INTRODUCTION

Coronary artery disease (CAD) is the foremost cause of death in many countries and hence, its early diagnosis is usually concerned as a major healthcare priority ***(Abbas Arjmand Shabestari, 2013)***. In developed countries coronary heart disease is the leading cause of death in men and women. In Europe CHD accounts for an estimated 1.95 million deaths each year ***(Peterson et al., 2005).***

Atherosclerosis represents a state of heightened oxidative stress which is characterized by lipid and protein oxidation in the vascular wall. Production of reactive oxygen species (ROS) is a particularly destructive aspect of oxidative stress. In the setting of CAD, reactive oxygen species are proposed to play a significant role in tissue necrosis and reperfusion injury. Increased free radicals and various inflammatory mediators in atherosclerosis can impair collagen synthesis, which is required for maintenance and repair of the fibrous cap and for triggering degradation of extracellular matrix macromolecules, which further weaken plaque's fibrous cap, enhance its vulnerability to rupture ***(Neha Uppal et al., 2014).***

The rationale behind stress testing is to increase myocardial oxygen demand by increasing heart rate, blood pressure and contractility. In patients with obstructive CAD, an imbalance between myocardial oxygen demand and supply will occur leading to myocardial ischemia. The earliest manifestation of myocardial ischemia is abnormal diastolic

function. With more prolonged ischemia, regional abnormalities occur. Later on, the ECG becomes abnormal and lastly, chest pain occurs ***(Marwick, 2003).***

Stress echocardiography represents a well validated tool in the diagnosis and assessment of patients with known or suspected coronary artery disease. Recently, data have emerged supporting the prognostic capabilities of stress echocardiography in patients with various levels of systolic dysfunction, diastolic abnormalities, and valvular heart disease ***(Cullen et al., 2011).***

The application of pneumatic sleeves around lower extremities is recognized for several purposes. The most common use is primarily for improving venous circulation and preventing venous stasis in broad population of postoperative patients in surgical wards but several studies have been conducted concerning the cardiovascular influence of different types of pneumatic sleeves ***(Amitia Bickel et al., 2010).***

Pneumatic compression is suspected to lead to an increase in the sensitivity of dobutamine stress echocardiography (DSE) by increasing in systemic vascular resistance, left ventricular wall stress and so it will increase the afterload and even shorten the time to a positive response, Gaining a positive response at an earlier stage not only shortens the test time but also shortens the time to restoration of the baseline HR ***(Dae-Won DW Sohn et al., 2008).***

AIM OF THE WORK

Is to assess whether pneumatic lower extremity compression during dobutamine stress echocardiography will increase the sensitivity of the test for detection of coronary artery disease compared to the regular dobutamine stress echocardiography.

Chapter One
DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Introduction:

The diagnosis of coronary artery disease was possible only through cardiac catheterization and invasive coronary angiography. To avoid the risks of an invasive procedure, stress testing is often employed for an initial assessment of patients with suspected coronary artery disease, serving as a gatekeeper for cardiac catheterization ***(Armin, 2012).***

Exercise test (ET) is the preferred initial noninvasive test for the diagnosis and risk stratification of coronary artery disease (CAD), however, its lower sensitivity may fail to identify patients at greater risk of adverse events ***(Arq. Bras. Cardiol et al., 2013).***

Exercise test (ET) plays an important role in the diagnosis and risk stratification of patients with known or suspected CAD However, it is established in the literature that left ventricle wall motion abnormalities detected by Stress Echocardiography (SE) appear earlier in the ischemic cascade than angina or ST segment changes ***(Picano et al., 2003).***

Pathophysiological mechanisms of stress echocardiography:

Stress echocardiography is the combination of 2D echocardiography with a physical, pharmacological, or electrical stress ***(Picano, 2003).***

Stress echocardiography is a low-cost, widely available procedure which is based on assessment of regional wall motion abnormality induced by exercise or increasing doses of dobutamine. Stress-induced new or worsening regional or global wall motion abnormality is a reliable predictor of ischaemia ***(Pakkal et al., 2011).***

The reduction of coronary reserve is the common pathophysiological mechanism. Regardless of the stress used and the morphological substrate, ischemia tends to propagate centrifugally with respect to the ventricular cavity: it involves primarily the subendocardial layer, whereas the subepicardial layer is affected only at a later stage if the ischaemia persists. In fact, extravascular pressure is higher in the subendocardial than in the subepicardial layer; this provokes a higher metabolic demand ***(Picano et al., 2003).***

Pharmacological stress echocardiography:

Pharmacological stress echocardiography is widely used for the diagnosis of coronary artery disease ***(Picano, 2008).***

i) Sympathomimetic stressors:

Several sympathomimetics have been used as stressors but, Dobutamine is by far the most widely used pharmacologic stressor and is suitable for most patients ***(Petros Nihoyannopoulos et al., 2009).***

ii) Vasodilator stressors:

The most widely used vasodilator stressors are Dipyridamole and Adenosine. Dipyridamole (or adenosine) mainly decreases subendocardial flow supply through its vasodilator effect. In the presence of coronary atherosclerosis, arteriolar dilation can paradoxically exert detrimental effects on regions already well perfused in resting conditions at the expense of regions or layers with a precarious flow balance ***(Sicari, 2008).***

iii) Combined stressors:

Combinations of dobutamine and dipyridamole have been used to simultaneously increase myocardial oxygen demand and accentuate flow discrepancy ***(William, 2005).***

Dobutamine Stress Echocardiography:

Mechanism of action of dobutaminme:

Dobutamine is a synthetic catecholamine resulting from the modification of the chemical structure of isoproternol. It has

a complex pharmacological profile with dose dependent effects on beta-1, beta -2 and alpha -1 adrenoreceptors ***(Picano, 2009).***

At low doses (up to 10 ug/kg per minute), marked inotropic effects occur, mediated by alpha-1 and beta-1 receptors stimulation which lead to stimulation of myocardial contractility in absence of significant increases in heart rate ***(Sawada, 2000).***

Higher doses of dobutamine induce a progressive increase of heart rate mediated by α_1-receptor stimulation. The result is an increase in the cardiac output as a result of both positive inotropic and chronotropic response. The drug also causes reduction of systemic vascular resistance mediated by β_2-receptor stimulation. The net result is usually a mild increase of systolic blood pressure, because the increase of cardiac output is partially counteracted by the reduction of systemic vascular resistance. The increase in heart rate and myocardial contractility results in an increase in myocardial oxygen demand, with subsequent hyperemia. This causes a secondary dilation of the coronary arteries and an increase in blood flow in normal coronary arteries ***(Elhendy, 2002).***

In myocardial regions supplied by a coronary artery with a critical stenosis, the increase in oxygen demand cannot be met by an adequate increase in blood flow. Hence, regional ischemia develops and causes regional wall motion abnormalities that can

be detected by two-dimentional echocardiography ***(Picano, 2009).***

Pharmacokinetics:

Dobutamine has proven to be a safe agent because of its short half life. The drug has an onset of action of 2 minutes and a maximum effect by 10 minutes. It is metabolized by catechol-o-Methyl transferase to inactive metabolites that are eliminated by the kidney by about 10 minutes after the interavenous infusion is discontinued ***(Crouse and Kramer, 2001).***

INDICATIONS

The principal indications of DSE are:

1) Patients who cannot exercise or exercise submaximally.
2) Patients with uninterpretable ECG caused by repolarisation abnormalities, pre-excitation, depression of ST segment at baseline, left bundle branch block.
3) Identification of viable myocardium.
4) Evaluation of severity of aortic stenosis with LV dysfunction.
5) Evaluation of patients of dilated cardiomyopathy.
6) Its role for evaluation of prosthetic valve function, severity of valvular regurgitation, provocation of outflow tract gradients in hypertrophic cardiomyopathy are yet to be validated for clinical use ***(Paul et al., 2004).***

Protocol

Protocols for DSE vary from institution to institution, particularly with regard to dobutamine dose (range 20 to 40 µg/kg per min), atropine addition (range 0 to 2 mg) and stage duration (range 2 to 8 min) ***(Paul et al., 2004; Sawada et al., 2001).***

Usually, centers that use lower peak doses of dobutamine use longer stage durations and stop beta-adrenergic blocking agent treatment more often before the test. To date, the most widely used protocol uses dobutamine up to 40 mg/kg per min, with the addition of atropine up to 1 mg ***(McNeill et al., 1992).***

According to this protocol, a rest electrocardiogram (ECG) and two-dimensional echocardiogram are acquired, intravenous access is secured, and dobutamine is then administered intravenously by an infusion pump, starting at 5 or 10 µg/ kg per min for 3 min, increasing by 10 µg/ kg per min. every 3 min up to a maximum of 40 µg/ kg per min.

In patients not achieving 85% of their theoretic maximal heart rate (220 beats/min minus age for men, 200 beats/min minus age for women) and without symptoms or signs of myocardial ischemia, atropine is administered on top of the maximal dose of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 min, with continuation of dobutamine infusion.

Throughout dobutamine infusion, the ECG (three leads) is continuously monitored and recorded (12 leads) at 1-min intervals. Blood pressure is measured and recorded by sphygmanometry or automatic device every 3 min.

The Echocardiogram is continuously monitored and recorded on video or quad screen during the final minute of each dobutamine (or atropine) stage and recovery.

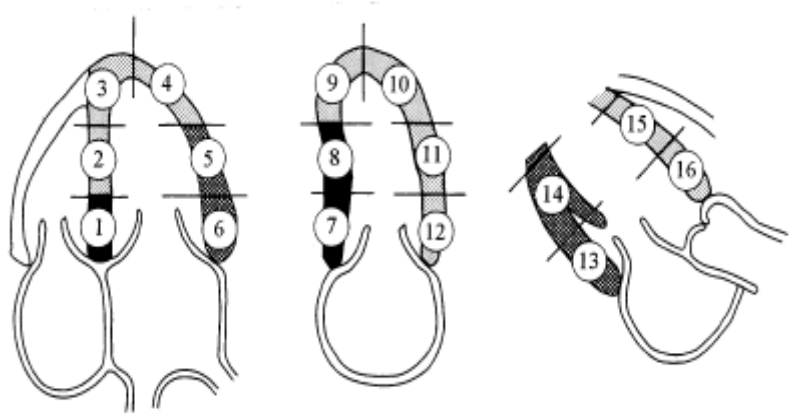

Figure (1): Diagrams showing the 16 regional wall segments and distribution of coronary perfusion. **Left**, apical four-chamber view; **middle**, apical two-chamber view; **right**, long-axis view. **Dotted areas** = left anterior descending coronary artery; **crosshatched areas** = left circumflex coronary artery; **solid areas** = right coronary artery.

Reasons for interruption of the test are severe or extensive new wall motion abnormalities; horizontal or downsloping ST segment depression >0.2 mV at an interval of 80 ms after the J point compared with baseline; ST segment elevation >0.1 mV in patients without a previous MI; severe angina; a symptomatic reduction in systolic blood pressure ≥ 40 mm Hg from baseline; hypertension (blood pressure ≥240/120

mm Hg); significant tachyarrhythmias; and any serious side effect regarded as due to dobutamine. A beta-blocker that can be injected intravenously must be available to reverse the effects of dobutamine if they do not revert spontaneously and quickly.

Contraindications to DSE include critical aortic stenosis, hypertrophic cardiomyopathy, uncontrolled hypertension, uncontrolled atrial fibrillation, known severe ventricular arrhythmias and electrolyte abnormalities (mainly hypokalemia) ***(Coma et al., 2005)***. The addition of atropine is contraindicated in patients with narrow angle glaucoma, myasthenia gravis, obstructive uropathy or obstructive gastrointestinal disorders.

DSE may be performed as an in–patient or out–patient procedure. A complete request with clinical diagnosis, reason for study and brief history is required. Any patient meeting any of the conditions of absolute contraindications (myocardial infarction less than 72 hours, unstable angina, hemodynamic instability, symptomatic ventricular arrhythmias, acute myocarditis/ pericarditis, intracardiac thrombus, uncontrolled hypertension, pregnancy, acutely ill patients) is excluded. The minimum personnel in attendance are a nurse, a technician and the physician who is to perform the test.

Any medication that can reduce the chronotropic response of the heart should be withheld in the morning. The subject should be fasting for a period of not less than 4 hours.

To ensure patient safety an emergency cart which is fully equipped with emergency medications, defibrillator etc. is kept ready. Upon arrival, physical assessment is done and an informed consent is obtained. Patient education before the test is of paramount importance ***(Paul et al., 2004).***

The vital parameters of the patient (heart rate, blood pressure, ECG, oxygen saturation) are monitored throughout the procedure. The patient is positioned properly (usually left lateral decubitus) for proper image acquisition. At baseline the resting images are acquired (parasternal long-axis and short-axis, apical two and four chamber views) which are digitized and stored ***(Paul et al., 2004).***

Echocardiographic interpretation

For purposes of analysis, the left ventricle is usually divided into the 16-segment model recommended by the American Society of Echocardiography **(Fig. 1)** ***(J Am Soc Echo et al., 1989)***.

Although the quad screen format (with rest, low and high dose and recovery images next to each other in one screen) facilitates wall motion analysis, it is not a prerequisite because videotape analysis seems to be as reliable ***(Castini et al., 1995)***.

Wall motion or thickening is reported according to an arbitrary numerical classification: 1= ***normal***, characterized by a uniform increase in wall excursion and thickening; 2 =

hypokinesia, denoted by reduced (< 5 mm) inward systolic wall motion; 3 = ***akinesia***, is marked by an absence of inward motion and thickening; 4 = ***dyskinesia***, indicated by systolic thinning and outward systolic wall motion. Hypokinetic segments can be further classified as *mild* (2A) or *severe* (2B) hypokinetic segments to refine the analysis.

A ***normal stress echocardiogram*** is defined by a uniform increase in wall motion and systolic wall thickening, with a reduction in end-systolic cavity area.

A ***positive test*** is denoted by development of new wall motion dyssynergy or by worsening of regional dyssynergy in one or more segments.

In patients with rest wall motion abnormalities, use of the "biphasic" response (i.e., initial improvement of dyssynergy at low dose followed by worsening of dyssynergy at high dose) has improved detection of CAD ***(Lahiri et al., 1999)***.

More subtle criteria for positive test are tardokinesia (delayed excursions) and relative failure to augment wall thickening. These more subtle criteria should be used with caution by inexperienced interpreters because too strict application could lead to substantial loss in specificity ***(Carstensen et al., 2005)***.

Moreover, isolated mild wall motion deterioration in mid- or basal inferoposterior segments needs to be interpreted

with caution because these segments are known to be less specific for CAD ***(Carstensen et al., 2005)***.

Several investigators have reported ***(Fioretti et al., 2005; Jeane, 2004)*** that the inclusion of rest wall motion abnormalities in addition to new or worsening wall motion abnormalities as a criteria for positive test results in a gain in sensitivity without a loss in specificity for the detection of CAD. However, the inclusion of rest wall motion abnormalities as a criterion for CAD is appropriate only in patients without a previous MI because in patients with a previous MI, this diagnosis is nearly certain and does not require further testing for this purpose.

Other possible dobutamine-induced markers of ischemia.

Abnormal left ventricular diastolic filling.

Changes in diastolic indexes are known to precede systolic changes and therefore may be a more sensitive indicator of myocardial ischemia.Despite the finding that left ventricular filling is predominantly mediated by a complex interaction of active myocardial relaxation, passive filling properties and left atrial pressure, one study clearly demonstrated ***(El-Said et al., 2004)*** that during dobutamine stress testing, an abnormal response of Doppler indexes of left ventricular early filling (E velocity) is a more sensitive marker for the detection of significant single vessel disease than are wall motion abnormalities. Other, confirmative publications are

needed to firmly establish the clinical utility of left ventricular filling indexes.

Sinus node deceleration.

Dobutamine stress-induced sinus node deceleration, defined as an initial increase and subsequent decrease in heart rate with progressive dobutamine infusion, occurs more often during dobutamine infusion than during exercise ***(Hopfenspirger et al., 1994)***.

In a small group of patients, it was reported to be a specific marker of inferior wall ischemia, as assessed by dobutamine perfusion scintigraphy. Currently, there are no stress Echocardiographic data reporting the pathophysiology of isolated sinus node deceleration. Cardiac slowing, in particular in combination with hypotension (see later), may also result from a neurally mediated cardiovascular vasodepressor reflex ***(Oakley et al., 2004)***.

Mitral regurgitation

Low dose dobutamine is known to have a beneficial effect on chronic mitral regurgitation, especially in patients with left ventricular dysfunction ***(Heinle et al., 1995)***. Although the mechanism of this beneficial effect remains unclear, it may be related to a decrease in afterload or mitral orifice size that results from the vasodilatory and inotropic effects of dobutamine ***(Tanimoto et al., 1995)***. It has been suggested that