INTRODUCTION

Dobutamine-atropine stress echocardiography (DASE) is well established in clinical practice, as it is considered to be one of the main methods of imaging to determine the presence of myocardial ischemia.

Currently, the use of the 3 min. protocol has become the most popular, beginning at 5 μg/kg/min infusion of dobutamine and reaching a maximum dose of 40 μg/kg/min, with the addition of atropine from the final stage on.

Even though atropine has been used more often at the end of the stress test to increase heart rate and accuracy, this agent is usually administered during or soon after the maximum dose of dobutamine, with the patients receiving prolonged amine infusions which may increase side effects. Besides, the test time is often extended.

Considering that a significant number of patients (32%) do not reach a dobutamine stress echocardiographic end point with the standard protocol ***(Weissman A et al., 1995)***, and the increasing use of Beta blockers as anti-ischemic or anti-hypertensive medication in the last decade, the following question should be considered: Are the protocols employed in stress echocardiography still in agreement with current medical practice?

If the range of the ideal heart rate, which is of extreme importance to the accuracy of the method, is compromised, then the need for a more homogenous protocol which counterbalances the employed therapeutic effect becomes relevant so as to avoid damage to the diagnostic and prognostic information of the test.

AIM OF THE WORK

The aim of this study is to assess the sensitivity, validity & safety of atropine when initiated early during dobutamine stress echocardiography in relation to its later usage.

STRESS ECHOCARDIOGRAPHY

Cardiac ultrasound was first demonstrated to be a promising diagnostic technique in the late 1960s. The overwhelming majority of clinical work in the early era involved evaluation of patients with pericardial and valvular heart disease. It was only later that echocardiographic techniques were used in the evaluation of patients with ischemic heart disease.

Clinical use in coronary artery disease (CAD) did not see fruition until well after the development and widespread dissemination of two-dimensional (2D) imaging platforms.

Reliance on the resting echocardiogram alone allowed detection of myocardial infarction and assessment of left ventricular (LV) function. The fortuitous observation that transient myocardial ischemia, as seen with spontaneous angina, resulted in wall-motion abnormalities suggested an opportunity to evaluate patients for the presence of provoked ischemia.

These early observations regarding the potential use of echocardiography in ischemic heart disease came at a time when the shortcomings of electrocardiographic (ECG) analysis alone for detecting CAD, and the advantages of evaluating myocardial function with radionuclide ventriculography and perfusion imaging during stress, were becoming well appreciated.

The impetus for development of stress echocardiography was the drive to gain an equivalent degree of clinical relevance, if not outright superiority, over the competing imaging techniques for evaluation of patients with known or suggested CAD. ***(William F et al. , 2008)***

EARLY FEASIBILITY AND VALIDATION

The initial reports of stress echocardiography were largely feasibility studies. It should be recognized that during the early days of stress echocardiography, 2D echocardiographic imaging was limited to 30-degree scanners with limited gray-scale resolution and remarkably low frame rates.

This, combined with the challenges of imaging a heart during exercise, presented formidable obstacles. Nevertheless, several pioneers, including investigators in the Indiana University Echocardiography laboratory (Indianapolis, IN), pursued the objective of 2D echocardiographic imaging during stress with supine bicycle exercise **Figure** (1-1) ***(William F et al. , 2008)***

In 1979 a landmark article, ***(Wann et al., 1979)*** demonstrated the feasibility of identifying exercise-induced wallmotion abnormalities with 2D echocardiography and their

resolution after successful coronary artery bypass surgery ***(William F et al., 2008).***

One of the first proposed solutions to the technical challenges of exercise echocardiography was to record the echocardiographic images immediately after treadmill exercise. This had the advantage of allowing exercise with a format more familiar than bicycle stress, while continuing to use protocols for ECG analysis that were of proven diagnostic accuracy.

Thus, the Echocardiographic imaging became an add-on to a standard treadmill exercise test, which was the accepted and traditional form of evaluating patients for known or suggested CAD. The initial studies were performed using standard methodology for recording of 2D echocardiograms on videotape allowing for sequential but not side-by-side evaluation of LV wall motion from videotaped images. ***(Robertson et al., 1983)***

Stress echocardiography languished for several years after these early reports of feasibility because of the cumbersome nature of acquiring exercise or postexercise imaging and the inability to compare rest and stress images in a side-by-side format for detection of subtle abnormalities.

It was not until the mid-1980s, when early offline digital acquisition systems became available, that this type of comparison became feasible. These systems allowed capture of individual echocardiographic loops, which then could be edited

to remove cycles that had marked translational motion or respiratory artifact. These were then played back as a continuous loop allowing for a more reliable evaluation of myocardial thickening and wall motion abnormalities. Side-by-side display of rest and post stress images became available shortly afterward ***(William F et al., 2008)***.

One of the early studies ***(O'Donnell et al., 1986)*** using digital methodology for evaluation of stress echocardiograms came from the echocardiography laboratory at Indiana University and was published in 1986.

Intriguingly, the title of this study "Complementary Value of Two-dimensional Exercise Echocardiography to Routine Treadmill Exercise Testing" concluded that the Echocardiographic portion would be additive and complementary to standard treadmill parameters when the ECG response was nondiagnostic.

The advent of digital systems for acquisition and display of echocardiograms resulted in an exponential increase in interest in stress echocardiography as a competitor to the well-established radionuclide-based techniques.Today, after multiple, far more advanced and larger studies than this modest study of 95 individuals, it has become apparent that the Echocardiographic data are far more robust than those obtained by analysis of the ECG alone, independent of the nature of the ECG response ***(William F et al. 2008)***.

The technical difficulty of acquiring images at the time of physical stress led to efforts at nonexercise forms of stress, such as handgrip exercise, which was demonstrated in early studies to be a feasible means of inducing ischemia. Subsequently, pharmacologic approaches to stress echocardiography were developed.

In the United States, based in part on cost considerations, dobutamine rapidly became the favored agent as a combined inotropic and chronotropic mimicker of physical exercise. In Europe, vasodilator stress with dipyridamole became the favored agent for stress echocardiography. The bias toward dipyridamole in Europe was similarly based on cost considerations. At the time of the early studies, a dose of dipyridamole in the United States was approximately $130 per testing dose compared with the cost of well under $1 in Europe, whereas the cost of dobutamine in Europe was 4 to 10 times higher than that in the United States. ***(William F et al., 2008)***.

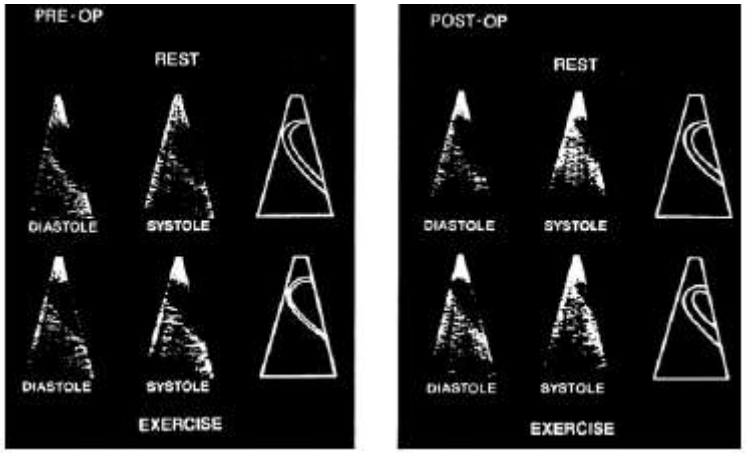

Figure (1-1):- Early two-dimensional stress echocardiogram using 30-degree scanner. Rest and stress images demonstrate apical dyskinesis at time of bicycle exercise (*left*) and resolution of exercise-induced ischemia after successful coronary artery bypass surgery (*right*).***(Wann et al.,1979).***

The search for an appropriate pharmacologic stressor in the United States included attempts at vasodilator stress and a pure heart rate increase with atropine. Other agents used in an effort to identify the ideal stressor included isoproterenol and dopamine. Dopamine was limited in its heart rate response and the downside of significant side effects if inadvertently extravasated from the intravenous space. Patient tolerance for isoproterenol infusion was poor. It rapidly became apparent that dobutamine was well tolerated by the overwhelming majority of patients and provided a relatively balanced inotropic and chronotropic response that mimicked the stages of physical exercise on a treadmill or bicycle ergometer ***(William F et al.,2008)***.

PATHOPHYSIOLOGY

Exercise and inotropic stress normally provoke a generalized increase of regional wall motion and thickening, with an increment of ejection fraction mainly caused by a reduction of systolic dimensions.

Regional systolic dysfunction is usually caused by coronary artery disease, but cardiomyopathies may also show regional variation in function. ***(Armstrong WF 2003)***.

Resting wall motion abnormalities are the hallmark of prior myocardial infarction, but do not necessarily imply that the segment is non-viable.The presence of residual viable tissue is more common in hypokinetic than akinetic segments, and least common in dyskinetic segments.

However, hypokinesis may also imply non-transmural infarction, and even perfusion data or the dobutamine response may not solve this ambiguity.

Ischemia is typically manifest as new or worsening wall motion abnormalities**,** delayed contraction, or (if severe) the development of left ventricular enlargement or a decrease in ejection fraction.

Regional systolic changes generally precede the development of ST segment changes and chest pain, but follow the initial development of abnormalities of diastolic function and regional malperfusion.

The presence of inducible wall motion abnormalities implies a significant limitation of blood flow at peak stress, and usually corresponds to a stenosis of > 50% diameter, although the anatomic severity and physiologic consequences are poorly related.

The provocation of ischaemia in the setting of relatively mild coronary stenoses is dependent on the performance of maximal stress. Inducible wall motion abnormalities often recover rapidly after stress, but may be persistent if ischaemia is severe and stunning is induced ***(Thomas H,2003)***.

Contraindications to stress testing

The following contraindications are from the AHA/ACC guidelines published in 1997.

Absolute contraindications :-

- Acute myocardial infarction (within 2 d).
- Unstable angina not previously stabilized by medical therapy.
- Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise.
- Symptomatic severe aortic stenosis.
- Uncontrolled symptomatic heart failure.
- Acute pulmonary embolus or pulmonary infarction.

- Acute myocarditis or pericarditis.
- Acute aortic dissection.

Relative contraindications: -

Relative contraindications can be superseded if the benefits of exercise outweigh the risks.

- Left main coronary stenosis.
- Moderate stenotic valvular heart disease.
- Electrolyte abnormalities.
- Severe arterial hypertension: In the absence of definite evidence, the committee suggests an SBP of greater than 200 mm Hg and/or a DBP of greater than 110 mm Hg.
- Tachyarrhythmias or Brady arrhythmias.
- Hypertrophic cardiomyopathy and any other forms of outflow tract obstruction.
- Mental or physical impairment leading to an inability to exercise adequately.
- High-degree atrioventricular (AV) block. ***(David & Sarath,2008)***.

Stress Echocardiography Methodology

Either physical or pharmacologic stress can be used **Table (1-1)**.

The choice of exercise (treadmill vs. bicycle) has become a matter of laboratory choice and patient acceptability.

With treadmill exercise, only post-exercise imaging is available. This results in the possibility of WMA resolving rapidly and hence a false-negative study. This effect is most likely with milder or single-vessel stenosis.

Bicycle exercise has the advantage of imaging the heart at peak exercise. This may result in detection of a greater extent of ischemia and in a theoretical increase in sensitivity.

If post-treadmill imaging is utilized, it is imperative that imaging be completed within 45 to 60 s to avoid resolution of stress-induced WMA ***(William A et al., 2005)***.

Exercise
Post-treadmill exercise.
Supine bicycle.
Upright bicycle.
Pharmacologic
Dobutamine infusion (±atropine).
Dipyridamole (±atropine).
Adenosine (±atropine).
Combined dobutamine–dipyridamole.
Other
Transesophageal atrial pacing.
Transvenous pacing (temporary or permanent).
Ergonovine. *
Hyperventilation. *
Cold pressor.

* For provocation of coronary vasospasm.

Table (1-1):-. Stress Echocardiography Methods

For patients incapable of adequate physical exercise, pharmacologic stress can be substituted. The most commonly employed agents are dobutamine and dipyridamole (or adenosine). Based on a number of factors, including cost, dobutamine has been the preferred agent in the U.S.

Combinations of dobutamine and dipyridamole have been used to simultaneously increase myocardial oxygen demand and accentuate flow discrepancy. Pacing stress, using either a temporary transvenous catheter, an implanted pacemaker, or transesophageal atrial pacing, is also an alternative to exercise. ***(William A et al.,2005)***.

For patients capable of exercise, in whom the question is the presence or absence of CAD or for evaluation of dyspnea and fatigue, exercise is preferred to pharmacologic testing because it allows a link to be drawn between physical activity and provokable abnormalities. Similarly, while the response of pulmonary artery pressures (measured from the tricuspid regurgitation jet) to exercise has been validated, the same conclusion cannot be made when using pharmacologic stress. ***(William A et al., 2005)***.

Table (1-2) outlines the commonly employed stress Echocardiographic methodologies that should be considered as primary, alternative, or not recommended depending on the clinical question to be addressed.