



**The prediction of pulmonary arterial hypertension
documented by echocardiography in patients with dilated
cardiomyopathy at Chris Hani Baragwanath hospital.**

By

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Submitted in fulfillment of the Degree of Masters in Technology

Clinical Technology: Cardiology

In the

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Durban, South Africa

April 2011

ABSTRACT

Background: Idiopathic dilated cardiomyopathy (IDC) is a primary myocardial disease of unknown cause characterized by left ventricular or biventricular dilatation and impaired myocardial contractility. Idiopathic dilated cardiomyopathy (IDC) is the second commonest cause of heart failure in Africa. Some patients with idiopathic dilated cardiomyopathy present with significant pulmonary hypertension (PHT) which maybe out of keeping with the usual degree of PHT seen in patients with this disorder.

Methods and Material: This is a prospective and longitudinal follow-up study of 66 patients with IDC who were evaluated after satisfying the inclusion and exclusion criteria of this study. The clinical evaluation of each patient included a complete medical history, physical examination, 12 lead electrocardiogram, 2D-echocardiography, continuous wave (CW), pulsed wave (PW), and tissue Doppler imaging (TDI).

Results: The mean age of all patients was 48.5 ± 12.8 , with 39/66 (59.1%) patients being male. The prevalence of pulmonary arterial hypertension (PAH) was documented in 47 patients (71.2%, 95% CI: 59 - 83%). Mean left ventricular ejection fraction (LVEF) was $25.3 \pm 8.8\%$, and mean left atrial volume index (LA volume) was 44.5 ± 19.8 ml/m². Mitral regurgitation (MR) occurred in 56/66 (84.8%) of patients with moderate or severe MR detected in 60.6% of all cases of IDC. The presence of a tricuspid regurgitant jet was found in 56/66 (84.9%), with (95% CI: 75 - 93%). Right ventricular dilatation was found in 65/66 (98.5%), with (95% CI: 95 - 101%).

Age, LA volume, LVEF and MR were included into a multivariate logistic regression model to predict PAH. Only MR presence was independently associated with PAH adjusted (OR 6.02, 95% CI: 1.15- 31.47) (p= 0.03).

Conclusion: The study has shown that there is a significant prevalence of pulmonary arterial hypertension (PAH), right heart involvement and tricuspid regurgitant jet in IDC patients. The present study also showed that in patients with dilated cardiomyopathy, the degree of mitral regurgitation was a good predictor of PAH.

PREFACE

This study represents original work by the author and has not been submitted in any other form to another University or University of Technology. Where the work of others was made of, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the cardiac clinic at Chris Hani Baragwanath Hospital, Johannesburg, under the supervision of Dr F.F.E Peters – Consultant at Chris Hani Baragwanath Hospital, and Prof J.K Adam – Head of Clinical Technology: Durban University of Technology.

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Acknowledgements

The author wishes to express sincere gratitude to the following persons for their assistance in the preparation of this research study.

1. To the many patients that participated in this study.
2. Dr F.F.E Peters for his assistance, guidance, support and encouragement.
3. Dr A.C Becker for his assistance, guidance, support and encouragement.
4. Dr E. Libhaber for her assistance in the statistical analysis of the results.
5. Prof J. K. Adams for her assistance, guidance and supervision.

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ABBREVIATIONS

A wave – Late diastolic mitral inflow velocity

BADCMO – Baragwanath dilated cardiomyopathy

CHBH – Chris hani baragwanath hospital

CHF – congestive heart failure

CW – Continuous wave Doppler

DCM – Dilated cardiomyopathy

DT – Deceleration time

ECG – Electrocardiogram

EDV- End-diastolic volume

EF- Ejection fraction

ESV- End-systolic volume

(ET-1)- Endothelin-1

E wave – Early diastolic mitral inflow velocity

DC – Idiopathic dilated cardiomyopathy

IVCT – Isovolumic contraction time

IVRT – Isovolumic relaxation time

IVS – Interventricular septum

LA- left atrium

LV – Left ventricle

LVEF- left ventricular ejection fraction

NO- Nitric oxide

PAH – Pulmonary arterial hypertension

(PDE-5)- phosphodiesterase

PE-pulmonary embolism

PGI₂ – prostacyclin

PHT- Pulmonary hypertension

PTED – Pulmonary thromboembolic disease

RA- Right atrium

RV- Right ventricle

RVEF- Right ventricular ejection fraction

S' – Peak systolic myocardial velocity

PW – Pulsed wave doppler

2D- echo – Two dimensional echocardiography

WHO – World Health Organization

CHAPTER 1

INTRODUCTION

Idiopathic dilated cardiomyopathy (IDC) is the second commonest cause of heart failure at Chris Hani Baragwanath Hospital (CHBH) (Sliwa, Wilkinson, Hansen, Nytyintyane, Tibazarwa, Becker, Steward, 2008). Some patients with idiopathic dilated cardiomyopathy present with significant pulmonary hypertension (PHT) which may be out of keeping with the usual degree of PHT seen in patients with this disorder. The reasons for this discrepancy is important since concomitant clinical problems such as pulmonary thromboembolic disease (PTED) can occur more frequently in patients with congestive cardiac failure (CCF) (Pengo, Lensing, Prins, Marchiori, Davidson, Tiozzo, Albanese, Biasiolo, Pegoraro, Iliceto, Prandoni, 2004). If undiagnosed and untreated it can be associated with significant mortality. Furthermore, in the Heart of Soweto Study a significant number of patients (42% male and 58% female) had right heart failure (Sliwa et al., 2008). Thus identifying right heart failure is important since this may either be related to pulmonary hypertension or due to intrinsic right ventricular (RV) myocardial abnormality similar to the same disease process affecting the left ventricle (LV). Distinguishing these various mechanisms is important and may alter therapy.

Apart from the pathophysiological mechanisms of PHT or right heart abnormalities in IDCMO both PHT and RV failure are independently associated with a worst prognosis in patients with heart failure (Cody, Haas, Kelley, Binkley, Capers, 1992).

Echocardiography is the first tool of investigation to study patients with CCF and IDC. It allows the noninvasive assessment of the size and function of both the left and right heart chambers. It enables the degree of atrioventricular valve regurgitation to be studied and it allows for the accurate measure of systolic pulmonary arterial pressure measurements. The causes of PHT can also be determined eg: severe LV dysfunction, severe mitral regurgitation and the consequences of PHT on the right heart chambers and function can be assessed (Bailey, Hatle, Tajik, Nishimura, 1994).

Thus we undertook a prospective and longitudinal study in patients with IDC which aimed at:

- 1) Determining the prevalence of PAH documented on echocardiography in patients with dilated cardiomyopathy.
- 2) Identifying the predictors of pulmonary hypertension in this population using echocardiography.
- 3) Determining the prevalence of right heart involvement and tricuspid regurgitation in dilated cardiomyopathy patients.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Idiopathic Dilated Cardiomyopathy (IDC)

Idiopathic dilated cardiomyopathy (IDC) is a primary myocardial disease of unknown cause characterized by left ventricular or biventricular dilatation and impaired myocardial contractility (Cohn, Wilen, Francoisa, Ziesche, 1983). IDC vies with rheumatic heart disease and hypertension as one of the leading causes of heart failure in Africa (Sliwa et al., 2008). A study involving 4549 patients in Africa presenting with heart failure showed that 17% to 48% of patients had IDC (Amoah and Kallen, 2000). Among 1500 patients seen at the cardiac clinic at Chris Hani Baragwanath Hospital in 2006 more than 30% presented with heart failure due to so called idiopathic dilated cardiomyopathy (Sliwa et al., 2008). This contrasts with studies of IDC in the United States and elsewhere, where the prevalence is reported to be 4 to 8 per 100 000 person-years and 36.5 per 100 000 individuals, respectively (Braunwald and Wynne, 2001).

The true natural history of IDC is difficult to determine, since asymptomatic cardiomegaly may be present for months or years (Ballard, Sugrue, Rodheffer, Codd, Fuster, Gersh, 1992). Although the rate of progression from asymptomatic left ventricular dysfunction to overt symptomatic heart failure is unknown, symptomatic patients generally have a poor prognosis. Survival data from tertiary referral centres are similar, with mortality rates of 25 to 30% at one year and approximately 50% at

five years (range, 35 to 62%) (Diaz, Obasohan, Oakley, 1987). The poor survival reported in these early retrospective studies may reflect a referral bias, since patients with more advanced disease or treatment failures may have been more likely than others to be referred. More recent observations suggest substantially better survival, with an average five-year mortality of 20% (Ballard et al., 1992). This change in mortality probably reflects their earlier detection of disease, a shift to population-based studies and better treatment (Ballard et al., 1992).

Although the majority of deaths occur within three years of the onset of symptoms, an additional 4 to 10 percent of patients die annually as a result of progression (Di Lenarda et al., 1990). A minority of patients may have a prolonged period of clinical stability. A spontaneous increase in the left ventricular ejection fraction (> 10 percentage points) has been reported in 20 to 45% (Coy, Rouillard, Fishbein, Don Michael, Siegel, 1991). Improvement in ventricular function is independent of the initial ejection fraction and most frequently occurs within six months of initial presentation, but such improvement can occur up to four years after the onset of symptoms (Coy et al., 1991). This variation in natural history may be partially explained by the lack of specificity in diagnosing IDC.

Some patients with IDC do badly, whereas most patients are stable on modern therapy. However as many as 20% of these patients with IDC will die each year (Hoffman, Meinertz, Kasper, 1998). A number of predictors can be identified with an adverse prognosis as listed in table 1 (Van Den Brock, Van Veldhuisen, De Graeff, 1998).

Table 1: Adverse prognosis of IDC (Van Den Brock, Van Veldhuisen, De Graeff, 1998).

1) New York Heart Association Class rating
2) Increasing Age
3) A low left ventricular ejection fraction (LVEF)
4) Exercise peak oxygen uptake (VO_2) of 11 to mL/ Kg/ min
5) High left ventricular filling pressure
6) Marked intraventricular conduction delay (Including a permanent pacemaker)
7) A complex ventricular arrhythmia

Echocardiography can be used to identify adverse prognostic factors such as an increased left atrial size, right ventricular enlargement and a reduced right ventricular ejection fraction (RVEF) (Juilliere, Barbier, Feldman, 1997). High left atrial pressures were also predictive of adverse outcomes which included a high early diastolic mitral inflow velocity, a short early diastolic mitral inflow velocity, a short early diastolic mitral inflow velocity deceleration time and a reduced pulmonary venous inflow velocity during ventricular systole (Boni, Cortigiani, Nannini, 1998). High left sided filling pressures may contribute to the development of PHT.

Pulmonary hypertension complicating left ventricular dysfunction is associated with a high mortality and incidence of heart failure (Abramson et al., 1992) and an even worse outcome of heart transplantation (Fowler, 1992). Such a grim prognosis underscores the importance of defining the determinants (Abramowicz, Naeije, Lipski, 1994) of the variable degree of pulmonary hypertension associated with left ventricular dysfunction (Cody, Haas, Binkley, Capers, Kelley, 1992).

2.2 Pulmonary Arterial hypertension (PAH)

Pulmonary arterial hypertension (PAH) > 35 mmHg on echocardiography is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and death (Rich, 2004).

2.2.1 Venice classification of Pulmonary Arterial Hypertension

The World Health Organisation (WHO) classification of pulmonary hypertension, designated five categories that are distinctive because they differ in their clinical presentation, diagnostic findings and response to treatment (Table 2).

Table 2: The WHO Classification of Pulmonary Hypertension (Simonneau, Galie, Rubin, Langleben, Seeger, Domenighetti, Gibbs, Lebrec, Speich, Beghetti, Rich, Fishman, 2004).

1. Pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic (IPAH)
 - 1.2. Familial (FPAH)
 - 1.3. Associated with (APAH):
 - 1.3.1. Collagen vascular disease
 - 1.3.2. Congenital systemic-to-pulmonary shunts
 - 1.3.3. Portal hypertension
 - 1.3.4. HIV infection
 - 1.3.5. Drugs and toxins
 - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
 - 1.4. Associated with significant venous or capillary involvement
 - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
 - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
 - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
 - 2.1. Left-sided atrial or ventricular heart disease
 - 2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
 - 3.1. Chronic obstructive pulmonary disease
 - 3.2. Interstitial lung disease
 - 3.3. Sleep-disordered breathing
 - 3.4. Alveolar hypoventilation disorders
 - 3.5. Chronic exposure to high altitude
 - 3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
 - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
 - 4.2. Thromboembolic obstruction of distal pulmonary arteries
 - 4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

2.2.2 Left heart failure causing Pulmonary Arterial Hypertension

Left heart disease probably represents the most frequent cause of pulmonary hypertension (PHT). Left-sided ventricular or valvular diseases may produce an increase in left atrial pressure, with passive backward transmission of the pressure leading to an increase in the pulmonary capillary wedge pressure. This backward pressure ultimately leads to PHT (Di Lenarda et al., 1993) (Figure 1). Pulmonary hypertension is also associated with neurohumoral activation (Burnett, Kao, Hu, 1986), in particular of endothelin-1 (Cody et al., 1992), a potent vasoconstrictor that is increased markedly in advanced heart failure (Lerman, Wei, Rodeheffer, 1994). An adaptive increase in pulmonary arteriolar resistance results from a prolonged duration of pulmonary venous hypertension. Amelioration is the primary approach of the underlying cause, although persistent vascular changes may persist after complete normalization of cardiac dysfunction.

Recent studies by Bailey et al., (1994), have suggested an association between abnormal left ventricular inflow velocity patterns assessed by doppler echocardiography and increased pulmonary arterial hypertension in left ventricular dysfunction. However, in left ventricular dysfunction, because of the frequent functional mitral regurgitation (Bailey, Tajik, Seward, Enriquez – Sarano, 1994) and the changes in the left atrial volume and compliance, which may affect left ventricular filling patterns (Nakano, Tomita, Zile, 1991), the independent determinants of pulmonary arterial hypertension are unclear (Cosyns, Robert, Rapheal, Vanoverscherde, 1990).

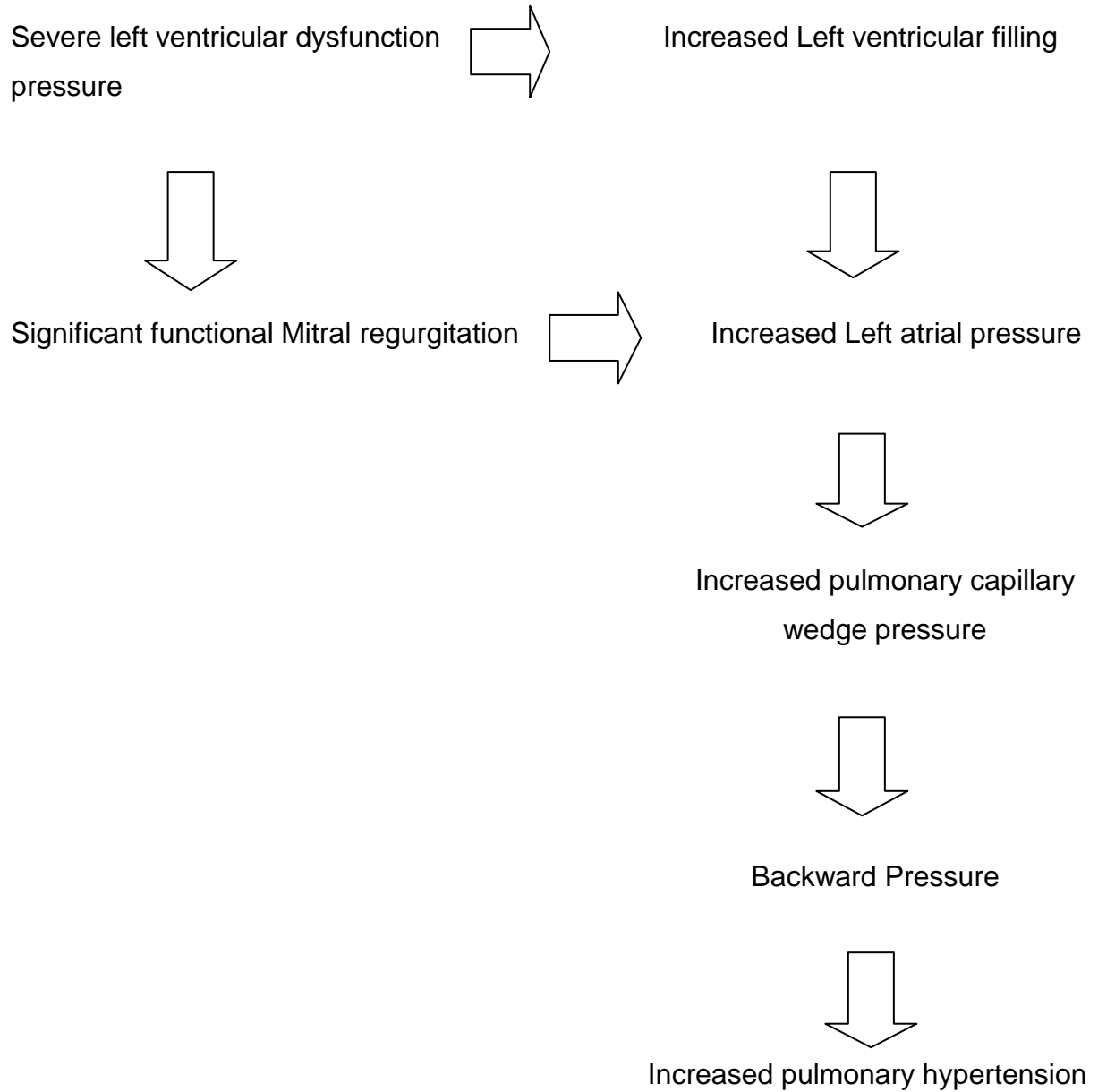


Figure 1: How left sided disease causes pulmonary hypertension

2.2.3 Pulmonary Arterial Hypertension and thromboembolism

Patients with IDC can develop thromboembolism. However according to the literature, the incidence is not known. The reasons that could result in patients with IDC developing thromboembolism could be due to venous stasis secondary to right heart failure, prolonged bed rest can lead to deep vein thrombosis and subsequently pulmonary embolism or uncommonly insitu thrombus formation in the right atrium (RA) or right ventricle (RV) that leads to pulmonary embolism.

2.2.4 Imbalance between vasodilators and vasoconstrictors

The imbalance between vasodilators and vasoconstrictors is plausible because of the neurohumoral abnormalities in chronic heart failure, however this has not been fully explored.

Prostacyclin

The action of prostacyclin synthase on arachidonic acid in endothelial cells results in the production of prostacyclin (PGI₂). In patients with PAH, prostacyclin synthase activity and prostacyclin levels are reduced, which leads to a relative deficiency of its potent vasodilatory and antiproliferative effects (Christman, McPherson, Newman, King, Bernard, Groves, Loyd, 1992). Thus, levels of the vasoconstrictor thromboxane are increased (Christman et al., 1992).

Endothelin

Endothelin-1 (ET-1) is a 21-amino acid peptide that is produced from big endothelin by endothelium-converting enzymes in endothelial cells. It possesses potent vasoconstrictor and mitogenic effects (Dubin, Pratt, Dzau, 1989). Patients with PAH have elevated endothelin levels, and the clearance of endothelin in the pulmonary vasculature is reduced (Stewart, Levy, Cernacek, Langleben, 1991). Endothelin acts at 2 different receptors: ET_A receptors on vascular smooth muscle cells and ET_B receptors on vascular smooth muscle cells and endothelial pulmonary vascular cells. Vascular smooth muscle cell proliferation are mediated by both ET_A and ET_B receptors. Vasoconstriction is mediated by ET_A receptors. Whereas, ET_B receptors may have a role in either vasoconstriction, via action on smooth muscle cell receptors, or release of both vasodilators (nitric oxide [NO] and PGI₂) and vasoconstrictors (thromboxane), via actions on endothelial cells, and also clear ET-1.

Nitric Oxide Pathway

Nitric oxide (NO), produced in endothelial cells from arginine by NO synthase, leads to vasodilation via a complex pathway that involves the production in vascular smooth muscle cells of cGMP. cGMP kinase is activated by cGMP, which in turn opens cell membrane potassium channels to allow potassium ion efflux, membrane depolarization and calcium channel inhibition. Phosphodiesterase-5 (PDE-5), 1 of 11 superfamilies of PDE enzymes, degrades cGMP, thus counteracting the vasodilatory pathway initiated by NO.

Evidence of decreased NO synthase expression is noted in patients with PAH, thus promoting vasoconstriction and cell proliferation (Giaid and Saleh, 1995). Potential sites of intervention include increased substrate (arginine), nitric oxide or nitrate donor agents, inhibition of PDE-5, or calcium channel blockade. The prostacyclin, endothelin and NO pathways are depicted in Figure 2.

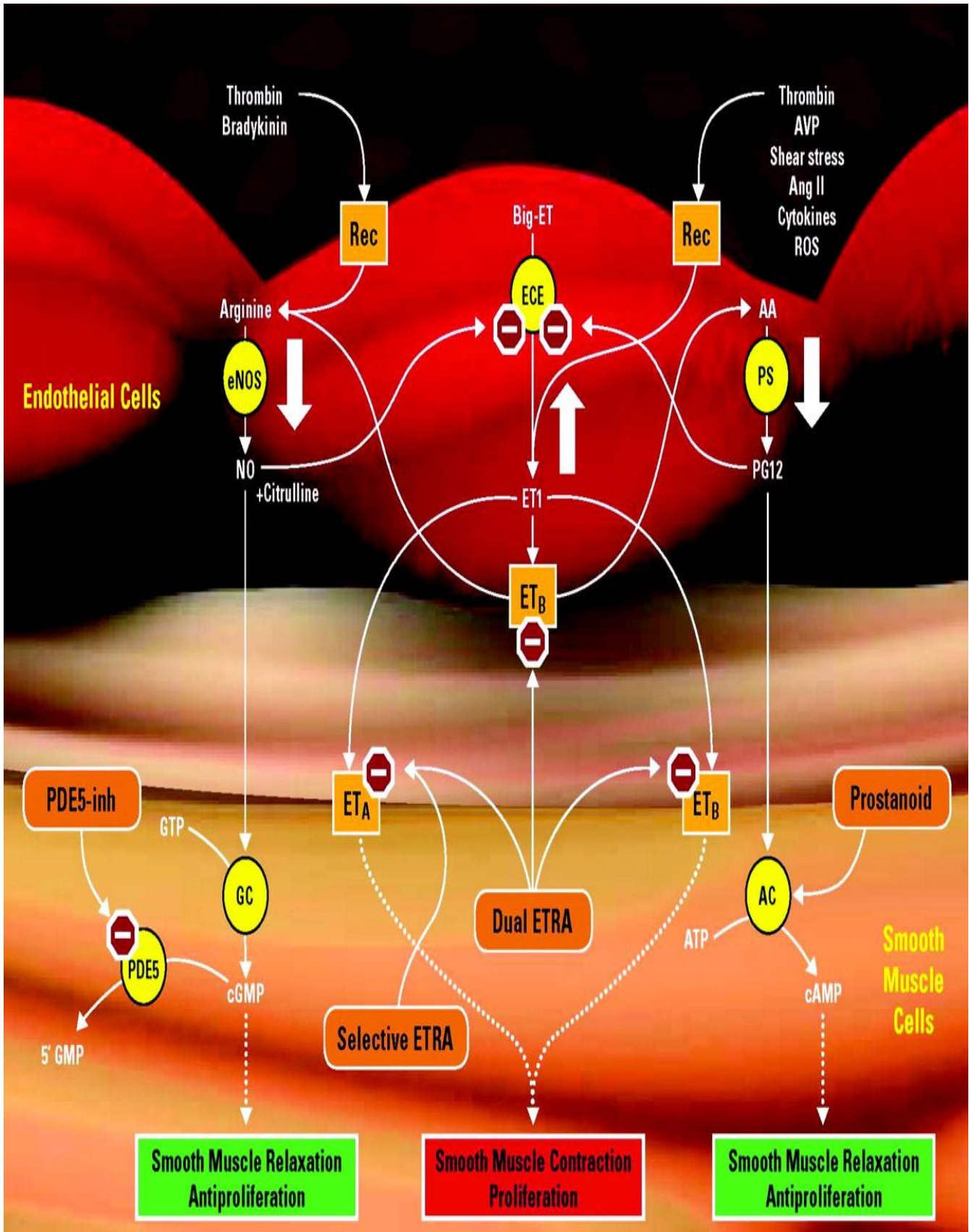


Figure 2: Three major mechanistic pathways known to be present in patients with PAH.

(Giad and Saleh, 1995)

The Nitric Oxide pathway: NO is created in endothelial cells by type III NO synthase (eNOS), which in turn induces guanylate cyclase (GC) to convert guanosine triphosphate (GTP) to cGMP, a second messenger that constitutively maintains pulmonary artery smooth muscle cell (PASMC) relaxation and inhibition of PASMC proliferation.

The endothelin (ET) pathway: Big-ET (or pro-ET) is converted in endothelial cells to ET-1 (21 amino acids) by endothelin-converting enzyme (ECE). ET-1 binds to PASMC ET_A and ET_B receptors, which ultimately leads to PASMC contraction, proliferation, and hypertrophy. ET-1 also binds to endothelial cell ET_B receptors.

The prostacyclin pathway: The production of PGI₂ (prostacyclin) is catalyzed by prostacyclin synthase (PS) in endothelial cells. In PASMCs, PGI₂ stimulates adenylate cyclase (AC), thus increasing production from ATP of cAMP, another second messenger that maintains PASMC relaxation and inhibition of PASMC proliferation. The pathways interact as illustrated, modulating the effect of any single pathway. They also are impacted by transmitters and stimuli that act at cell membrane receptors (Rec). Examples of these include but are not limited to thrombin, bradykinin, arginine vasopressin (AVP), vessel-wall shear stress, angiotensin II (Ang II), cytokines, and reactive oxygen species (ROS). In addition, the effect of a transmitter depends on its specific site of action (such as PASMC ET_A or ET_B receptors vs endothelial cell ET_B receptor). The large white arrows (Figure 2) depict aberrations observed in these pathways among patients with PAH. The orange boxes (Figure 2) represent agents that have reported clinically beneficial effects in patients with PAH. PDE5-inh indicates PDE-5 inhibitor, eg, sildenafil; ETRA, endothelin receptor antagonist, eg, bosentan (dual), ambrisentan, and sitaxsentan (receptor A selective). Prostanoids, eg, epoprostenol, treprostinil, and iloprost, supplement exogenously deficient levels of PGI₂. Red stop signs (Figure 2) signify an inhibitory effect of depicted agents.

Dotted arrows (Figure 2) depict pathways with known and unknown intervening steps that are not shown. (Giaid and Saleh, 1995)

2.2.5 Associated cormobid lung disorders causing hypoxia

In this category, the predominant cause of PHT is alveolar hypoxia as a result of lung disease, impaired control of breathing, or residence at high altitude. The prevalence of PHT in all of these conditions remains largely unknown. About 66% of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV chronic obstructive lung disease have some degree of PHT, which is generally mild (Scharf, Iqbal, Keller, Criner, Lee, Fessler, 2002).

2.3 Right heart function

Intrinsic contractile dysfunction, a change in loading conditions beyond physiological limits, as well as an altered performance of the left ventricle (LV) can all have detrimental effects on RV function.

An acute change in afterload of sufficient magnitude, as produced by pulmonary embolism (PE), can quickly result in RV failure as the RV has little ability to cope with this condition (Goldhaber, 2004). A chronic exposure to an increased afterload results in RV hypertrophy and altered geometry, which temporarily reduces wall stress but ultimately results in RV failure (Belik, Light, 1989). In addition, the flattening or displacement of the interventricular septum (IVS) seen in chronic RV pressure overload impairs LV compliance and filling (Lurz, Puranik, Nordmeyer,

Muthuranga, Hansen, Schievano, 2009). The mechanisms leading to RV failure in patients with chronic pulmonary hypertension are not fully understood. However, potential mechanisms include: RV myocardial ischaemia, altered inflammatory and oxidative stress, abnormalities in endothelin and nitric oxide systems and myocyte apoptosis.

Volume overload is a condition which is better tolerated by the RV, but, if sustained, will also ultimately lead to RV functional decline (Davlourous, Niwa, Webb, Gatzoulis, 2006). Left ventricular failure may directly impact on RV function by ventricular interaction in that an exaggerated displacement of the septum into the RV may impair both filling and contractility of the RV (Alpert, 1986).

2.3.1 Difficulties of assessing the right ventricle – Anatomy and Physiology

In a normally developed RV with atrioventricular and ventriculo-arterial concordance and normal tricuspid and pulmonary valves, three anatomical parts of the RV can be distinguished: 1) the inlet part which accommodates the tricuspid valve, 2) the trabeculated apical part, 3) and the outlet part (Anderson, Razavi, Taylor, 2004). The myocyte arrangement in the RV wall differs from that of the three-layered LV. Myocytes are predominantly oriented in the longitudinal direction in the subendocardial layer. Circumferentially oriented myocytes are found in the thinner subepicardium (Anderson, Smerup, Sanchez-Quintana, Loukas, Lunkenheimer, 2009). Consequently, the RV contraction pattern is predominantly longitudinal (Leather, Ama', Missant, Rex, Rademakers, Wouters, 2006). To further differentiate the RV from the LV, rotational deformation plays only a minor role in RV contraction.

The thickness of the RV free wall is in the range of only 3-5 mm as measured by echocardiography (Lang, Bierig, Devereux, Flachskampf, Foster, Pellikka, 2006), and the RV mass is approximately one-fourth of that of the LV (Sandstede, Lipke, Beer, Hofman, Pabst, Kenn, 2000). Despite the lower muscle mass because of the lower impedance and greater distensibility of the pulmonary artery bed, the RV is able to pump blood at the same rate and volume as the LV.

The ability of both ventricles to maintain a normal cardiac output, ensuring sufficient organ perfusion, depends on three key factors: 1) the contractile status of the myocardial tissue, 2) the preload, which represents the initial stretching of cardiac myocytes prior to contraction, 3) and the afterload, defined as the load against which the heart must contract to eject blood (Opie, 2008). In addition, RV performance is directly influenced by LV functional status owing to ventricular interaction (Sheehan and Redington, 2008). The interventricular septum, the pericardium and common muscle fibers all play an important role in facilitating the transfer of force from the LV to the RV during the cardiac cycle (Santamore and Dell'Italia, 1998). Around one-third of the pressure generated in the RV is determined by LV contraction (Yamaguchi, Harasawa, Li, Zhu, Santamore, 1991).

Right ventricular function is adversely affected by an elevated afterload, with a small range of pressure against which it can maintain a normal cardiac output (Chin, Kim, Rubin, 2005). In contrast, it tolerates volume overload much better which alters RV geometry, but does not influence the pattern of ejection (Redington, Rigby, Shinebourne, Oldershaw, 1990).

The particular haemodynamic environment of the right heart has direct implications on the phases of the cardiac cycle in the RV. Under normal circumstances, the low end-diastolic pressure in the pulmonary artery is quickly exceeded by the pressure rise in the RV, resulting in a very short or even absent isovolumic contraction time (Redington, Gray, Hodson, Rigby, Oldershaw, 1988). Another element that separates RV from LV physiology is the existence of a hang-out period during ejection. During this time interval RV pressure fall below pulmonary artery pressure until pulmonary valve closure. The ejection of blood is maintained most likely as a consequence of the high capacitance of the pulmonary circulation which allows the preservation of blood momentum. Similar to the isovolumic contraction, isovolumic relaxation is very short or may even be absent under normal conditions (Redington et al., 1988). Thus when the right ventricular end diastolic pressure is elevated, an indicator of this on echocardiography is an abnormally prolonged isovolumic relaxation time (IVRT).

Right ventricle (RV) function is a major determinant of functional capacity and prognosis in PAH (Voelkel et al., 2006). While RV hypertrophy and dilatation are initiated by increased afterload [i.e., elevated pulmonary vascular resistance (PVR)], the adequacy of the RV's compensatory response (preservation of stroke volume) is quite variable amongst individuals with RV failure occurring under loading conditions that appear not to induce RV failure amongst other individuals. It is unclear why there is a thinning and dilatation of the RV, and a reduce RV ejection fraction are the hallmarks of RV decompensation on echo. RV function could potentially be improved

by discovering effective therapies to regress pulmonary vascular obstruction or by directly improving RV contractile function.

2.3.2 Echocardiography and assessment of Right Ventricle

A) Technical difficulties

The RV is positioned directly behind the sternum, anterior to the left ventricle (LV). It has a complex geometry, appearing triangular when viewed from the front, and crescentic when viewed in a transverse section of the heart, with the septum being the most important determinant of shape. Under normal loading conditions, the septum arches into the RV both in systole and diastole. This complex geometry cannot be fitted to simple geometric models, which presents important limitations for the estimation of RV volume and function based on two-dimensional (2D) tomographic views.

B) Studies/ recommendations to assess Right Ventricular size, Tricuspid Regurgitation Jet and Systolic Excursion Velocity (RV S')

Right Ventricular size

The accurate assessment of RV morphology and function requires integration of multiple echocardiographic views, including parasternal long and short axis, RV inflow, apical 4-chamber and subcostal. Although multiple methods for quantitative

echocardiographic RV assessment have been described, in clinical practice assessment of RV structure and function remains mostly qualitative.

Compared with LV, the RV is a thin-walled structure under normal conditions. The normal RV is accustomed to a low pulmonary resistance and, hence, low afterload. Thus, normal RV pressure is low and RV compliance high. Therefore, the RV is sensitive to changes in afterload, and alterations in RV size and function are indicators of increased pulmonary vascular resistance and load transmitted from the left sided chambers. Elevations in RV afterload in adults are manifested acutely by RV dilatation and chronically by concentric RV hypertrophy. In addition, intrinsic RV abnormalities, such as infarction or RV dysplasia can cause RV dilatation or reduced RV wall thickness (Yoerger, Marcus, Sherrill, Calkins, Towbin, Zareba, 2005). Thus, assessment of RV size and wall thickness is integral to the assessment of RV function.

Qualitative assessment of RV size is easily accomplished from the apical 4-chamber view (Figure 3). In this view, RV area or mid-cavity diameter should be smaller than that of the LV. In cases of moderate enlargement, the RV cavity area is similar to that of the LV and it may share the apex of the heart. As dilatation progresses, the cavity area will exceed that of the LV and the RV will be apex forming. Quantitative assessment of RV size is also best performed in the apical 4-chamber view. Care must be taken to obtain a true non-foreshortened apical 4-chamber view, oriented to obtain the maximum RV dimension, before making these measurements.

Measurements of the mid-cavity and basal RV diameter in the apical 4-chamber view at end diastole is a simple method to quantify RV size (Figure 3). In addition, RV longitudinal diameter can be measured from this view. Table 3 provides normal RV dimensions from the apical 4-chamber view (Weyman 1994; Schenk, Globits, Koller, Brunner, Artemiou, Klepetko, 2000).

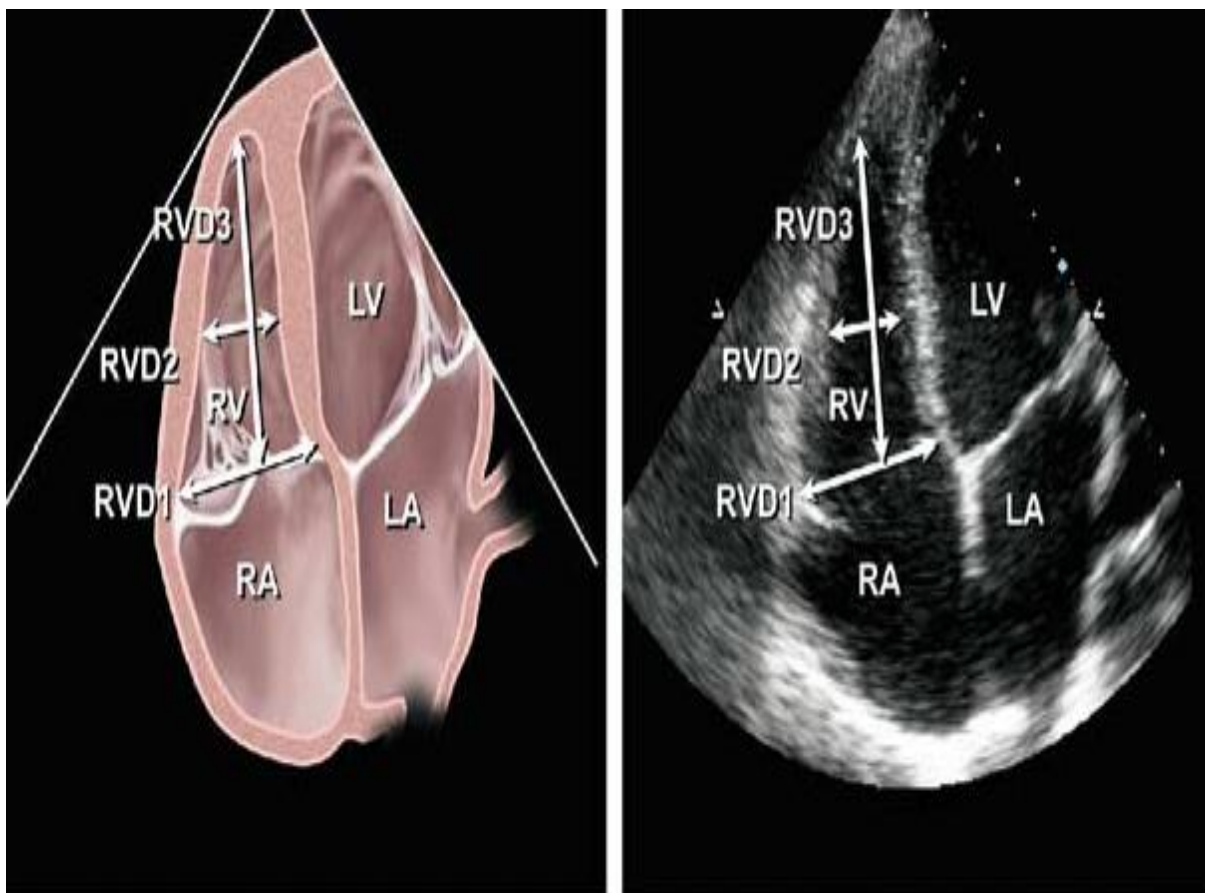


Figure 3: Right ventricular diameter measured in apical 4-chamber (Schenk, Globits, Koller, Brunner, Artemiou, Klepetko, 2000).

Table 3: Reference limits and values of right ventricular measurements (Schenk, Globits, Koller, Brunner, Artemiou, Klepetko, 2000)

RV Dimensions (Figure 2)	Reference Range	Mildly abnormal	Moderately abnormal	Severely abnormal
Basal RV diameter (RVD 1), cm	2.0 – 2.8	2.9 – 3.3	3.4 – 3.8	≥3.9
Mid RV diameter (RVD2), cm	2.7 – 3.3	3.4 – 3.7	3.8 - 4.1	≥4.2
Base to apex length (RVD 3), cm	7.1 – 7.9	8.0 – 8.5	8.6 – 9.1	≥9.2

Tricuspid Regurgitation Jet

An integrative approach is recommended for evaluation of TR (Table 4). It includes evaluation of the size of right sided chambers, septal motion and various Doppler parameters. Attention to the vena contracta, flow convergence and the direction and size of the jet should be done when performing color flow Doppler mapping. CW Doppler recording of the TR jet should be recorded to evaluate the signal intensity and contour of the jet, and estimate pulmonary artery systolic pressure. The size of the inferior vena cava and response to respiration will help evaluate right atrial pressure and adaptation to the volume overload. With the lack of extensive data on quantitation of TR, information from all available parameters must be intergrated

(Table 4). The more congruent the findings regarding severity, the more confident the diagnosis.

Table 4: Echocardiographic and Doppler parameters used in grading tricuspid regurgitant severity (Tribouilloy, Enriquez-Sarano, Bailey, Tajik, Seward, 2000).

<u>Parameter</u>	<u>Mild</u>	<u>Moderate</u>	<u>Severe</u>
<u>Tricuspid valve</u>	Usually normal	Normal or abnormal	Abnormal / flail leaflet / poor coaptation
<u>RV / RA / IVC size</u>	Normal	Normal or dilated	Usually dilated
<u>Jet area –central jets (cm²)</u>	< 5	5 – 10	>10
<u>Vena contracta width (cm)</u>	Not defined	Not defined, but < 0.7	>0.7
<u>Jet density and contour – CW</u>	Soft and parabolic	Dense, variable contour	Dense, triangular with early peaking

Systolic Excursion velocity (RV S')

The most reliable and reproducible imaged region of the right ventricle is the tricuspid annulus segment. This region can be assessed by pulsed wave tissue Doppler imaging to measure the longitudinal velocity of excursion. This velocity has been termed RV S' or systolic excursion velocity. To perform this measurement, an apical 4-chamber window is used with a color tissue Doppler, the region of interest is

highlighted on the lateral tricuspid annulus. The pulsed Doppler sample volume is placed on the tricuspid annulus of the RV (Figure 4). Because this technique uses Doppler, care must be taken to ensure that the beam is parallel and not more than 20 degrees off axis so as not to avoid underestimating the measured velocity.

Advantages: A simple, reproducible technique with good discriminatory ability to detect normal versus abnormal RV function, pulsed Doppler is available on all modern ultrasound equipment and does not require additional software.

Disadvantages: This technique is less reproducible for non-basal segments and is angle dependent, and there are limited normative data in all ranges and in both sexes. Moreover, it assumes that the function of a single segment represents the function of the entire right ventricle, which is not likely in conditions that include regionality, such as infarction or pulmonary embolism.

Recommendations: Interrogation of S' by pulsed tissue Doppler is a simple and reproducible measure to assess basal RV free wall function and should be used in the assessment of RV function. $S' < 10$ cm/s should raise the suspicion for abnormal RV function (Lindqvist, Waldenstrom, Henein, Morner, Kazzam, 2005). However, there were no studies published about assessing the right ventricle in combination with the various techniques in patients with IDC.

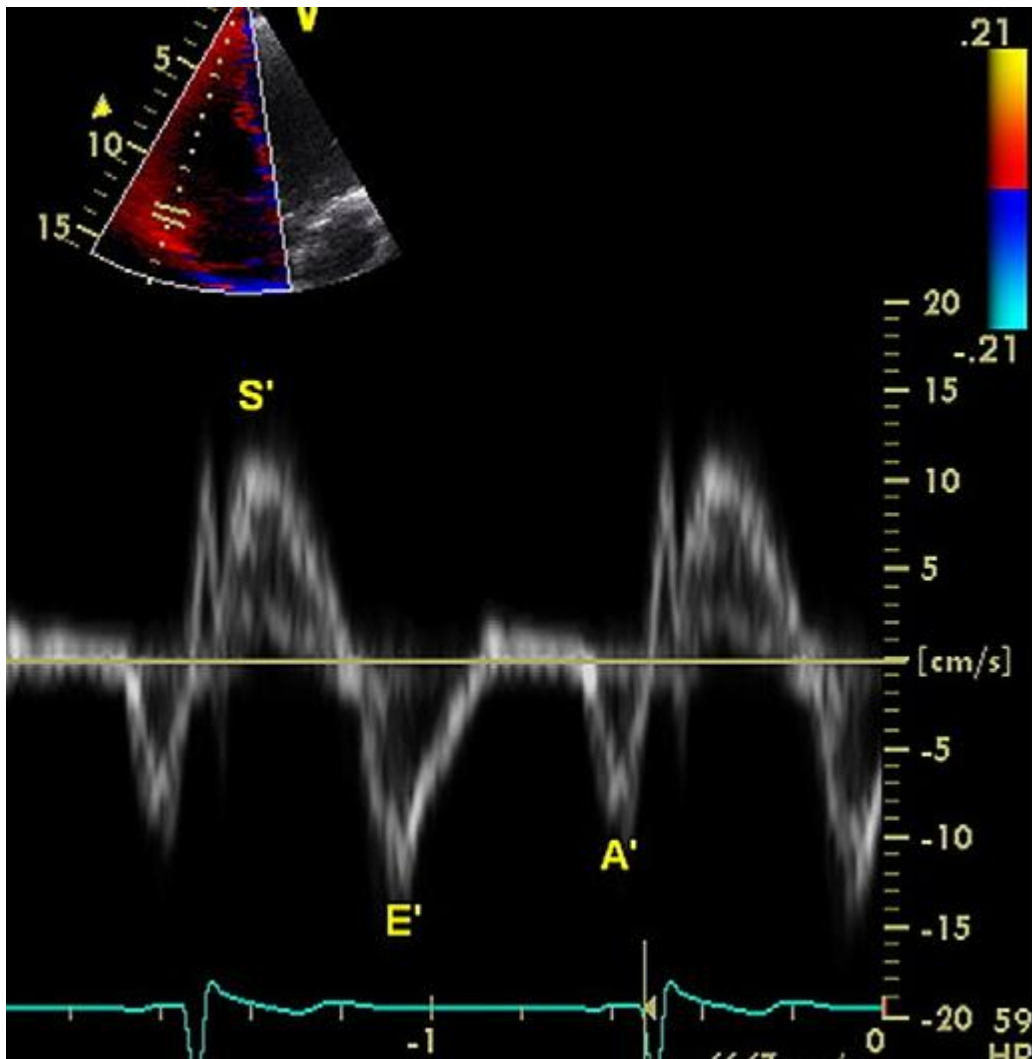


Figure 4: Tissue Doppler of the tricuspid annulus in a patient with normal right ventricular systolic function (Lindqvist et al., 2005).

CHAPTER 3

Materials and Methods

3.1 Consent

All patients who met the inclusion criteria received an information letter as well as informed consent form. The clinical evaluation of each patient included a complete medical history, physical examination, 12 lead electrocardiogram, 2D-echocardiography, Continuous Wave Doppler (CW), Pulsed Wave Doppler (PW), and Tissue Doppler Imaging (TDI).

The procedures and nature of the study was explained to the patients and consent was requested (Appendix A). Each patient was advised that they were not compelled to participate in the study and that if at any time they wished not to continue they were at liberty to withdraw themselves from the research project. The patients were informed that if they preferred not to be included in the study, their decision would not hinder any of their future assessment or testing if required in the echocardiography laboratory. Each patient was ensured that anonymity and confidentiality will be maintained.

3.2 Research Design

This was a prospective and longitudinal follow-up study of 66 patients with idiopathic dilated cardiomyopathy, presented at the cardiac clinic at Chris Hani Baragwanath

Hospital in Gauteng. The aim of the study was to 1) determine the prevalence of PAH documented on echocardiography in patients with dilated cardiomyopathy, 2) Identify the predictors of pulmonary hypertension in this population using echocardiography and 3) determine the prevalence of right heart involvement and tricuspid regurgitation in dilated cardiomyopathy patients. All patients 18 years and older presenting to the cardiac clinic during January 2009 to current were included in the study.

3.3 Location of the Study

This study was conducted at the Chris Hani Baragwanath Hospital (CHBH). The Baragwanath Dilated Cardiomyopathy (BADCMO) registry has ethics approval from the University of Witwatersrand. The hospital provides medical care to a large population from Soweto and other areas enabling the treatment to about 120 000 patient's visiting the department of Internal Medicine & Cardiology.

3.4 Data Collection

All patients were recruited from the dilated cardiomyopathy clinic. Every patient in the clinic received a screening echo to determine whether they were suited for the study. All patients who met the inclusion criteria, were enrolled. Thereafter, all patients were seen by a consultant who then performed a full physical examination and documented their medical history. Each patient received a routine baseline electrocardiogram (ECG) and their height and weight were documented. All the above mentioned information was then placed into a file that was created for each

patient. Once a file was created for the patient, a detailed echocardiogram was performed according to a standardized protocol (Appendix B). The patients studied in the echocardiographic laboratory were imaged in the left lateral decubitus position with a Phillips IE 33 system utilizing a broadband S5-1 transducer (frequency transmitted 1.7 mhz and received 314 mhz). Once the study was complete all data was transferred to an Xcelera workstation where all measurements were made offline.

Personal information was kept confidential and in the results, patients will not be able to be identified by name, record number or other similar identifying information.

3.5 Recruitment of Participants

A sample size of 66 consecutive patients who met the inclusion criteria were selected. All patients who underwent two dimensional (2D) echocardiography between the periods of January 2009 to November 2010 were selected.

Recruitment was just and fair. It was based on sound scientific and ethical principles and no person was unjustly excluded on basis of race, age, sexual orientation, disability, religious beliefs, marital status, ethnic or social origin.

Inclusion Criteria

- 1) Patients 18 years and older.
- 2) Patients with idiopathic dilated cardiomyopathy.

Exclusion Criteria

- 1) Coronary disease.
- 2) Significant organic valvular disease.
- 3) Renal failure
- 4) Co morbid cancer
- 5) Patients with an underlying cause for dilated cardiomyopathy
(i.e: peripartum)

3.6 The Electrocardiogram (ECG)

A 12 lead electrocardiographic recording was performed on all patients using a Phillips page writer trimmer II ECG recorder. The electrocardiogram showed nonspecific repolarization abnormalities. The ECG's performed on the DCMO patients presented with conduction abnormalities which included first-degree atrioventricular block, left bundle-branch block, left anterior hemiblock and nonspecific interventricular conduction delays. Atrial fibrillation, which is often poorly tolerated, develops in 20 percent of patients but has not been associated with a worse prognosis (Ballard et al., 1992). The ECG also provided suggestive or supportive evidence of pulmonary hypertension by demonstrating right ventricular hypertrophy and strain and right atrial dilation. Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with pulmonary arterial hypertension (Barst, McGoon, Torbicki, Sitbon, Krowka, Olchewski, Gane, 2004) (Figure 5). The ECG has inadequate sensitivity (55%) and specificity (70%) to be the screening tool for detecting significant pulmonary hypertension (Barst et al., 2004).

35-YR OLD FEMALE

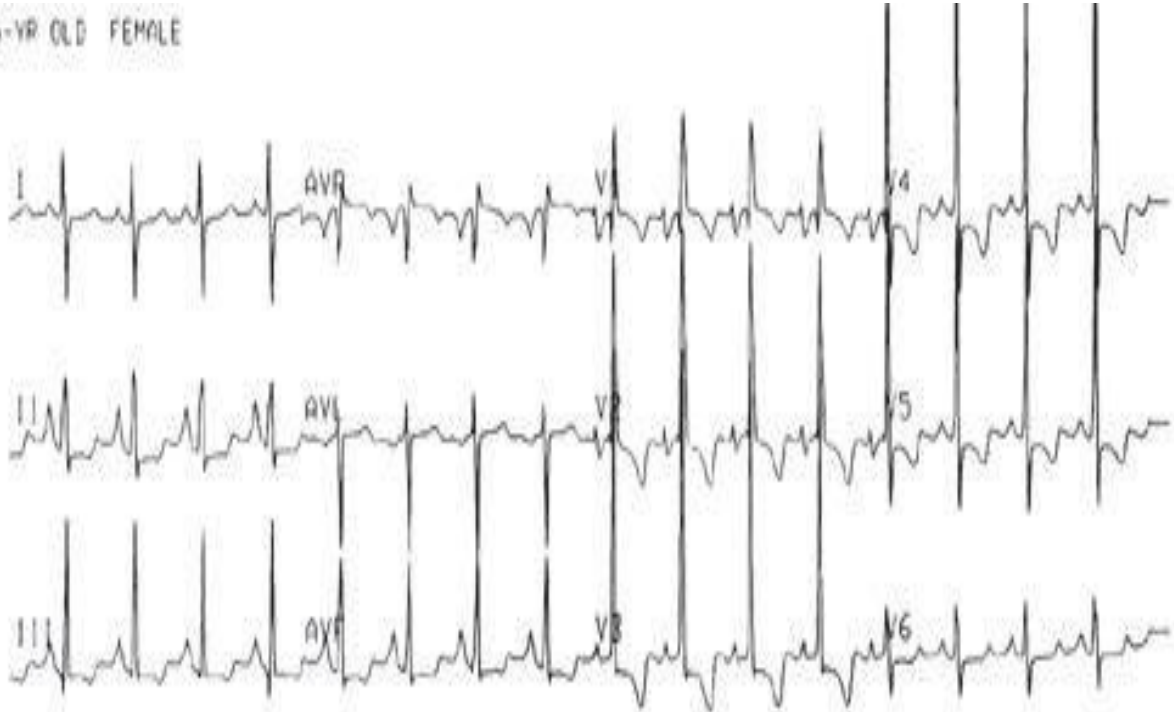


Figure 5: ECG in PAH. ECG of the same patient reveals right atrial enlargement, right ventricular hypertrophy and strain, and right axis deviation of the QRS complex (Barst et al., 2004).

3.7 Echocardiography

3.7.1 Quantification of the Left Ventricle (LV)

In the present study, echocardiographic measurements that were performed included left ventricular (LV) dimensions, volumes and wall thicknesses (Gottdiener, Bednarz, Devereux, Gardin, Klein, Manning, 2004). LV size and performance are still

frequently visually estimated. However, qualitative assessment of LV size and function may have significant interobserver variability and is a function of interpreter skill. Therefore, it should regularly be compared with quantitative measurements, especially when different views qualitatively suggest different degrees of LV dysfunction. Similarly, it is also important to cross-check quantitative data using the eyeball method, to avoid over emphasis on process-related measurements, which at times may depend on structures seen in a single still frame. Methods for quantitation of LV size, mass, and function using two-dimensional (2D) imaging have been validated (Helak and Reichek, 1981). There are distinct advantages and disadvantages to each of the accepted quantitative methods (Table 5).

Table 5: Left ventricular quantification methods: Use, advantages, and limitations (Helak and Reichel, 1981)

Dimension/volumes	Use/advantages	Limitations
Linear M-mode 2D- Guided	Reproducible -High frame rates -Wealth of accumulated data -Most representative in normally shaped ventricles -Assures orientation perpendicular to ventricular long axis	-Beam orientation frequently off axis -Single dimension may not be representative in distorted ventricles. -Lower frame rates than in M-mode -Single dimension only
Volumetric Biplane Simpsons Area Length	-Corrects for shape distortion -Minimizes mathematic assumptions - -Partial correction for shape distortion	-Apex frequently foreshortened -Endocardial dropout -Relies on only to planes -Few accumulated data on normal population -Based on mathematic assumptions Few accumulated data

2D, Two-dimensional; LV, left ventricle

3.7.2 General Principles for Linear Left Ventricular Measurements

The recordings were made from the parasternal long-axis acoustic window in order to obtain accurate linear measurements of interventricular septal wall thickness (SWT), posterior wall thickness (PWT), and LV internal dimensions. The LV internal dimensions (left ventricular end diastolic dimension (LVEDD) and left ventricular end-

systolic dimension (LVESD), respectively) and wall thicknesses were measured at the level of the LV minor axis, approximately at the mitral valve leaflet tips.

The LVEDD, SWT and PWT were measured at end diastole and end systole from 2D recordings, (Schiller, Shah, Crawford, DeMaria, Devereux, Feigenbaum, 1989) preferably on several cardiac cycles (figure 6). Refinements in image processing have allowed improved resolution of cardiac structures. Therefore, it was now possible to measure the actual visualised thickness of the ventricular septum and other chamber dimensions as defined by the actual tissue-blood interface, rather than the distance between the leading edge echoes, which had previously been recommended (Feigenbaum, Armstrong, Ryan, 2005). The use of 2D echocardiographically derived linear dimensions in the current study, helped overcome the common problem of oblique parasternal images resulting in overestimation of cavity and wall dimensions from M-mode.

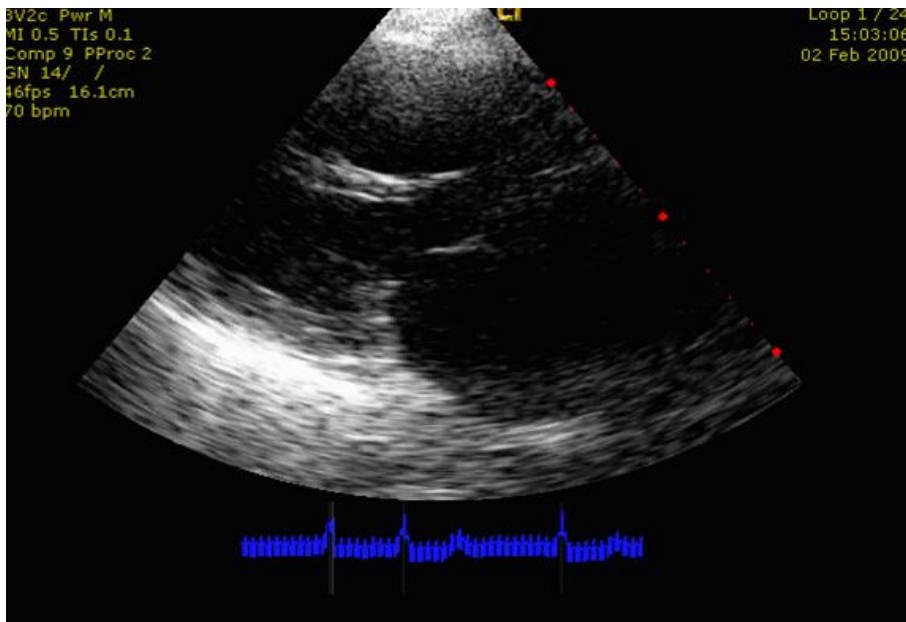


Figure 6: Measurement of left ventricular end-diastolic diameter (*EDD*) made from a parasternal long axis view (Echo Lab Chris Hani Baragwanath Hospital., 2009).

3.7.3 Left Ventricular Systolic Function: Linear and Volumetric Measurements

In the current study the ejection fraction (EF) was measured using the modified Simpson's method in the apical four-chamber view. The biplane method of disks (modified Simpson's rule) was used as the 2D measurement for volume measurements (figure 7). The principle underlying this method is that the total LV volume is calculated from the summation of a stack of elliptical disks. The height of each disk is calculated as a fraction (usually 1/20) of the LV long axis based on the

longer of the two lengths from the four-chamber view. The cross sectional area of the disk is based on the two diameters obtained from the four-chamber view. When two adequate orthogonal views are not available, a single plane can be used and the area of the disk is then assumed to be circular. The limitations of using a single plane are greatest when extensive wall-motion abnormalities are present.

End-diastolic volume (EDV) and end-systolic volume (ESV) are calculated by the method described above and the EF is calculated as follows:

$$\text{Ejection Fraction} = (\text{EDV} - \text{ESV}) / \text{EDV}$$

Partition values for recognizing depressed LV systolic function follow the conventional practice of using the same cutoffs in women and men (Table 6); however, emerging echocardiographic data suggest that LVEF and other indices are somewhat higher in apparently healthy women than in men (Celentano, Palmieri, Arezzi, Mureddu, Sabatella, Di, 2003).

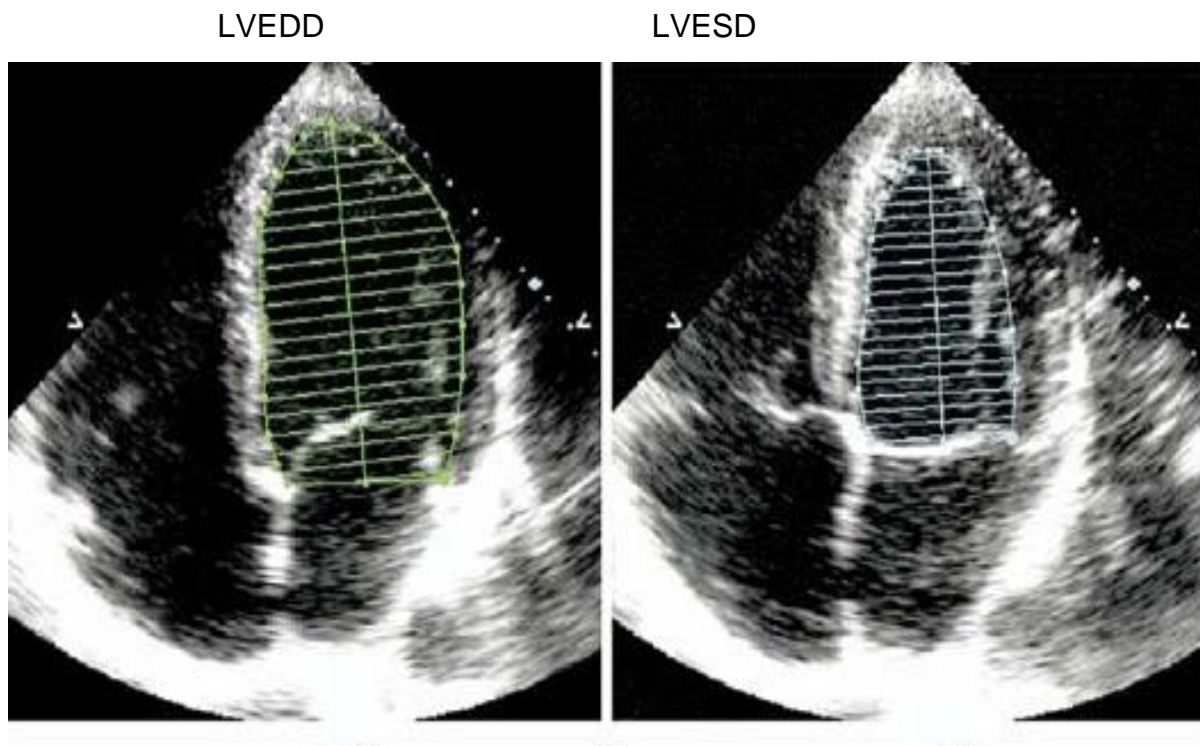


Figure 7: Two dimensional measurements for volume calculations using biplane method of disks (modified Simpson's rule) in apical 4-chamber (A4C) at end diastole (LVEDD) and at end systole (LVESD) (Echo Lab Chris Hani Baragwanath Hospital., 2009).

3.7.4 Reference Values for Left Ventricular Measurements

As shown in Tables 6-7, reference values for LV linear dimensions have been obtained from an ethnically diverse population of 510 normal-weight, normotensive and nondiabetic white, African American, and American Indian adults without recognized cardiovascular disease (Ilercil et al., 2001). Reference values for volumetric measurements have also been obtained in a healthy adult population (Wahr, Wang, Schiller, 1983).

Table 6: Reference values of left ventricular size (Ilercil et al., 2001)

	Reference range	<u>WOMEN</u> Mildly abnormal	Moderately abnormal	Severely abnormal
LV Dimension				
LV diastolic diameter, cm	3.9 – 5.3	5.4 – 5.7	5.8 – 6.1	≥6.2

	Reference range	<u>MEN</u> Mildly abnormal	Moderately abnormal	Severely abnormal
LV Dimension				
LV diastolic diameter, cm	4.2 – 5.9	6.0 – 6.3	6.4 – 6.8	≥6.9

BSA, body surface area; LV, left ventricle.

Table 7: Reference limits and values of left ventricular function (Ilercil et al., 2001).

	Reference range	<u>WOMEN</u> Mildly abnormal	Moderately abnormal	Severely abnormal
2D Method				
Ejection fraction, %	≥55	45-54	30-44	<30

	Reference range	<u>MEN</u> Mildly abnormal	Moderately abnormal	Severely abnormal
2D Method				
Ejection fraction, %	≥55	45-54	30-44	<30

3.7.5 Quantification of Left Atrial Size

The left atrium (LA) fulfils 3 major physiologic roles that impact on LV filling and performance. The LA acts as a contractile pump that delivers 15% to 30% of the LV filling, as a reservoir that collects pulmonary venous return during ventricular systole, and as a conduit for the passage of stored blood from the LA to the LV during early ventricular diastole (Spencer, Mor-Avi, Gorcsan, De Maria, Kimball, Monaghan, 2001). Increased LA size is associated with adverse cardiovascular outcomes (Tsang, Barnes, Gersh, Takemoto, Rosales, Bailey, 2003; Kizer, Bella, Palmieri, 2005). An increase in atrial size most commonly is related to increase wall tension as a result of increased filling pressure (Simek, Feldman, Haber, Wu, Jayaweera, Kaul, 1995). Although increased filling volumes can cause an increase in LA size, the adverse outcomes associated with increased dimension and volume are more strongly associated with increased filling pressure. Relationships exist between increased LA size and the incidence of atrial fibrillation and stroke, (Barnes, Miyasaka, Seward, Gersh, Rosales, Bailey., 2004) and risk of death and hospitalization in patients with dilated cardiomyopathy (Rossi, Cicoira, Zanolta,

Sandrini, Golia, Zardini, 2002; Dini, Cortigiani, Baldini, Boni, Nut, Barsotti, 2002). LA enlargement is a marker of both the severity and chronicity of diastolic dysfunction and magnitude of LA pressure elevation (Simek et al., 1995).

The LA size was measured at end-ventricular systole when the LA chamber is at its greatest dimension. While recording images for computing LA volume, care should be taken to avoid foreshortening of the LA. The base of the LA should be at its largest size indicating that the imaging plane passes through the maximal short-axis area. The LA length should also be maximized ensuring alignment along a true long axis of the LA. When performing planimetry, the LA, the confluences of the pulmonary veins and LA appendage should be excluded.

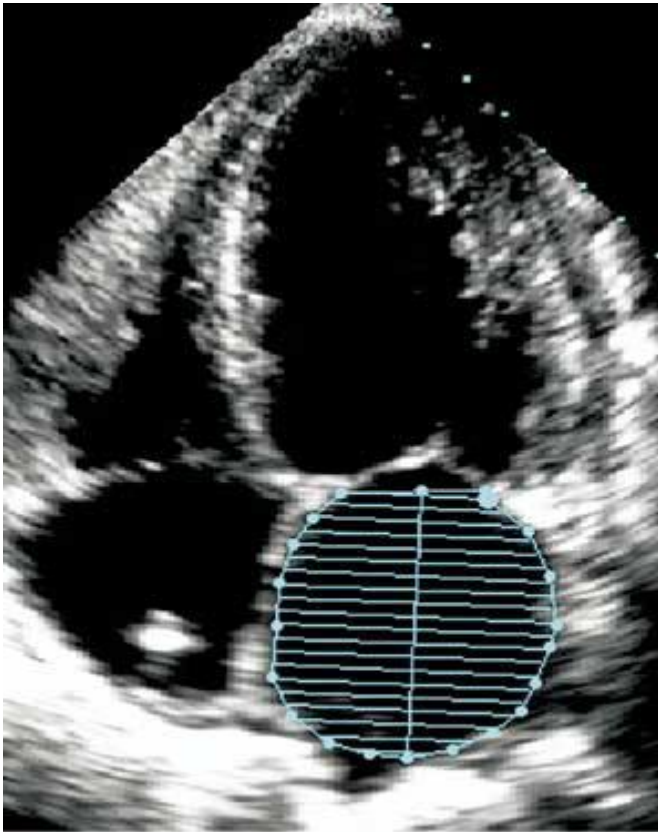
3.7.5.1 Left Atrial Volume Measurements

When LA size is measured in clinical practice, volume determinations allow accurate assessment of the asymmetric remodelling of the LA chamber (Lester, Ryan, Schiller, Foster, 1999). The Simpson's rule was used in the current study to measure LA volume, similar to its application for LV measurements, which states that the volume of a geometric figure can be calculated from the sum of the volumes of smaller figures of similar shape (Tshang, Barnes, Gersh, Bailey, Seward, 2002; Thomas, Levett, Boyd, Leung, Schiller, Ross, 2002) . Most commonly, Simpson's algorithm divides the LA into a series of stacked oval disks whose height is h and whose orthogonal minor and major axes are $D1$ and $D2$ (method of disks). The volume of the entire LA can be derived from the sum of the volume of the individual

disks. $\text{Volume} = \pi/4 (h) \sum (D1) (D2)$. The formula is integrated with aid of a computer and the calculated volume provided by the software package (Figure 8).

The use of the Simpson's method in this way requires the input of biplane LA planimetry to derive the diameters. Optimal contours was obtained orthogonally around the long axis of the LA using transthoracic echocardiography (TTE) apical views. The inferior border should be represented by the plane of the mitral annulus.

As shown in Table 8, reference values for left atrial dimensions and volumes have been obtained from a Framingham Heart Study cohort of 1099 participants between the ages of 20 and 45 years who were not obese, of average height, and without cardiovascular disease (Table 8) (Vasan, Larson, Levy, Evans, Benjamin, 1997). In the current study absolute LA volume was indexed to body surface area (BSA) which accounted for variations in body size and was therefore used. As cardiac risk and LA size are closely linked, more importantly than simply characterizing the degree of LA enlargement, normal reference values for LA volume allow prediction of cardiac risk. Consequently, indexed LA volume measurements should become a routine laboratory measure because they reflect the burden and chronicity of elevated LV filling pressure and are a strong predictor of outcome.



A4C

Figure 8: Measurement of left atrial (LA) volume from biplane method of disks (modified Simpson's rule) using apical 4-chamber (A4C) view during ventricular end systole (maximum LA size) (Echo Lab Chris Hani Baragwanath Hospital., 2009).

Table 8: Reference limits and values for left atrial dimensions / volumes (Vasan et al., 1997; Weyman, 1994)

	Reference range	<u>WOMEN</u> Mildly abnormal	Moderately abnormal	Severely abnormal
ATRIAL DIMENSIONS				
LA diameter, cm	2.7 – 3.8	3.9 – 4.2	4.3 – 4.6	≥4.7
LA diameter/BSA, cm/m ²	1.5 – 2.3	2.4 – 2.6	2.7 - 2.9	≥3.0
ATRIAL VOLUMES				
LA volume, ml	22 – 52	53 – 62	63 – 72	≥73
LA volume/BSA, ml/m ²	22 +/- 6	29 – 33	34 – 39	≥40

	Reference range	<u>MEN</u> Mildly abnormal	Moderately abnormal	Severely abnormal
ATRIAL DIMENSIONS				
LA diameter, cm	3.0 – 4.0	4.1 – 4.6	4.7 – 5.2	≥5.2
LA diameter/BSA, cm/m ²	1.5-2.3	2.4-2.6	2.7-2.9	≥3.0
ATRIAL VOLUMES				
LA volume, ml	18 – 58	59 – 68	69 -78	≥79
LA volume / BSA, ml/m ²	22 +/- 6	29 – 33	34 – 39	≥40

BSA, Body surface area; LA, left atrium

3.7.6 Quantification of the Inferior Vena Cava (IVC)

Examination of the inferior vena cava (IVC) was performed from the subcostal view using 2D echocardiography. The diameter of the IVC was measured at 1.0 to 2.1cm from the junction with the RA, using the long axis view (Figure 9). For accuracy, this measurement was made perpendicular to the IVC long-axis. The diameter of the IVC decreases in response to inspiration when the negative intrathoracic pressure leads to an increase in RV filling from the systemic veins. The diameter of the IVC and the percent decrease in the diameter during inspiration correlate with RA pressure. The relationship has been called the collapsibility index (Moreno, Hagan, Holmen, Pryor., Strickland, Castle, 1984). Evaluation of the inspiratory response often requires a brief sniff, as normal inspiration may not elicit this response.

The normal IVC diameter is ≤ 2.1 cm. There is a 50% decrease in the diameter when the RA pressure is normal (0-5mm Hg). A normal IVC with an inspiratory collapse of less than 50% is suggestive of a mildly elevated RA pressure (6 - 10mm Hg). A dilated IVC with an inspiratory collapse of more than 50% results in the RA pressure being between (10-15mm Hg). Finally, a dilated IVC without any collapse suggests a markedly increased RA pressure of greater than 20mm Hg. The use of the IVC size and dynamics is encouraged for estimation of RA pressure. Therefore, this estimate was used in the estimation of the pulmonary artery pressure based on the tricuspid regurgitant jet velocity.

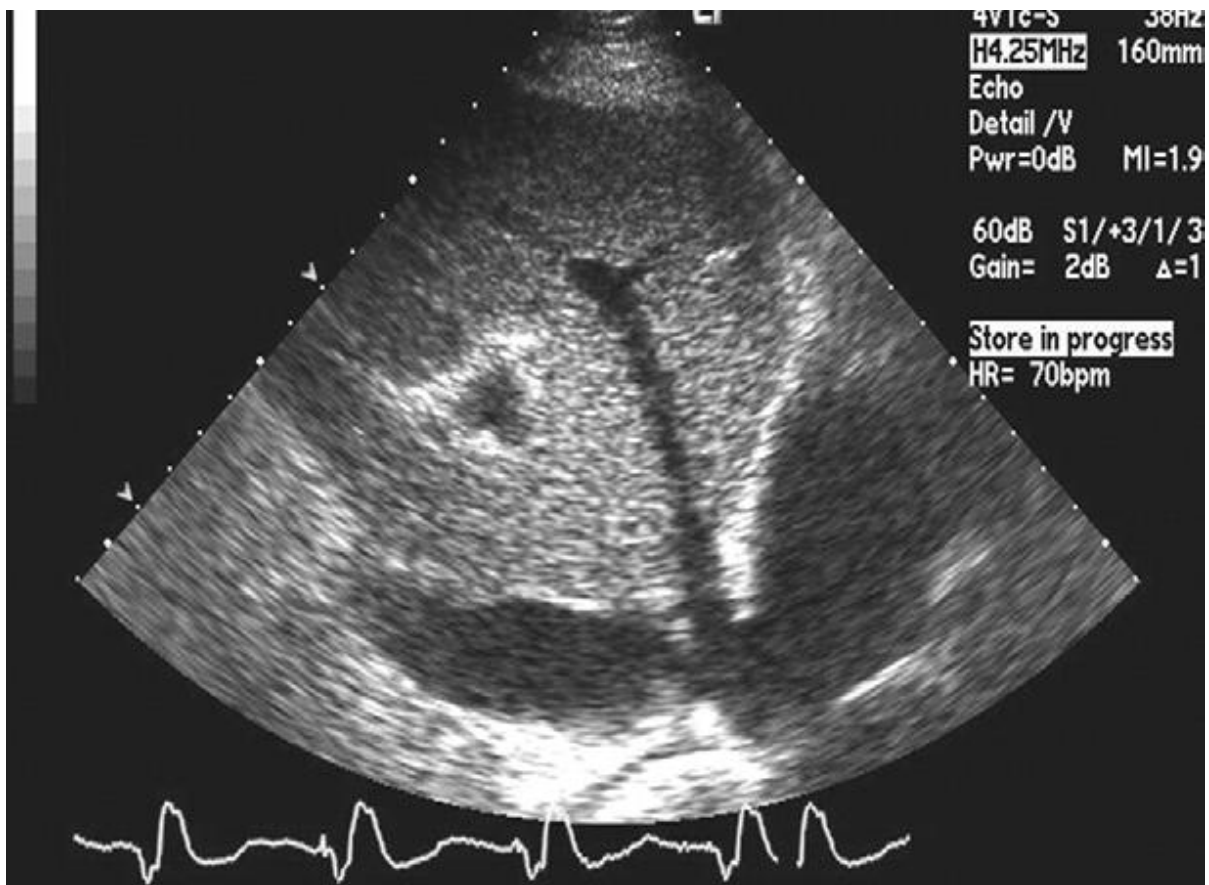


Figure 9: Subcostal view of inferior vena cava (IVC) during expiration for patient with dilated cardiomyopathy. Note dilated IVC (2.5 cm). Inspiration resulted in minimal change in IVC diameter consistent with elevated right atrial pressure (Echo Lab Chris Hani Baragwanath Hospital., 2009).

3.7.7 Mitral Regurgitation

3.7.7.1 Role of Two-dimensional Echocardiography

The anatomy of the mitral valve apparatus was evaluated using 2D echocardiography which is critically important in assessing the severity of mitral

regurgitation (MR). The mitral apparatus is made up of the leaflets, chordate tendinae, annulus and the papillary muscles with their supporting LV walls. In order to define the mechanism of MR and yield clues to its severity one has to carefully evaluate these structures. For example, Severe MR is associated with a prominent flail leaflet. In the setting of LV dilatation and/or systolic dysfunction, it is important to determine whether MR is functional (i.e. due to LV dilatation) or primary (i.e. due to an abnormality of the valve apparatus). Functional MR, results from the leaflets being tethered by outward displacement of the LV walls and papillary walls, with or without annular dilatation (Otsuji, Handschumacher, Schwammethal, Jiang, Song, Guerrero, 1997). Evaluation of left atrial size and LV size and function provides clues to the severity of MR, its acuteness and chronicity, are important in determining the necessity and timing of surgery (Carabello and Crawford 1997).

3.7.7.2 Doppler Methods

A) Color Flow Doppler

Color flow Doppler mapping was used to screen the presence of MR. In roughly 40% of healthy normal volunteers a small color flow jet is seen which is considered a normal variant (Yoshida, Yoshikawa, Shakudo, Akasaka, Jyo, Takao, 1988). As age increases the incidence of mild regurgitation increases. In this study the two methods used for quantifying the severity of MR using color Doppler flow mapping were: regurgitant jet area and vena contracta.

Regurgitant jet area: In the current study it was noted that large jets that extended deep into the LA represented more MR than small thin jets that appeared just

beyond the mitral leaflets. Hypertensive patients with mild MR may have a large jet area, whereas patients with acute severe MR, in whom blood pressure is low and LA pressure is elevated may have a small eccentric color flow jet area. Color flow jets that are directed centrally into the LA generally appear larger because they entrain red blood cells on all sides of the jet. In contrast, eccentric jets that hug the LA wall cannot entrain blood on all sides and tend to appear smaller than central jets of similar or lesser severity (Enriquez-Sarano, Tajik, Bailey, Seward, 1993). Mild MR is defined as small non-eccentric jets with an area $<4.0\text{cm}^2$ or $<20\%$ of the LA area (Table 9). Conversely, large jets that penetrate into the pulmonary veins are more likely to be haemodynamically significant. The use of jet area as an index of severity should be avoided when there is detection of eccentric wall impinging jets and use other more appropriate methods such as vena contracta.

Vena contracta: The vena contracta was imaged in high-resolution, and views were zoomed in for the largest obtainable proximal jet size for measurements. Whenever possible one should search in multiple planes perpendicular to the commissural line (such as the parasternal long-axis view) (Figure 10). The width of the neck or the narrowest portion of the jet was then measured. Several studies have shown that the width of the vena contracta is accurate in assessing the severity of MR, using 2D echocardiography (Heinle, Hall, Brickner, Willett, Grayburn, 1998). Mild MR is denoted with a vena contracta of $<0.3\text{cm}$ whereas the cut off for severe MR has ranged between 0.6 to 0.8cm (Heinle et al., 1998).

Table 9: Qualitative and quantitative parameters useful in grading mitral regurgitation severity (Enriquez-Sarano, Tajik, Bailey, Seward, 1993; Heinle, Hall, Brickner, Willett, Grayburn, 1998).

	MILD	MODERATE	SEVERE
<u>Structural parameters</u>			
LA size	Normal	Normal or dilated	Usually dilated
LV size	Normal	Normal or dilated	Usually dilated
Mitral leaflets or support apparatus	Normal or abnormal	Normal or abnormal	Abnormal / flail leaflet / ruptured papillary muscle
<u>Doppler parameters</u>			
Color flow jet area	Small, central jet (usually $<4\text{cm}^2$ or $<20\%$ of LA area)	Variable	Large central jet (usually $>10\text{cm}^2$ or $>40\%$ of LA area) or variable size wall impinging jet swirling in LA
Jet density –CW	Incomplete or faint	Dense	Dense
Jet contour-CW	Parabolic	Usually parabolic	Early peaking-triangular
<u>Quantitative parameters</u>			
Vena contracta width (cm)	< 0.3	$0.3 - 0.69$	≥ 0.7

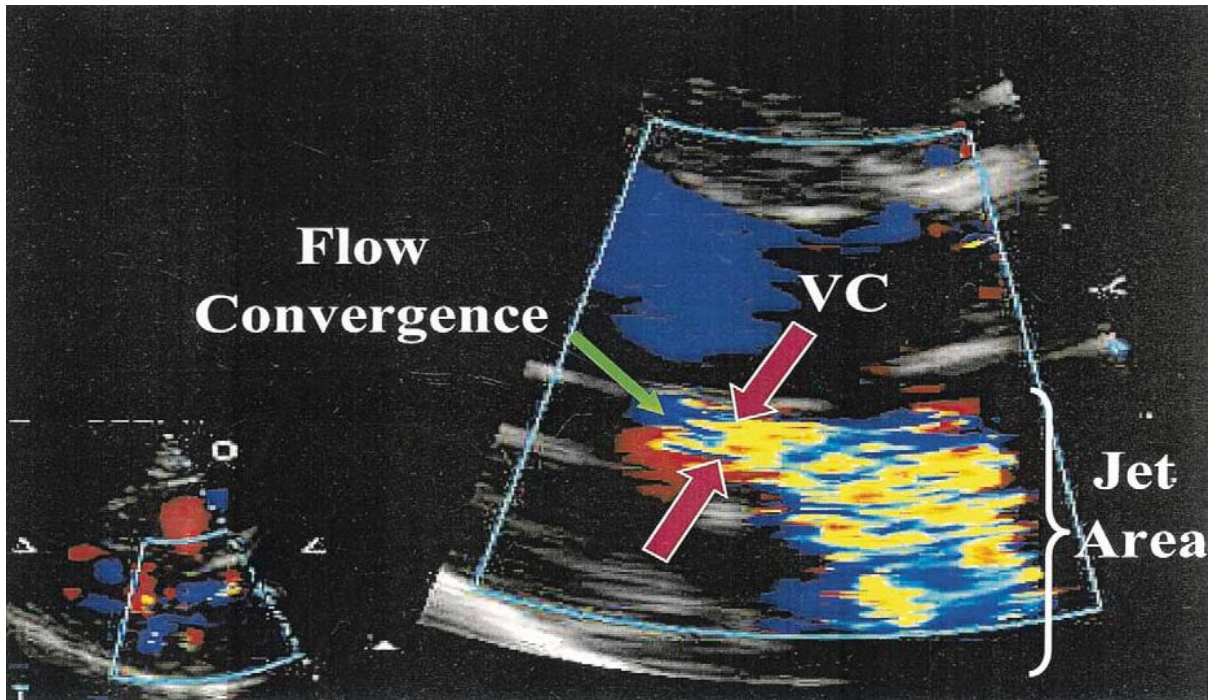


Figure 10: Color flow recording of a mitral regurgitation jet obtained from a zoomed view in the parasternal long axis depicting the 3 components of the regurgitant jet: flow convergence, vena contracta (VC), and jet area in the left atrium. Measurement of the vena contracta is shown between the *red arrows* (Echo Lab Chris Hani Baragwanath Hospital., 2009).

B) Continuous Wave Doppler.

In most patients, because of the high systolic pressure gradient between the LV and left atrium (LA) the MR velocity was 4 to 6 m/s. The velocity itself does not provide useful information about the severity of MR. However, the density and the contour of the velocity profile were useful. Elevated LA pressure or a prominent regurgitant pressure wave in the LA was indicated by a truncated, triangular jet contour with early peaking of the maximal velocity (Figure 11). The density of the CW Doppler is a qualitative index of MR severity. Significant MR was suggestive when a dense signal approaches the density of antegrade flow, whereas faint signal, with or without an

incomplete envelope was suggestive of mild or trace MR, assuming that the recording is made through the vena contracta (Figure 10).

CW Doppler

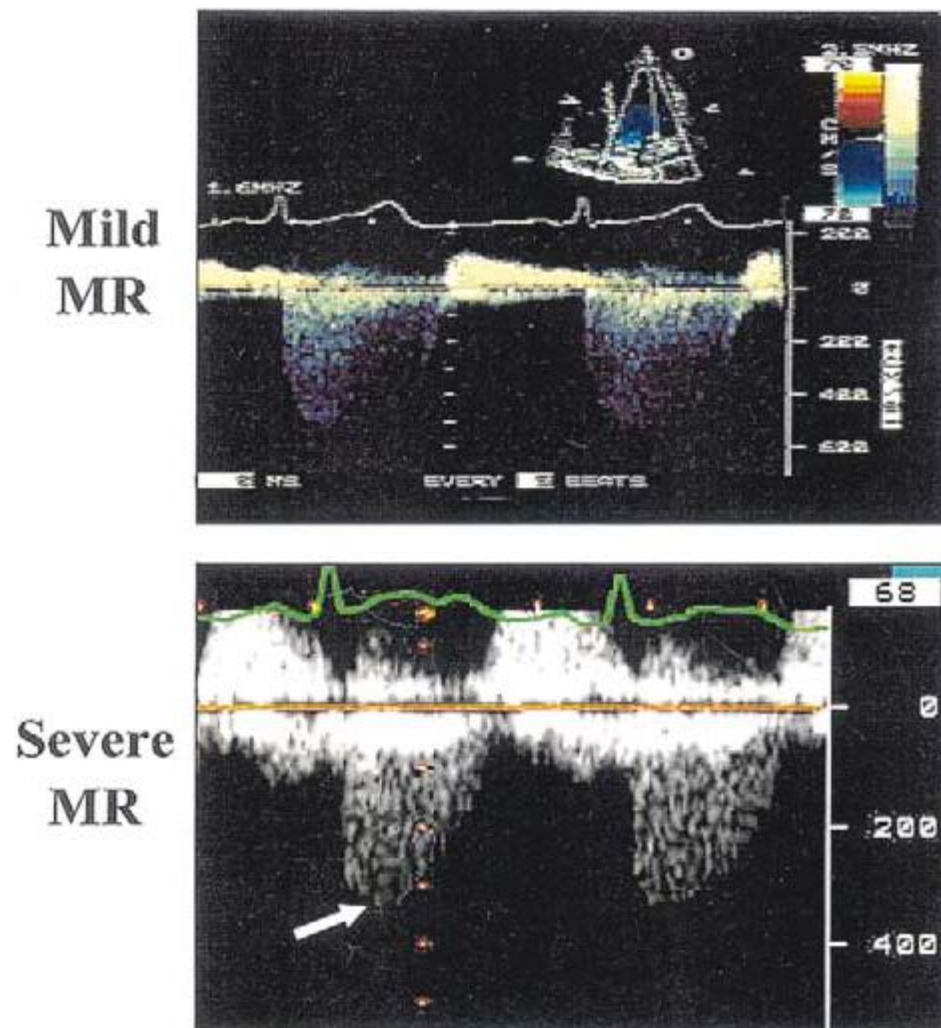


Figure 11: Example of findings of continuous wave (CW) Doppler recordings with mild and another with severe mitral regurgitation (MR). In mild MR, spectral recording of the jet has a soft density with a parabolic, rounded contour of the regurgitant velocity whereas in severe MR, the jet is dense with a triangular, early peaking of the velocity (*arrow*) (Echo Lab Chris Hani Baragwanath Hospital., 2009).

3.7.7.3 Assessment of Mitral Regurgitant Severity

Evaluating MR severity integrates multiple parameters rather than depending on a single measurement. This helps reduce the effects of technical or measurement errors that are inherent to the various methods discussed. Distinguishing between the amount of MR and its haemodynamic consequences are also important. For example, a modest regurgitant volume that develops acutely into a small, non-compliant LA may cause severe pulmonary congestion and systemic hypotension. Conversely, some patients with chronic severe MR remain asymptomatic due to compensatory mechanisms and a dilated, compliant LA.

Parameters that were used in the current study to measure amount of MR included vena contracta width, regurgitant volume and fraction. When the evidence from the different parameters was congruent, it was easy to grade MR severity with confidence. However, when different parameters were contradictory, careful consideration was made for technical and physiologic reasons to explain any discrepancies and to rely on the components that have the best inherent quality of the primary data and are the most accurate considering the underlying physiologic condition.

3.7.8 Tricuspid Regurgitation

About 70% of normal individuals have a small degree of tricuspid regurgitation (Singh., Evans., Levy., Larson., Freed., Fuller., 1999). Pathologic regurgitation is

often a result of right ventricular and tricuspid annular dilatation secondary to pulmonary hypertension or RV dysfunction.

Due to the lack of a quantitative standard of severity has resulted in the evaluation of TR severity being hampered. Surgical intervention for severe TR is uncommon, in contrast to left sided lesions. When TR is significant, tricuspid annuloplasty is performed as an adjunct to other cardiac surgery. The echocardiographic examination therefore seeks to determine the etiology of regurgitation and provides a semi-quantitative estimate of severity. Table 10 shows the various parameters used in the evaluation of TR. During the current study, the TR velocity was measured using CW Doppler, which provided an estimation of RV systolic pressure.

Table 10: Echocardiographic and Doppler parameters used in the evaluation of tricuspid regurgitation severity: Utility, advantages and limitations (Tribouilloy, Enriquez-Sarano.,Bailey, Tajik, Seward, 2000).

<u>Parameter</u>	<u>Utility / Advantages</u>	<u>Limitations</u>
RV / RA / IVC size	Enlargement sensitive for chronic significant TR. Normal size virtually excludes significant chronic TR.	Enlargement seen in other conditions. May be normal in acute significant TR
TV leaflet alterations	Flail valve specific for significant TR	Other abnormalities do not imply significant TR
Paradoxical septal motion (volume overload pattern)	Simple sign of severe TR	Not specific for TR
Jet area- color flow	Simple, quick screen for TR	Subject to technical and hemodynamic factors, Underestimates severity in eccentric jets
Vena contracta width	Simple, quantitative, separates mild from severe TR	Intermediate values require further confirmation
Jet profile – CW	Simple, readily available	Qualitative, complementary data

3.7.8.1 Role of 2D Echocardiography

Two dimensional echocardiography is important in determining the etiology of TR upon evaluating the tricuspid valve apparatus. Accompanying significant chronic TR are usually secondary findings such as right atrial and RV enlargement. This evaluation is usually qualitative. The absence of enlarged right-sided chambers suggests milder degree of TR even though it is not specific for significant regurgitation. Severe TR can cause RV volume overload resulting in paradoxical ventricular septal motion. However, this sign is not specific to TR as it is affected by many factors (DePace, Ross, Iskanfrain, Nestico, Kotler, Mintz, 1984).

3.7.8.2 Doppler Methods

A) Color Flow Doppler

Color flow imaging was used to evaluate TR severity and to establish the characteristics, direction and size of the regurgitant jet. Jets that extended deep into the right atrium represented more TR than small central jets that appeared just superior to the tricuspid leaflets (Figure 12). Similar to MR, flow jets that are directed centrally into the right atrium generally appear larger by color Doppler than eccentric, wall-impinging jets with similar or worse severity.

Visualization of the vena contracta width can be utilized either quantitatively or qualitatively (Tribouilloy, Enriquez-Sarano.,Bailey, Tajik, Seward, 2000). A jet width

>0.7cm identifies severe TR with a sensitivity of 89% and a specificity of 93% (Tribouilly et al., 2000). The vena contracta method is more accurate in determining TR severity in central jets compared to eccentric jets, and it appears to be more accurate than jet area. However, there can be overlap in values of jet width between mild and moderate TR. In 20-30% of patients underestimation of severe TR also occurs when using jet area (Grossman, Stein, Kochs, Hoher, Koenig, Hombach, 1998).

B) Continuous Wave Doppler

The noninvasive measurement of the pulmonary artery systolic pressure was made by the recording of a TR jet velocity in the apical four chamber view. It is important to understand that TR jet velocity, is not related to the volume of regurgitant flow. Massive TR is often associated with a low jet velocity (<2m/s), as there is near equalization of RV and right atrial pressures (Figure 12). Conversely, mild regurgitant may have a very high jet velocity, when pulmonary hypertension is present.

The signal intensity and the contour of the velocity curve, are the features of TR jet by CW Doppler that help in evaluating severity of regurgitation (figure12). With severe TR, a dense spectral recording is seen along with a triangular, early peaking of the velocity because of a prominent regurgitant pressure wave.

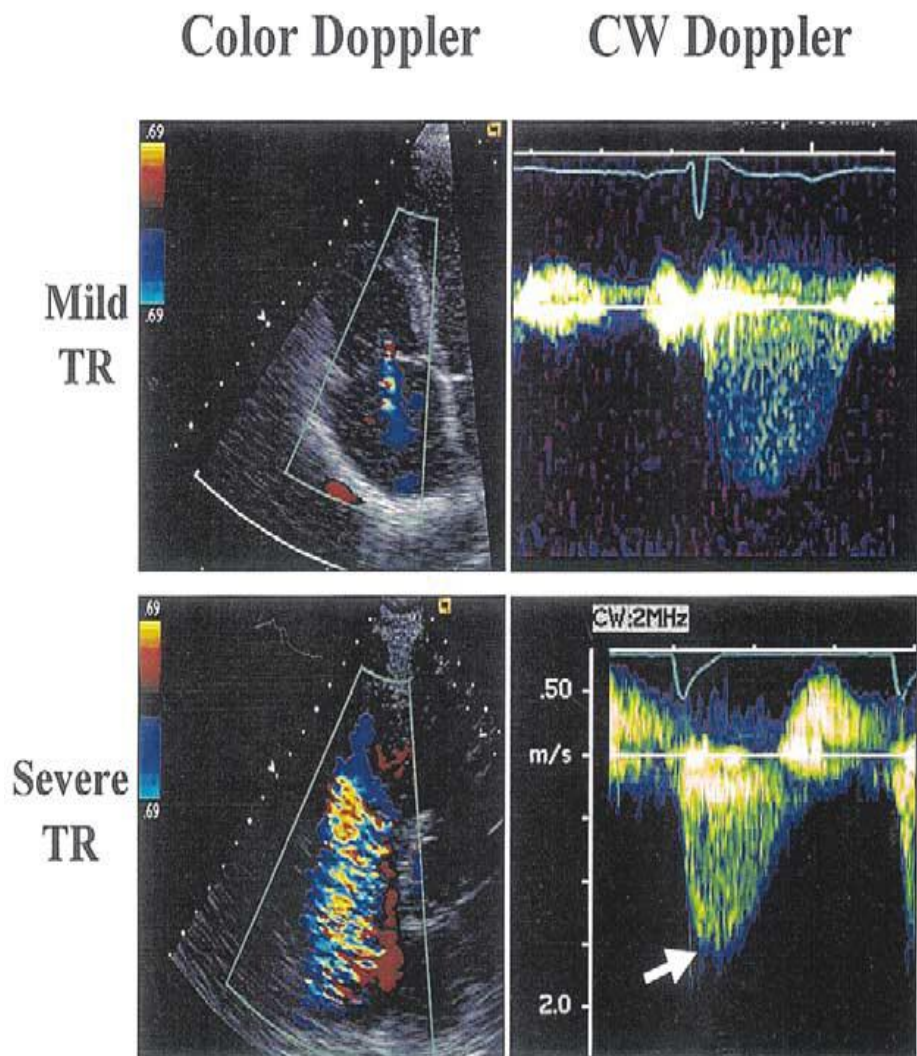


Figure 12: Examples of jet recordings by color Doppler and continuous wave (CW) Doppler. The case of mild TR shows a small central color jet with minimal flow convergence in contrast to the severe TR with a very large flow convergence and jet area in the right atrium. CW Doppler recording shows a parabolic spectral display in mild TR whereas in severe TR, early peaking and triangular shape of the velocity is seen (*arrow*) (Echo lab Chris Hani Baragwanath Hospital., 2009).

3.7.9 Systolic Pulmonary Artery Pressure

Two-dimensional correlates. Flattening of the interventricular septum (D-shaped LV) is compatible with abnormal RV haemodynamics (Ryan, Petrovic, Dillon, 1985) (Weyman, Wann, Feigenbaum, 1976). Rapid early systolic correction of diastolic septal flattening qualitatively suggests RV volume overload, whereas failure of early systolic septal curvature correction suggests RV pressure overload (Feneley and Gavaghan, 1986). The presence of RV dilatation, hypertrophy, and decreased systolic function are also important additional clues to the presence of pulmonary hypertension.

Doppler correlates. Pulmonary artery systolic pressure (PASP) is equivalent to RV systolic pressure in the absence of obstruction to flow between the RV and PA. The best validated Doppler technique for evaluation of PASP in the current study was the application of the modified Bernoulli equation to the measurement of TR velocity ($4TRV_{max}^2$) (Skjaerpe and Hatle, 1986). This measured the RV to right atrial pressure (RAP) gradient and, therefore, an estimation of RAP was added. The estimation of RAP, derived by methods noted above, is that of a mean RAP. In the setting of severe TR a significant v wave may be present and, thus, the estimate of RAP added to the TRV may underestimate the true RV systolic pressure. This is most notable when the RA is small.

$$PASP = 4TRV_{max}^2 + \text{estimated RAP}$$

The threshold for clinically significant pulmonary hypertension when detected by Doppler echocardiography is not precisely defined. Commonly used echocardiographic definitions of pulmonary hypertension are a PASP of greater than 35mm Hg (Barst, McGoon, Torbicki, 2004). Pulmonary hypertension was defined as mild (36 -45mmHg), moderate (46 -55mmHg) or severe (>55mmHg) (Schachna, Wigley, Chang, White, Wise, Gelber, 2003). However, there is no consensus on the classification of mild, moderate, and severe pulmonary hypertension on the basis of a study performed in patients with scleroderma which classified patients that had mild, moderate and severe pulmonary hypertension, therefore in the present study a similar classification was applied to patients with IDC. The specific thresholds suggested are confounded by the lack of uniformity or consistency in the use of constants for RAP. It has additionally been proposed that normal values be adjusted for age, sex and body mass index (McQuillan, Picard, Leavitt, 2001). Conceptually, such adjustments are unique in the interpretation of right-sided haemodynamics and are not general practice for left-sided haemodynamic parameters, such as systolic blood pressure. Therefore, this was not applied in the present study.

As the PASP increases, there is a conformational change in the RVOT spectral Doppler signal such that the time to peak velocity (acceleration time {AT}) shortens. Therefore, there is an inverse relationship between the RV AT with PA pressure (Dabestani, Mahan, Gardin, 1987). The AT is dependent on cardiac output and heart rate. Therefore, in the setting of a left-to-right shunt the increased flow through the right heart chambers may cause the AT to be normal despite an increase in PA pressure. Although there is a linear inverse relationship, the measured interval is short and dependent on both heart rate and the cardiac output, limiting interobserver

reproducibility and clinical use. A value less than 90 to 100 milliseconds implies elevated PA pressures. To formally measure the AT the ascertainment of the RVOT VTI was obtained by placing a 1 to 2 –mm pulsed wave Doppler sample volume in the proximal RVOT. The sample volume is placed so that the closing but not the opening click of the pulmonary valve could be visualised.

3.7.9.1 Diastolic Pulmonary Artery Pressure

Pulmonary artery end-diastolic pressure is frequently used as an estimate of pulmonary capillary wedge pressure. The presence of pulmonary regurgitation (PR) can be exploited to estimate PA end-diastolic pressure. The application of the modified Bernoulli equation to the end-diastolic PR velocity, adding to this an estimate of RAP, provides an estimation of PA diastolic pressure (Lee, Lord., Plappert, 1989) (Figure 13).

$$\text{Diastolic PA pressure} = 4V^2 \text{ end PR} + \text{estimated RAP}$$

3.7.9.2 Mean Pulmonary Artery Pressure

Although mean PA pressure can be calculated from Doppler determination of both the PASP and diastolic PA pressure, this technique may lack precision as it is dependent on the accuracy of two independent Doppler variables. As noted above, RV AT also correlates with mean PA pressure with similarly noted limitations (Dabestani et al., 1987).

The position of the dicotic notch on the PA pressure wave form approximates the mean PA pressure. Peak diastolic pressure gradient between the PA and the RV approximates mean PA pressure and, therefore, application of the modified Bernoulli equation to the peak PR velocity with a RAP estimate can be used to estimate mean PA pressure (Figure 13) (Abbas, Fortuin, Schiller, 2003).

$$\text{Mean PA pressure} = 4V_{\text{pr}}^2 \text{ peak velocity}^2 + \text{estimated RAP}$$

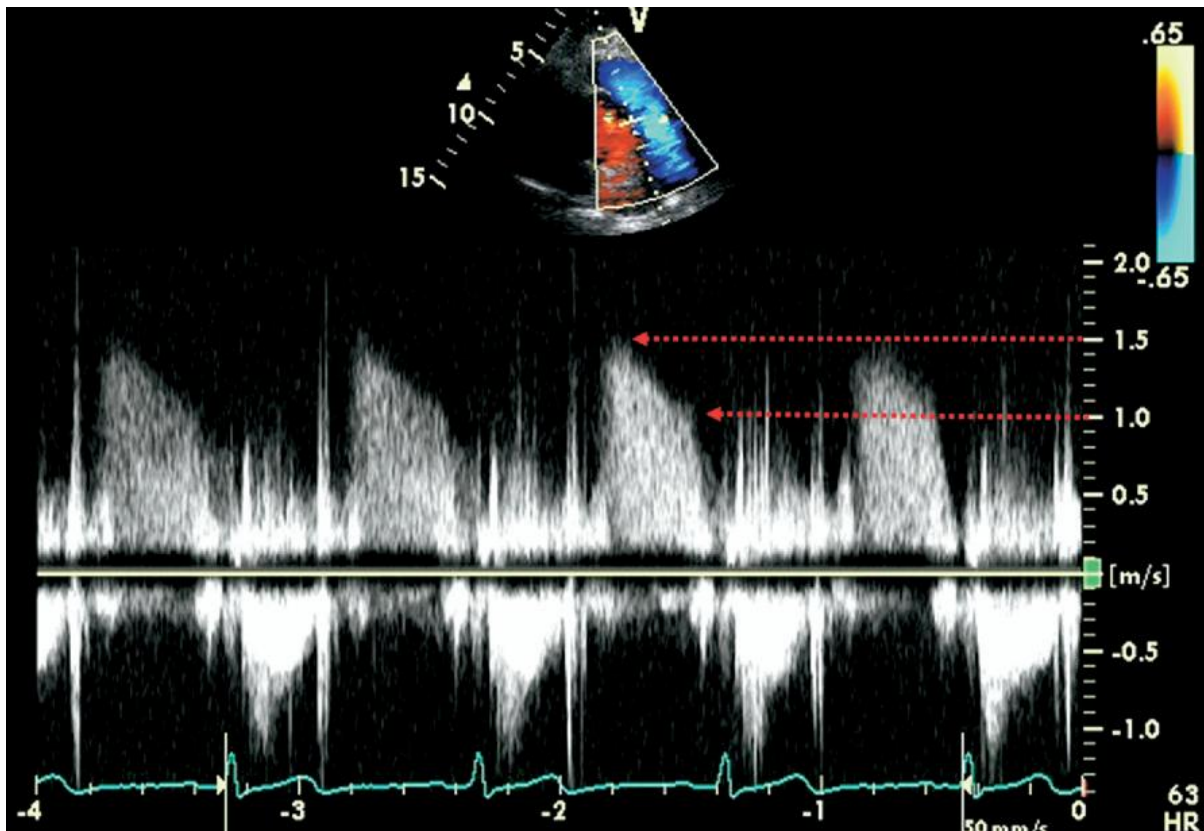


Figure 13: Continuous wave Doppler spectrum of pulmonary regurgitation velocity demonstrating assessment of mean pulmonary artery (PA) pressure and PA diastolic pressure. Peak early diastolic regurgitant velocity is 1.5 m/s. Mean PA pressure, therefore = $4 \times (1.5)^2 + \text{right atrial pressure (RAP)}$ (estimated in this patient at 10 mm Hg), or 19 mm Hg. End-diastolic regurgitant velocity is 1.0 m/s. PA diastolic pressure is, therefore = $4 \times (1)^2 + \text{RAP}$, or 14 mm Hg (Abbas, Fortuin, Schiller, 2003).

3.7.10 Estimated Pulmonary Vascular Resistance

Pressure is the product of flow and resistance. Assignment of pathology to a value of PASP is incomplete without an understanding of associated resistance. In addition, a measure of pulmonary vascular resistance (PVR) is important clinically in the evaluation and treatment of patients with various cardiovascular disorder.

Two dimensional correlates:

Due to the close relationship between pressure and resistance, many of the 2D correlates of elevated PA pressure in the current study were also associated with increased PVR. As PVR increases, there is earlier and enhanced reflection of the pressure wave propagated from the RVOT into the pulmonary trunk. This is reflected by a conformational change in RVOT velocity-time integral (VTI), where midsystolic notching and premature deceleration of pulmonary flow occur, leading to a decreased RV ejection time (Figure 14 B) (Hirschfeld, Meyer, Schwartz, 1975).

Doppler Correlates:

Numerous qualitative Doppler abnormalities are associated with elevated PVR and there is a significant overlap between findings associated with elevated PA pressures because of their interrelationship.

Estimation of PVR by echocardiography was performed using Doppler measurements obtained from TRV and pulmonary forward systolic flow. Therefore, it is dependent on obtaining technically optimal measurements. Numerous correlates have been proposed that have mostly proven to be unreliable because of the complex interrelationship among heart rate, resistance and flow.

The method of choice in current study for estimating PVR was by extrapolation, an echocardiographic Doppler correlate of transpulmonary pressure: (TRV) and transpulmonary flow (RVOT VTI). The ratio of TRV: RVOT VTI has been shown to correlate with PVR with a correlation of $r = 0.93$ (95% confidence interval 0.87 – 0.96) (Abbas, Fortuin, Schiller, 2003). A 1 to 2 mm pulsed wave Doppler sample volume was placed in the RVOT when imaged from the parasternal short axis view to obtain the RVOT VTI, while continuous wave Doppler was used to determine the maximum TRV (using methods as described to obtain PASP). A simplified equation for noninvasive calculation of PVR is:

$$PVR (WU) = 10 \times TRV/RVOT VTI$$

Assigned dichotomously, a TRV / RVOT VTI ratio greater than or equal to 0.2 predicts a PVR value greater than 2 WU with a sensitivity of 70% and a specificity of 94% (Figure 14 A) (Abbas et al., 2003).

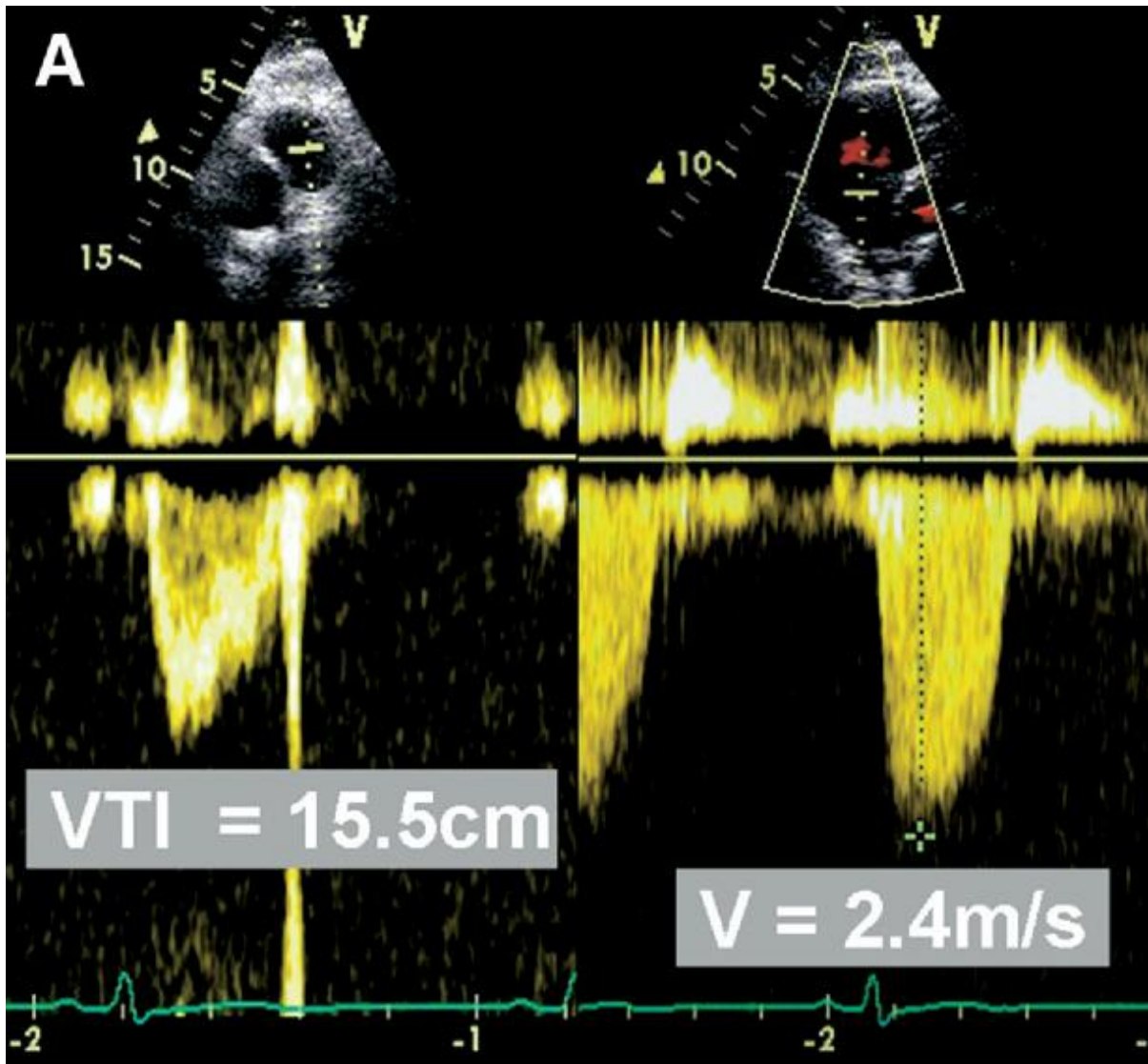


Figure 14 A: Images showing peak tricuspid regurgitation velocity (TRV) and right ventricular outflow tract (RVOT) velocity - time integral (VTI) in patient with normal pulmonary vascular resistance (PVR). TRV is 2.40 m/s. RVOTVTI is 15.5 cm. Ratio of TRV/RVOTVTI = $2.40/15.5 = 0.15$. PVRECHO calculated based on linear regression equation $PVRECHO = TRV/RVOTVTI \times 10 + 0.16 = 1.66$ Wood's units (WU) (Abbas et al., 2003).

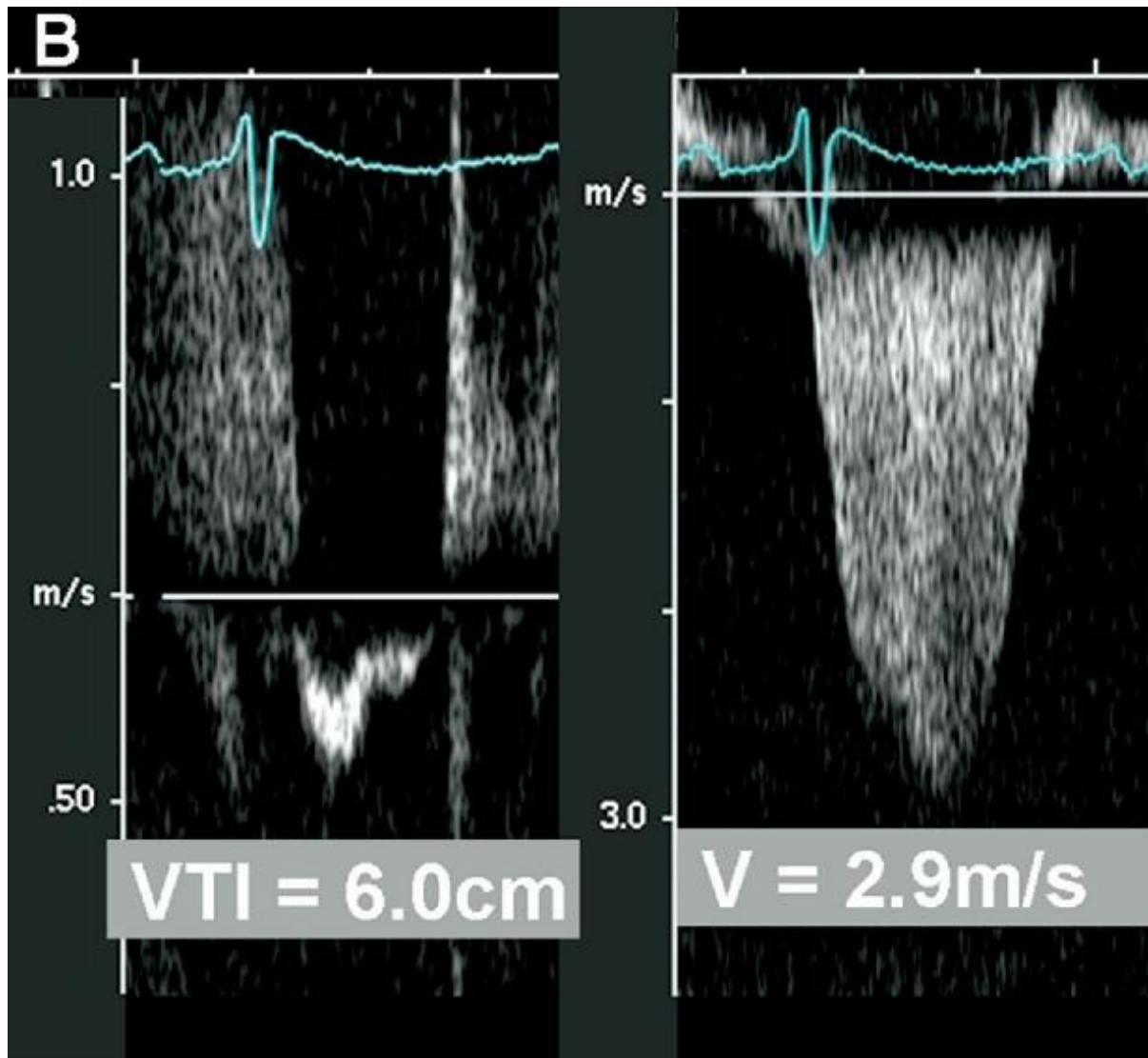


Figure 14 B: Images showing TRV and RVOT VTI in patient with elevated PVR. TRV is 2.9 m/s. RVOT VTI shows midsystolic notching and is calculated 6.0 cm. Ratio of TRV/RVOTVTI = $2.9/6.0 = 0.48$. PVR ECHO = $0.48 \times 10 + 0.16 = 4.96$ WU (Hirschfeld, Meyer, Schwartz, 1975).

3.7.11 Mitral Inflow Velocities

The mitral inflow velocities were recorded using pulsed wave Doppler echocardiography by positioning the sample volume at the tip of the mitral leaflets from the apical four-chamber view. From the mitral valve inflow velocity curve the following measurements were made: early diastolic mitral inflow velocity (E) and late diastolic mitral inflow velocity (A) wave velocities, their ratio and the deceleration time of the E wave.

3.7.12 Statistical Analysis

Data was captured into the excel spreadsheet and analysed with SAS version 9.1 (SAS Institute Inc, Cary, NC). Normal distributed continuous data are presented as mean \pm SD. Categorical variables are summarized as frequencies and percentages. Percentages are accompanied by 95% CI where appropriate. Comparisons of continuous variables for categorical chi square test was performed. A probability value less than 0.05 was considered statistically significant. Univariate logistic regression was performed for age, mitral regurgitation, left atrial volume index and ejection fraction to predict PAH. Multiple logistic regression was performed using the independent variables that showed significant odds ratio by univariate analysis of pulmonary arterial hypertension.

CHAPTER 4

RESULTS

4.1 Baseline Characteristics

Sixty six participants were enrolled in the study. The baseline characteristics of the group are presented in Table 11. The mean age was 48.5 ± 12.8 years. Of the 66 patients, 39 (59.1%) were male and 27 (40.9%) female. The body mass index was 26.9 ± 5.8 kg/m², and surface area 1.8 ± 0.2 m².

Table 11: BASELINE CHARACTERISTICS

Demographic Profile	All patients (n=66)
Age (years)	48.5 ± 12.8
Male n (%)	39 (59.1)
Female n (%)	27 (40.9)
Anthropometric features	
BMI (kg / m ²)	26.9 ± 5.8
BSA (m ²)	1.8 ± 0.2

Data are presented as mean \pm standard deviation or proportions

BMI = body mass index; BSA = body surface area

4.2 Baseline Echocardiographic Characteristics

The baseline echocardiographic characteristics are represented in Table 12. The mean ejection fraction was $25.3 \pm 8.8\%$. 20/66 (30.3%) of the patients had a moderately depressed EF and 46/66 (69.7%) had severely depressed EF. Mitral regurgitation occurred in 56/66 (84.8%) of patients which was further categorized into mild 16/66 (24.2%), moderate 28/66 (42.4%) and severe 12/66 (18.2%). The remaining 10/66 (15.2%) had no mitral regurgitation.

The LA volume index was measured in all subjects. The mean volume was $44.5 \pm 19.8 \text{ ml/m}^2$. The LA volume index was categorized into mildly abnormal 6/66 (9.1%), moderately abnormal 13/66 (19.7%) and severely abnormal 35/66 (53.0%). The remaining 12/66 (18.2%) had a normal LA volume index.

The function of the right ventricle as assessed by (RV S') was measured in all patients, with a mean of 9.5 ± 2.7 . The right ventricular function was normal in 18/66 (27.3%), whereas 48/66 (72.7%) had an abnormal right ventricular function. The estimated pulmonary vascular resistance was normal in 19/66 (28.8%) and abnormal 47/66 (71.2%).

Left ventricular diastolic function was measured using the E peak (early mitral inflow velocity) with a mean of $85.1 \pm 26.5 \text{ cm/s}$ and, A peak (late mitral inflow velocity) had a mean of $53.7 \pm 24.6 \text{ cm/s}$. The E/A ratio had a mean of 1.9 ± 1.0 and the DT a mean of $101.1 \pm 40.6 \text{ ms}$ (Table 12).

Table 12: BASELINE ECHOCARDIOGRAPHIC CHARACTERISTICS

	All patients (n=66)
EF	25.3 ± 8.8
Moderately depressed n(%)	20 (30.3)
Severely depressed n(%)	46 (69.7)
MR	56 (84.8)
Nil n(%)	10 (15.2)
Mild n(%)	16 (24.2)
Moderate n(%)	28 (42.4)
Severe n(%)	12 (18.2)
LA VOLUME INDEX mL/m ²	44.5 ± 19.8
Mildly abnormal n(%)	6 (9.1)
Moderately abnormal n(%)	13 (19.7)
Severely abnormal n (%)	35 (53)
RV S'	9.5 ± 2.7
Normal n (%)	18 (27.3)
Abnormal n (%)	48 (72.7)
ESTIMATED PVR (WU)	4.0 ± 1.9
Normal n (%)	19 (28.8)
Abnormal n (%)	47 (71.2)
E peak, cm/s	85.1 ± 26.5
A peak, cm/s	53.7 ± 24.6
E / A ratio	1.9 ± 1.0
DT, ms	101.1 ± 40.6

Data are presented as mean ± standard deviation or proportions.

EF = ejection fraction; MR = mitral regurgitation; LA volume = left atrial volume

RV S' = systolic excursion velocity; PVR = pulmonary vascular resistance; E peak = early diastolic mitral inflow velocity; A peak = late diastolic mitral inflow velocity; DT = deceleration time; WU = woods unit

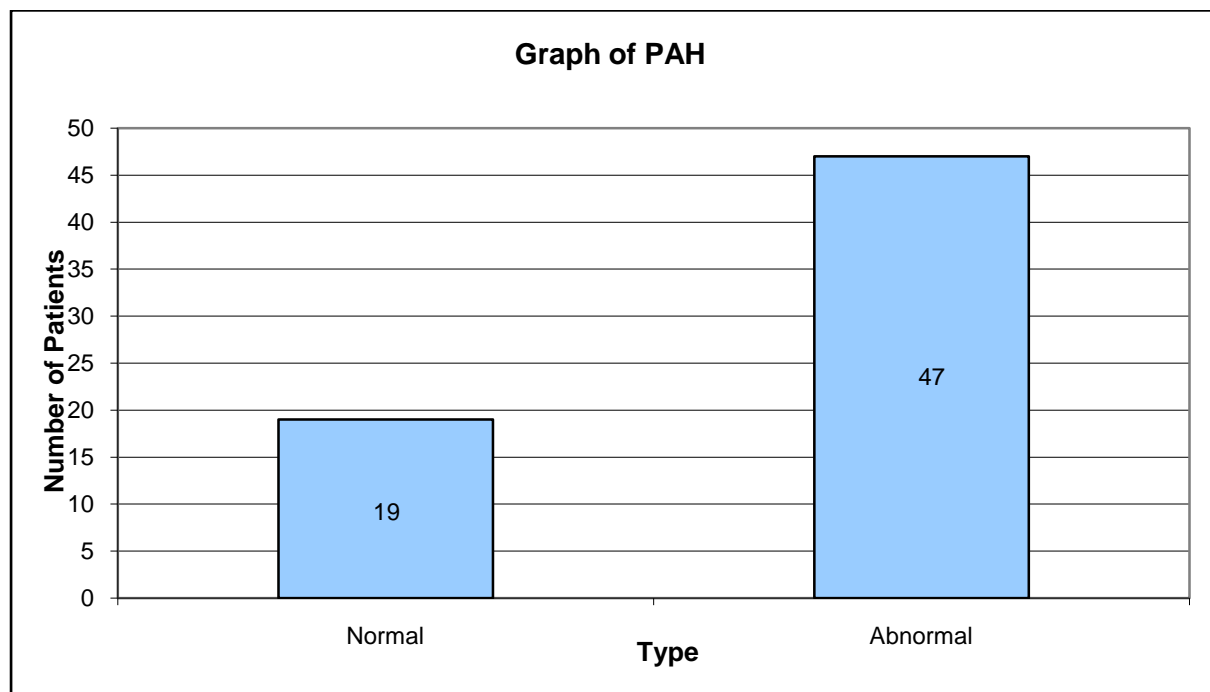
4.3 Prevalence of Pulmonary Arterial Hypertension in Idiopathic Dilated Cardiomyopathy Patients

Pulmonary arterial hypertension was found in 47/66 (71.2%, 95% CI 59 - 83%) patients, with no PAH in 19/66 (28.8%) (Table 13) (Graph 1).

Table 13: PREVALENCE OF PULMONARY ARTERIAL HYPERTENSION IN DILATED CARDIOMYOPATHY PATIENTS

VARIABLE	n, (%)	95% CONFIDENCE INTERVAL
PAH n (%)	47 (71.2)	(59 - 83%)

PAH = pulmonary arterial hypertension



Graph 1: Patients with and without Pulmonary arterial hypertension

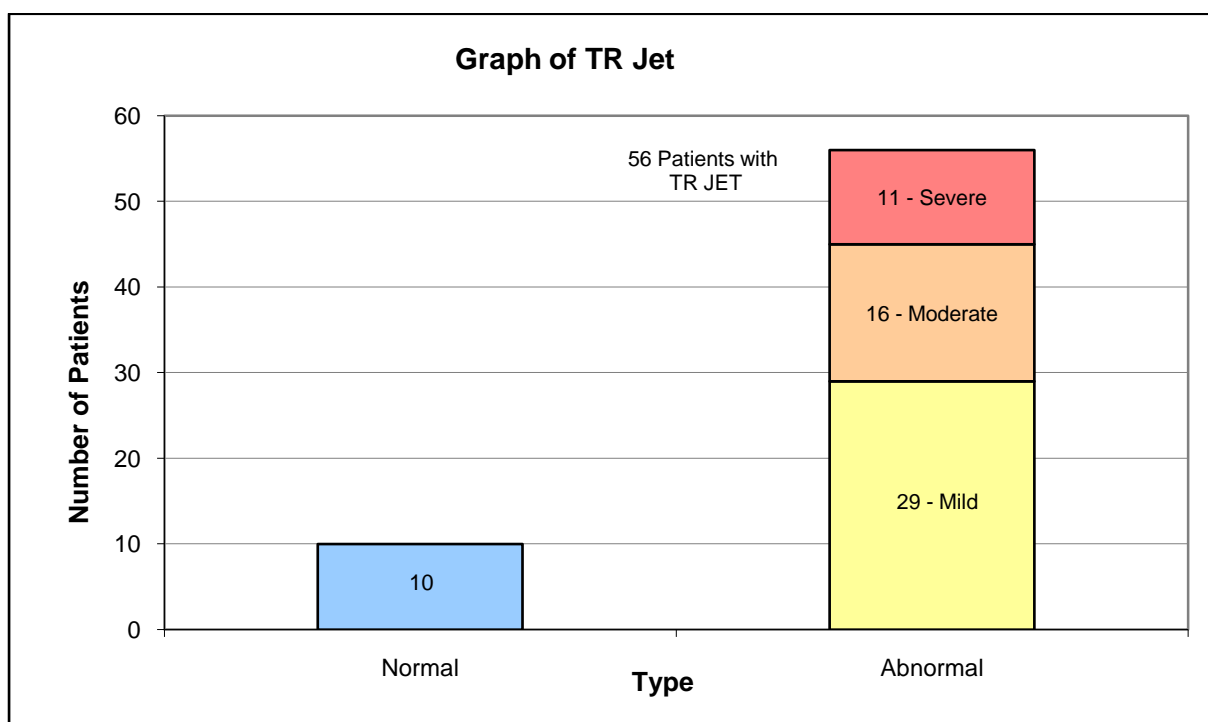
4.4 Prevalence of Tricuspid Regurgitant Jet Involvement in Idiopathic Dilated Cardiomyopathy Patients

The presence of a tricuspid regurgitant jet was found in 56/66 (84.9%, 95% CI 75 - 93%) patients, whereas 10/66 patients presented with no tricuspid regurgitation (Table 14) (Graph 2).

Table 14: PREVALENCE OF TRICUPID REGURGITANT JET INVOLVEMENT IN IDIOPATHIC DILATED CARDIOMYOPATHY PATIENTS

VARIABLE	n, (%)	95% CONFIDENCE INTERVAL
TR JET n (%)	56 (84.9)	75 - 93%

TR Jet = tricuspid regurgitant jet



Graph 2: Patients with and without tricuspid regurgitation jet

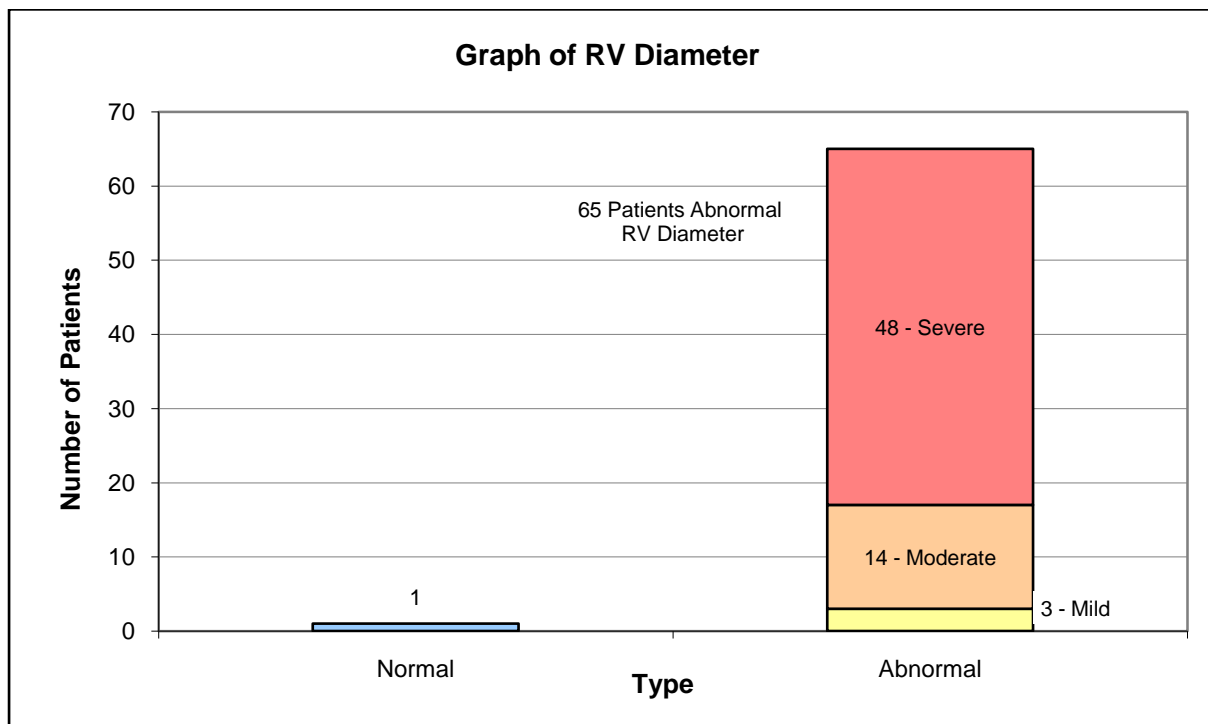
4. 5 Prevalence of Right Ventricular Diameter Involvement in Idiopathic Dilated Cardiomyopathy Patients

Right ventricular involvement was found in 65/66 (98.5%, 95% CI 95 - 101%) patients, whereas 1 patient presented with a normal right ventricular diameter (Table 15) (Graph 3).

TABLE 15: PREVALENCE OF RIGHT VENTRICULAR DIAMETER INVOLVEMNET IN DILATED CARDIOMYOPATHY PATIENTS

VARIABLE	n, (%)	95% CONFIDENCE INTERVAL
RV DIAMETER	65 (98.5)	95 - 101%

RV Diameter = right ventricular diameter



Graph 3: Patients with normal and dilated right ventricles.

4.6 Predictors of Pulmonary Arterial Hypertension

The predictors of PAH included age, LA volume index, mitral regurgitation and ejection fraction. In patients with PAH the mean age was 50.1 ± 13.1 years, whereas those that presented with no PAH had a mean age of 44.6 ± 11.2 years, $p = 0.19$. The mean LA volume index in patients with PAH was 47.1 ± 18.5 ml/m², and those presenting with no PAH had a mean of 37.9 ± 21.8 ml/m², $p = 0.09$. In patients with PAH 69.7% had mitral regurgitation, 15.2% presented with mitral regurgitation but had no PAH, and the remaining 15.2% of patients had no mitral regurgitant. The mean ejection fraction in patients with PAH was $24.8 \pm 9.0\%$, however those that did not have PAH had a mean ejection fraction of $26.5 \pm 8.4\%$ (Table 16).

TABLE 16: PREDICTORS OF PULMONARY ARTERIAL HYPERTENSION

Variables	ALL (n=66)	With PAH	Without PAH	P VALUE
AGE	48.5 ± 12.8	50.1 ± 13.1	44.6 ± 11.2	0.19
LA VOLUME INDEX (ml/m ²)	44.5 ± 19.8	47.1 ± 18.5	37.9 ± 21.8	0.09
MR n (%)	66 (100)	46 (69.7)	10 (15.2)	0.01
EF	25.3 ± 8.8	24.8 ± 9.0	26.5 ± 8.4	0.5

Data presented as mean ± standard deviation or proportions

LA volume = left atrial volume; MR = mitral regurgitation; EF = ejection fraction;

PAH = pulmonary arterial hypertension

4.7 Univariate Logistic Regression for Pulmonary Arterial Hypertension

In the univariate logistic regression analysis mitral regurgitation was a predictor of PAH with an unadjusted (OR 8.56, 95% CI: 1.92 – 38.17) ($p= 0.01$) (Table 17). The other variables measured to determine whether they were predictors of PAH included age with an unadjusted (OR 1.04, 95% CI: 0.99 – 1.07) ($p= 0.12$), LA volume index showed an unadjusted (OR 1.03, 95% CI: 1.00 – 1.07) ($p= 0.09$) and the ejection which showed an unadjusted (OR 0.98, 95% CI: 0.92 – 1.04) ($p=0.50$). However, the p values of age, LA volume index and ejection fraction were > 0.05 and therefore not good predictors of PAH.

TABLE 17: UNIVARIATE LOGISTIC REGRESSION OF PULMONARY ARTERIAL HYPERTENSION

	ODDS RATIO UNAJUSTED	95% CONFIDENCE INTERVAL	P VALUE
AGE (years)	1.04	0.99 – 1.07	0.12
MR	8.56	1.92 – 38.17	0.01
LA VOLUME INDEX (ml/m ²)	1.03	1.00 – 1.07	0.09
EF (%)	0.98	0.92 – 1.04	0.50

MR = mitral regurgitation; LA volume = left atrial volume; EF= ejection fraction

4.8 Multiple Logistic Regression for Pulmonary Arterial Hypertension

The multivariate analysis was also performed to identify whether there was more than one variable that could be a predictor of PAH (Table 18). Despite this however, MR was still the only predictor of PAH with an adjusted (OR 6.02, 95% CI: 1.15 – 31.47) ($p=0.03$). Age showed an adjusted (OR 1.02, 95% CI: 0.98 – 1.05) ($p= 0.50$). The LA volume index had an adjusted (OR 1.03, 95% CI: 0.99- 1.05) ($p= 0.50$). EF showed an adjusted (OR 0.98, 95% CI: 0.91- 1.05) ($p= 0.51$). The p values of age, LA volume index and EF were >0.05 and therefore not good predictors of PAH.

TABLE 18: MULTIPLE LOGISTIC REGRESSION OF PULMONARY ARTERIAL HYPERTENSION

	ODDS RATIO ADJUSTED	95% CONFIDENCE INTERVAL	P VALUE
AGE (years)	1.02	0.98 – 1.05	0.50
MR	6.02	1.15 – 31.47	0.03
LA VOLUME INDEX (ml/m ²)	1.03	0.99 – 1.05	0.50
EF (%)	0.98	0.91 – 1.05	0.51

MR = mitral regurgitation; LA volume = left atrial volume; EF = ejection fraction

CHAPTER 5

DISCUSSION

It has been documented that IDC is the second commonest cause of heart failure in Africa (Sliwa et al., 2008) and thus an important public health problem. Furthermore, IDC is associated with PAH and consequent right heart failure, a condition which is often difficult to treat with limited available options in the developing world. Despite this, no data exists on the prevalence and/or predictors of PAH in patients presenting with IDC. The purpose of this research was to establish the prevalence of PAH and its predictors in black South Africans with IDC in an attempt to better understand the condition and hopefully establish predictors which may be used for its prevention.

After examining a cohort of 66 patients with poor left ventricular function, the present study established that 71.2% of the patients presented with PAH. This study confirmed that patients with moderately as well as severely depressed ejection fraction develop PAH. The prevalence of right ventricular dilatation and tricuspid regurgitation was also determined in the cohort of patients and showed results of 99% and 84% respectively. Pulmonary arterial hypertension, right ventricular dilatation and tricuspid regurgitation ultimately play a role in development of right heart dysfunction and failure.

Multiple logistic regression analysis was performed to establish any predictors of PAH and mitral regurgitation emerged as the only predictor. According to Di Lenarda et al. (1993) left sided ventricular or valvular diseases may produce an increase in

left atrial pressure, with passive backward transmission of the pressure leading to an increase in the pulmonary capillary wedge pressure, and this backward flow leading to PAH. Thus explaining how MR may contribute to PAH.

Based on the present finding, it would seem reasonable to actively look for the presence of MR in patients with IDC and manage it appropriately in an attempt to halt the progression of, or even prevent, PAH and its complications. This hypothesis, however, would have to be validated in future prospective studies. Currently available and emerging technologies such as three dimensional echocardiography and percutaneous valve management may facilitate the diagnosis and treatment of IDC related MR in the future.

5.1 LIMITATIONS OF THE STUDY

Although this study represents the only available data on the prevalence and predictors of PAH in IDC, the total number of patients is modest and thus the results have to be interpreted cautiously and a larger study sample may reveal further predictors. Echocardiographic data is highly operator dependent and thus subject to inter and intra-operator variability. In terms of specific echocardiographic techniques, annular velocities may vary with the site of sampling, and thus, the utility of this method is independent of the location of the sample volume.

Pulmonary pressure was calculated noninvasively by doppler echocardiography and not by catheterization. The TR jet obtained in patients in the present study were technically good. The TR jet was not measured in a few patients, therefore PAH

could not be calculated. The noninvasive method has, however, been fully validated (Chan, Currie, Seward, 1985) and currently represents a standard approach to pulmonary hypertension (Tramarin, Torbicki, Marchandise, Laaban, Morpurgo, 1991). By avoiding the potential selection bias of catheterization, doppler echocardiography has the advantage of analysing a group of patients representative of those seen routinely for congestive heart failure (CHF). The doppler diagnosis of pulmonary hypertension using tricuspid regurgitant jet velocity is a powerful diagnostic indicator in left ventricular dysfunction and thus represents a valid end point.

Concurrent invasive haemodynamic measurements were not performed in this prospective cohort study. The estimation of PVR by TRV/RVOT VTI does not account for some potentially confounding haemodynamic variables including right atrial pressure and pulmonary capillary wedge pressure. Previous validation studies correlating TRV/RVOT VTI to invasively measured PVR, however, showed a robust correlation even in patients with increased right atrial pressure and pulmonary capillary wedge pressure (Abbas et al., 2003). Right ventricular parameters were not compared to gold standard magnetic resonance imaging. Since the TR jet could not be measured in a few patients PAH could not be calculated, thus potentially underestimating the prevalence of PAH. No reliable data on left sided filling pressures were obtained due to the difficulty in obtaining Tissue doppler imaging in all patients. Pulmonary thromboembolic disease was not actively excluded in patients with PAH.

CHAPTER 6

CONCLUSION

There are minimal quantitative data overall on RV size and function in normal controls and disease states. A gradual shift to more quantitative approaches for the assessment of RV size and function will help standardize assessment of the right ventricle and allow clinicians to better incorporate assessment of the right heart into an echocardiographic evaluation. Doppler echocardiography has shown to be a powerful non invasive tool in the detection of PAH.

In conclusion, there is a high prevalence of PAH with associated right ventricular dilatation in black South African patients with IDC. The presence of mitral regurgitation in this population predicts the presence of PAH and may emerge as an important target for treatment in this important group of patients. Further studies to confirm these findings and establish the importance of varying grades of MR on the prediction of PAH are warranted.

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APPENDIX A

Letter of Information and Consent

Title of the Research Study:

The prevalence of pulmonary arterial hypertension documented on echocardiography in patients with dilated cardiomyopathy.

Principal Investigator:

Mr K. Naidoo, student in Master's Degree: Clinical Technology (Cardiology) at Durban University of Technology.

Brief Introduction and Purpose of the Study:

Idiopathic dilated cardiomyopathy, a disease of the heart muscle of unknown origin, is characterized by impaired systolic function and dilatation of the left and right ventricles. This study aims to determine the prevalence of pulmonary arterial hypertension by using echocardiography

Outline of the Procedures:

People with **dilated cardiomyopathy (large hearts)** will be invited to participate in the study. You will **come** to the Cardiac Clinic, Chris Hani Baragwanath Hospital, Johannesburg. When you arrive, a cardiac doctor will take your medical history, examine you and arrange for you to have a chest X-ray; and electrocardiogram, an echocardiogram (which is "heart scan" method of examining the heart using sound waves) as well as blood tests. You will be required to sign consent for the study.

Risks or Discomforts to the Subject:

There will be no risk to the participants, as all the test being conducted as part of this study are recommended in all patients with **idiopathic dilated cardiomyopathy** and represent the best international standard of care.

Benefits:

The new information gained from the study will help to improve diagnosis and treatment of patients with **idiopathic dilated cardiomyopathy**.

Reason/s why the Subject May Be Withdrawn from the Study:

The subject may be withdrawn from the study they are **hypertensive or if they have valvular disease**.

Remuneration:

There will be no remuneration given to the participant.

Costs of the Study:

The participant will be liable for the normal costs for the routine medical procedures needed; no extra costs will be added for the research.

Confidentiality:

Participants will be identified by a code and not by name. Their details will be kept confidential in a subject file, which will be stored in a locked office in the department of Cardiology, Chris Hani Baragwanath Hospital.

Research-related Injury:

There will not be any research related injuries.

Persons to Contact in the Event of Any Problems or Queries:

Mr Krinesh Naidoo	Prof J. K Adam	Dr. F.F.E. Peters
Principal Investigator	Supervisor	Supervisor
0786864940	031 373 5291	0829278697

Statement of Agreement to Participate in the Research Study:

(I,.....subject's full name,
 ID number....., have read this document in its
 entirety and understand its contents. Where I have had any questions or queries,
 these have been explained to me byto my
 satisfaction. Furthermore, I fully understand that I may withdraw from this study at
 any stage without any adverse consequences and my future health care will not be
 compromised. I, therefore, voluntarily agree to participate in this study.

Subject's name **Subject's signature**.....

Date:.....

Researcher's name **Researcher's signature**.....

Date:.....

Witness name **Witness signature**.....

Date:.....

Supervisor's name..... **Supervisors signature**.....

Date:.....



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APPENDIX A

Incwadi yokuchaza nesivumelwano

Isihloko socwaningo

Xxxxxxxxxxxxxxxxxxxx

Umncwaningi

K. Naidoo, umfundi we- Master's Degree: Clinical Technology (Cardiology) at Durban University of Technology.

Incazelo nenjongo yocwaningo.

Uvavanyo lwentliziyo:

Simema abantu abanesifo samanzi ajikeleza intliziyo esibangwa sisifo sephepha ukuba bathabathe inxaxheba koluphando. Uzakuthi uthunyelwe kwicandelo lesifo sentliziyo kwisibhedlela saseGroote Schuur, eKapa. Ekufikeni kwakho ugqirha uzakukujonga imbali yokugula kwakho, akuxilonge, alungisele ukuba ujongwe ukubetha kwentliziyo, ukusebenza kwentliziyo kunye novavanyo lwegazi.

Uzakutshikitsha isivumelwayo sokutsalwa kwamanzi entlizini, uvavanyo kanye nokuba ingxenye yophando.

Uzakuyiswa egumbini labucala elilungiselwe ukuvavanywa nokutsalwa kwamanzi kwintliziyo. Kuyakuthi kutsalwe incindi okanye amanzi akwintliziyo Inaliti iyawufakwa kodonga olungasentliziyweni kanye nasemlenzeni, kutsalwe incindi namanzi akwintliziyo, ukuphanda ngakumbi. Kuzakuthi kujongwe nokubetha kwentliziyo.

Emva kokuba sekwenziwe konke okhu, uzakuya egumbini lwentliziyo, apho uzakwenziwa uvavanyo lokukhangela ukusebenza kwentliziyo (i-echocardiogram). Emva kwakho uzakukhululwa ukuba uye ekhaya. Loluphando uludingi ukuba ubuyele esibhedlela ozokwenza olunye uvavanyo,

Ubungozi okanye ubuhlungu

Ukuba yingxenywe yoluphondo akuzukufaka impilo yakho engozi ngokuba konke okuhlolwa okuzokwenziwa kuyingxenywe yokwelashwa kwesisifo ngokomgangatho kazwelonke.

Umvuzo:

Ulwazi olutsha esizakulifumana lwawukwenza sizame ukuohucula unyango lwesisifo.

Isizathu sokuba ungakhutshwa koluphando:

Isiguli singakhutshwa kolupha uma ezinye inchukatsha ngesifo zingafumaneki.

Ukubhatalwa:

Akukho mvuzo wemali ofumanekayo ngokuba iingxenywe yoluphando.

Imali ezakuyibhatala ngoluphando

Awuzubhatala nto koluphando

Imfihlakalo:

Yonke incukacha neziphumo ziyawugcinwa ngokufihlekileyo kwisibhedlela I Chis Hani Baragwanath Hospital eGoli. Igama lomguli alizikusetshenziswa.

Ukonzakala okumayelana nophando:

Uphando alukubeki encupheni yokonzakala nangaluphi uhlobo

Abantu ongabathinta mayelana nemibuzo okanye ingxaki ngoluphando:

Mr K. Naidoo	Dr J. K Adam	Dr. F.F.E. Peters
Principal Investigator	Supervisor	Supervisor
0786864940	031 373 5291	0829278697

Isivumelwano sokuthabatha inxaxheba koluphando:

(Mina.....(igama lakho ngokugcwele)

(inombolo yeID).....,ndifundile futhi ndiyaqonda lencukacha yoluphando. Apho ndinemibuzo, ndiye ndafumana incazelo egculisayo ku..... ngaphezu kokho ndiyaqonda ukuba ndingayeka ukuba ingxenye yophando ngaphandle kokuphazamiseka konyango lwami. Ndiyavuma ukuba yingxenye yoluphando.

.

Igama lomguli.....Tyikitya.....Usuku.....

Umphandi.....Tyikitya..... Usuku.....

Lingqina.....Tyikitsa.....Usuku.....

APPENDIX B

IMAGING PROTOCOL ECHO LAB CHRIS HANI BARAGWANATH HOSPITAL

Long axis

ACQUIRE 2D FIRST THEN COLOUR WHERE RELEVANT.

- 1) Parasternal long axis (M MODE)
- 2) RV in flow view. Do colour across tricuspid valve and then CW.
- 3) RV outflow view.

Short axis views

ACQUIRE 2D VIEWS FIRST, THEN COLOUR WHERE RELEVANT

- 1) MPA level. Colour Doppler in RVOT and MPA. CW Doppler and then PW in RVOT below acceleration (closing click).
- 2) Aortic valve.
- 3) Base-mitral leaflets.
- 4) Papillary muscles.
- 5) Apex.

Apical 4 chamber (no apical foreshortening)

- 1) Acquire 2D view ensuring the apex is not foreshortened.
- 2) Perform colour Doppler of mitral valve, tricuspid valve and interatrial septum.
- 3) Perform Doppler of mitral valve (CW, PW at tips of mitral leaflets, and then PW in LVOT).
- 4) Perform Doppler of aortic valve (CW then PW in LVOT below acceleration point).
- 5) Perform Doppler of tricuspid valve (CW then PW at tips of leaflets).
- 6) Perform tissue Doppler of lateral and medial mitral annulus and finally lateral tricuspid annulus.
- 7) Perform TAPSE of lateral tricuspid annulus using M mode.

Apical 2 chamber (2D and colour of the Mitral valve).

Apical 3 chamber (2D, COLOUR OF MITRAL AND AORTIC VALVES WITH CW OF AORTIC IN AORTIC STENOSIS).

SUBCOSTAL VIEW (VISUALISE INTERATRIAL SEPTUM AND IVC)

SUPRASTERNAL VIEW