"UTILITY VALUE OF TISSUE DOPPLER IN AORTIC STENOSIS; E/Ea VALUES PREDICT SYMPTOMS AND FUNCTIONAL CAPACITY IN PATIENTS WITH AORTIC STENOSIS"

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AUGUST 2010

"Learn to heal"

CERTIFICATE

This is to certify that the dissertation entitled **"UTILITY VALUE OF TISSUE DOPPLER IN AORTIC STENOSIS; E/Ea VALUES PREDICT SYMPTOMS AND FUNCTIONAL CAPACITY IN PATIENTS WITH AORTIC STENOSIS"** is the bonafide original work of **DR.C.KRISHNAKUMAR** in partial fulfillment of the requirements for D.M. Branch-II (CARDIOLOGY) examination of THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY to be held in August 2010. The period of post-graduate study and training was from July 2007 to July 2010.

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DECLARATION

I **Dr. C.KRISHNAKUMAR,** solemnly declare that this dissertation entitled, **"UTILITY VALUE OF TISSUE DOPPLER IN AORTIC STENOSIS; E/Ea VALUES PREDICT SYMPTOMS AND FUNCTIONAL CAPACITY IN PATIENTS WITH AORTIC STENOSIS"** is a bonafide work done by me at the department of Cardiology, Madras Medical College and Government General Hospital during the period 2007 – 2010 under the guidance and supervision of the Professor and Head of the department of Cardiology of Madras Medical College and Government General Hospital, Professor **Geetha Subramanian, M.D.D.M.** This dissertation is submitted to The Tamilnadu Dr.M.G.R Medical University, towards partial fulfillment of requirement for the award of **D.M. Degree (Branch-II) in Cardiology.**

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Dr.C.KRISHNAKUMAR

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CONTENTS

INTRODUCTION

Aortic stenosis (AS) continues to be an important valvular heart disease that leads to significant morbidity and mortality. The natural history of aortic stenosis is limited by onset of left ventricular systolic dysfunction. Nowadays the importance of identifying diastolic dysfunction in patients with aortic stenosis is being recognized since it contributes significantly to the onset of symptoms and prognosis[1].

Left ventricular (LV) hypertrophy is an adaptive process that compensates for pressure overload associated with aortic stenosis and is responsible for changes in systolic and diastolic functions[2-4]. This process is accompanied by a remodeling of the LV that involves the muscular and non muscular compartments of the ventricle. As a result of this remodeling process, muscle fiber hypertrophy and abnormalities of the collagen network occur that are responsible for changes in systolic and diastolic functions[5,6].

Although it has been previously shown that aortic valve replacement may lead to immediate hemodynamic improvement and to prolongation of survival[7], it has been reported that regression of myocardial hypertrophy after relief of the hemodynamic burden is a process that may continue for decades after valve replacement[2]. However, abnormal exercise hemodynamics may persist late after valve replacement despite a normal systolic function, suggesting impaired diastolic function in these patients.

LV systolic function may be normal in the presence of advanced diastolic dysfunction in aortic stenosis. Patients with aortic stenosis develop variable grades of diastolic dysfunction even before the onset of symptoms[7].

Changes in the structures within the extracellular matrix (ECM) can also affect diastolic function. The myocardial ECM is composed of 3 important constituents:

(1) fibrillar protein, such as collagen type I, collagen type III, and elastin;

(2) proteoglycans;

(3) basement membrane proteins, such as collagen type IV, laminin, and fibronectin

It has been hypothesized that the most important component within the ECM that contributes to the development of diastolic heart failure is fibrillar collagen. The evidence that suggests that changes in ECM fibrillar collagen play an important role in the development of diastolic dysfunction and diastolic heart failure in the following three ways[11-15].

First, disease processes that alter diastolic function also alter ECM fibrillar collagen, particularly in terms of its amount, geometry, distribution, degree of crosslinking, and ratio of collagen type I versus collagen type III.

Second, treatment of these disease processes, which is successful in correcting diastolic function, is associated with normalization of fibrillar collagen.

Third, experiments in which a chronic alteration in collagen metabolism is accomplished result in an alteration of diastolic function[16-21]. The role played by other fibrillar proteins, the basement membrane proteins, and the proteoglycans remains largely unexplored.

Whether to perform valve replacement in patients with asymptomatic, but severe aortic stenosis is controversial. Physician usually reluctant to refer patients with severe aortic stenosis for valve replacement as long as they remain asymptomatic. However, there remains concern about the risk of irreversible myocardial damage or

sudden death among such patients who do not undergo surgery. In contrast to patients with valvular regurgitation, patients with severe aortic stenosis who are still asymptomatic but already have impaired left ventricular function are very rare.

Once severe degrees of diastolic dysfunction develop in the pre operative period, patients will be persistently symptomatic even after aortic valve replacement. These patients also have increased short and long term mortality. This is due to persistence of left ventricular diastolic dysfunction in those patients which results in increased morbidity and mortality.

So, it is very important to identify the patients with aortic stenosis and normal LV function, before they develop higher grades of LV diastolic dysfunction. They should undergo aortic valve replacement eventhough their systolic function is normal.

According to ACC/AHA 2006 (American college of cardiology / American heart association) guidelines for operability in valvular heart disease, class 1 indication for isolated aortic valve replacement in patients with severe aortic stenosis and normal LV systolic function is the presence of symptoms[22]. So, in this study our aim is to find out an echocardiographic diastolic index which correlates with LV diastolic dysfunction and symptoms.

In this study to test the functional capacity and the severity of symptoms six minute walk test (6MWT) was performed. The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality.

Echocardiography has been and continues to be the most commonly used and most readily available investigation modality for the assessment of diastolic dysfunction.

Various echo parameters have been in use, like the early and late transmitral filling velocities (E & A), deceleration time of E slope, isovolumic relaxation time, pulmonary vein systolic and diastolic velocities, pulmonary vein atrial flow reversal velocity and duration etc. Each of them lacks sensitivity and specificity when applied individually; they have their own drawbacks, and even the combination of various parameters always can not give a better and more accurate estimate of diastolic dysfunction. Even routine grading of diastolic dysfunction also has limitation in differentiating

1. Pseudo normal and normal patterns
2. Grade 3 and grade 4 diastolic dysfunctions,

and most of the times it needs tissue doppler imaging to differentiate them.

Tissue Doppler derived indices like Ea and E/Ea may be used to identify the presence and severity of diastolic dysfunction. E/Ea value of more than fifteen correlates with pulmonary capillary pressure of more than 20 mmHg. In the presence of severe LV systolic dysfunction, increased E value and DT of less than 130 msec both correlate to elevated PCWP. But with normal LV systolic function both lose their correlation to PCWP. E/Ea value is not modified by the presence of LV systolic dysfunction. E/Ea is preload, afterload and heart rate independent index. So, it is more reliable even in circumstances which modify the above factors.

Apart from these, other methods available for measuring diastolic dysfunction are cardiac catheterization and magnetic resonance imaging (MRI). Cardiac catheterization has limitation in the form of being invasive and cumbersome calculations. MRI has limited availability and being costlier. Echocardiography will continue to be the first line investigation of choice for the assessment of diastolic dysfunction for the time to come.

AIM OF THE STUDY

- To find out the tissue doppler derived E/Ea values in patients with moderate and severe aortic stenosis.
- To assess the presence of diastolic dysfunction in patients with aortic stenosis.
- To find out the relationship between the E/Ea values and presence of symptoms in patients with AS.
- To correlate the six minute walk distance to E/Ea values in patients with moderate and severe AS.
- To find out the relationship between various diastolic indices and symptoms in patients with AS

REVIEW OF LITERATURE

Etiology and pathogenesis of aortic stenosis:

Valvular heart disease continues to be an important threat to human community across all part of the world. Valvular aortic stenosis accounts for almost two thirds of aortic valve replacements done recently. Obstruction to left ventricular outflow may occur at the valvular, sub valvular and supra valvular levels. Left ventricular out flow obstruction commonly at the level of aortic valve (valvular AS) is being studied in this thesis.

Valvular AS has three principal causes;

1. Degenerative (calcific)
2. Rheumatic etiology
3. Congenital bicuspid aortic valve stenosis (BCAV)

Other rare causes of aortic stenosis include atherosclerosis, severe hyper cholesterolemia, rheumatoid arthritis, ochronosis and alkaptonuria.

Congenital aortic stenosis;

Congenital malformations of aortic valve may be unicuspid, bicuspid, tricuspid and dome shaped valve stenosis. Unicuspid valve produces severe obstruction in infancy and is the cause for most of the fatal aortic stenosis under one year of age. Bicuspid aortic valve is more frequent in men than in women with ratio being 4:1. It is transmitted in autosomal dominant pattern[23,24]. A mutation in NOTCH1 gene has been described as the cause for bicuspid aortic valve[25].

A bicuspid aortic valve normally functions in childhood. Most of the patients with BCAV develop severe aortic stenosis in later in adulthood. They typically present with

severe AS above the age of fifty years. They have associated medial abnormality and present with post stenotic dilatation of ascending aorta. Although the histopathology of BCAV with aortic stenosis is no different than that of tricuspid aortic valve stenosis, the turbulent flow and leaflet stress cause the BCAV to present earlier with stenosis than tricuspid aortic valve.

Calcific aortic stenosis:

Age related calcific AS of tricuspid and bicuspid aortic valve has emerged as the most important cause of aortic stenosis in elderly. Calcific AS was formerly termed as senile or degenerative AS. Above 65 years of age 2% of general population have severe calcific AS and nearly 29% have age related sclerosis of the aortic valve without stenosis. Patients with calcific valve disease irrespective of the degree of obstruction have 50% increased mortality from coronary artery disease and cardiovascular deaths[26-28].

The risk factor for development of calcific AS is the same as for atherosclerosis like elevated serum levels of LDL cholesterol, diabetes mellitus, smoking and hypertension. Calcific AS also linked to inflammatory markers and components of metabolic syndrome. Retrospective studies have proved that treatment with statins reduces the progression of calcific AS and this effect has been demonstrated in animal models.

Rheumatic aortic stenosis:

Rheumatic heart disease most commonly affects mitral valve in the form of either stenosis or regurgitation. Aortic valve involvement in rheumatic etiology is most often associated with mitral valve involvement. Only a less number of patients have isolated aortic valve involvement in rheumatic heart disease.

Rheumatic AS results from fusion of commisures and cusps. There is also revascularization of leaflets of valve ring. This leads to stiffening of the free borders of the cusps. Calcific nodules develop on both side of the cusps and the orifice is reduced small triangular or round opening. As a consequence the rheumatic valve is often regurgitant as well as stenotic. With the decline in rheumatic fever, the incidence of rheumatic AS declines in western part of the world; it remains to be an important problem worldwide.

NORMAL AORTIC VALVE

Figure1; Normal aortic valve showing three leaflets, there is no calcification

DEGENERATIVE AORTIC STENOSIS

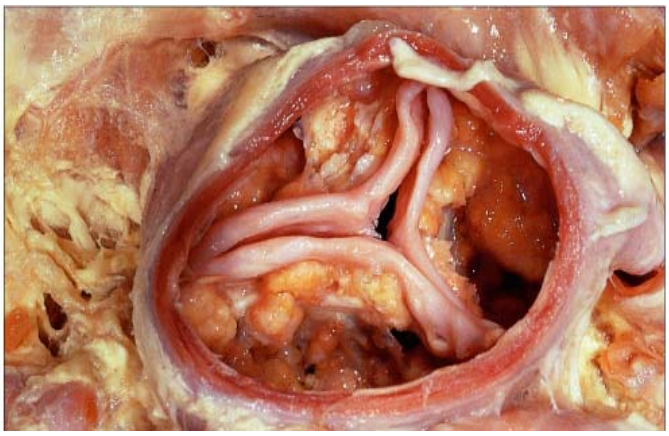

Figure 2; Degenerative AS showing thickened and heavily calcified leaflets

Pathophysiology of aortic stenosis:

In adults with AS, the severity of stenosis develops over prolonged period. Left ventricular systolic function is well maintained in patients with AS because the left ventricle (LV) adapts to slowly developing increase in wall stress. Even in patients with severe AS the cardiac output is maintained by the presence of severe LV hypertrophy. The presence of LV hypertrophy which sustain a large pressure gradient across the aortic valve for many years with out reduction in cardiac output, LV dilatation, or the development of symptoms.

According to ACC/ AHA guideline for valvular heart disease in 2006, severe AS is defined as

1. Peak velocity across the aortic valve more than 4 m/sec
2. Mean gradient across the aortic valve of more than 40 mmHg.
3. Aortic orifice by continuity equation, less than $1cm^2$ ($0.6cm^2$ / m^2 body surface area)
4. Left ventricular outflow tract TVI / Aortic valve TVI $\leq$ 0.25 (TVI-time velocity integral)

Moderate aortic stenosis is defined as,

1. Peak velocity across the aortic valve between 3 and 4 m/sec
2. Mean gradient across the aortic valve between 25 and 40 mmHg
3. Aortic valve orifice between 1 and 1.5 cm^2

However the degree of stenosis associated with symptom onset varies between patients and there is no single number that defines the severe or critical AS in an individual patient. Clinical decisions are based on the consideration of symptom status

and the LV response to chronic pressure overload, in conjunction with hemodynamic severity.

Chronic pressure overload typically results in concentric LV hypertrophy with increased wall thickness and a normal chamber size. The increased wall thickness allows normalization of wall stress (afterload) so that LV contraction is maintained. However increased cell mass and interstitial matrix results in development of diastolic dysfunction, which may persist even after the relief of AS. Gender differences in LV performances in patients with aortic stenosis have been demonstrated; with women more frequently have normal LV performance with smaller, thick walled, concentrically hypertrophied LV with diastolic dysfunction with normal or even subnormal systolic wall stress. Men more frequently have eccentric left ventricular hypertrophy, excessive wall stress, systolic dysfunction and chamber dilation.

The ventricular changes caused by chronic pressure overload and reflected in left ventricular and left atrial pressure wave forms and in Doppler velocity curves. As the contraction of the left ventricle becomes progressively more isometric, the Doppler velocity curve exhibits a progressively later systolic peak. The elevated left ventricular end diastolic pressure and corresponding changes in doppler filling velocities which are characteristic of severe AS, reflects delayed relaxation and eventually decreased compliance of hypertrophied left ventricular wall. In patients with severe AS large a waves appear in left atrial pressure pulse and in Doppler left ventricular filling curve because of the combination of enhanced contraction of the hypertrophied left atrium and diminished left ventricular compliance.

Atrial contraction plays an important role in filling of left ventricle in AS. It increases left ventricular end diastolic pressure with elevation of mean left atrial pressure.

This booster pump function of left atrial contraction helps from prevention of developing pulmonary congestion, while at the time maintaining LV end diastolic pressure at the level to produce adequate cardiac output. Loss of atrial contraction as in atrial fibrillation or inappropriately timed atrial contraction as in atrioventricular dissociation leads to rapid clinical deterioration in patients with aortic stenosis.

Systemic vascular resistance also contributes to left ventricular afterload in patients with AS. Concurrent hypertension may affect the evaluation of severity of AS. Exercise physiology is altered in patients with moderate to severe AS and even asymptomatic patients will have reduced exercise tolerance. Although cardiac output is normal at rest, there is blunted response to exercise induced increase in cardiac output and mediated primarily by increase in heart rate with little change in stroke volume.

Even though the stroke volume is unchanged, transvalvular flow rate increases due to shortened systolic ejection time so that aortic jet velocity and transvalvular gradient increase proportionately. There will be small increase valve area during exercise in patients with AS, but when severity increases the valve area becomes fixed, resulting in greater jet velocity and gradient. At this point there is an abnormal blood pressure response to exercise in the form of fall or failure to rise in systolic blood pressure more than 10 mmHg, signifying severe AS.

Myocardial function in aortic stenosis:

The development of left ventricular hypertrophy is the one of the important mechanism by which left ventricle adapts to increased hemodynamic burden. The increased wall stress leads to increase in number of sarcomeres in parallel and leads to concentric hypertrophy. The increase in wall thickness is important in counterbalancing increase in systolic wall stress, as the AS develops slowly the wall stress remains normal.

In some patients inadequate wall thickening results in dilatation of LV cavity and left ventricular failure. This is called as afterload mismatch. There is true depression of left ventricular systolic function. In this group surgery is less effective.

Diastolic properties in patients with aortic stenosis:

Although left ventricular hypertrophy is a key adoptive mechanism in aortic stenosis to the pressure load imposed by AS, it has an adverse consequence in the form of decreased left ventricular compliance. As a result a greater intracavitary pressure is required for LV filling. Some patients with AS have an increase in stiffness of left ventricle, simply because of increased muscle mass with no alteration in diastolic properties of each unit of myocardium (normal muscle stiffness); where as others exhibit increases in both chamber and muscle stiffness. This increased stiffness constitutes to elevated left ventricular filling pressure. Diastolic dysfunction may revert towards normal after aortic valve replacement. However some people continue to have morbidity and mortality due to diastolic dysfunction even though they underwent aortic valve replacement.

Changes in the transmitral pressure gradient are demonstrated accurately by mitral inflow Doppler velocities, which reflect the relation between LV and LA pressures during diastole. The three type of myocardial fiber are the longitudinal, radial, and circumferential fibers. Normal myocardial relaxation is a result of the well-coordinated motion of these fibers, which causes the twisting and untwisting of the heart.

It is most practical for echocardiography to record the longitudinal motion of the myocardium with myocardial relaxation the LV cavity elongates and expands laterally. The longitudinal motion of the mitral annulus has been shown to reflect the rate of myocardial relaxation. The velocity of the mitral annulus can be recorded with tissue

Doppler imaging, which has become an essential part of the echocardiographic evaluation of diastolic function.

For each person, the proportion of LV filling during the early and late phase of diastole depends on elastic recoil, the rate of the myocardial relaxation, chamber compliance, and LA pressure. In cardiac disease, the status of these variables depends on the interaction of the disease process, the baseline diastolic properties, and LV volume. The LV filling pattern is the result of the transmitral pressure gradient produced by these various factors.

Therefore, after the 2D echocardiographic study, LV diastolic filling is analyzed the transmitral pressure gradient. In most patients the LV diastolic filling pattern can be determined with 2D echocardiography and mitral inflow recording. However a definitive assessment of diastolic filling and estimation of filling pressure may require tissue Doppler pulmonary vein Doppler, hepatic vein Doppler and color M-mode imaging of mitral inflow, occasionally, with an alteration in the loading condition.

Clinical presentation:

Symptoms:

The cardinal symptoms in patients with aortic stenosis are exertional dyspnoea, angina, syncope and ultimately heart failure. The mechanism of exertional dyspnoea may be left ventricular diastolic dysfunction with elevation of LV end diastolic pressure leading to pulmonary congestion. Exertional symptoms may be due to limited ability to increase cardiac output with exercise. More severe exertional dyspnoea with orthopnoea and paroxysmal nocturnal dyspnoea are relatively very late symptoms.

Angina pectoris occurs in two thirds of patients with severe AS with half of whom have obstructive coronary artery disease. Angina in AS may be due to increased demand

due to increased LV mass, increased systolic workload, prolonged ejection time, reduced coronary flow reserve and coexisting coronary artery disease. Very rarely angina results from calcific emboli.

Syncope is most commonly due to reduced cerebral perfusion that occurs during exertion when arterial pressure decreases as a consequence to systemic vasodilatation and fixed cardiac output. Syncope is also attributed to malfunctioning baroreceptor response and transient ventricular fibrillation occurs during exertion in patients with AS.

Other late findings in AS includes atrial fibrillation, pulmonary hypertension and systemic hypertension. Gastrointestinal bleeding may occur due to acquired deficiency in Von Willebrand factor, which is correctable by aortic valve replacement.

Diastolic dysfunction:

Diastolic dysfunction accounts for nearly 50% of patients with heart failure. These patients have heart failure even though their systolic function is normal. Abnormal myocardial relaxation and increased filling pressures have to be demonstrated to establish the diagnosis of diastolic heart failure[29]. Therefore, the following three conditions must be met to consider cardiac function to be entirely normal:

1) Normal systolic function,

2) Normal myocardial relaxation, and

3) Normal diastolic filling pressure at rest and with exertion.

Doppler echocardiography is the most practical method for assessing filling patterns and myocardial relaxation and for estimating LV filling pressures at rest and with exertion by recording flow velocities from the atrioventricular valves, central veins, and myocardial tissue.

Although patients with primary diastolic heart failure do not have an obvious abnormality of either systolic function or a major cardiac structure, a two-dimensional (2D) echocardiography study is rarely normal. The thickness of the LV wall is frequently increased and the left atrium (LA) is usually enlarged because of the chronic increase in LV filling pressure. The increase in LV wall thickness may be due hypertrophic cardiomyopathy infiltrative cardiomyopathy, or obesity.

The normal cycle of cardiac contraction and relaxation requires a precise, transient increase and decrease in the intracellular concentration of calcium ions. The sarcoplasmic reticulum helps orchestrate the movement of calcium during each contraction end reach relaxation. The contraction of cardiac muscle is initiated by the cellular action potential that causes the opening of L-type sarcolemmal calcium channels through which calcium ions results in the release of more calcium ions from the adjacent sarcoplasmic reticulum through ryanodine receptor channels, a process called calcium-induced calcium release. This calcium ions bind to Troponin C, which ultimately disinhibits the inter-action of actin and myosin and result in the formation of cross-bridges.

Myocardial relaxation is accomplished primarily by the removal of calcium ions from Troponin C by an enzyme in the sarcoplasmic reticulum-called saroplasmic reticulum adenosine triphosphastase (SERCA2), and the sarcolemmal sodium-calcium exchanger. In humans, approximately 75% of calcium ions are removed by SERCA2 and 25% by the sodium-calcium exchanger[30].

The activity of SERCA2 is modulated by phospholamban, a protein located near SERCA2 sarcoplasmic reticulum. Through phosphorylation by protein kinase A and other kinases, phospholamban enhances calcium ion uptake by SERCA2.Failure of the

mechanisms of reuptake of calcium ions extruded during contraction can result in the slowing of the relaxation or the inability of the cytosolic calcium concentration to return to normal diastolic levels. The latter cause diastolic calcium overload and incomplete relaxation (includes excessive diastolic tension or stiffening).

An experimental model of senescence has demonstrated that decreased uptake of calcium ions by the sarcoplasmic reticulum during relaxation is associated with a decrease in the concentration and activity of SERCA2 more recently; SERCA2 levels were found to be greatly decreased in senescent human myocardium[31]. This decrease was associated with impaired myocardial function at baseline, and further deterioration occurred during hypoxic conditions.

Thus a decrease in SERCA2 concentration and associated decrease in uptake of calcium ions by the sarcoplasmic reticulum are thought to influence diastolic dysfunction. Despite normal systolic function, the vulnerability of calcium reuptake is a contributing factor to abnormal LV relaxation early in cardiac disease.

Completely normal 2D echocardiographic findings (i.e, normal LVEF wall thickness LA size, and ventricular septal motion) usually exclude diastolic dysfunction, but a comprehensive Doppler examination is required to assess diastolic function. Measurement of LA volume is also helpful in assessing diastolic function. The cardiac atria are actively remodeled during the evolution of heart failure.

Normal LA volume in a patient with advanced diastolic dysfunction is most unusual unless the LV filling pressure increases abruptly because of the sudden onset of a structural abnormality, such as severe mitral or aortic regurgitation due to sudden valvular disruption. LA volume is a good predictor of the development of atrial fibrillation and long-term outcome in various cardiac disorders.

Assessment of diastolic dysfunction:

Diastolic filling usually is classified on the basis of the peak mitral flow velocity of the early rapid filling wave (E), peak velocity of the late filling wave due to atrial contraction (A), and the E/A ratio. To measure E and A velocities reliably, the Doppler velocity recording should be satisfactory. Tachycardia or first-degree atrioventricular block may result in fusion of the E and A velocities. In fact, A velocity may be relatively increased if it starts before E velocity has reached zero. Generally, if E velocity is more than 20 cm/s at the beginning of A velocity (E at A), both the A velocity and E/A ratio may be affected by the fusion of the E and A velocities.

The diastolic filling pattern is characterized further by measuring the deceleration time (DT), the interval from the peak of the E velocity to its extrapolation to baseline. In patients with a relaxation abnormality as the predominant diastolic dysfunction, DT is prolonged because, with a slower and continued decrease in LV pressure until mid to late diastole, it takes longer for LA and LV pressures to equilibrate. DT is shortened if there is rapid filling due to vigorous LV relaxation and elastic recoil, as in normal young subjects, or, conversely, if there is a decrease in LV compliance or marked increase in LA pressure.

The isovolumic relaxation time (IVRT) is the interval from aortic valve closure to mitral valve opening. It generally parallels DT, being prolonged with abnormal relaxation and shortened with rapid relaxation or increasing filling pressure (or both). The duration of mitral flow with atrial contraction is useful for estimating LV end-diastolic pressure (LVEDP)[32,33] , because it is shortened with a higher LVEDP.

In a patient with impaired relaxation and mild-to-moderate increase in filling pressures, the mitral flow pattern resembles a normal filling pattern because of the

opposing effects of myocardial relaxation and increased filling pressures on mitral velocity variables. Therefore, the normalized filling pattern due to moderate diastolic dysfunction has been termed pseudonormalized mitral inflow. We need to demonstrate impaired relaxation or increased filling pressure to characterize a normal-appearing mitral inflow as a pseudonormalized pattern.

The Valsalva manoeuvre, which is performed by forceful expiration (about 40 mm Hg) against a closed nose and mouth, produces a complex hemodynamic process involving four phases. Frequently, during a physical examination, this manoeuvre is used to assess a cardiac murmur; it is also helpful in the echocardiographic assessment of diastolic function. Because LV preload is reduced during the strain phase (phase II) of the Valsalva manoeuvre, this manoeuvre decreases E velocity, lengthens DT of the E velocity, and increases A velocity if the patient has already increased filling pressure. In patients with normal filling pressure, the Valsalva manoeuvre decreases both the E and A velocities and lengthens DT. Therefore, the Valsalva manoeuvre is used to differentiate a normal mitral inflow velocity pattern from a pseudonormal pattern[34]. In patients with a restrictive filling pattern, the reversibility of advanced diastolic dysfunction is assessed with the Valsalva manoeuvre. However, not all patients can perform a Valsalva manoeuvre satisfactorily.

Mitral Annulus Velocities:

Although the movement of the mitral annulus can be recorded with M-mode echocardiography, tissue Doppler imaging is the method of choice for recording the longitudinal velocities of the mitral anulus[35,36]. These velocities are recorded from the apical four-chamber view by placing a 2 to 5-mm sample volume over the lateral or medial portion of the mitral annulus. Normally, three distinct velocities are recognized:

systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities. Additional isovolumic or mid-diastolic velocities may be recorded. Ea velocity is essential for classifying the diastolic filling pattern and estimating filling pressures. It also is extremely helpful in distinguishing between constrictive pericarditis and other forms of myocardial diastolic heart failure. Aa velocity has been studied less well, but it has been found to correlate with LA function[37].

Ea velocity reflects relaxation of the myocardium. In normal subjects, Ea increases as the transmitral gradient increases with exertional or increased preload; however, in patients with impaired myocardial relaxation, Ea is reduced at baseline and does not increase as much as in normal subjects with increased preload[38]. Therefore, a decrease in Ea is one of the earliest markers for diastolic dysfunction, and this decrease is present in all stages of diastolic dysfunction[39]. Ea decreases with aging even earlier than the decrease in mitral inflow E velocity. Because Ea velocity remains reduced and mitral E velocity increases with higher filling pressure, the ratio between E and Ea, E/Ea, correlates well with LV filling pressure or pulmonary capillary wedge pressure. Normally, the Ea velocity from the lateral annulus is higher than the Ea velocity from the medial annulus (normal, 15 cm/s vs. 10 cm/s).

Mitral Inflow Propagation Velocity (Vp):

Normal LV relaxation induces an active suction of blood and creates diastolic intraventricular gradients. Courtois and colleagues[41] demonstrated that pressures at the apex are lower than those at the base of heart, and this intraventricular gradient decreases or disappears with a decrease in myocardial relaxation. The intraventricular pressure gradient implies that there are regional differences in myocardial relaxation, with the

apex segment showing the earliest relaxation in a normal heart. Color M-mode of mitral inflow displays color-coded mean velocities from the annulus area to the apex over time[42-44]. Color M-mode is obtained by placing a cursor line along the central part of the mitral inflow blood column. The colour flow baseline needs to be shifted to lower the Nyquist limit so the central highest velocity jet is blue.

There are several ways to measure Vp from colour M-mode. The most practical way is to trace the slope of the first aliasing velocity (red to blue) from the mitral valve plane to 4 cm distal to the LV. The normal flow propagation velocity is 50 cm/s or higher. It correlates with myocardial relaxation. Although Vp initially was thought to be independent of preload, subsequent studies have suggested that it depends on preload and cardiac size[45]. Vp has been used to estimate pulmonary capillary wedge pressure (PCWP) as follows:

- $PCWP = 4.5 - [10^3/(2 \times IVRT) + Vp] - 9$
- $PCWP = (5.27 \times E/Vp) + 4.6$

Pulmonary Vein Flow Velocities:

A pulmonary vein Doppler recording has four distinct velocity components two systolic velocities (PVS1 and PVS2), diastolic velocity (PVd), and atrial flow reversal velocity (PVa). The first systolic forward flow, PVS1, occurs early in systole and is related to atrial relaxation, which decreases LA pressure and fosters pulmonary venous flow into the LA. The second systolic forward flow, PVS2, occurs in mid to late systole and is produced by the increase in pulmonary venous pressure.

At normal LA pressure, the late systolic increase in pulmonary venous pressure is larger and more rapid than LA pressure. However, at elevated filling pressures, the late systolic pressure increase in the LA is equal to or more rapid than that in the pulmonary

vein, resulting in earlier peak velocity of PVS2. The remaining pulmonary vein flow velocity components (PVd, PVa, PVS1) follow phasic changes in LA pressure[47]. With normal atrioventricular conduction, the systolic components are closely connected, and a distinct PVS1 peak velocity may not be identified in 70% of patients. During diastole, forward flow velocity (PVd) occurs after opening of the mitral valve and in conjunction with the decrease in LA pressure. With atrial contraction, the increase in LA pressure may result in flow reversal into the pulmonary vein. The extent and duration of the flow reversal are related to LV diastolic pressure, LA compliance, and heart rate. The diastolic phase of pulmonary venous flow resembles early mitral flow (E).

The peak velocity and DT correlate well with those of mitral E velocity because the LA functions mainly as a passive conduit for flow during early diastole. The DT of pulmonary vein diastolic forward flow velocity (PVd) becomes shorter as PCWP increases[48]. Both peak velocity (PVa) and duration of pulmonary vein atrial flow reversal (PVa duration) are important measurements that increase with higher LVEDP.

Myocardial Performance Index:

Left ventricular myocardial performance was calculated as follows. The mitral inflow is interrogated by pulse wave doppler in the apical 4 chamber view and the time interval from end of A wave to the onset of the following E wave is noted as a in milliseconds. Then the aortic valve is interrogated by pulse wave doppler in the apical five chamber view. The total aortic ejection time is noted as b. Five consecutive cardiac cycles were averaged to obtain each value for ‘a’ and ‘b’ to correct for heart rate variation and measurement errors.

The time interval ‘a’ denotes combination of isovolumetric contraction time (IVCT), ejection time (ET) and isovolumetric relaxation time (IVRT). As the doppler

period b is the aortic ET, the sum of IVCT and IVRT is derived by subtracting b from a. MPI is calculated as MPI = a-b/b and a valueless ratio is obtained. Normal value of MPI is 0.39 ± 0.05.

Left Atrium:

The LA, located as a conduit between the pulmonary vein and LV, reflects the burden of LV diastolic filling. Experiments have demonstrated a progressive increase in the dimension of the LA chamber with atrial remodelling in heart failure[49]. Mechanical stretch of the LA induces hypertrophy of LA myocytes and, subsequently, fibrosis, which predispose to the development of atrial fibrillation. It has been shown that the size and volume of LA increase as diastolic dysfunction progresses.

Therefore, LA volume has been termed glycosylated haemoglobin of diastolic dysfunction. Whereas the mitral inflow velocity pattern reflects instantaneous changes in filling pressure, LA volume reflects the chronicity of diastolic dysfunction. Therefore, not unexpectedly, LA volume is predictive of future cardiovascular events such as atrial fibrillation, heart failure, stroke, and death. LA volume is helpful in assessing diastolic function: an entirely normal LA volume can exclude clinically important diastolic dysfunction[50]. A normal-appearing mitral inflow velocity pattern usually represents a pseudonormalized pattern if LA volume is increased.

Grading of Diastolic Dysfunction (or Diastolic Filling Pattern):

- Grade 1 = impaired relaxation pattern with normal filling pressure

  1a = impaired relaxation pattern with increased filling pressure
- Grade 2 = pseudonormalized pattern
- Grade 3 = reversible restrictive pattern
- Grade 4 = irreversible restrictive pattern

Normal Diastolic Filling Pattern:

The rates of myocardial relaxation and compliance change with aging, so that different diastolic filling patterns are expected for different age groups. In normal young subjects, LV elastic recoil is vigorous and myocardial relaxation is swift; therefore, most filling is completed during early diastole, with only a small contribution at atrial contraction. Therefore, E/A is usually 1.5 or higher, DT 160 to 230 milliseconds (septal), Ea 10 cm/s or more, E/Ea less than 8, and Vp 50 cm/s or more.

With the Valsalva manoeuvre, both E and A velocities decrease with lengthening of DT, so that the E/A ratio remain the same. With normal myocardial relaxation, the longitudinal mitral annulus diastolic velocity pattern mirrors that of normal mitral inflow: early diastolic velocity (Ea) is higher than the late diastolic velocity (Aa). The lateral annulus velocity is always higher than septal Ea. Ea increases with an increasing transmitral gradient in healthy subjects, so that E/Ea is similar at rest and with exercise (usually <8). Mitral inflow propagation velocity is normally 50 cm/s or greater.

With aging, the rate of myocardial relaxation and elastic recoil gradually decrease, resulting in slow LV pressure declines and slower filling. With normal LA pressure, the pressure crossover between the LV and LA (i.e., mitral valve opening) occurs later and the early transmitral pressure gradient is decreased. Hence, the IVRT becomes longer and the E velocity in normal subjects gradually decreases with increasing age. Decreased filling in early diastole retards the equilibration of pressure between the LV and LA, resulting in a longer DT. Because early LV filling is reduced, the contribution of atrial contraction to LV filling becomes more important. This results in a gradual increase in A velocity with aging.

At the age of 65 years, E velocity approaches A velocity, and in persons older than 70 years, the E/A ratio is usually less than 1.0. Pulmonary vein flow velocities show similar changes with aging: diastolic forward flow velocity decreases as more of the LV fills at atrial contraction, and systolic forward flow velocity becomes more prominent. This is similar to the grade 1 filling pattern.

Abnormal Patterns:

Grade 1 Diastolic Dysfunction (Impaired Myocardial Relaxation):

In nearly all types of cardiac disease, the initial abnormality of diastolic filling is slowed or impaired myocardial relaxation. Typical examples of cardiac lesions that produce impaired relaxation include LV hypertrophy, hypertrophic cardiomyopathy, and myocardial ischemia or infarction. The IVRT is prolonged. Mitral E velocity is decreased and A velocity is increased, producing an E/A ratio less than 1, with prolonged DT. Whenever the E/A ratio is less than 1, impaired relaxation is usually present. (The reverse is not true.) PVd parallels mitral E velocity and is also decreased, with compensatory increased flow in systole. The duration and velocity of PVa are usually normal, but they may be increased if the LVEDP is high.

Ea is also reduced, usually less than 7 cm/s (at the septal annulus), and mitral flow propagation velocity is reduced, less than 50 cm/s. In most patients with the described mitral inflow velocity pattern, diastolic filling pressure is not increased and E/Ea is 8 or less (20). In a subgroup of patients, E/Ea is greater than 15, with E/A less than 1. This pattern has been designated as grade 1a diastolic dysfunction to emphasize that filling pressure is increased in the presence of a typical grade 1 mitral inflow velocity pattern.

Grade 2 Diastolic Dysfunction (Pseudonormalized Pattern):

As diastolic function deteriorates, the mitral inflow pattern goes through a phase that resembles a normal diastolic filling pattern, that is, the E/A ratio is 1 to 1.5 and DT is normal at 160 to 220 milliseconds. This is the result of a moderately increased LA pressure superimposed on a relaxation abnormality. This is referred to as the pseudonormalized mitral flow filling pattern, and it represents a moderate stage of diastolic dysfunction. The pseudonormal pattern can be distinguished from a true normal pattern by the following:

- The best way to identify a pseudonormalized pattern is to demonstrate impaired myocardial relaxation by Ea less than 7 cm/s and increased filling pressure by E/Ea greater than 15. Frequently, there is mid-diastolic flow due to marked impairment of myocardial relaxation.
- In patients with an LV of abnormal size or systolic dysfunction or with increased wall thickness, impaired relaxation is expected as the baseline diastolic function without increased filling pressure, and a normal E/A ratio suggests that increased LA pressure is masking the abnormal relaxation.
- A decrease in preload, by having the patient sit, perform the Valsalva manoeuvre, or take sublingual nitro-glycerine, may be able to unmask the underlying impaired relaxation of the LV, causing the E/A ratio to decrease by 0.5 or more and reversal of the E/A ratio[24]. In normal subjects, both the E and A velocities decrease more proportionally with a decrease in filling.
- A pseudonormal pattern is demonstrated by showing a shortening of mitral A duration in the absence of a short PR interval or by demonstrating prolonged PVa exceeding mitral A duration.

- Colour M-mode of mitral inflow can determine the rate of flow propagation in the LV[45]. With worsening diastolic function, myocardial relaxation is always impaired and flow propagation is slow, even when LA pressure and mitral E velocity are increased. This is less reliable in patients who have a normal LV cavity size.

Grade 3 and 4 Diastolic Dysfunction (Restrictive Filling):

The term restrictive diastolic filling, or restrictive physiology, should be distinguished from restrictive cardiomyopathy. Restrictive physiology can be present in any cardiac abnormality or in a combination of abnormalities that produce decreased LV compliance and markedly increased LA pressure. The increase in LA pressure results in earlier opening of the mitral valve, shortened IVRT, and an increased initial transmitral gradient (high E velocity).

Early diastolic filling in a noncompliant LV causes a rapid increase in early LV diastolic pressure, with rapid equalization of LV and LA pressures producing a shortened DT. Atrial contraction increases LA pressure, but A velocity and duration are shortened because LV pressure increases even more rapidly. When LV diastolic pressure is markedly increased, there may be diastolic mitral regurgitation during mid-diastole or with atrial relaxation. Therefore, restrictive physiology is characterized by mitral flow velocities that show increased E velocity, decreased A velocity (<<E), and shortened DT (<160 milliseconds) and IVRT (<70 milliseconds). Typically, the E/A ratio is more than 2.0 and occasionally increases to 5 (e.g., E velocity of 1.5 m/s and A velocity of 0.3 m/s).

It should be emphasized, however, that myocardial relaxation continues to be impaired in patients with restrictive filling (except for those with a sudden disruption of cardiac structure), but it is masked by decreased LV compliance with markedly increased

LA pressure. Systolic forward flow velocity in the pulmonary vein is decreased because of increased LA pressure and decreased LA compliance. Pulmonary vein forward flow stops at mid to late diastole, reflecting the rapid increase in LV pressure; at atrial contraction, the increase in LA pressure can produce a prolonged PVa; however, PVa may not be seen if atrial contraction occurs when the pulmonary vein flow velocity is relatively high because of tachycardia.

Because myocardial relaxation is impaired in patients with a restrictive filling pattern, mitral annulus Ea is reduced (<7 cm/s) and flow propagation velocity is usually reduced. E/Ea is usually more than 15. Flow propagation velocity may not be reduced in restrictive filling when the LV cavity is small and systolic function is well preserved. The Valsalva manoeuvre may reverse a restrictive filling pattern to a grade 1 or 2 pattern, indicating the reversibility of high filling pressure (grade 3 diastolic filling). However, even if the restrictive filling pattern does not change with the Valsalva manoeuvre, reversibility cannot be excluded because the Valsalva manoeuvre may not be adequate or filling pressure may be too high to be altered by the manoeuvre. Diastolic filling should be graded as irreversible restrictive (grade 4) only when there is objective evidence of a persistent restrictive pattern with normal filling pressure.

Techniques for Diastolic Doppler Parameters:

Transducer position: The ultrasound beam needs to be parallel with the direction of blood flow to obtain the optimal flow signal. Because of the location of the papillary muscles, normal mitral inflow is directed toward the mid-to-distal portion of the posterolateral wall of the LV, which is approximately 20 degrees lateral to the apex. An optimal transducer position for recording flow velocities in the pulmonary veins varies depending on which view and which vein is to be interrogated. Usually, an apical four-

chamber view is used to record flow velocities from the right upper pulmonary vein. Color-flow imaging may be helpful in guiding the ultrasound beam so it is parallel with mitral inflow or pulmonary venous flow

Sample volume size and location: To record peak mitral inflow velocities, the pulsed wave Doppler technique is used, with a sample volume of 1 to 2 mm placed between the tips of the mitral leaflets during diastole. The sample volume may be moved toward the mitral annulus to better record the duration of the A velocity.

To measure IVRT (i.e., the interval from aortic valve closure to mitral valve opening), a 3 to 4-mm sample volume is placed in the area of the mitral leaflet tips. Next, the transducer beam is angulated toward the LV outflow tract until aortic valve closure appears above and below the baseline. An alternative technique is to use continuous wave Doppler echocardiography to record aortic and mitral flow simultaneously.

Hepatic vein Doppler velocities are recorded with subcostal imaging, using a 2 to 5-mm pulsed wave sample volume placed 1 to 2 cm proximal to the junction with the inferior vena cava. Flow velocity in the SVC is obtained with a 2 to 5-mm pulsed wave sample volume at a depth of 5 to 7 cm from the right supraclavicular area.

Mitral annulus velocity is recorded by tissue Doppler imaging. Sample volume size can vary from 2 to 5 mm over the lateral or septal mitral annulus. For the color M-mode of mitral flow, a cursor is placed along the center of mitral inflow on color flow imaging. The color flow sector should be adjusted so it is slightly wider than the width of mitral inflow and it should be extended all the way to the apex.

Velocity scale and filter: These should be adjusted according to the peak velocities of Doppler recording. Compared with mitral and tricuspid flow velocities (range, 0.5-1.5 m/s), venous flow velocities are lower (range, 0.1-0.5 m/s), and because

of this, velocity scales should be expanded and the velocity filter should be low. For tissue Doppler velocity recording, the Doppler gain and velocity filter need to be lowered.

Invasive measurement of left ventricular stiffness:

Stiffness or elastance is defined as the relationship between the change in stress and the resulting strain. On the chamber level, the elastance of the LV varies over the cardiac cycle (time-varying elastance), and end-systolic and end-diastolic elastance are defined by the changes in systolic or diastolic pressure associated with a change in end-systolic or end-diastolic volume (40). Increases in LV diastolic stiffness will mandate higher LA pressures to maintain filling and thus promote elevated pulmonary venous pressures and pulmonary congestion when LA pressures are elevated or reduced cardiac output when LA pressures are not elevated.

The time constant of relaxation (tau, t) describes the rate of LV pressure decay during isovolumic relaxation. Measurement of tau requires high-fidelity manometer tipped LV catheters for precise determination. The pressure (P) and time (t) data during the period from end-systole (peak - dP/dt) to the onset of LV filling (determined from LA to LV crossover pressure, or estimated as 5 mm Hg above the end-diastolic pressure) is used to calculate tau. The pressure-time data during isovolumic relaxation are fit to various equations to derive the value of tau. The equations used make different assumptions regarding the LV minimum pressure obtained.

The Weiss equation is LV $P = P_o e^{-t/\tau}$ (τ -tau)

Where P0 = LV P at end ejection, assumes a zero asymptote (or that the LV minimum pressure must be positive) and thus derives tau as the negative inverse of the slope of the relationship between the natural log (ln) of LV pressure and time during

isovolumic relaxation). The “logistic” equation lets the data drive the asymptote and allows for negative LV minimum pressures, as has been documented in animal studies. With all methods, the larger the value of tau, the longer it takes for the LV to relax and the more impaired is relaxation. A normal value for tau is less than 40 milliseconds in most age groups and relaxation is complete by 3.5 × tau (less than 140 milliseconds).

Treatment of aortic stenosis:

The most important principle in management of adults with AS is patient education regarding the disease course and typical symptoms. Patients should be advised to report promptly the development of any symptoms possibly related to AS. Patients with severe AS should be cautioned to avoid vigorous athletic and physical activity. However, such restrictions do not apply to patients with mild obstruction. Evolving recommendations for infective endocarditis prophylaxis should be explained. Although medical therapy has not been shown to affect disease progression, adults with AS (as any other adult) should be evaluated and treated for conventional coronary disease risk factors, as per established guidelines.

Echocardiography is recommended for initial diagnosis and assessment of AS severity, for assessment of LV hypertrophy and systolic function, for reevaluation in patients with changing signs or symptoms, and for re-evaluation annually for severe AS, every 1-2 years for moderate AS, and every 3 to 5 years for mild AS. Because patients may tailor their lifestyles to minimize symptoms or may ascribe fatigue and dyspnoea to deconditioning or aging, they may not recognize early symptoms as important warning signals, although these symptoms often can be elicited by a careful history. Exercise testing may be helpful in apparently asymptomatic patients to detect covert symptoms,

limited exercise capacity, or an abnormal blood pressure response. Exercise stress testing should be absolutely avoided in symptomatic patients.

Symptomatic patients with severe AS are usually operative candidates because medical therapy has little to offer. However, medical therapy may be necessary in patients who are considered to be inoperable (usually because of comorbid conditions that preclude surgery). Although diuretics are beneficial when there is abnormal accumulation of fluid, they must be used with caution because hypovolemia may reduce the elevated LV end-diastolic pressure, lower cardiac output, and produce orthostatic hypotension. ACE inhibitors should be used with caution but are beneficial in treating patients with symptomatic LV systolic dysfunction who are not candidates for surgery. They should be initiated at low doses and increased slowly to target doses, avoiding hypotension. Beta-adrenergic blockers can depress myocardial function and induce LV failure and should be avoided in patients with AS.

Atrial flutter or fibrillation occurs in less than 10 percent of patients with severe AS, perhaps because of the late occurrence of left atrial enlargement in this condition. When such an arrhythmia is observed in a patient with AS, the possibility of associated mitral valvular disease should be considered. When AF occurs, the rapid ventricular rate may cause angina pectoris. The loss of the atrial contribution to ventricular filling and a sudden fall in cardiac output may cause serious hypotension. Therefore AF should be treated promptly, usually with cardioversion. New onset AF in a previously asymptomatic patient with severe AS may be a marker of impending symptom onset.

Management of concurrent cardiac conditions, such as hypertension and coronary disease, is complicated in patients with asymptomatic AS by the concern that vasodilatory effects of medications may not be offset by a compensatory increase in

cardiac output. Despite this concern, AS patients should receive appropriate treatment for concurrent disease, although medications should be started at low doses and slowly titrated upward with close monitoring of blood pressure and symptoms. Adults with asymptomatic severe AS can undergo noncardiac surgery and pregnancy with careful hemodynamic monitoring and optimization of loading conditions. However, when stenosis is very severe, elective AVR prior to noncardiac surgery or a planned pregnancy may be considered.

Aortic valve replacement:

AVR is recommended in adults with symptomatic severe AS, even if symptoms are mild. AVR also is recommended for severe AS with an ejection fraction less than 50 percent and in patients with severe asymptomatic AS who are undergoing coronary bypass grafting or other heart surgery. In addition, AVR may be considered for severe AS when exercise testing provokes symptoms or a fall in blood pressure. In asymptomatic patients with severe AS and a low operative risk, AVR may be considered when markers of rapid disease progression are present or when AS is very severe, depending on patient preferences regarding the risk of earlier intervention versus careful monitoring with intervention promptly at symptom onset. Coronary angiography should be performed before valve replacement in most adults with AS Surgical AVR is the procedure of choice for relief of outflow obstruction in adults with valvular AS.

If surgical repair is not feasible as attempts at debridement of valve calcification have not been successful. Balloon aortic valvotomy has only a modest hemodynamic effect in patients with calcific AS and does not favourably impact long-term outcome. Thus balloon aortic valvotomy is not recommended as an alternate to AVR for calcific AS. In selected cases, balloon valvotomy might be reasonable as a bridge to surgery in

unstable patients or as a palliative procedure when surgery is very high risk. Newer percutaneous methods for implantation of prosthetic valves in seriously ill patients who are not candidates for surgery are under development. Limited clinical experience has been reported to date Symptoms of pulmonary congestion (exertional dyspnoea) and of myocardial ischemia (angina pectoris) are relieved in almost all patients, and most patients will have an improvement in exercise tolerance, even if only mildly reduced prior to surgery.

Hemodynamic results of AVR are also impressive; elevated end diastolic and end-systolic volumes show significant reduction. Impaired ventricular performance returns to normal more frequently in patients with AS than in those with AR or MR. However, the finding that the strongest predictor of postoperative LV dysfunction is preoperative dysfunction suggests that patients should, if possible, be operated on before LV function becomes seriously impaired. The increased LV mass is reduced toward (but not to) normal within 18 months after AVR in patients with AS, with further reduction over the next several years. Coronary flow reserve and diastolic function also demonstrate considerable improvement after AVR. However, interstitial fibrosis regresses more slowly than myocyte hypertrophy so that diastolic dysfunction may persist for years after successful valve replacement.

In patients with moderately or severely calcified valves in whom serial echocardiographic testing reveals a marked increase in aortic-jet velocity, the outcome is significantly worse, and an 80 percent event rate at two years can be expected. Because patients do not always report symptoms promptly, and in consideration of the elevated risk of death while patients await surgery, as well as the higher operative risk in symptomatic patients and those undergoing urgent surgery, it may be worthwhile

to consider early elective valve replacement instead of waiting for symptoms to develop in this high-risk group.

In the study by Pellikka et al[52], only aortic-jet velocity and ejection fraction were independent predictors of the risk of subsequent cardiac events, whereas age, sex, and the presence or absence of hypertension, diabetes mellitus, left ventricular hypertrophy, electrocardiographic strain pattern, ventricular ectopic activity, and coronary artery disease, smoking status, and the use or nonuse of digoxin or diuretic drugs were not. In the study by Otto et al,[26] the only predictors of outcome were aortic-jet velocity, the rate of change in this velocity, and functional status, but not age, sex, cause of aortic stenosis, left ventricular mass, or ejection fraction. Neither of these studies allowed any conclusions to be drawn about how to select high-risk patients who might benefit from early elective surgery.

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MATERIAL AND METHODS

This study was performed in the Department of Cardiology, Government General Hospital, Chennai, during the year 2007 – 2010. The study is a prospective observational study involving 40 patients.

Study group selection:

Ethical committee clearance was obtained to conduct the study in our hospital.

All subjects provided written informed consent to participate in the study before inclusion.

Inclusion criteria:

1. Moderate to severe aortic stenosis with normal LV systolic function

Severe AS – peak velocity more than 4 m/sec or mean gradient more than 40 mmHg

Moderate AS – peak velocity between 3 and 4 m/sec or mean gradient of 25 to 40 mmHg

2. Age 30 – 75 years
3. Both sexes
4. Sinus rhythm

Exclusion criteria:

1. more than mild aortic insufficiency
2. other valvular lesions (except mild MR)
3. LV systolic dysfunction (LVEF 55%)
4. systemic hypertension
5. diabetes mellitus
6. cardiomyopathies
7. chronic obstructive airway disease

8. symptomatic respiratory disease (bronchial asthma, pulmonary tuberculosis, bronchiectasis, etc)
9. chronic kidney disease
10. hypothyroidism
11. cardiac surgeries in the past
12. patients not in sinus rhythm

Patient Characteristics:

68 patients with valvular AS were screened for study. 8 of them were eliminated because of coexisting more than mild aortic regurgitation and another 10 patients were eliminated because of mild to moderate LV systolic dysfunction. Among the remaining 50 patients one had associated mild mitral stenosis and two of them had more than mild mitral regurgitation. Another 7 patients were excluded due to presence of respiratory disease in the form of abnormal pulmonary function tests and diabetes mellitus.

40 patients (male-28 / female-12) who met the inclusion criteria had isolated aortic valve disease in the form of degenerative calcific aortic stenosis (No.23), bicuspid aortic stenosis (No.13) and rheumatic etiology (No.4). Three patients had associated mild mitral regurgitation.

Among the 40 patients included in the final phase of the study, 30 of them had severe AS and 10 of them had moderate AS. 28 patients (male-18 / female-10) were symptomatic and 12 (male-10 / female-2) were asymptomatic. Mean age of patients in this study was 49 ± 3.8 years

Male population consists of 64% (n=18) of symptomatic group and 83% (n=10) of asymptomatic group. Among female gender (total-12), 10 patients were symptomatic and 2 were asymptomatic.

Out of 30 patients with severe AS, 26 patients (87%) were symptomatic and 4 patients were asymptomatic. Among 10 subjects with moderate AS only 20% were symptomatic.

All the patients entered the study had detailed questionnaire. History was meticulously elicited with leading questions to bring out even subtle symptoms. Study population was subjected to routine blood investigations, chest X ray, ECG and detailed clinical examination. Informed written consent obtained from subjects after explaining the process of the study.

To test the functional capacity objectively, we had decided to subject the patients to six minute walk test. Because it is easily performed by even severely symptomatic individuals and has excellent reproducibility

Six minute walk test (6MWT):

The 6MWT was performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test was performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is required. The length of the corridor should be marked every 3 m. The turnaround points were marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Patient preparation includes,

1. Comfortable clothing

2. Appropriate shoes for walking
3. Patients used their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen was continued.
5. A light meal before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

Advantages of six minute walk test includes,

1. Easy to perform
2. Can be done in patient with marked limitation of physical activity
3. Excellent reproducibility
4. Correlates with symptoms
5. Can be repeated on the same day on different times
6. No instruments / hardware needed

Six minute walk test was selected as a tool to measure the functional capacity since most of the population was around 60 years and being symptomatic. Six minutes walk test was performed according to American thoracic society protocol.

30 meters even, hard walk surface was selected, measured and marked. Chairs were kept on the sides for patients to take rest in between the test. They were educated about the test and were encouraged to walk at possible maximum speed. Stop clock was being used. One individual was allowed to walk at a time. 6 minute walk distance was measured meticulously. Their baseline and post exercise blood pressure were recorded. They were informed to convey their symptom during exercise. Symptoms were identified and correlated during the six minute walk test.

Patients were requested to undergo echocardiographic examination with prior proper information. Mean pressure gradient and peak velocity across the aortic valve is used to define the severity of aortic stenosis and defined as follows,

Severe AS - mean gradient > 40 mm Hg, V max > 4 m/sec.

Moderate AS - mean gradient 25 - 40 mmHg, V max 3 - 4 m/sec.

2D and M-Mode echocardiogram was performed many times in all possible views to obtain the diastolic parameters apart from routine echocardiographic examination. Among 2D parameters left atrial size, LV systolic and diastolic dimensions, early and late mitral filling velocities (E & A) were obtained. E deceleration time (DT), A duration and E-A duration was also measured. Pulmonary vein systolic (S) and diastolic (D) flows and flow reversal were measured.

Then tissue Doppler study was performed in apical 4 chamber view using pulse doppler sample to obtain septal mitral annulus velocities namely Ea and Aa. Indices like isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT) and ejection time (ET) to calculate myocardial performance index (MPI) also obtained. LV end diastolic volume and LV end systolic volume were obtained using modified Simpson's method and ejection fraction was calculated.

To record peak mitral inflow velocities, the pulsed wave Doppler technique is used, with a sample volume of 1 to 2 mm placed between the tips of the mitral leaflets during diastole. The sample volume may be moved toward the mitral annulus to better record the duration of the A velocity.

Measurement of aortic stenosis severity using CW doppler

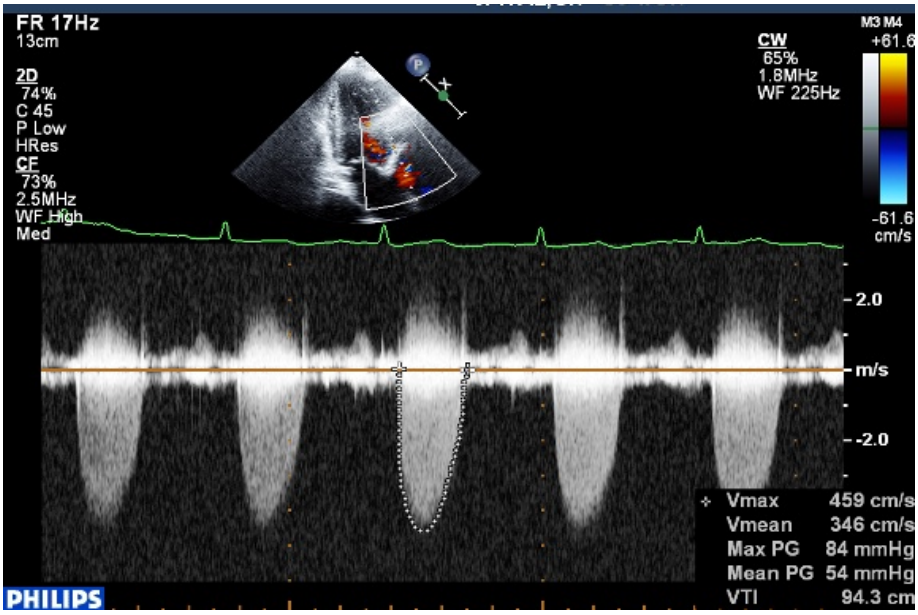

Figure 3; Continuous wave doppler across the aortic valve showing peak velocity of 4.59 m/s and mean gradient of 54 mmHg, suggestive of severe AS.

Early and late transmitral filling velocities

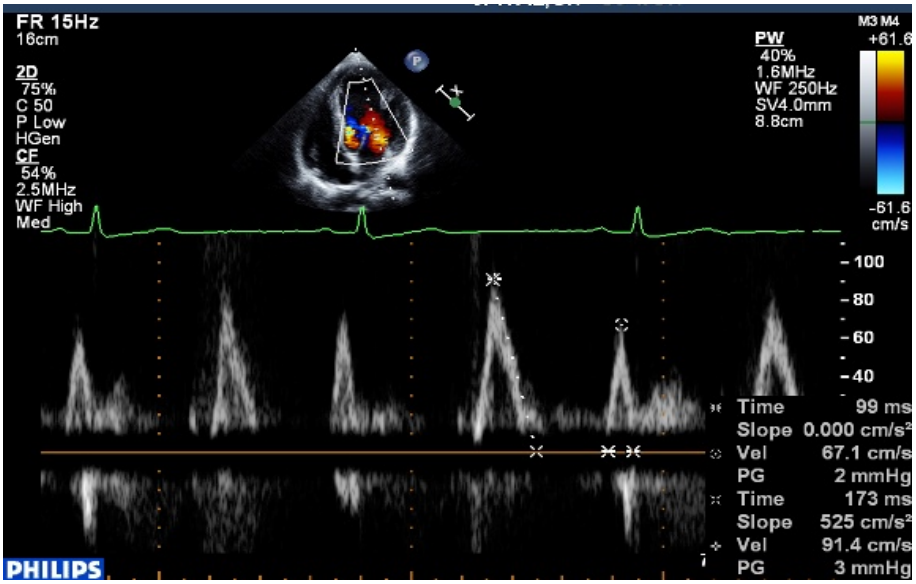

Figure 4; Transmitral doppler showing E value of 91.4 cm/s, A value of 67.1 cm/s and DT of 173 msec, suggestive of normal filling pattern.

Tissue Doppler – measuring velocities of septal mitral annulus

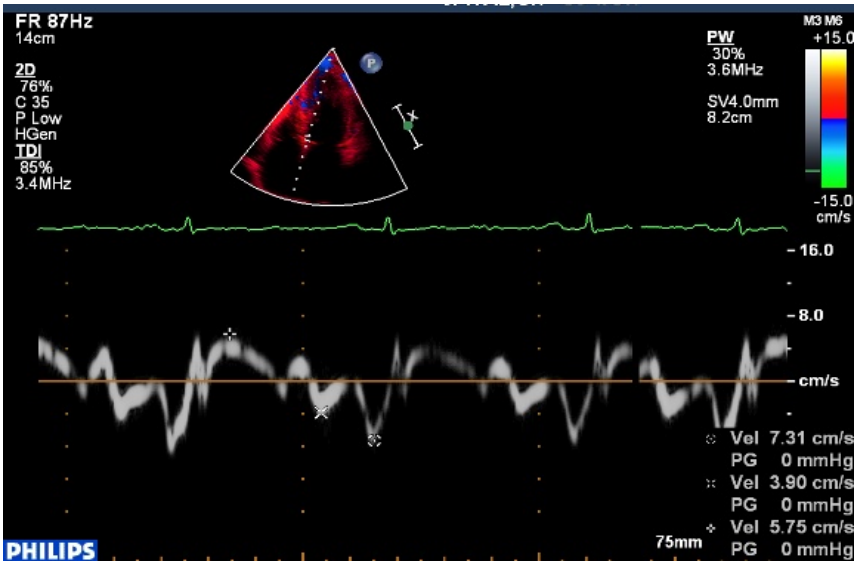

Figure 5; Tissue doppler across medial mitral annulus showing reduced Ea value of 3.9cm/s and E/Ea value of this patient was 23.4, which is markedly abnormal.

Pulmonary vein Doppler – systolic, diastolic forward flow and diastolic reversal velocities

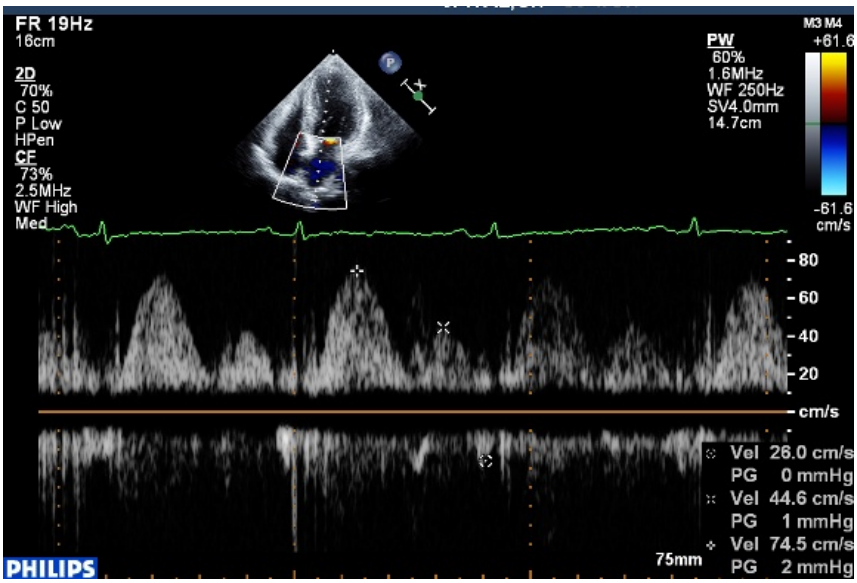

Figure 6; pulse wave doppler across pulmonary vein showing S-74.5cm/s and D-44.6cm/s with S/D ratio of more than 1, which is normal.

Velocity scale and filter adjusted according to the peak velocities of Doppler recording. Compared with mitral and tricuspid flow velocities (range, 0.5-1.5 m/s), venous flow velocities are lower (range, 0.1-0.5 m/s), and because of this, velocity scales expanded and the velocity filter was kept low. For tissue Doppler velocity recording, the Doppler gain and velocity filter was adjusted to lower aliasing velocity.

Tissue Doppler study was done in apical 4 chamber view with pulse wave doppler using 1-2 mm sample volume. Early and late mitral annulus velocities (Ea, Aa) were measured. Velocity scale adjusted to lower aliasing velocity.

Echocardiography was performed using Phillips IE 33 machine by experienced consultants and average of three readings was taken as final. Velocities and durations were meticulously calculated to avoid observer bias.

PROFORMA

Serial no:	Initials:	Contact no:
Age :	sex:	Address:
CD no:		
Diagnosis :		

SHT:	DM:	CKD:
COPD:	CAD:	HCM:
Hypothyroidism:		

Symptoms :

1.Dyspnoea;

2.Angina;

3.Syncope;

4.others;

Six minute walk distance:

Symptoms:

Blood pressure:	Pulse:
CVS:	RS:

Investigations:

Bld.sugar;

Sr.creatinine:

Hb%;

CBC;

CXR-PA view;

ECG;

Pulmonary function test;

Exclusion criteria:

CAD; COPD;

CKD; ASTHMA;

SHT; HYPOTHYROIDISM;

DM; HCM;

OTHER VALVULAR DISEASE;

ECHO parameters: **2 D, M Mode and Doppler study:**

LVIDD; LVISD;

EF;

LA size:

E velocity: E - DT:

A velocity: A- duration: E-A;

E/A:

PV-S: D: S/D:

PVa velocity: PVa duration:

TR peak velocity:

Tissue Doppler Indices:

Septal mitral annular velocities:

Ea: Aa:

E/Ea:

IVRT; IVCT; MPI;

RESULTS

Statistics of echocardiographic parameters had been done with student's t test (p values). Comparison of symptomatic and asymptomatic patients was done with chi square test. Gender comparison was done with chi square test. Mean age of the study population was 52±9 years, the lowest being 32 and the highest was 71 years.

Table 1; General and clinical characteristic of patients based on symptoms

Variables	Asymptomatic (n=12)	Symptomatic (n=28)	p Value
Age, years	47.9 ± 9.2	53.7 ± 8.8	0.082
Male, n %	10 (83.3%)	18(64.3%)	0.207
Sev AS	4 (33.3%)	26 (92.9%)	< 0.001
E	85.2 ± 9.5	85.8 ± 10.3	0.881
A	81.9 ± 24.1	78.6 ± 26.6	0.699
E/A	1.1 ± 0.3	1.1 ± 0.4	0.784
Ea	8.9 ± 2.9	4.4 ± 0.8	< 0.001
Aa	8.3 ± 1.3	7.9 ± 1.7	0.466
E/Ea	10.6 ± 3.8	20.2 ± 3.5	< 0.001
PV S/D	1.4 ± 0.3	1.3 ± 0.4	0.362
MPI	0.6 ± 0.2	0.8 ± 0.1	0.008
EF	65.8 ± 5.4	61.2 ± 5.0	0.021
6 MWD	389.4 ± 63.8	214.8 ± 36.8	< 0.001

In the study group 28 patients were males and 12 were females. 10 patients had moderate AS and 30 patients had severe AS. 28 patients were symptomatic and 12

patients had no symptoms. 26(92%) patients with severe AS and 2(20%) patients with moderate AS had symptoms. Mean E/A ratio in symptomatic group was 1.1 ± 0.3 vs asymptomatic group was 1.1 ± 0.4(p-0.7), which did not show any significance. Mean Ea value was reduced in symptomatic group than in asymptomatic group. Mean Ea value in asymptomatic group was 8.9 ± 2.9 vs symptomatic group 4.4 ± 0.8 (p<0.001).

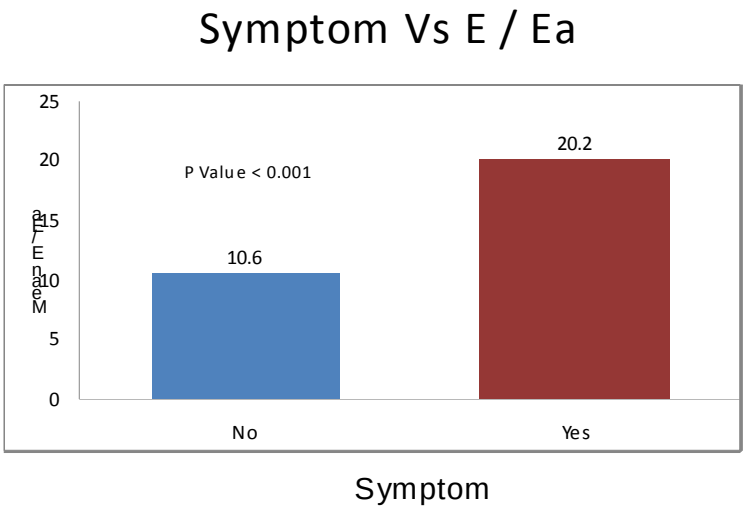

Figure 7; Mean E/Ea was elevated (nearly doubled) in symptomatic patients when compared to asymptomatic group.

E/Ea ratio is very much reduced in symptomatic patient s than in asymptomatic group. Mean E/Ea ratio in symptomatic group was 20.2 ±3.5 vs asymptomatic group 10.6 ± 3.8 (p<0.001). Other parameters like E, A, Aa, PV S/D and MPI did not statistically differ between symptomatic and asymptomatic patients.

In symptomatic patients the mean six minute walk distance was very much reduced when compared to asymptomatic group. (symptomatic group - 389.4 ± 63.8 meters vs asymptomatic group - 214.8 ± 36.8 meters with P value of less than 0.05). In this study functional capacity was objectively tested using six minute walk testing, which revealed whether the symptomatic patients had reduced walk distance or not.

Table 2; Clinical and echocardiographic variables according to severity of AS

Variables	AORTIC STENOSIS		p – Value
	Moderate (n=10)	Severe (n=30)	
Age, years	49.7 ± 7.8	52.7 ± 9.6	0.334
Male, n (%)	7 (70%)	21 (70%)	NS
Symptom, n(%)	2 (20%)	26 (86.7%)	< 0.001
E	88.9 ± 9.2	84.5 ± 10.1	0.212
A	74.4 ± 20.2	81.3 ± 27.2	0.400
E/A	1.3 ± 0.3	1.1 ± 0.4	0.187
Ea	9.3 ± 3.1	4.5 ± 0.9	0.001
Aa	8.1 ± 1.8	8.0 ± 1.5	0.871
E/Ea	11.3 ± 6.6	19.4 ± 3.7	0.003
PV S/D	1.5 ± 0.3	1.2 ± 0.4	0.041
MPI	0.6 ± 0.2	0.7 ± 0.1	0.163
EF	64.4 ± 7.2	62.0 ± 4.8	0.345
6MWD(mt)	378.7 ± 92.8	230.0 ± 57.0	0.001

Table 3; Cross table comparing severity of aortic stenosis and presence of symptoms

Count		AS		
		Moderate	Severe	Total
Symptom	No	8	4	12
	Yes	2	26	28
	Total	10	30	40

Table 4; Table shows various formulas used for statistical power

	Value	Df	symp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	15.873[a]	1	.000		
Continuity Correction[b]	12.857	1	.000		
Likelihood Ratio	15.301	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	15.476	1	.000		
N of Valid Cases	40				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.00.

b. Computed only for a 2x2 table

Most of the patients with severe AS had symptoms (86.7%) and reduced 6 minute walk distance (230 ± 57 meters). Only 20% of the patients with moderate AS had symptoms. Mean 6 minute walk distance in moderate AS group was 378± 92.8 meters. Ea values in severe AS group was lower than that of moderate AS group. Mean Ea value in moderate AS group was 9.3 ± 3 vs severe AS group was 4.5 ± 0.9 (p-0.001). Mean E/Ea ratio in the moderate AS was 11.3 ± 6.6 vs severe AS 19.4 ±3.7 (p-0.003). Other

parameters like E, A, E/A, PV S/D, MPI and Aa did not significantly differ moderate and severe AS groups.

The mean LV ejection fraction in asymptomatic group was 65.8% vs symptomatic group 61.2% which reveals LV ejection fraction in both the groups are normal and has no role in determining the symptoms.

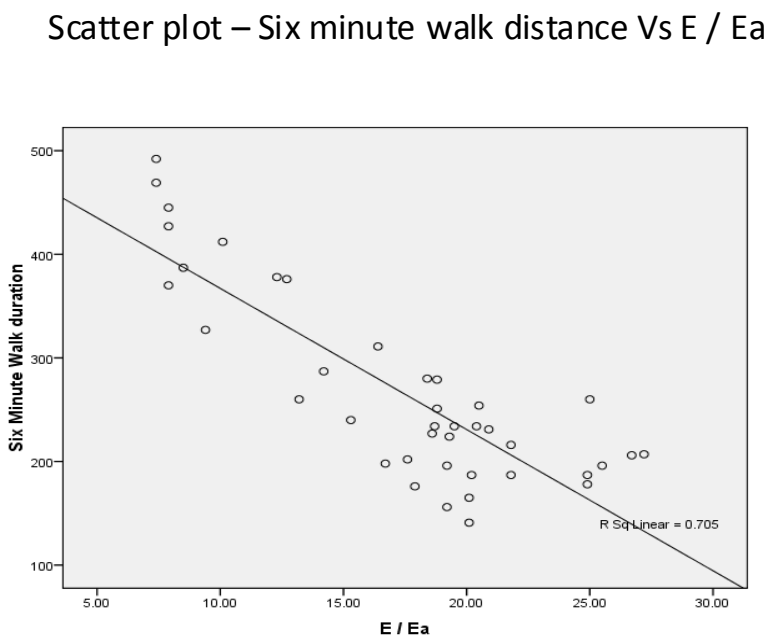

Figure 7; scatter plot shows linear inverse correlation between mean E/Ea value and six minute distance with R sq linear value of more than 0.7 suggests statistical significance.

Six minute walk distance was 214.8 ± 36.8 meters in symptomatic group and 389 ± 63.8 meters in asymptomatic group (r value -0.087 & $p < 0.001$) which is statistically very significant. Six minute walk distance did not differ between both sexes and it was altered only by the E/Ea value and Ea, not by difference in age.

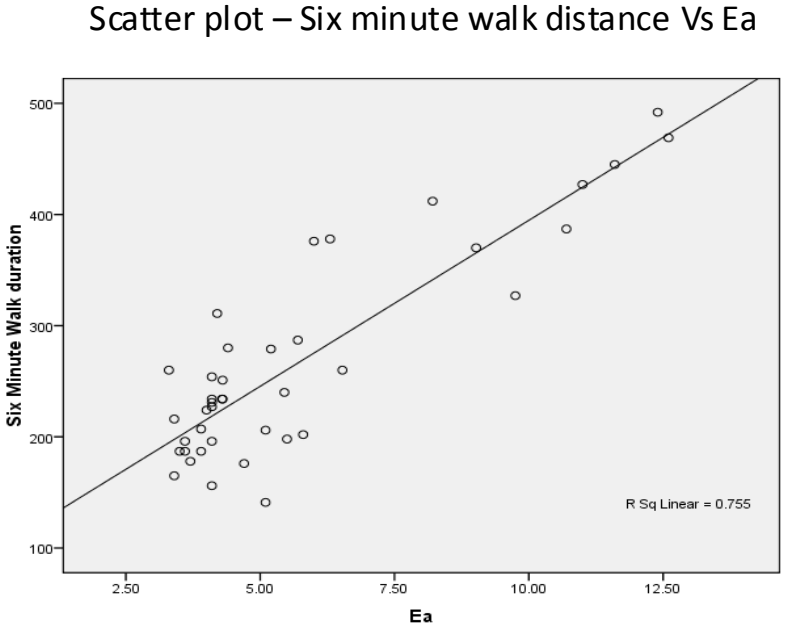

Figure 8; scatter plot shows linear direct correlation between Ea and six minute walk distance with R sq linear value of more than 0.7 which is statistically significant.

Table 5; Correlation between six minute walk test and echo or clinical variables

Variables	**r – value**	**p-Value**
Ea	0.869	< 0.001
E / Ea	-0.840	< 0.001
MPI	-0.459	0.003
EF	0.405	0.009
Symptom	-0.871	< 0.001
Age, years	-0.236	NS
Sex	-0.053	NS
Dx	-0.701	< 0.001

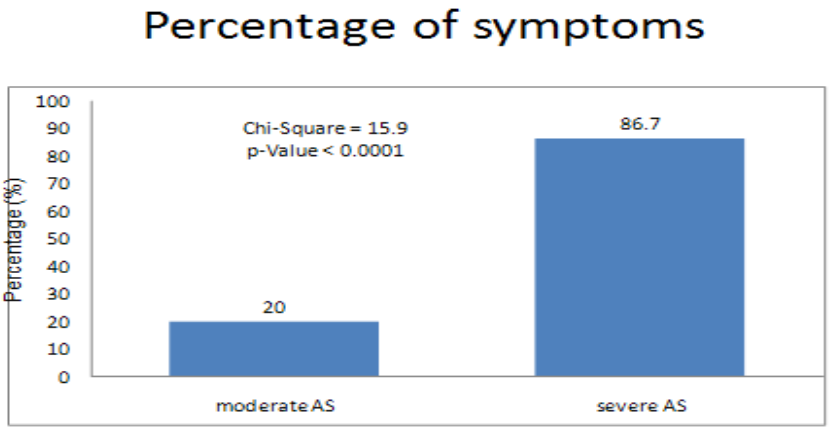

Figure 9; shows percent of patients with symptoms in moderate AS and severe AS group

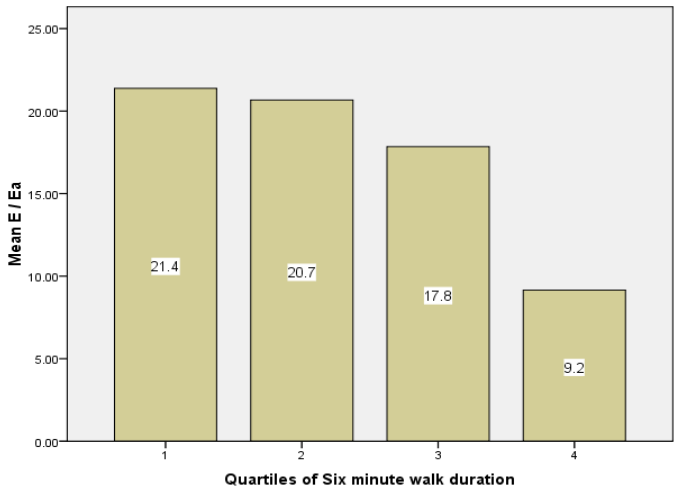

Figure 10; Bar chart showing upto third quartile of patients with reduced 6MWD had elevated E/Ea value

After the analysis, it is found that most of the patients with symptoms have reduced six minutes walk distance. Diastolic parameters like transmitral filling velocities E, A, E/A ratio, pulmonary vein S/D and myocardial performance index (MPI) did not consistently associated with symptoms or six minute walk distance.

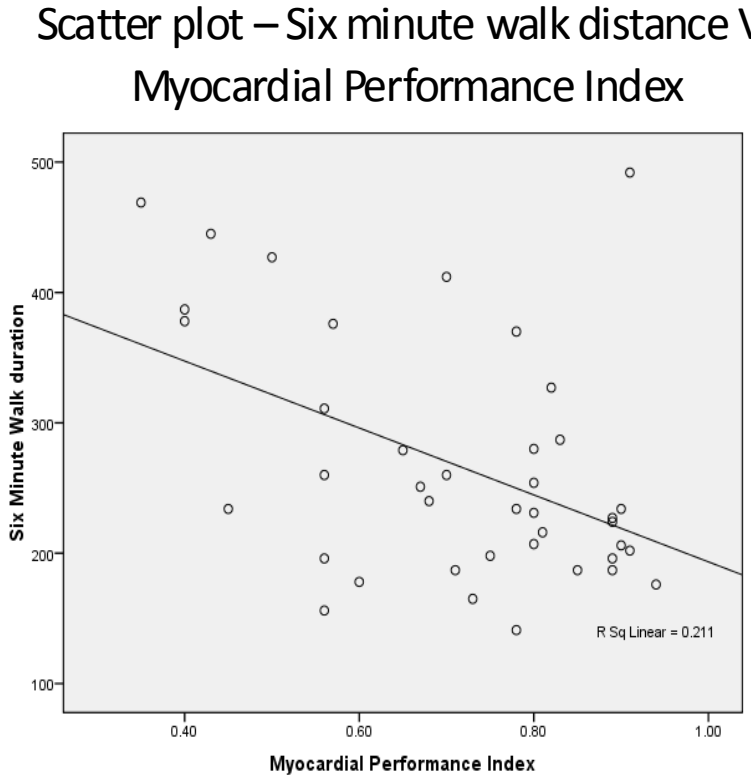

Figure 11; Scatter plot showing correlation between 6MWD and MPI. R sq linear value did not show any statistical significance between variables.

This study demonstrates LV diastolic filling pressure, as represented by increased E/Ea correlates well with the symptoms and inversely associated with six minute walk

distance. Among all the diastolic indices Ea and E/Ea were found to be statistically significant and consistently inversely associated with six minute walk distance.

E/Ea value of less than eight is normal which correlate to normal pulmonary capillary wedge pressure (PCWP). When E/Ea is elevated more than fifteen (using lateral mitral annulus > 10) reflects PCWP of more than 20 mmHg. In this study Ea values obtained from medial septal annulus which is usually less than that obtained from lateral annulus.

In this study symptomatic individuals had higher E/Ea values and reduced six minute walk distance. They also had reduced Ea values. The other diastolic indices like E/A, deceleration time, isovolumic relaxation time, pulmonary vein S/D, and myocardial performance index were not statistically altered between symptomatic and asymptomatic patients.

Most patients with symptoms have severe aortic stenosis and reduced Ea and elevated E/Ea ratio. In patients with moderate aortic stenosis who were symptomatic had significantly increased E/Ea ratio. Among four patients with asymptomatic severe aortic stenosis with elevated E/Ea ratio had reduced six minute walk distance. This unmasks the patients' natural tendency to reduce the exertion and become functionally asymptomatic. They constitute the subgroup of patients who may develop significant diastolic dysfunction before the onset of symptoms. They should be identified and subjected for aortic valve replacement.

DISCUSSION

In most patients with aortic stenosis, long-term survival after aortic valve replacement is excellent. In the absence of coronary artery disease, operative mortality is less than 2-3% and 10-years survival is more than 85%. Early and late mortality is dependent on various factors such as age, clinical symptoms, severity of valve disease, left ventricular function, presence of coronary artery disease etc

Lund *et al* [51] observed an adverse early and late outcome in patients with diastolic dysfunction either alone or in combination with systolic dysfunction.

Left ventricular diastolic dysfunction has been found in 50 to 60% of all patients with aortic stenosis and has been considered a major cause for the development of congestive heart failure. The most common cause of diastolic dysfunction in patients with aortic stenosis is left ventricular hypertrophy.

In the study of Villari *et al* [46] diastolic dysfunction was defined either as abnormal relaxation, decreased diastolic filling or increased myocardial stiffness. Diastolic dysfunction was observed in approximately 50% of all patients with a normal systolic ejection performance, but was found in 95% of those with depressed systolic function.

Late after aortic valve replacement (up to 10 years) both diastolic stiffness and relaxation improve due to the regression of both muscular and collagen tissue. Thus, reversal of diastolic dysfunction in aortic stenosis takes years and is accompanied by a slow regression of interstitial fibrosis, whereas reversal of systolic dysfunction occurs more rapidly due to mechanical unloading, with a rapid decrease in muscle mass. Diastolic filling, however, remains unchanged after valve replacement, indicating that

this parameter is relatively insensitive to changes in diastolic function but is highly influenced by age, loading conditions and hypertrophy. Excessive hypertrophy is, however, associated with a significant increase in postoperative mortality[51].

Older studies have used catheterisation derived data for assessment of diastolic dysfunction[9,10]. More recent studies use MRI[8], 2D and M mode echocardiographic variables[1,10] for the assessment of diastolic dysfunction. This study is the first of its kind to assess the diastolic dysfunction with tissue doppler echocardiography and symptom correlation in patients with aortic stenosis.

Hildo J. Lamb, Hugo P et al[8] studied diastolic function in patients with AS. They used MRI parameters like twisting and untwisting for assessment of diastolic dysfunction. They correlated their data well with catheterization findings.

Villari et al and Lund et al[46,51] used cardiac catheterization for measurement of LV diastolic dysfunction, they graded the diastolic dysfunction according to catheterization data and submitted the patients for surgery. They found that there was regression of diastolic dysfunction in those patients who underwent aortic valve replacement.

Bech-Hanssen, Peter Gjertsson et al[1] used two dimensional and M mode echocardiography to find out the aortic stenosis patients with LV diastolic dysfunction. They used routine diastolic grading for assessment of severity of diastolic dysfunction. They did not use the tissue doppler parameters for the identification of diastolic dysfunction. They found that patients with advanced diastolic dysfunction continue to be symptomatic and had more morbidity and mortality after aortic valve replacement.

Kristensen et al[10] also used two dimensional and M mode echocardiography for preoperative assessment of diastolic dysfunction in AS. They found that patients with

higher degree of diastolic dysfunction had poor prognosis even after aortic valve replacement. In this study tissue Doppler was not used.

A recent study conducted at mayo clinic in patients with aortic stenosis by Grace.C et al[4], found that E/Ea was directly correlated with pulmonary artery systolic pressure. In this study patients with other conditions producing diastolic dysfunction were not excluded. Patient with elevated E/Ea value were more symptomatic than with lower E/Ea values. Symptoms were not tested objectively by doing exercise testing. The study group consisted of patients with left ventricular systolic dysfunction also. They did not correlate the symptom to E/Ea values.

In the presence of severe LV systolic dysfunction, increased E value and DT of less than 130 msec both correlate to elevated PCWP. But with normal LV systolic function both lose their correlation to PCWP.

E/Ea may be used to identify the presence and severity of diastolic dysfunction. E/Ea ratio of more than fifteen correlates with pulmonary capillary pressure of more than 20 mmHg. In the presence of severe LV systolic dysfunction, increased E value and DT of less than 130 msec both correlate to elevated PCWP. But with normal LV systolic function both lose their correlation to PCWP.

E/Ea value is not modified by the presence of LV systolic dysfunction. E/Ea ratio is preload, afterload and heart rate independent index. So, it is more reliable even in circumstances which modify the above factors.

This study demonstrates LV diastolic filling pressure, as represented by increased E/Ea ratio correlates well with the symptoms and inversely associated with six minute walk distance. Among all the diastolic indices Ea values and E/Ea ratio were found to be

statistically significant and consistently inversely associated with six minute walk distance.

In this study asymptomatic patients with severe AS with elevated E/Ea ratio had reduced six minute walk distance. It is evidenced from this study that patients with normal LV function and severe aortic stenosis developed increase in filling pressure (increased E/Ea ratio), even before the development of symptoms. It was proven by many studies that presence of higher degree of irreversible diastolic dysfunction may develop in individuals with asymptomatic severe aortic stenosis in the pre operative period and it is associated with reduced long term and short term mortality, if they were operated after the development of symptoms[1].

This study demonstrates E/Ea as a single most reliable diastolic parameter to predict onset of symptoms and reduction in functional capacity in patients with aortic stenosis. This study undermines the importance of identifying the asymptomatic patients with aortic stenosis and elevated filling pressures.

Aortic valve replacement in patients with asymptomatic but severe aortic stenosis is controversial. Patients with severe aortic stenosis have not been referred for valve replacement as long as they remain asymptomatic. However, there remains concern about the risk of irreversible myocardial damage or sudden death among such patients who do not undergo surgery.

Higher degree of diastolic dysfunction is irreversible even after aortic valve replacement, so those asymptomatic patients should be identified at an early date, before the development of severe diastolic dysfunction[1]. Since our study group contains small number of asymptomatic individuals, it needs a large multicentre randomized trial to

decide whether the patients with elevated E/Ea value and asymptomatic severe aortic stenosis to be subjected for aortic valve replacement.

Aortic valve replacement (AVR) is advised in symptomatic patients, presence LV dysfunction or concurrent intra cardiac surgeries. In the absence of above indications AVR is not coming under class1 indication. All other indications come under class IIb. So, it is frequent for patients with AS and diastolic dysfunction may go unoperated because of lack of symptoms or LV dysfunction. But this patient may develop higher degree of LV dysfunction which may not reverse after AVR. This population of patients with severe diastolic dysfunction may be benefitted by early aortic valve replacement. In this study asymptomatic patients with elevated E/Ea values have reduced six minute walk distance. So, they may be candidate for aortic valve replacement.

CONCLUSIONS

1. Diastolic dysfunction develops in patients with aortic stenosis even in the presence of normal left ventricular systolic function.
2. E/Ea ratio is elevated in symptomatic patients with aortic stenosis.
3. Among diastolic parameters increased E/Ea ratio correlates with severity of symptoms.
4. E/Ea ratio has highly significant inverse correlation and Ea velocity has direct correlation with functional capacity.
5. TDI derived E/Ea ratio could be an early marker for aortic valve replacement in asymptomatic patients with severe aortic stenosis.

LIMITATIONS OF THE STUDY

1. The number of patients included in this study is less.
2. Our study population was highly selective and restricted to one geographical area.
3. Since female sample size was smaller, significant difference between the two genders was not demonstrated.
4. This study results may be applicable only in severe grades of AS

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GLOSSARY & ACRONYMS

AS - Aortic stenosis

BCAV - Bicuspid aortic valve

CAD - Coronary artery disease

LDL - Low density lipoprotein

LV – Left ventricle

TTE - Trans Thoracic Echocardiogram.

MRI - Magnetic Resonance Imaging.

LVEF - Left Ventricular Ejection Fraction.

EDD – End Diastolic Diameter

MPI – Myocardial Performance Index

EF – Ejection Fraction

ECG - Electrocardiography

IVCT – Isovolumetric Contraction Time

IVRT – Isovolumetric Relaxation Time

TDI – Tissue Doppler Imaging

Ea – Early phase of diastolic myocardial velocity

Aa – Late phase of diastolic myocardial velocity

PCWP – pulmonary capillary wedge pressure

LVEDP – left ventricular end diastolic pressure

TVI – time velocity integral

AVR – aortic valve replacement

ACC – American college of cardiology

AHA – American heart association

6 MWD – six minute walk distance

6MWT – six minute walk test

MASTER CHART

S.NO	NAME	CD NO	age	sex	Dx	E	A	IVRT	DT	E/A	Ea	Aa	E/Ea	LA size	PV S/D	MPI	EF	symptom	6MWD-mt
1	Indirani	24367	45	F	Sev	84	137	116	266	0.6	4.29	10.8	19.5	4.1	1.54	0.78	61	Y	234
2	Valli	25212	69	F	Sev	78.8	93.5	98	240	0.84	3.9	7.3	20.2	4.3	1.67	0.71	64	Y	187
3	Lailakumari	27008	41	F	Sev	81	64	90	179	1.27	4.4	4.8	18.4	3.8	1.41	0.8	68	Y	280
4	Kesavan	36297	57	M	Sev	83.6	89.6	102	228	0.93	5.45	8.29	15.3	3.7	1.28	0.68	63	Y	240
5	Elumalai	37558	42	M	Mod	91.4	67	88	182	1.36	9.75	5.75	9.4	3.4	1.24	0.82	61	N	327
6	Elumalai	39114	49	M	Sev	86.4	74.5	79	195	1.16	6.53	9.94	13.2	4	1.31	0.56	59	Y	260
7	Perumal	24882	37	M	Mod	71.4	69	91	166	1.03	9.02	9.2	7.9	3.7	1.7	0.78	70	N	370
8	Rajan	17895	58	M	Sev	102.1	67	76	152	1.52	5.8	8.8	17.6	4.2	0.7	0.91	58	Y	202
9	Shanmugam	19774	48	M	Sev	69	59.9	81	178	1.15	4.2	8.7	16.4	4.8	1.1	0.56	65	N	311
10	Manimegalai	40765	51	F	Mod	82.8	79.3	86	192	1.04	8.21	9.5	10.1	3.5	0.99	0.70	59	N	412
11	Kaleel	36142	63	M	Sev	78.7	92	120	256	0.86	4.1	9.6	19.2	5	0.81	0.89	63	Y	196
12	Ramesh	29555	32	M	Sev	76.1	97.4	98	270	0.78	6	7.8	12.7	3.6	1.2	0.57	66	N	376
13	Appavu	40123	47	M	Mod	92.7	78	76	169	1.19	11.6	6.7	7.9	4.1	1.6	0.43	73	N	445
14	Kuppan	39607	59	M	Mod	106.1	56	60	154	1.89	3.9	9.7	27.2	5.1	1.21	0.8	55	Y	207
15	Malaisamy	12085	62	M	Sev	97.5	72.1	85	178	1.35	5.2	8.6	18.8	4.8	1.34	0.65	62	N	279
16	Radhabai	28956	71	F	Sev	82.4	90.6	97	231	0.91	3.3	8.1	25	4.3	2.3	0.7	60	Y	260
17	Venkatesan	41034	55	M	Sev	78.7	92.9	106	229	0.85	4.1	6.9	19.2	3.9	1.43	0.56	64	Y	156
18	Pitchaimani	32850	42	M	Sev	78	130	121	269	0.6	6.3	7.9	12.3	2.9	0.87	0.4	66	N	378
19	Muthuraj	28461	49	M	Sev	102.5	96.1	80	170	1.07	5.1	8.2	20.1	4.1	0.99	0.78	63	Y	141
20	Chandran	40281	57	M	Sev	80.5	78.3	91	161	1.03	4.3	7.2	18.7	3.7	1.2	0.45	56	Y	234
21	Thangadurai	31398	52	M	Sev	76.4	87.4	98	201	0.87	3.5	8.9	21.8	4.2	1.21	0.89	62	Y	187
22	Munian	16783	45	M	Mod	93.6	78.4	78	172	1.19	12.6	9.8	7.4	2.7	1.72	0.35	70	N	469
23	Mariammal	23516	62	F	Sev	76.3	10.1	97	189	0.75	4.1	6.4	18.6	3.8	1.1	0.89	55	Y	227
24	Veni	41827	59	F	Sev	84	120.1	116	263	0.7	4.1	7.8	20.5	3.9	0.7	0.8	65	Y	254
25	Sundaramoorthy	27418	41	M	Sev	91.7	78	85	163	1.12	3.6	5.9	25.5	4.9	1.3	0.56	55	Y	196
26	Sundaram	49122	54	M	Sev	116	56	56	142	2.1	5.1	10.9	26.7	4.7	0.7	0.9	60	Y	206
27	Kalaiarasi	47278	47	F	Mod	81.1	63.9	84	176	1.26	4.3	5.0	18.8	3	1.62	0.67	58	Y	251
28	Vetrivel	11187	60	M	Sev	92	67	73	180	1.4	5.5	8.3	16.7	4.2	1.4	0.75	61	Y	198
29	Vennila	32456	39	F	Sev	84	89.5	98	230	0.94	4.7	6.6	17.9	4.8	0.8	0.94	59	Y	176
30	Pazhamalai	45329	53	M	Mod	91.1	59	63	151	1.54	10.7	9.7	8.5	3.7	1.4	0.4	76	N	387
31	Natarajan	24398	42	M	Sev	74	97	90	210	0.76	3.4	7.9	21.8	4.6	2.1	0.81	57	Y	216
32	Sivakumar	19267	48	M	Sev	83.9	40	99	138	2.1	4.1	8.5	20.4	4	0.7	0.9	56	Y	234
33	Chandrasekar	41362	59	M	Sev	80.9	62.7	72	167	1.3	5.7	5.6	14.2	3.6	0.69	0.83	78	Y	287
34	Saraswathy	27130	64	F	Sev	92.3	68.1	79	198	1.4	3.7	8	24.9	4.4	1.1	0.6	66	Y	178
35	Padmanaban	49621	45	M	Sev	77.2	56	92	201	1.36	4	6.3	19.3	3.2	1.7	0.89	55	Y	224
36	Rajeswari	31627	42	F	Sev	71	62.5	84	154	1.13	3.4	7.4	20.1	4.8	1.76	0.73	64	Y	165
37	Shek sulaiman	25409	63	M	Mod	87.3	127	122	269	0.69	11	8.71	7.9	3.1	1.65	0.5	62	N	427
38	Thirumalai	42945	57	M	Sev	85.6	135	113	248	0.63	4.1	10.8	20.9	4.4	1.65	0.8	66	Y	231
39	Selvi	17436	53	F	Mod	92	66	86	175	1.39	12.4	7.2	7.4	2.6	1.9	0.91	60	N	492
40	Benjamin	24534	59	M	Sev	89.9	75	79	183	1.19	3.6	8.4	24.9	4.9	1.4	0.85	63	Y	187