed to correlate with exercise duration (Starling et al., 1980). In addition, high peaks HR at low work loads have implied a poor prognosis, presumably indicating an impaired myocardial function and low stroke volumes. Naturally, HR and BP responses will be blunted if the patients are taking beta blockers, nitrates or antihypertensive medications.

ST segment elevation

Exercise-induced ST segment elevation is common in subjects with post-MI stress tests in leads where Q waves are present (De Feyter et al., 1982; Taylor et al., 1980).

6.6 **Interpretation of the EST** (Gibbons et al., 2002)

Interpretation of the exercise test should include exercise capacity and clinical, hemodynamic, and ECG response. The occurrence of ischemic chest pain consistent with angina is important, particularly if it forces termination of the test. Abnormalities in exercise capacity, SBP response to exercise and HR response to exercise are important findings. The most important ECG findings are ST depression and elevation. The most commonly used definition for visual interpretation of a positive exercise test result from an ECG standpoint is greater than or equal to 1 mm of horizontal or downsloping ST segment depression or elevation for at least 60 to 80 milliseconds (ms) after the end of the QRS complex (Eagle et al., 1999). By these criteria, the test has approximately 65-70% sensitivity and 75-80% specificity in detecting patients with anatomically significant coronary disease. The stress test is considered marked positive if one or more of the following signs of severe ischemic heart disease occur: 1) the ischemic ECG changes develop in the first 3 minutes of exercise or persist 5 minutes after exercise has stopped, 2) the magnitude of the ST segment depression is $\geq$ 2 mm, 3) the SBP decreases during exercise, 4) high grade ventricular arrhythmia develop, 5) the patient cannot exercise for at least 2 minutes because of cardiopulmonary limitations. Patients with markedly positive tests are more likely to have severe and multivessel coronary disease.

The utility of a stress test may be affected by the patient's medication. For example, β-blockers or certain calcium channel blockers may blunt the ability to achieve the target heart rate. In these situations, one must consider the purpose of the stress test. If it is to determine whether ischemic heart disease is present, then those medications are typically withheld for 24-48 hours before the test. On the other hand, if the patient has known ischemic heart disease and the purpose of the test is to assess the efficacy of the current medical regimen, then testing should be performed while the patient takes his or her usual antianginal medications.

6.7 Type of treadmill protocols

Bruce protocol

Bruce protocol is a multistage treadmill protocol. The workload is increased by changing both the treadmill speed and percent grade. During the first stage of the test, the normal individual walks at a 1.7 mph pace at 10% grade. At the start of the second stage (minutes 4 to 6), increase the grade by 2% and the speed to 2.5 mph. In each subsequent stage of the test, increase the grade 2% and the speed by either 0.8 0r 0.9 mph until the patient is exhausted. Prediction equations for this protocol have been developed to estimate the $\dot{V}O_{2,max}$ of active and sedentary women and men, cardiac patients, and people who are elderly (Bruce et al., 1973). The Bruce protocol formula for estimating $\dot{V}O_{2,max}$ are present in below;

For men ;

$$\dot{V}_{O2,max} = 14.8 - (1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)$$

For women;

$$\dot{V}_{O2,max} = 4.38 \times T - 3.9$$

T = Total time on the treadmill measured as a fraction of a minute

Table 3 The incline and speed in the Bruce protocol

Stage	Speed (mph)	Grade (%)	Time (min)	METs
Rest/recovery	1.2	0	3	1.9
1	1.7	10	3	4.6
2	2.5	12.4	3	7
3	3.4	14	3	10.1
4	4.2	16.5	3	12.9
5	5	18	3	15
6	5.5	20	3	16.9
7	6	22	3	19.1