THE IMPACT OF PERCUTANEOUS CORONARY INTERVENTION (PCI) ON DIASTOLIC DYSFUNCTION IN CORONARY ARTERY DISEASE

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ABSTRACT

Background

Diastolic dysfunction is increasingly recognized as a major contributor to cardiac morbidity and mortality in a background ischaemic heart disease. This study determined the effect of percutaneous coronary intervention (PCI) on diastolic dysfunction in patients with coronary artery disease.

Methods

Forty two patients with coronary artery disease who underwent PCI for ACS at HUSM from December 2013 to May 2014were enrolled in the study. All patients had PCI and underwent Doppler Echocardiographic examination within 48hours before PCI, 48 hours after PCI and at 3 months after PCI for evaluation of LV function. Mean differences in Echo was determined using Multifactorial repeated measure ANOVA.

Results

The mean age of the study patients was 59.3 ± 8.1 years. Thirty six patients were male with 6 female patients. Almost all patients (40 patients) had mild to moderate degree of left ventricular diastolic dysfunction before PCI. All the study patients had severe coronary artery disease with more than 70% occlusion of the involved coronary artery. The E/A ratio before PCI (0.99+0.43) compared with post PCI within 48 hours (1.12±0.46) showed significant improvement but no progressive improvement at three months of PCI (1.10±0.31). Isovolumic relaxation time (IVRT) of 106.8±24.5 before PCI versus 89.0±23.8 at 48 hours versus 89.9±19.5 at 3 months after PCI also showed remarkable improvement. Improvement was also noted in deceleration time DT, 224.0±49.5 versus 211±45.6 versus 201±37.3. The E'/A' obtained from Tissue Doppler imaging also showed improvement noticeable within 48 hours 0.65+ 0.33 versus 1.06± 0.52 versus 1.05±0.35. It was statistically significant (*P*=0.006) that diastolic dysfunction improved within 48 hours of PCI. There was no significantsustained/progressive improvement after 48 hours of PCI to three months of PCI (*P*=0.965).. Left anterior descending artery (LAD) disease patients were found to have more heart failure as a complication following MI.A significant difference was found between pre-PCI and 48hours post-PCI (p=0.006) and between pre-PCI and 3 months post-PCI (0.001). No significant difference was found between 48 hours post-PCI and 3 months post-PCI.There was association found between the severity of LAD disease and severity of diastolic dysfunction.Also there was association between LAD disease and diastolic dysfunction.

Conclusion

Improvement of diastolic dysfunction after PCI as demonstrated in this study showed that PCI is an effective mode of treatment for diastolic dysfunction in patients with significant coronary artery disease. This may significantly reduce morbidity and mortality in these patients.

Professor Dato ZurkurnaiYusof: Main Supervisor

Dr. Ng SengLoong: Co-Supervisor

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BY

DR UMAR BELLO TAMBUWAL

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (INTERNAL MEDICINE)

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This thesis is dedicated to

To my Mother (Aisha) my Father (Alh Umar) My beloved wife (Safiya) and my children

Acknowledgment

All praise be to Allah, the Almighty for giving me the opportunity and courage to undertake this research.

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ABBREVIATION

ACS	Acute coronary syndrome
ACE -I	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
ARB	Angiotensin receptor blocker
AS	Aortic stenosis
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CRP	C reactive protein
DT	Deceleration time
ECG	Electrocardiogram
HDL	High density lipoprotein
HPT	Hypertension
HOCM	Hypertrophic obstructive cardiomyopathy
HUSM	Hospital Universiti Sains Malaysia
IHD	Ischemic heart disease
IVRT	Isovolumic relaxation time
LA	Left atrium

LAD	Left anterior descending artery
LCX	Left circumflex artery
LDL	Low density lipoprotein
LMS	Left main stem
LV	Left ventricle
LVFP	Left ventricular filling pressure
LVEF	Left ventricular ejection fraction
MOH	Ministry of Health
MVI	Mitral Valve Inflow
NSTEMI	Non ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
RCA	Right coronary artery
RV	Right ventricle
STEMI	ST elevation myocardial infarction
TDI	Tissue Doppler imaging
USA	United states of America
WHO	World Health Organization

KESAN INTERVENSI KORONARI PERKUTANEOUS (PCI) PADA DISFUNGSI DIASTOLIK DALAM PENYAKIT ARTERI KORONARI

ABSTRAK

Penyakit koronari arteri merupakan penyebab kardiovaskular yang penting dan utama yang menyebabkan kematian di seluruh dunia. Terdapat banyak kemajuan dalam pengurusan penyakit arteri koronari terutamanya dalam revaskularisasi saluran darah tersumbat. Fungsi diastolik tidak normal semakin diiktiraf sebagai penyumbang utama kepada morbiditi jantung dan kematian dalam kes penyakit jantung iskemia. Oleh kerana itu, peranan intervensi perkutaneus koronari (PCI) sebagai terapi untuk penyakit arteri koronari(CAD) perlu dinilai dalam meningkatkan disfungsi diastolik. Objektif kajian ini adalah untuk menilai kesan PCI pada disfungsi diastolik pada pesakit yang mempunyai penyakit arteri koronari melalui parameter Doppler Ekokardiografik.

Kaedah: Empat puluh dua pesakit yang mempunyai penyakit arteri koronari yang memenuhi kriteria kemasukan telah mendaftar dalam kajian ini. Semua pesakit mempunyai PCI dan semua pesakit telah menjalani pemeriksaan Doppler Ekokardiografik pada 3 bulan PCI, untuk penilaian fungsi LV.

Hasil: Purata umur pesakit kajian adalah 59.3 $\pm$ 8.1 tahun. 36 pesakit lelaki dengan 6 pesakit perempuan. Hampir semua pesakit (40 pesakit)mempunyai tahap disfungsi diastolik daripada lemah kepada sederhana sebelum PCI. Semua pesakit kajian mempunyai penyakit arteri koronari yang teruk dengan lebih daripada 70% arteri koronari yang terlibat .

Nisbah EIA sebelum PCI (0.99 $\pm$ 0.43) berbanding dengan kedudukan selepas PCI dalam masa 48 jam (1.12 $\pm$ 0.46) menunjukkan peningkatan yang ketara tetapi tiada peningkatan progresif pada 3 bulan daripada PCI (1.10 $\pm$ 0.31). Masa rehat Isovolumic (IVRT) daripada 106.8 $\pm$ 24.5

sebelum PCI berbanding 89.0 ± 23.8 pada 48 jam selepas PCI berbanding 89.9 ± 19.5 pada 3 bulan PCI juga menunjukkan peningkatan yang luar biasa .

Peningkatan juga dicatatkan dalam masa Kelembapan (DT) 224.0 ± 49.5 berbanding 211 ± 45.6 berbanding 201 ± 37.3. E'/A' diperolehi daripada tisu pengimejan Doppler juga menunjukkan peningkatan yang ketara dalam tempoh 48 jam PCI 0.65 ± 0.33 berbanding 1.06 ± 0.52 berbanding 1.05 ± 0.35.

Ia adalah statistik yang signifikan (P-0.006) bahawa disfungsi diastolik bertambahbaik dalam tempoh 48 jam PCI. Tiada perubahan yang berterusan atau progresif yang ketara selepas 48 jam PCI hingga 3 bulan selepas PCI (P-0.965). Tiada perkaitan di antara tahap keterukan penyakit arteri koronari dan tahap disfungsi diastolik. Pesakit yang menghidap penyakit arteri kiri 'anterior descending' (LAD) didapati mempunyai kegagalan jantung yang lebih teruk akibat komplikasi MI.

Kesimpulan: Peningkatan disfungsi diastolik selepas PCI seperti yang ditunjukkan dalam kajian ini menunjukkan bahawa PCI ialah mod rawatan berkesan untuk disfungsi diastolik pada pesakit dengan significant penyakit arteri koronari. Ini boleh mengurangkan morbiditi dan kematian dalam kalangan pesakit-pesakit ini.

ABSTRACT

Background

Coronary artery disease is an important and major cardiovascular cause of morbidity and mortality worldwide. There has been much progress made in the management of coronary disease especially in revascularisation of the occluded coronary blood vessel. Abnormal diastolic function is increasingly recognised as a significant contributor to cardiac morbidity and mortality in the setting of ischemic heart disease; because of this, the role of percutaneous coronary intervention (PCI) as a therapy for coronary artery disease (CAD) should be evaluated in improving diastolic dysfunction. The objective of this study is to evaluate the impact of PCI on diastolic dysfunction in CAD patients by Doppler Echocardiographic parameters.

Methods

Forty two patients with coronary artery disease who fulfilled the inclusion criteria were enrolled in this study. All the patients had PCI and all patients underwent Doppler Echocardiographic examination within 48 hours before PCI, within 48 hours after PCI and at three months of PCI for evaluation LV function.

Results

The mean age of the study patients was 59.3 $\pm$ 8.1 years. Thirty six patients were male with 6 female patients. Almost all patients (40 patients) had mild to moderate degree of left ventricular diastolic dysfunction before PCI. All the study patients had severe coronary artery disease with more than 70% occlusion of the involved coronary artery. The E/A ratio before PCI (0.99+0.43) compared with post PCI within 48 hours (1.12$\pm$0.46) showed significant improvement but no progressive improvement at three months of PCI (1.10$\pm$0.31). Isovolumic

relaxation time (IVRT) of 106.8±24.5 before PCI versus 89.0±23.8 at 48 hours versus 89.9±19.5 at 3 months after PCI also showed remarkable improvement. Improvement was also noted in deceleration time DT, 224.0±49.5 versus 211±45.6 versus 201±37.3. The E'/A' obtained from Tissue Doppler imaging also showed improvement noticeable within 48 hours 0.65+ 0.33 versus 1.06± 0.52 versus 1.05±0.35. It was statistically significant (*P*=0.006) that diastolic dysfunction improved within 48 hours of PCI. There was no significantsustained/progressive improvement after 48 hours of PCI to three months of PCI (*P*=0.965). There was association found between the severity of coronary artery disease and severity of diastolic dysfunction. Left anterior descending artery (LAD) disease patients were found to have more heart failure as complication following MI.

Conclusion

Improvement of diastolic dysfunction after PCI as demonstrated in this study showed that PCI is an effective mode of treatment for diastolic dysfunction in patients with significant coronary artery disease. This can significantly reduce morbidity and mortality in these patients.

CHAPTER ONE

1.1 Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide. It is characterized pathophysiologically by progressive occlusive atherosclerosis, acute plaque rupture and thrombosis (Owan *et al.*, 2006). ACS encompasses a broad spectrum of clinical conditions from unstable angina (UA) to non-ST-segment elevation infarct (NSTEMI) with micro-necrosis and through to trans mural ST-elevation myocardial infarction (STEMI) (Libby, 2001; Gaasch *et al.*, 2009).

There has been much progress made in the management of coronary heart disease, especially in revascularisation of the occluded coronary blood vessels. Abnormal diastolic function is increasingly recognized as a major contributor to cardiac morbidity and mortality in the setting of ischaemic heart disease. Advances in echocardiographic assessment of left ventricular diastolic function can lead to replacement of invasive hemodynamic methods in vast majority of patients.

Diastolic dysfunction and coronary artery disease (CAD) are interrelated. The complications of CAD, myocardial ischemia or infarction, are major causes of diastolic dysfunction. Noninvasive measurement of diastolic dysfunction during stress testing can detect myocardial ischemia, and the presence of resting diastolic dysfunction identifies patients with poor prognosis. About half of heart failure patients, acute or chronic, have preserved ejection function, heart failure with preserved ejection fraction: HFpEF (Braunwald *et al.*, 2002).The WHO estimated that CAD will be the single largest cause of the disease burden in many countries worldwide by the year 2020. In the USA, every year nearly 1.2 million patients are hospitalized for ACS.

It is estimated that more than 16 million Americans have coronary artery disease (CAD) and 8 million have had a myocardial infarction (MI). Based on data from the Framingham trial nearly 50% of males and 30% of females over the age of 40 years will develop coronary artery disease (Owan *et al.*, 2006).

According to the epidemiological databases of cardiovascular disease in Malaysia, (Medical record according of AMI death in the government hospital Malaysia 1990-1998)(MOH, 1990-1998). Cardiovascular disease accounted for 25% of all deaths in Malaysia. In 2001, ACS apparently accounted for nearly 35,000 acute admissions into Government hospitals in Malaysia.Half of heart failure causes are related to left ventricular diastolic dysfunction, and heart failure is one of the important causes of mortality in heart disease patients (Vasan *et al.*, 1995; Betocchi and Hess, 2000). In 2006, there were 12,534 admissions due to ACS in Malaysia. As an estimate, the incidence of CAD in Malaysia is 141 per 100,000 population according to provision of coronary care services in Malaysia,

Development of left ventricular diastolic dysfunction is a frequent complication after acute myocardial infarction (AMI), and it is associated with an increased risk of heart failure.Coronary artery disease is most commonly due to atherosclerotic occlusion of the coronary arteries(Poulsen *et al.*, 1999). The main risk Factors for Atherosclerotic Coronary Artery Disease are:

1. Dyslipidemias; particularly high low density cholesterol (LDL-C) and low high density cholesterol (HDL-C). (ATP III classification of LDL, total and HDL cholesterol; LDL-C: Optimal < 100 mg/dL, Near or above optimal 100-139 mg/dL, Borderline high 140-159 mg/dL, high > 160 mg/dL, total cholesterol: desirable < 200mg/dl, borderline high 200-239 mg./dL, high > 240 mg./dL, HDL: Low < 40 mg./dL. (Owan *et al.*, 2006)

2. Hypertension; According to WHO, about 1.5billion people suffer from Hypertension worldwide, seven million die each year due to hypertension. Hypertension (50 million in the US, 1/3 undiagnosed, 3/4 under treated). (Classification of HTN Normal BP: systolic < 120 mmHg AND diastolic < 80 mmHg, Pre-hypertension: systolic 120-139mmHg OR diastolic 80-89 mmHg, Hypertension: systolic >140mmHg OR diastolic > 90 mmHg. The 7th Joint National Committee (7JNC) (Snow *et al.*, 1990).

3. Diabetes mellitus (8% of US population). According to Malaysian National Health survey, DM has risen to 11.6% in 2006. (Classification: Normal fasting glucose < 110 mg/dL (6.1mmol/l) Impaired 110- 126 mg/dL (6.1-7mmol/l), diabetes > 126 mg/dL)(>7mmol/l).

4. Smoking (most important modifiable risk factor), CAD accounts for 35%-40% of all smoking related deaths.

5. Family history of premature coronary artery disease (CAD); First degree male relatives < 55 years or females < 65 years.

6. Obesity (18% of US population) and lack of exercise

7. Male sex and advanced age

8. Others (20% of CAD occurs in individuals without any of the classical risk factors); homocysteinemia, high sensitivity C reactive protein (hs-CRP), Fibrinogen, Lipoprotein a (Lpa), infection (? *Chlamydia pneumoniae*). These are emergent newer risk factors.

1.2 Pathophysiology of Ischemic Heart disease

Coronary atherosclerosis is initially characterized by fatty streaks, which are associated by functional alterations of the endothelium without significant reductions in the vessel diameter. Hypercholesterolemia, circulating vasoactive amines, chemical irritants such

as tobacco smoke, and inflammatory processes promote endothelial dysfunction. These early lesions also involve accumulation of lipids, macrophages, and T-lymphocytes

in the arterial vessel wall. Fatty streaks are never associated with cardiac symptoms and may disappear or develop into atheromata. Platelets, endothelial cells, and macrophages may secrete several growth factors that initiate proliferation and migration of smooth muscle cells to other layers of the vessel wall. Endothelial dysfunction and smooth muscle cell proliferation may result in lesions of the more inward (intimal) layers of the coronary vascular wall. These coronary lesions display fibrin deposits and/or lipid-laden phagocytes (i.e., foam cells). Endothelial activation can be caused by low-density lipoprotein (LDL) cholesterol modification by oxidation resulting in the release of phospholipids. Platelets first respond to activated endothelium and may further increase endothelial activation by their glycoproteins (Ib and IIb/IIIa). Subsequently, a capsule-like fibrous layer of smooth muscle cells is formed, which covers the lipid lesion and predominantly collagen-based matrix. The atherosclerotic lesion is infiltrated by T-cells, macrophages, and mast cells, particularly at sites where the plague grows. These activated immune cells produce inflammatory cytokines which can be detected in the systemic circulations. Atherosclerotic plagues at the advanced stage of CAD are characterized by severe damage to all layers of the vessel wall, including the elastic lamina. Because of the thin layer of lipid-laden lesions, plague rupture can easily occur, causing blood-clot formation and development of severe vascular lesions, even when obstructive luminal narrowing has not yet been developed.

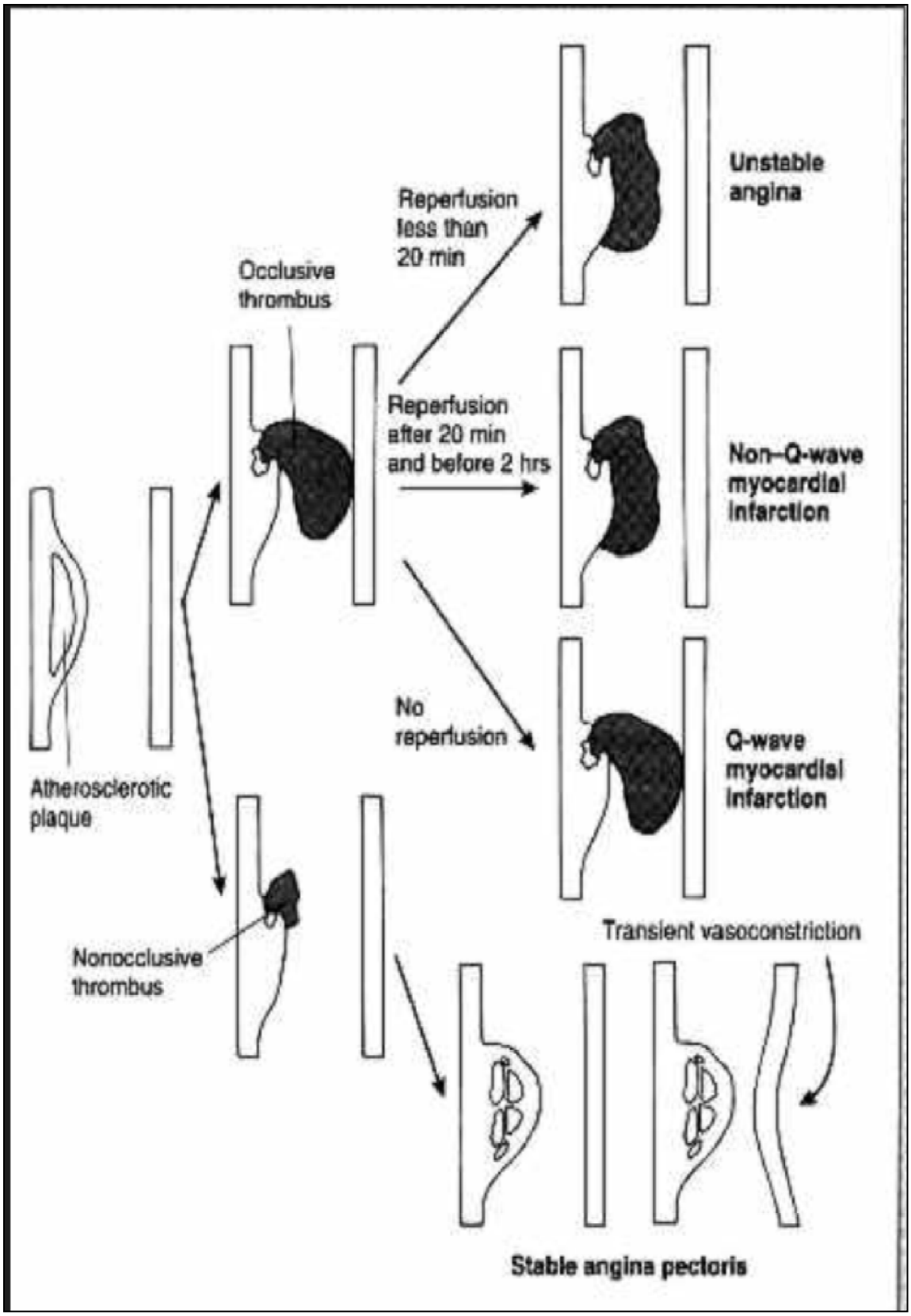

Figure 1 Pathophysiology of ischemic Heart disease Adopted from (Otto, 2012)

CHAPTER TWO

LITERATURE REVIEW

2.1 Diastolic function

Diastolic function encompasses several distinct haemodynamic phases which are fundamentally different in their properties. Echocardiography has been the mainstay for understanding the physiology of diastolic function and identifying the pathophysiology of diastolic dysfunction.

2.1.1 Physiology of diastole

Diastole was defined by Wiggers in physiologic terms as a process extending from the opening of the mitral valve i.e. the onset of ventricular filling to the onset of the contraction. For clinical application, diastole commence at the onset of the second heart sound indicating closure of the aortic valve and ended with the first heart sound, indicating closure of the mitral valve(Galiuto *et al.*, 2011). It is divided into four phases;

1. Isovolumic relaxation – which is the time between aortic valve closure and mitral valve opening.
2. Rapid early filling – account for 80% of ventricular filling.
3. Slow filling / Diastasis – account for less than 5%.
4. Late filling from atrial contraction.

1. Isovolaemic relaxation

By definition this is a period that extends from the time of aortic valve closure to mitral valve opening, and it occurs without a change in LV volume. It is an energy dependent process which occurs until mid-diastole.

2. Early rapid filling phase

This starts with opening of the mitral valve. The blood leaves the left atrium and enters the left ventricle passively down a pressure gradient generated by continued ventricular relaxation. This phase is therefore commonly termed the passive filling phase of ventricle, even though relaxation is active, an energy requiring process. Left ventricular suction, continued LV relaxation and elastic recoil leads to a continued fall in LV pressure, resulting in development of LA to LV pressure gradient with subsequent blood acceleration. This gradient is influenced by the level of left atrial pressure at mitral valve opening and rate of decline of ventricular pressure. Blood rapidly enters the LV from LA during the early filling period with approximately 70% of stroke volume received by the LV during the first third of diastole(Galiuto *et al.*, 2011).

3. Diastasis

This term is applied to the phase in diastole when LA and LV pressure are essentially in equilibrium following the rapid filling phase and little or no filling occurs; hence diastasis occurs between rapid filling and atrial contraction phase. It accounts for less than 5% of ventricular filling.

4. Late filling phase (atrial systole)

In the presence of sinus rhythm, synchronous electrical activation of the left atrium is followed by atrial contraction and ejection of further amount of blood into the left ventricle. Increase end diastolic volume by 25-30% of total filling volume of the ventricle. Naturally this phase of ventricular filling is absent in AF. Normally very little retrograde flow of blood into pulmonary veins occurs, and practically all the blood ejected by the atrium enters the ventricle.

2.1.2 Determinants and Properties of LV Diastolic Function

The following are major determinants of diastolic function;

1) Active myocardial relaxation

2) LV compliance

3) LA function

4) Heart rate

5) The pericardium

1. Active myocardial relaxation

Relaxation maybe defined broadly as the process by which muscle returns from its contracted state to that which existed before the initiation of the contraction. Abnormalities of relaxation may occur with myocardial ischaemia with hypoxia (such as in coronary artery disease), myocardial hypertrophy, hypothyroidism, hypothermia, aging, and a variety of other conditions. 3 main controlling mechanisms has been identified, these are; inactivation, load and in the case of intact ventricle, heterogeneity of inactivation of the ventricular chamber.

- Inactivation: refers to the disengagement of actin-myosin cross bridges within the myocardial cell, the prior formation of which is the subcellular mechanism responsible for myocardial contraction.

- Load: relaxation loads are those loads that are presence during the period of relaxation. Of there, internal restoring forces refer to the intrinsic forces created by the deformation of myocardial geometry resulting from contraction.

- Heterogeneity of relaxation: when different segments of the ventricle relax assynchronously, some segment may commence relaxation when others are almost fully relaxed. The resulting effect is a reduction in chamber or global relaxation rate. Such heterogeneity of regional relaxation may occur because of regional ischaemia or infarction in CAD or as a result of an

abnormal sequence of electrical depolarization seen with ventricular pacing or intra-ventricular conduction defect.

2. LV Compliance

Ventricular compliance is the ratio of change in volume to change in pressure (dv/dp) and stiffness is the mathematical inverse of compliance (dp/dv). Compliance is the net result of a variety of factors; visco-elastic nature of the myocardium, chamber size, shape, and wall thickness, RV and LV pressure volume interactions, pleural pressure and pericardial characteristics.

3. Left atrium

LA predominantly acts as a passive reservoir of blood during early LV filling, and as an active pump at end diastole. Atrial systolic function (active phase) may be essential to maintain cardiac output in disease states.

4. Heart rate

Heart rate has a direct effect on cardiac output in cases of diastolic dysfunction. As heart rate increases, diastolic filling period preferentially decreases with respect to the systolic ejection period.

Other factors that affect diastolic function include neuro-hormonal activation, conduction abnormalities and the stiffness of pericardium.

2.2 Echocardiographic Assessment of Diastolic Function

Although LV diastolic function can be assessed by cardiac catheterization, non-invasive methods such as Doppler recording of trans mitral and pulmonary venous flow and Tissue Doppler can provide adequate and accurate information and are currently the most widely used in clinical practice.

Echocardiography has been the mainstay for understanding the physiology of diastolic function and identifying the pathophysiology of diastolic dysfunction. A large number of parameters have been used to measure many aspects of diastolic function, and this diversity in itself reflects the absence of a single index that is ideal or universally acceptable. Therefore the combination of different techniques and/or maneuvers is needed in order to allow for an effective clinical staging of LV diastolic dysfunction.

In current clinical practice, the clinician has a number of techniques in the evaluation of diastolic function which include traditional and widely used Doppler techniques - mitral inflow and pulmonary vein flow ; and newer techniques such as Color M-mode Doppler and tissue Doppler imaging.

Doppler techniques of evaluating diastolic function

1) Mitral inflow:

In the evaluation of diastolic function of the left ventricle (mitral inflow), perform PW Doppler in the apical 4 chamber view with the sample volume placed at the tips of the mitral valve leaflets. Obtain a PW Doppler trace and measure:

- Peak E wave velocity
- Peak A wave velocity
- E/A ratio
- E wave deceleration time (DT)
- Isovolaemic relaxation time (IVRT)

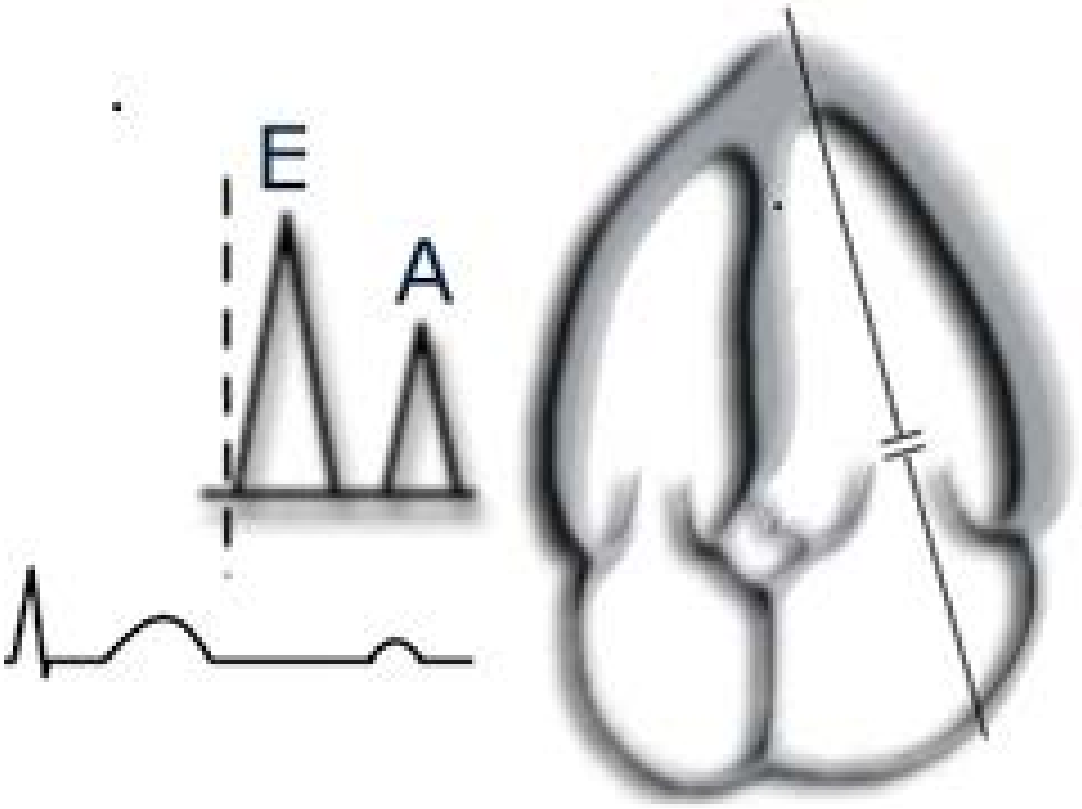

Figure 2 Mitral Inflow at apical 4 chamber view Adopted from (Houghton and Gray, 2008)

E wave

Represent the early filling phase of Left ventricle. In healthy individual, the early flow coincide with the mitral E-wave spectra, exceeds the later flow which occur with atrial systole - *the A-wave* (peak atrial systolic velocity spectra)

DT

E-wave deceleration time is the time period between the peak of the E-wave and the end of the E-wave, measured by extrapolating the E-wave deceleration slope down to the baseline and is normally 150-240 millisecond.

IVRT

This is the time period between aortic valve closure and mitral valve opening, during which LV pressure falls but there is no change in LV volume. There are various methods of measuring IVRT. The simplest is to tilt the probe, obtain a 5 chamber view and adjust the PW Doppler sample volume to lie between the mitral and aortic valves (so that both the mitral inflow and aortic outflow traces are seen on the same PW Doppler trace). Freeze the spectral trace and measure the time period between the end of aortic outflow trace and the start of the mitral inflow trace, this is the IVRT and normally 50-100 milliseconds.

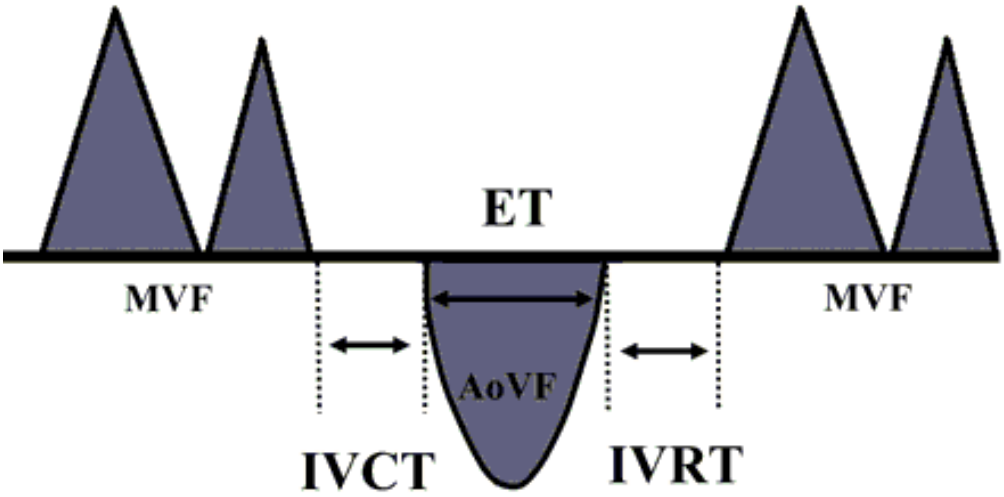

Figure 3 Isovolumic Relaxation Time (IVRT) Adopted from (CACP, 2007)

2) Tissue Doppler Imaging (TDI) of the mitral annulus

In the recent time, there has been tremendous interest in the prognostic implications of TDI diastolic variables. TDI of the mitral annulus is undertaken in the apical 4-chamber view, place the sample volume in the myocardium of the septum and/or lateral wall. The optimal location is 1cm before the mitral annulus. In each location a tissue doppler recording should be made using a low gain setting and aliasing velocity 12-20cm/s. TDI can be used as stand-alone technique or combine with mitral inflow pattern. TDI recording shows an early

myocardial velocity (Em or E') which corresponds to the early diastolic relaxation, the myocardium moving away from the transducer.

This is followed by a further movement away from the transducer corresponding to the atrial contraction (Am or A'). Normally E’ > A' when E’/A’ ratio is in the range of 1-2. If there is diastolic dysfunction, this ratio reverses. The ratio between the peak LV inflow E wave and E' should also be calculated, it reflects LA pressure. Normal E/E' ratio are less than 8 at the septum and less than 10 at the lateral wall.

The normal ratio of E' to A' is over 1.0. A reduced E' to A' ratio indicates impaired relaxation. The pattern of E’ to A' also helps to distinguish normal LV filling from the pseudo normalization pattern seen in patients with moderate diastolic dysfunction.

Approximate values for TDI derived variables are:

E' - 10 ± 2.0cm/s

A' - 5.8 ± 1.6cm/s

E'/A' - 2.1± 0.9

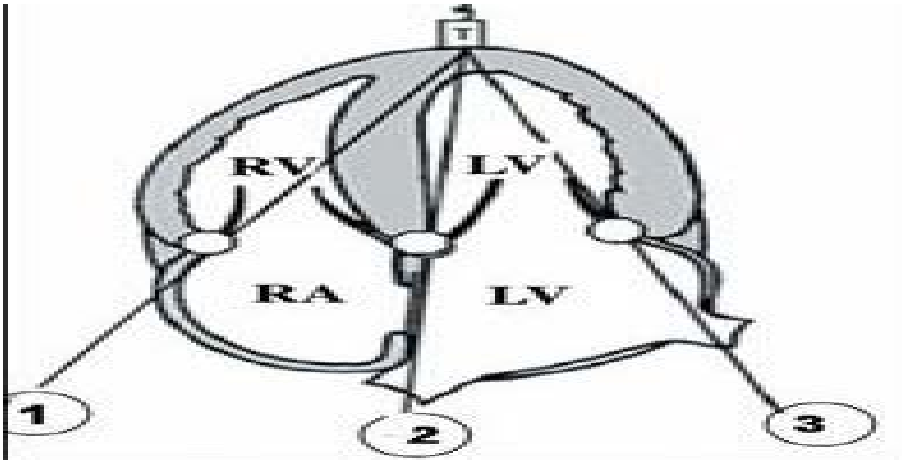

Figure 4 Tissue Doppler Imaging Technique Adopted from (Otto, 2012)

1) Tricuspid annulus; 2) Basal ventricular septum; 3) Mitral annulus.

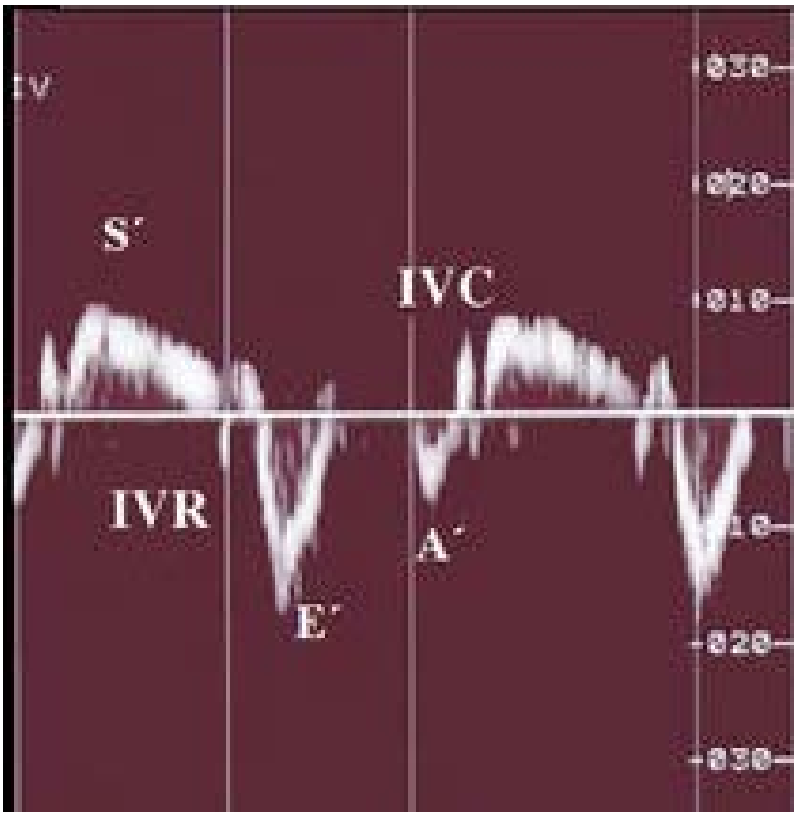

Figure 5 Doppler tissue imaging adopted from (Saccheri *et al.*, 2006)

A' indicates atrial systole; E', rapid ventricular filling; S', systolic contraction; IVC, isovolumic contraction; IVR, isovolumic relaxation; RA, right atrium; LA, left atrium.

3) Pulmonary venous flow

To assess pulmonary venous flow, obtain PW Doppler in the apical 4-chamber view with the sample volume placed inside one of the pulmonary veins, the right upper pulmonary vein is usually easiest to locate(Otto, 2012).

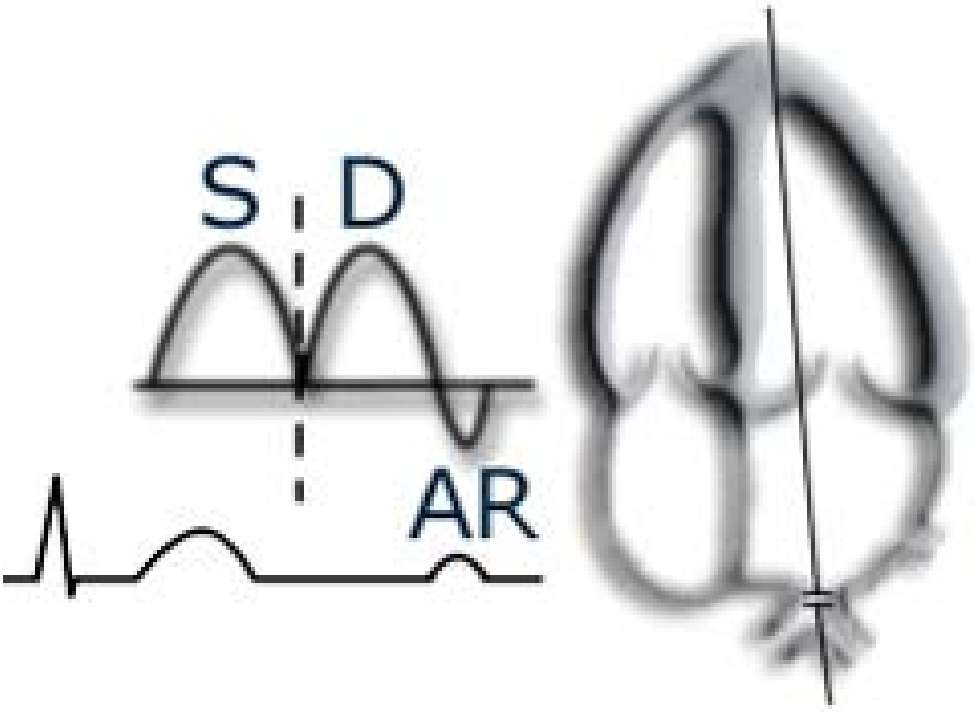

Figure 6 Pulmonary vein Flow Technique Adopted from (Otto, 2012)

Pulmonary vein flow normally consists of three (3) components:

- The S-wave represents forward flow into the left atrium during the ventricular systole.
- D-wave which is smaller represents forward flow during ventricular diastole.
- 'a' wave - if the patient is in sinus rhythm, the S and D waves are followed by 'a' wave representing flow reversal in the pulmonary vein during atrial systole.

Obtain a PW Doppler trace and measure;

- peak systolic (S wave) velocity (PV_S)
- peak diastolic (D wave) velocity (PV_D)
- peak atrial reversal (a wave) velocity (PV_a)
- duration of atrial reversal (a_{dur})

Normally $PV_S > PV_D$, and $PV_a < 0.35$ms

4) Color M-mode flow propagation velocity

Colour M-mode of the mitral inflow recorded by placing the M-mode cursor in the direction of the mitral inflow jet may be used to assess LV relaxation. The slope method is the most widely used in calculating velocity flow propagation [Vp cm/s]. In normal LV, values of Vp are greater than 30cm/s. In myocardial ischaemia or heart failure, there is slowing of Vp which is consistent with a reduction in apical suction. In normal subjects during diastole, there is a wave of relaxation originating at apex and moving toward the base which result in LV base to apex pressure gradient and allows blood flow to be sucked into the LV.

2.3 Mechanism of Diastolic Dysfunction

The evolution of diastolic dysfunction is complex, it involves the following:

Myocardial relaxation is an active process influencing isovolumic relaxation phase and part of the early filling phase. Factors affecting myocardial relaxation includes intracellular calcium overload (e.g. ischemia) which can delay or prolonged myocardial relaxation such that it impinges on early filling phase of diastole. Ventricular compliance is passive process that influences all three phases of diastole.

Besides myocardial relaxation and ventricular compliance, characteristics of pulmonary veins, left atrium and mitral valve are also involved in diastolic function. Heart rate is also a determinant of diastolic function. In the presence of bradycardia; most of the LV filling occurs before atrial contraction. In contrast, in presence of tachycardia, early filling is truncated and there is no diastasis phase.(Bursi *et al.*, 2006).

2.4 Diastolic dysfunction

Diastolic dysfunction is an abnormal function of the heart during atrial relaxation phase and compromises the heart ability to relax and fill.

Increase in left ventricular filling pressure (LVFP) is the main pathophysiological consequence of diastolic dysfunction. It is mainly determined by filling and passive properties of LV walls and can be additionally controlled by incomplete LV relaxation and alterations of myocardial diastolic tone.

Many patients with ischaemic heart disease show abnormal diastolic function on TDI despite having normal systolic function. In acute myocardial infarction, a pattern of delayed relaxation is seen acutely.

Causes of diastolic dysfunction

1) Ischaemic heart disease

2) LV hypertrophy e.g., hypertension, AS, HOCM

3) Restrictive cardiomyopathy

4) Constrictive pericarditis

5) Left ventricular infiltrations e.g., amyloid, sarcoid, carcinoid, hemochromatosis

6) Aging effects

Causes often co-exists e.g., hypertension, coronary artery disease

2.4.1 Mechanism of Diastolic Dysfunction

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2.4.2 Grading of diastolic dysfunction

There are 4 grades of diastolic dysfunction;

Grade 1: Represent impaired/ slows early left ventricular relaxation. At this point a patient is usually asymptomatic with normal filling pressure.

Doppler findings include:

- E/A ratio <1.0
- Deceleration time >240 msec.
- IVRT >90 msec.
- Pulmonary vein ‘’a’’ wave flow reversal <25 cm/sec.

Grade 2 : Pseudo normalisation. At this stage the effect of impaired/ slow early left ventricular relaxation on early diastolic filling become opposed by the elevated left atrial pressure and the early diastolic trans mitral pressure gradient and mitral flow velocity pattern return to normal, this phenomenon is called pseudo-normalisation to indicates that although left ventricular filling appears normal, significant abnormalities of diastolic function are present. This can be unmasked by valsalva manoeuvre or more evaluated by TDI method.

Grade 3: Restrictive but reversible represent a severe decrease in left ventricular chamber compliance but is reversible.

Grade 4: Restrictive but irreversible, diastolic filling pressures are elevated and the patient is markedly symptomatic. The left atrium is dilated and hypo-contractile.

Doppler findings:

- E/A ratio >1.5
- IVRT < 60m/sec
- Deceleration time < 160 m/sec

Normal echocardiographic diastolic function parameters

- E/A ratio: normal 1.1 to 1.5
- Deceleration time: 160 to 240 msec.
- IVRT: 76 +/- 13 (>40 years)

  69 +/- 12 (<40 years)
- Pulmonary vein "a " wave flow reversal < 25 cm/ sec

Normally E>A

Abnormal relaxation E<A

Pseudo-normal filling E>A

Restrictive filling E>>

TABLE 11-2 Criteria Used to Define the Grade of Diastolic Dysfunction

Criteria	*Normal Young*	*Normal Adult*	*Impaired Relaxation (Grade 1)*	*Pseudonormal (Grade 2)*	*Restrictive Reversible (Grade 3)*	*Restrictive Irreversible (Grade 4)*
E/A ratio	1-2	1-2	<1.0	1-1.5 (reverses with Valsalva maneuver)	>1.5	1.5-2.0 (Doppler values similar to grade 3 except no change with Valsalva maneuver)
Deceleration time (ms)	<240	150-240	≥240	150-200	<150	<150
IVRT (ms)	70-90	70-90	>90	<90	<70	<70
PV S_2/D ratio	<1	≥1	≥1	<1	<1	<1
$Ar_{dur} - A_{dur}$ (ms)	≥30	≤0	≤0 or ≥30	≥30	≥30	≥30
Ar velocity (cm/s)	<35	<35	<35	≥35	≥35	≥35
Propagation velocity (cm/s)	>55	>55	>45	<45	<45	<45
Mitral E′ velocity (cm/s)	>10	>8	<8	<8	<8	<8
Left atrium	Normal	Normal	Normal or mildly enlarged LA	Mild to moderate LA enlargement	Severe LA enlargement	Severe LA enlargement

Adapted from Bursi F, Weston SA, Redfield MM: Systolic and diastolic heart failure in the community. *JAMA* 296:2209-2216, 2006; Garcia MJ, et al: New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 32:865-875, 1998; and Yamada H, Klein AL. Diastology 2010: Clinical approach to diastolic heart failure. *J Echocardiogr* 8:65-79, 2010.

A_{dur}, Duration of transmitral atrial velocity; *Ar*, pulmonary vein atrial reversal velocity; Ar_{dur}, duration of pulmonary vein atrial reversal velocity; *D*, diastolic wave; *E/A*, ratio of early to late diastolic filling velocities; *IVRT*, isovolumic relaxation time; *PV*, pulmonary vein; *S*, systolic wave.

Figure 7 Grading of Diastolic Dysfunction adopted from (Otto, 2012)

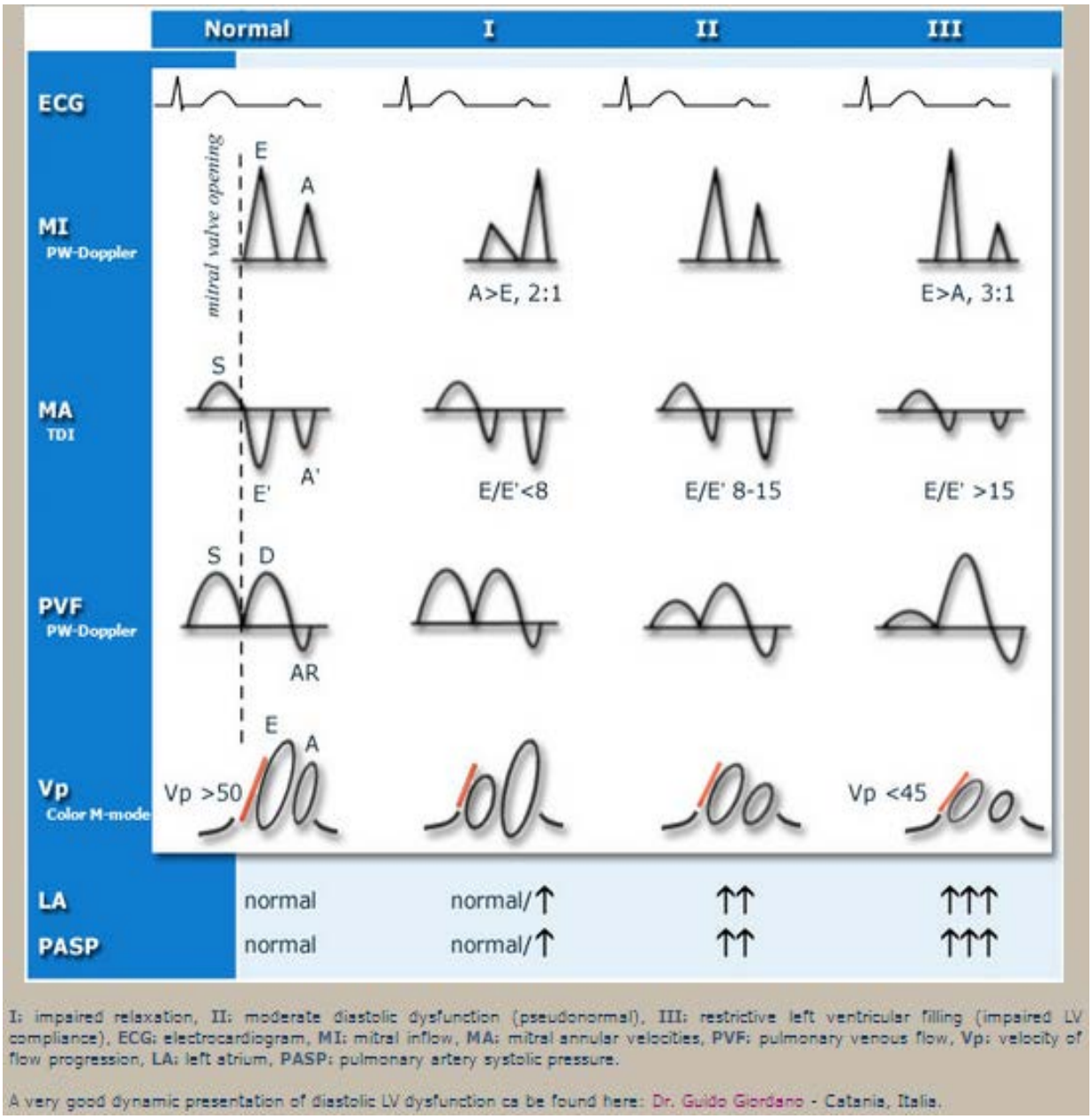

Figure 8 Echocardiographic Grading of Diastolic Dysfunction (Adopted from (http://www.echobasics.de/diastole-en.html))

2.5 The Ischemic cascade

The Ischaemic cascade is a sequence of hemodynamic and cardiac electro physiologic changes that culminates in angina. It is initiated by an imbalance between myocardial oxygen supply and demand.

Abnormal myocardial perfusion is the first detectable event of the ischaemic cascade as follows:

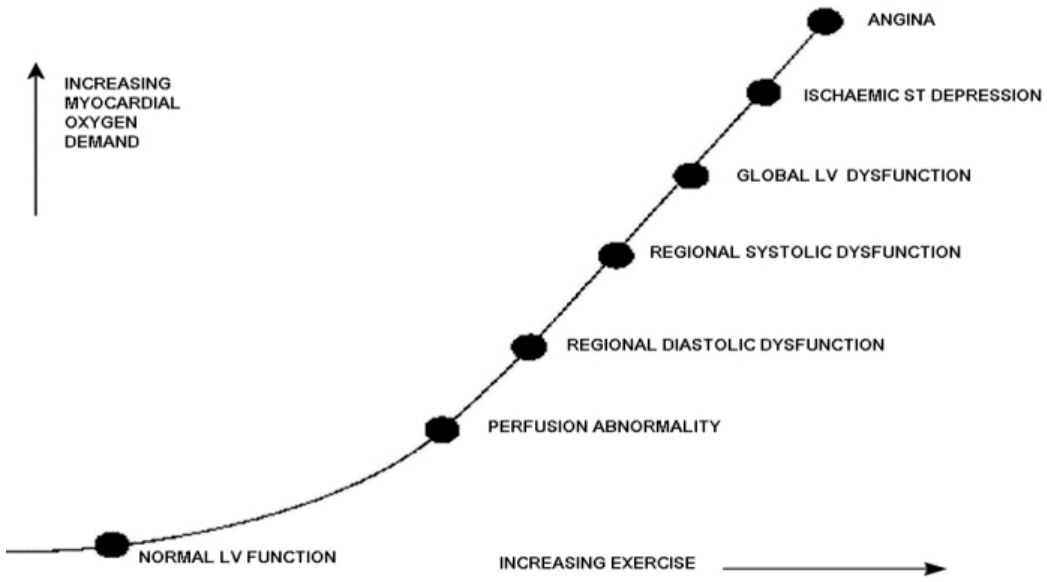

Figure 9 Ischemic cascade adopted from (Galiuto *et al.*, 2011)

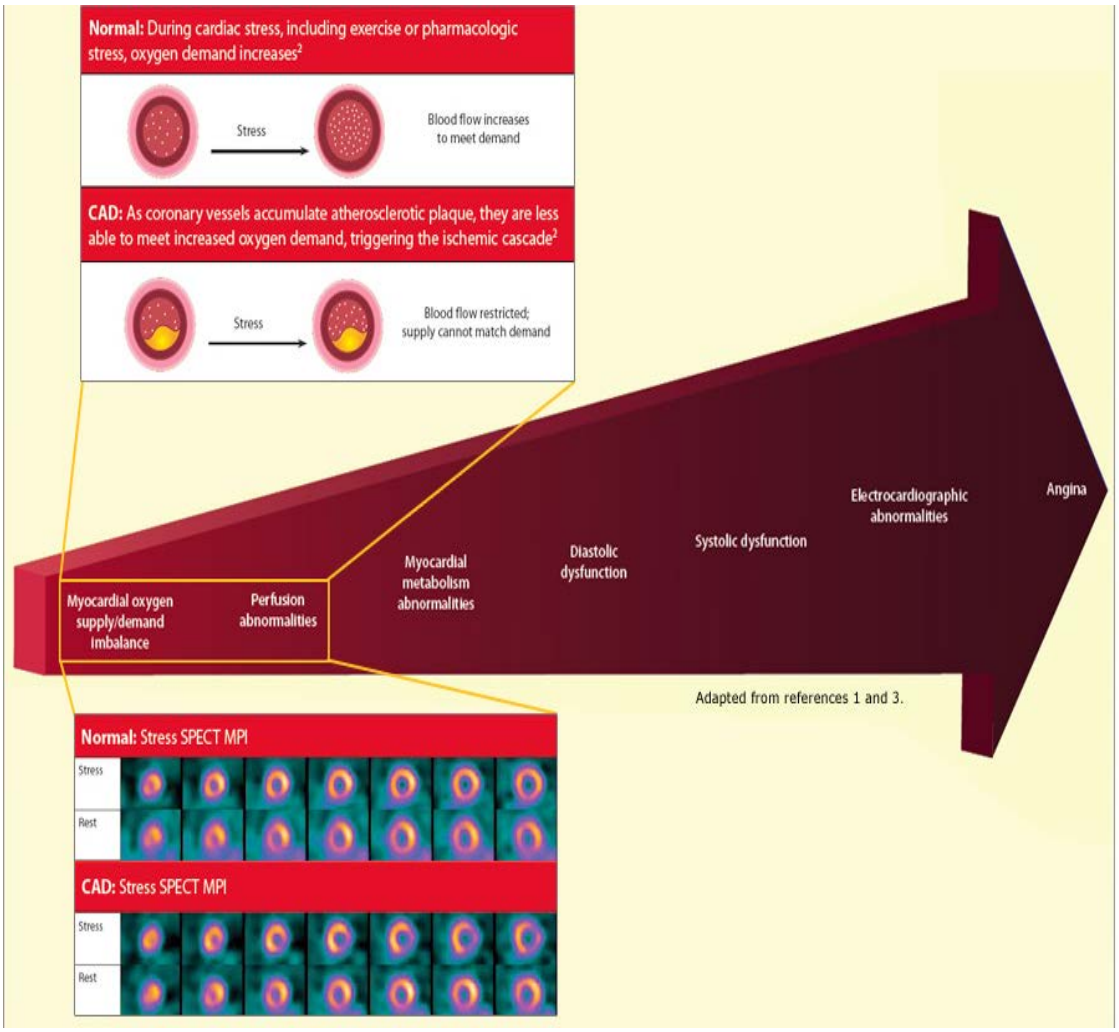

Figure 10 Sequence of ischemic cascade adopted from (CACP, 2007)

2.6 Percutaneous coronary intervention (PCI)

Since the first human percutaneous trans luminal coronary angioplasty (PTCA) procedure was performed in 1977, the use of percutaneous coronary intervention (PCI) has increased dramatically becoming one of the most common medical interventions performed. Coronary angioplasty has multiple indications including: unstable angina, acute myocardial infarction and multi-vessel coronary artery disease. With the combination of sophisticated equipment, experience operator and modern drug therapy, PCI has evolved into an effective non-surgical modality for treating patients with coronary artery disease. Annually, PCI is done in one million cases in the United States and two million around the world (Cutlip *et al.* 2007).

PCI is performed through the femoral, radial or brachial artery. A guiding catheter is placed in the ostium of the diseased coronary artery, a 0.014inch guide wire is advanced through the lesion and a balloon catheter is introduced over the guide wire and placed in the stenosed area. Usually the balloon is inflated for 15-30 seconds by 6 atmospheres.

Opening the thrombotic occlusion of the infarct related coronary artery in acute MI is effective in reducing the infarct size thereby preserving the LV function. In 1997, Weaver at el. showed a 32% mortality reduction in primary PCI compared to fibrinolysis. The CADILLAC trial demonstrated additional benefit of stenting versus balloon angioplasty in AMI. Diastolic abnormalities of left ventricular relaxation and filling now appear to be the earliest manifestation of myocardial ischemia and contribute to hemodynamic derangement and symptomatology. It has been suggested that abnormalities of left ventricular diastolic functions may actually proceed left ventricular systolic dysfunction in CAD and therefore serve as an early and sensitive marker of ischemia.