THE USE OF ECHOCARDIOGRAPHY IN PREDICTING LEFT VENTRICLE THROMBUS IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY AT CHRIS HANI BARAGWANATH HOSPITAL.

by

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AUTHORS DECLARATION

This study represents original work by the author. It has not been submitted in any other form to any other Tertiary Institution. Where use of the work of others was made, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Biomedical and Clinical Technology, Faculty of Health Sciences, Durban University of Technology, Durban, South Africa under the supervision of Doctor F.E.E. Peters and Prof J.K. Adam (Department of Biomedical and Clinical Technology, Durban University of Technology).

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I hereby certify that the above statement is correct.

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SIGNED: _____ **Prof J.K. Adam**
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DEDICATION

I dedicate this work to:

My late father, Antonio Ferreira Dos Santos - for always believing in me. You are a great inspiration in my life and I miss you every day.

ABSTRACT

Background: Cardiomyopathies and their resultant heart failure (HF) remain a major cause of cardiovascular morbidity and mortality (Wood and Picard, 2004). Idiopathic dilated cardiomyopathy (IDCMO) is a primary myocardial disease of unknown cause, characterized by left ventricular (LV) or biventricular dilatation and impaired myocardial contractility. Dilated cardiomyopathy (DCMO), along with rheumatic heart disease and hypertension (HPT), is one of the leading causes of HF in Africa. In fact, in an epidemiology study of 884 patients in Soweto, IDCMO was the second major cause of HF. Thirty five percent of patients in the study, with HF, had IDCMO (Sliwa, Damasceno, Mayosi, 2005).

Methodology: Patients referred to the cardiomyopathy (CMO) clinic at Chris Hani Baragwanath hospital, situated in the echocardiographic lab, were recruited, provided they satisfied the exclusion and inclusion criteria and were enrolled after obtaining voluntary informed consent. From May 2009 to September 2010, 70 patients with IDCMO were recruited for this trial. Patients with DCMO were identified by means of echocardiographic criteria which included a left ventricular ejection fraction (LVEF) of less than 45% and an end diastolic dimension (EDD) of greater than of 52 mm (2D in long parasternal axis).

Results: In the present study the prevalence of left ventricular (LV) thrombus in patients with IDCMO was 18.6%. When using Univariate logistic regression, the only independent predictors of LV thrombus formation was LVEF and age. However, when multivariate logistic regression analysis was applied to the data, the only predictor with a significant association was age. The reason for this is not clear. It is postulated that perhaps younger patients have differences in the pathophysiology of their disease such as a greater smoldering inflammatory component which may therefore predispose them to thrombus formation. For example the presence of IL-6 may be important in the formation of LV clot in

cases of LV dysfunction (Sosin, Bhatia, Davis, Lip, 2003). The association between LVEF and LV thrombus was borderline significant.

Conclusion: The prevalence of LV thrombus formation in this cohort of patients with IDCMO was 18.6%. Echocardiographic parameters alone cannot predict which patients are more likely to develop thrombus formation.

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2D	-	two dimensional
3D	-	three dimensional
ACE	-	angiotensin converting enzyme
AF	-	atrial fibrillation
ASE	-	American society of echocardiography
BMI	-	body mass index
BSA	-	body surface area
CAD	-	coronary artery disease
CMO	-	cardiomyopathy
CHF	-	congestive heart failure
COPD	-	chronic pulmonary obstruction disease
CW	-	continuous wave
DCMO	-	dilated cardiomyopathy
ECG	-	electrocardiography
EF	-	ejection fraction
EDD	-	end diastolic dimension
HF	-	heart failure
HPT	-	hypertension
IDCMO	-	idiopathic dilated cardiomyopathy
IL	-	interleukin
IVC	-	inferior vena cava
INR	-	international normalized ratio
LV	-	left ventricle
LVEDD	-	left ventricular end diastolic dimension

LVEF	-	left ventricular ejection fraction
MI	-	myocardial infarction
MPA	-	main pulmonary artery
MR	-	mitral regurgitation
Pf4	-	platelet factor 4
PW	-	pulsed wave
RV	-	right ventricle
SEC	-	spontaneous echo contrast
SV	-	stroke volume
TAPSE	-	tricuspid annular plane systolic excursion
TAT4	-	thrombin-antithrombin 4 complex
TEE	-	transesophageal echocardiography
TDI	-	tissue Doppler imaging
THI	-	tissue harmonic imaging
TR	-	tricuspid regurgitation
TNF	-	tumour necrosis factor
TV	-	tricuspid valve
VC	-	vena contracta
WHO	-	world health organization

CHAPTER ONE: INTRODUCTION

1.1 Introduction

Heart failure (HF) due to dilated cardiomyopathy (DCMO) is a large and expanding public health problem. Cardiomyopathy (CMO), an often irreversible form of heart muscle disease is associated with a dismal outcome and is endemic to Africa (Sliwa, Damasceno, Mayosi, 2005). Unlike other parts of the world in which CMO are rare, DCMO is a major cause of HF throughout Africa. In an epidemiology study of 844 patients in Soweto, idiopathic dilated cardiomyopathy (IDCMO) was the second major cause of HF. Thirty five percent of patients that presented with HF in this study had IDCMO (Sliwa *et al*., 2005).

The World Health Organization (WHO) defines DCMO as a myocardial disease characterized by dilatation and impaired contractility of the left or both ventricles (Richardson, McKenna, Bristow, Maisch, Mautner, O'Connell, Olsen, Thiene, Goodwin, Gyarfas, Martin, Nordet, 1996; Wood and Picard, 2004) in the absence of a recognized aetiology (Nihoyannopoulos and Kisslo, 2009). This disorder can be progressive and have a deteriorating clinical course with a high mortality (Chetty and Mitha, 1990). In addition it can occur at any age and is characterized by congestive heart failure (CHF) (Armstrong and Ryan, 2009). Once patients have developed symptoms, their prognosis is poor (Armstrong and Ryan, 2009). According to Armstrong and Ryan (2009), most studies show a mortality rate of 50% at one year and 75% at two years. The mode of death is either, sudden death, CHF or arrhythmia.

In most studies, 47% of cases of DCMO are idiopathic, which means specific causes cannot be identified (Fogoros, 2007). The generalized dilatation of the 4 chambers and the global ventricular dysfunction can cause stasis in any cardiac chamber (Fuseno, Mukai, Nakamura, Yoshikawa, Shomura, 1991). As a consequence, these patients have a high incidence of intracardiac thrombi,

particularly in the left ventricle (LV). Left ventricular thrombus is a common finding in patients with DCMO (Fuseno *et al*., 1991) to the extent that studies have found that LV thrombi are found in about 60% of these patients (Regitz and Rudolph, 1985). The consequences of LV thrombus formation are cardioembolism which can result in stroke or acute limb ischaemia (Crawford, 2002).

Many authors such as Nihoyannopoulos *et al* (2009), Choi *et al* (2010) and Wood *et al* (2004) have agreed that echocardiography has an important role in the detection of LV thrombus (Nihoyannopoulos and Kisslo, 2009; Choi, Jeong, Yang, Kang, Jun, Lee, Huh, 2010; Wood and Picard, 2004). Echocardiography can quickly establish the diagnosis of LV systolic dysfunction and demonstrate ventricular dilatation (Nihoyannopoulos and Kisslo, 2009). It is noninvasive, cost effective and relatively widely available in South Africa. However, serial monitoring for LV clot detection is not cost effective. Furthermore, it may not always be clinically meaningful if patients are seen every 6 months or even annually at specialist care level in South Africa.

Therapy for LV clot formation in South Africa, at this stage, implies the use of the anticoagulant drug, warfarin, which can be very effective in preventing and treating LV clots. Treating every patient will certainly reduce the mortality and morbidity associated with cardioembolism (Kelley and Minagar, 2003). However, there are a number of problems with such a strategy, in that it exposes all patients with IDCMO to the side effects of warfarin which includes major, at times, life threatening bleeding (Baker and Wright, 1994). Furthermore, it implies that monitoring patients' therapy with International Normalized Ratio (INR) measurements would be crucial. This adds to the cost of patient care and can cause significant problems for patients from outlying areas that may not have access to a laboratory service.

Hence, the ideal would be to identify patients with IDCMO who are at high risk for LV clot formation and treat them with warfarin prophylactically. To do this, one needs to know the prevalence and ideally the incidence of LV clot formation in IDCMO patients in South Africa and then determine if a risk model can be created to identify patients who would benefit most from warfarin. Thus, this study intended to prospectively evaluate patients with IDCMO to determine the prevalence and the clinical and echocardiographic predictors of LV thrombus in patients with IDCMO.

CHAPTER TWO: STUDY BACKGROUND AND LITERATURE REVIEW

2.1 Study background

2.1.1 Definition of IDCMO

Dilated CMO is a disorder involving the heart muscle. It is defined by the presence of a poorly functioning and dilated LV in the absence of abnormal loading conditions, such as hypertension (HPT), valvular disease or ischaemic heart disease (IHD) sufficient to cause global systolic impairment. If no identifiable cause is found it is referred to as idiopathic DCMO (Elliot, 2000; Davies, 2000).

The WHO/International Society and Federation of Cardiology Task Force suggested the term CMO be reserved for heart muscle diseases of unknown origin. A more recent report of the WHO/International Society and Federation of Cardiology Task Force suggests that cardiomyopathies be classified by their dominant pathophysiology, or if possible by the aetiologic/pathogenetic factor (McKenna, 1996). There has been some confusion surrounding CMO definitions and nomenclature. Classification schemes have proven to be exceedingly complex. Dilated CMO is characterized by ventricular chamber enlargement and systolic dysfunction with normal LV wall thickness (Davies, 2000). Usually diagnosis is made with 2D echocardiography (Mestroni, Maisch, McKenna, Schwartz, Charron|, Rocco, Tesson, Wilke, Komajda, 1999). Dilated CMO may be related to secondary causes or it may be idiopathic (Table 1) (Elliott, 2000).

Table 1 Known causes of DCMO (Elliott, 2000)

Young
Myocarditis (infective/toxic/immune)
Carnitine deficiency
Selenium deficiency
Anomalous coronary arteries
Arteriovenous malformation
Kawasaki disease
Endocardial fibroelastosis
Non-compacted myocardium
Calcium deficiency
Familial IDCMO
Barth syndrome
Adults
Familial IDCMO
X linked
Alcohol
Myocarditis (infective/toxic/immune)
Tachycardiomyopathy
Mitochondrial
Arrhythmogenic right ventricular cardiomyopathy
Eosinophilic (Churg Strauss syndrome)
Drugs – anthracyclines
Peripartum
Endocrine
Nutritional – thiamine, carnitine deficiency, hypophosphataemia, hypocalcaemia

2.1.2 The importance of IDCMO as a cause of HF

The dominant causes of death and disability in Africa remains mostly nonischaemic (Sliwa *et al*., 2005). Idiopathic DCMO is second to valvular heart disease as a cause of CHF in blacks in southern Africa (Chetty and Mitha, 1990). Dilated CMO, along with rheumatic heart disease and HPT, is one of the leading causes of HF in Africa (Sliwa *et al*., 2005). Dilated CMO is endemic in Africa and has several causes. The most common cause is idiopathic, some of which might be due to burnt-out untreated HPT (in which, after HF, blood pressure falls to normal therefore hindering diagnosis) (Stewart, Wilkinson, Hansen, Vaghela, Mvungi, McMurray, Sliwa, 2008). Idiopathic DCMO was more prevalent than HPT-related CMO in blacks compared with other race/ethnic groups (Albert, 2008).

2.1.3 Consequences and its impact on mortality and morbidity

Regarding DCMO, when LV dysfunction is severe, stasis of blood flow within the heart can occur. This stasis promotes thrombus formation. A possible consequence of LV thrombus is cardioembolism and CHF. A possible consequence of cardioembolism is an embolic stroke. The degree of LV dysfunction correlates with the risk of CHF and the risk of stroke correlates with the severity of LV dysfunction (Kelley and Minagar, 2003). In many industrial countries, stroke is the leading cause of death. Cardiogenic embolism is responsible for 15% to 30% of ischaemic strokes with about two thirds of these embolic events leading to serious morbidity or death (Kelley and Minagar, 2003; Stratton, 1989). Cardiogenic sources of emboli must be identified as soon as possible because the outcome after cardiogenic stroke is particularly poor, with 50% mortality after 3 years (Pepi, Evangelista, Nihoyannopoulos, Flachskampf, Athanassopoulos, Colonna, Habib, Ringelstein, Sicari, Zamorano, 2010).

2.1.4 Prevalence and incidence

The incidence of IDCMO is difficult to quantify due to a lack of reliable epidemiological evidence. However, an American study claimed that the prevalence of IDCMO varies from 36 per 100,000 in the United States to 14 per 100,000 in Japan (Cooper Jr., 2005). In the United Kingdom, the incidence rate is 0.87 cases per 100,000 individuals (Andrews, Fenton, Ridout, Burch, 2008).

Cardiomyopathy is one of the major causes of cardiovascular disease (CVD). Although the causes of HF due to CMO vary within and between African countries, the pathogenesis remains mostly nonischaemic (Sliwa *et al*., 2005). In South Africa, DCMO accounts for 10% to 17% of all cardiac conditions encountered at autopsy (Sliwa *et al*., 2005). Between 17% and 48% of patients are hospitalized for HF. However, there are no population based data on the burden of DCMO in Africa (Sliwa *et al*., 2005). Dilated and peripartum cardiomyopathies and endomyocardial fibrosis account for 20% of all cases of HF in the sub- Saharan Africa and idiopathic DCMO is second to valvular heart disease as a cause of CHF in blacks in southern Africa (Fogoros, 2007). In about 50% of patients presenting with a DCMO, no definite cause is identified, even after a detailed history, physical examination and laboratory evaluation, including a heart biopsy. This represents a deficiency in the ability to understand the nature of this heart muscle dysfunction at a cellular and subcellular level (Fogoros, 2007).

2.1.5 Symptoms, prognosis and treatment

Most patients with IDCMO are between 20 and 50 years of age, but the disorder can also strike children (Davidson, Haslett, Chilvers, Boon, Colledge and Hunter. 2002). Men are affected more than twice as often as women. Although IDCMO can exist at any age, morbidity and mortality rates rise sharply with age and are

highest in the elderly (Baughman, 2006) (Chen, Sanderson, Mayosi, Yusuf, Reddy, Hu, Timmis, 2007). The natural history of DCMO remains incompletely understood. This is because the diagnosis clearly contains a variety of aetiologies and patients have variable presentations. Patients' presentation can range from asymptomatic LV dysfunction to mild, moderate or severe CHF (Crawford, 2002). Patients with IDCMO will more typically present with signs and symptoms of pulmonary congestion and/or low cardiac output (CO), often accompanied by fatigue on exertion. However, the first presentation of IDCMO may be systemic embolism or sudden death (Elliott, 2000) which may occur at any stage (Davidson *et al*., 2002). Once patients with DCMO have developed symptoms, their prognosis is usually poor (Armstrong and Ryan, 2009). Most studies show a mortality rate of 50% at one year and 75% at two years (Armstrong and Ryan, 2009). The mode of death is either progressive irreversible HF or arrhythmia (Armstrong and Ryan, 2009).

The outlook for people with DCMO has improved significantly in the last ten years due to new drug treatments such as ACE (angiotensin converting enzyme) inhibitors and beta-blockers (Elliott, 2000). Some patients are considered for implantation of a cardiac defibrillator and/or cardiac resynchronization therapy (Davidson *et al*., 2002). A cardiac transplantation is actually the only viable alternative if myocardial injury persists or if conventional treatment does not alleviate the symptoms (Mahon, Parker, Wehbi, Douglass, 2002). A number of clinical and diagnostic measures may be monitored to predict prognosis (Mahon *et al*., 2002). The best predictors are the New York Heart Association (NYHA) failure functional class, the LVEF and the peak oxygen consumption (Mahon *et al*., 2002).

2.1.6 Thrombus formation in IDCMO

The natural history of LV thrombus complicating DCMO is unclear because no clinically obvious event identifies the initiation of thrombus formation (Crawford,

2002). Patients with DCMO have ventricular dilatation with diffuse hypokinesia. Diffuse hypokinesia causes a decline in left ventricular ejection fraction (LVEF). Low ejection fraction (EF) causes an elevation in LV filling pressures and a reduction in stroke volume (SV) with a consequent reduction of systolic blood flow. Low CO, abnormal flow with low intraventricular velocities passing through dilated and poorly contracting cardiac chambers may all predispose to intracardiac thrombus formation because of relative stasis of blood within the LV cavity (Lip, 1996; Nihoyahhopoulus and Kisslo, 2009). This thrombus within the LV cavity predisposes patients to subsequent thromboembolism (Lip, 1996; Nihoyahhopoulus and Kisslo, 2009). The underlying mechanisms for thrombus formation in patients with DCMO are complex and multifactorial and most likely involve mechanical (low velocity in the LV) and the activation of haemostatic factors that interact together in a cooperative manner (Mohr, Choi, Grotta, Weir, Wolf, 2004). The intracavitary flow velocity is chronically reduced in these patients. Therefore, the risk of thrombus formation is constant (Mohr *et al.*, 2004).

LV thrombus formation has been associated with Virchow's triad (Lip, 1996). Virchow's triad represents 3 factors that are thought to lead to the development of thrombosis (Lip, 1996).

The three components consist of:

(1) Abnormalities in the blood vessel wall which include injuries to the vascular endothelium and the endocardium (Lip, 1996).

(2) Abnormalities of blood constituents which involve imbalance between procoagulant and anticoagulant factors which increases the tendency of blood to coagulate (Chung and Lip, 2003/2004).

(3) Abnormalities in blood flow; the most common being blood stagnation (Özdemir, Kaymaz, Daglar, Karakaya, Akcay, Özkan, 2002; Lip, 2004).

Abnormalities in haematological function and prothrombotic markers intrinsic to LV dysfunction may contribute to the thromboembolic risk in patients with cardiac

impairment (Lip, 1996). Many studies suggest that there is increased thrombogenesis or a hypercoagulable state in patients with cardiac impairment (Lip, 1996).

A study by Jafri *et al* (1993) found that, regardless of the aetiology, patients with HF show significant abnormalities in platelet activation, reflected by the platelet factor 4 (pf4), beta- thromboglobulin and markers of haemostasis such as thrombin-antithrombin 4 complex (TAT4), fibrinopeptide A and fibrin D-dimer (Lip, 1996; Ozawa, Manmmen, Levine, Johnson, Goldstein, 1993). Abnormalities of haemostasis were also shown by Sbarouni *et al* (1994), who reported an increase in blood and plasma viscosity, platelet activation, fibrinopeptide A, fibrin D-dimer and von Willebrand factor in patients with HF (Sbarouni, Bradshaw, Andreotti, Tuddenham, Oakley, Cleland, 1994; Lip, 1996). Finally, Yamamoto and co-workers found abnormal haemostasis in a small study of patients with DCMO (Lip, 1996; Jafri, Ozawa, Manmmen, Levine, Johnson, Goldstein, 1993; Sbarouni *et al*., 1994).

Previous studies indicated that proinflammatory cytokines such as interleukin IL-1 and IL-6, tumour necrosis factor (TNF) and their receptors have been contributors to CHF and the underlying process of adverse LV remodeling leading to progressive LV dysfunction (Sosin *et al*., 2003). Proinflammatory cytokines such as IL-6 have been documented to be associated with an increase in LV thrombus formation in peripartum CMO and thus may equally play a role in clot formation in IDCMO (Sosin *et al*., 2003).

Congestive HF in DCMO is associated with abnormalities of flow due to low CO and dilated cardiac chambers, vessel wall (endothelial dysfunction) and abnormalities of blood constituents (abnormalities of platelets and haemodynamics) (Sosin *et al*., 2003). Thus, it fulfils all of Virchow's triad of characteristics of a prothrombotic state (Sosin *et al*., 2003).

2.2 Literature review

2.2.1 Prevalence of thrombus in IDCMO

The prevalence of LV thrombus, a well recognized complication of DCMO, differs in various published reports.

Regitz and Rudolph (1985) demonstrated that 60% of those who die with DCMO can be found to have intracardiac thrombi. Takamoto and co-workers (1985) found that 11% (2 of 19) of patients with CMO had mural thrombi. The thrombi noted in the 2 patients with CMO were both remarkably large with partial adhesion to the LV wall and extended well into the LV (Takamoto, Kim, Urie, Guthander, Gordon, Keren, Popp, 1985).

Yokota, Kawanishi, Hayakawa, Kumaki, Takarada, Nakanishi and Fukuzaki, (1989) studied the relationship between LV thrombus and LV dynamics in DCMO, by echocardiography and postmortem examination. The total amount of DCMO patients were 57, 40 were survival patients examined by echocardiography and 17 were autopsy patients. Intracardiac thrombus was detected in 11 of 40 (27%) survival patients and was found in 8 of 17 (47%) autopsy patients.

Coats *et al* (1992), in a study conducted at the Boston City Hospital, performed 2D echocardiograms in 21 patients with non ischaemic DCMO to determine the prevalence of LV thrombus in DCMO. All these patients were not receiving anticoagulation. A LV thrombus was present on initial echocardiogram in 11 (44%) patients. Thrombus became present during follow-up in an additional 4 and disappeared in 2 (Coats, Falk, Foster, 1992). In a study by Gottdiener *et al* (1983), 123 patients (average age 56 +/- 6 years) with chronic DCMO were studied for the presence of LV thrombus. On 2D echocardiography, thrombus

was present in 44 patients (36%) (Gottdiener, Gay, VanVoorhees, DiBianco and Fletcher, 1983).

2.2.2 Thrombus detection by echocardiography

Echocardiography can quickly establish the diagnosis of DCMO by demonstrating LV systolic dysfunction and by demonstrating ventricular dilatation (Nihoyannopoulos and Kisslo, 2009). Echocardiography serves as a noninvasive tool for establishing the presence and type of CMO and may provide information regarding its aetiology (Wood and Picard, 2004). The diagnosis of CMO, however, is more of a diagnosis of exclusion and ruling out CAD is essential (Nihoyannopoulos and Kisslo, 2009).

Echocardiography can also be used to accurately characterize the physiological abnormalities associated with CMO and 2D echocardiography has been confirmed to be an essential tool in the detection of LV thrombi (Choi *et al*., 2010). The American College of Cardiology/American Heart Association guidelines for management of CHF, consider echocardiography a Class I diagnostic test, implying that it is generally indicated and useful in all patients with CHF and suspected CMO (Pepi *et al*., 2010).

Left ventricular thrombus is defined as an echogenic mass in the LV with margins that are distinct from the endocardium and seen throughout diastole and systole (Figure 1). It may be homogeneously echogenic or have a heterogeneous texture with a central lucency (Pepi *et al*., 2010). Thrombi usually appear in 2D echo examination as dense intracavitary echoes and the apical 4 chamber view has been found to be the most useful view to diagnose LV thrombus (Choi *et al*., 2010). Masses may be laminar, immobile (fixed along LV wall) or pedunculated (Armstrong and Ryan, 2009). The thrombus may appear to move with the underlying myocardium or, more often, only a portion of the thrombus is mobile. They are most commonly situated in the LV apex or adjacent to the anterior wall.

Therefore it is critical to image the apex (Pepi *et al*., 2010).

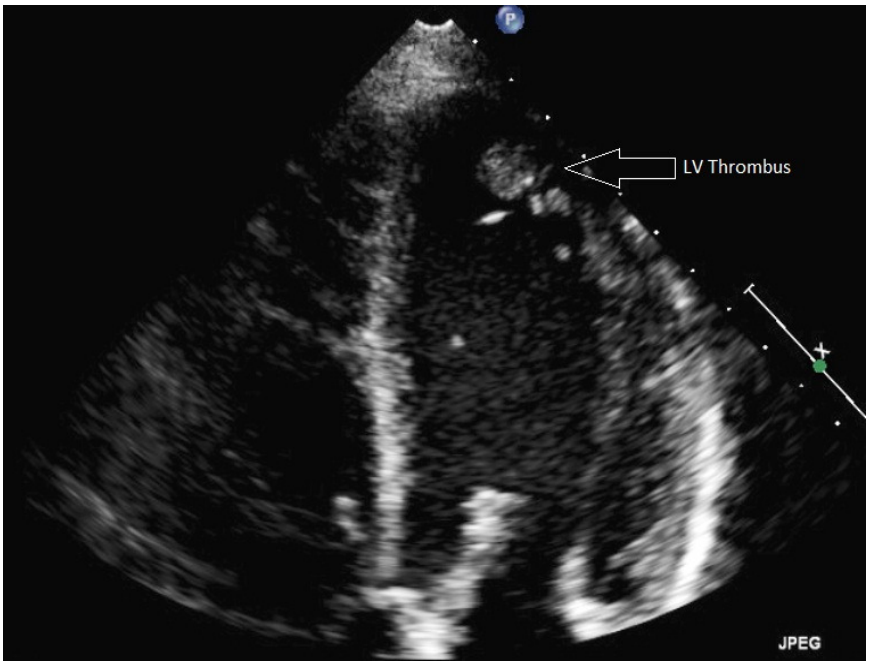

Figure 1 LV thrombus (Baragwanath Hospital, 2010)

The likelihood of subsequent embolic events increases with thrombi that are either pedunculated or mobile (Armstrong and Ryan, 2009). Mobility tends to be seen in fresher rather than chronic thrombi (Armstrong and Ryan, 2009). Chronic thrombi are likely to be covered completely by an endothelial layer and presumably have a relatively low embolic potential (Armstrong and Ryan, 2009). Embolic rates are increased to 40% when pedunculated or mobile thrombi are involved (Armstrong and Ryan, 2009). It has been noted that the duration of intracardiac thrombus is a valid factor in thromboembolism (Armstrong and Ryan, 2009). A recently formed, poorly attached thrombus is more likely to dislodge than an older thrombus which is likely to be more firmly attached by fibroblastic infiltration (Lip, 1996). Regarding cardioembolism, Lip (2006), found that size or location of thrombus were not as important as thrombus mobility, adjacent hyperkinesis and thrombus protrusion.

For the detection of LV thrombus, echocardiography has several limitations. Of all echocardiographs performed, 5% to 10% can be technically poor. This means that the presence of thrombus cannot always be adequately excluded (Armstrong and Ryan, 2009; Pepi *et al*., 2010). Left ventricular thrombi are sometimes mistaken for anatomical structures such as papillary muscles, false tendons, prominent trabeculations, chest wall or dense apical scars (Armstrong and Ryan, 2009; Pepi *et al*., 2010). This causes "false-positive" studies. Other causes of false-positive studies can be caused by artifacts due to noise or resolution problems or due to reverberation from the echocardiographic transducer. This is the most common false diagnosis of thrombus (Armstrong and Ryan, 2009; Pepi *et al*., 2010).

Furthermore, echocardiography may still miss smaller thrombus (especially those <5 mm in diameter) that may only be seen in transesophageal echocardiography (TEE) and that are still capable of producing strokes and other serious thromboembolic complications (Lip, 1996). However, echocardiography is still the most preferred method for diagnosing LV thrombus as it is relatively inexpensive, widely available and does not expose patients to any harmful radiation (Armstrong and Ryan, 2009). The sensitivity of echocardiography in the detection of LV thrombi has been reported as 77% to 95% and a positive echocardiogram has a specificity of 88% to 95% (Armstrong and Ryan, 2009). In one large study the predictive value of a positive test was 86% and that of a negative test, 98% (Armstrong and Ryan, 2009).

Thrombus may be very difficult to detect if the LV apex is not clearly defined (Pepi *et al*., 2010). This is due to the characteristically wall thinning, the sector angle being 90 degrees and the apex usually being too near the probe in the 4 chamber view (Lip, 1996). A final limitation of echocardiography is that, it provides a snapshot in time. It is unable to reflect thrombus activity, whether or not ongoing thrombogenesis is present (Lip, 1996).

The use of a contrast ultrasound agent (injected intravenously) improves the quality of the image allowing superior thrombus detection (Pepi *et al*., 2010). It will also decrease both the inter-observer and intra-observer variability (Pepi *et al*., 2010). The actual ultrasound machine and frequency of the transducer may also be a study limitation. Furthermore, some patients are technically difficult to echocardiograph due to obesity and chronic obstruction pulmonary diseases (COPD) (Pepi *et al*., 2010).

2.2.3 Predictors of thrombus in IDCMO patients

2.2.3.1 Left ventricular EF as a predictor of thrombus

Many predictors of LV thrombi in DCMO have been studied. Various studies stressed the importance of LV dysfunction as a principal predictor (Crawford, 2002). It has been suggested that patients with severe LV dysfunction tend to have higher rates of LV thrombi and systemic embolisation (Kim and Park, 2009). A decline in EF produces elevated LV filling pressures and a drop in SV with a consequent reduction of systolic blood flow. The reduced SV creates stasis within the LV that promotes thrombus formation and an increased risk of thromboembolic events (Mohr *et al*., 2004).

The Kalaria *et al* (1985) study found that among patients with DCMO, LVEF is the factor most associated with LV thrombus formation (Kalaria, Passannanta, Shah, Modik, Weisse, 1985). Yokota *et al* (1989) found that patients with a cardiac thrombus had a lower EF than patients without a thrombus (25% vs. 39 %, $P<0.001$). In addition, 9 of 11 patients with thrombi had severe apical dyskinesis or akinesis compared with 12 of 29 patients without thrombi ($P<0.05$).

2.2.3.2 End diastolic dimension as a predictor of thrombus

It is plausible that the greater the dilatation of the ventricle the more likely stasis will occur and thus intracavitary flow haemodynamics will be altered, predisposing patients to thrombus formation. However, a literature search using various search engines revealed that no studies found the increased LV internal diastolic dimension to be an independent predictor of LV thrombus in patients with IDCMO.

2.2.3.3 Mitral regurgitation as a predictor of thrombus

Mitral regurgitation (MR) has been shown to decrease the incidence of thrombus formation (Özdemir *et al*., 2002). Lip (1996), claimed that the protective effect of MR may be as a result of increased inflow velocities and may result in a lower tendency for thrombus formation. The Kalaria *et al* (1985) study, involved in the effect of MR on LV thrombus formation found that 10.8% of the patients with DCMO had LV thrombi present. Kalaria *et al* (1985) also found that although MR was equally present in all patients, severe MR was found only in the group of patients that did not have any thrombi. However, not all the patients in the Kalaria *et al* (1995) study presented with IDCMO.

Ninety-one patients with DCMO were studied by echocardiography to detect and quantify MR to record apical flow velocities in systole and diastole; and to detect the presence of LV thrombi (Blondheim, Jacobs, Kotler, Costacurta, Parry, 1991). Thrombus was present in 40% of the patients and MR was detected in 57%, but the occurrence of both MR and thrombus was rare (8%) (Blondheim *et al*., 1991). Apical flow velocity was significantly higher throughout the cardiac cycle in the group with MR ($p<0.001$ for both systole and diastole) (Blondheim *et al*., 1991). Higher apical flow velocities could be the reason for less thrombus in this group (Blondheim *et al*., 1991).

2.2.3.4 Spontaneous echo contrast as a predictor of thrombus

Spontaneous echo contrast (SEC) known as smoke, consists of dynamic, smoke- like echoes with a characteristic swirling motion (Weissman and Adelman, 2004). It is a manifestation of increased red blood cell aggregation seen in slow-flow states (Weissman and Adelman, 2004). The increased amplitude of backscattered ultrasonic signals causes the typical smoke appearance (Weissman and Adelman, 2004). Spontaneous echo contrast has been considered a predisposition to thromboembolism and cerebrovascular accident (CVA). However, there have been few reports on the prevalence and role of SEC in DCMO and the importance of thrombi and SEC in patients with DCMO is uncertain.

Between October 2001 and January 2008, transthoracic echocardiography with tissue harmonic imaging (THI) was performed by Gottdiener *et al* (1983), for the recognition of SEC in patients with DCMO. Twenty four patients (10.9%) had SEC in the LV. Gottdiener and co-workers (1993) divided their cohort of patients into 2 groups, one with SEC and the other group without SEC. In this study all the patients with SEC were diagnosed without thrombi in the LV. There were no significant differences in other echocardiographic findings, including LVEF, between the two groups (Gottdiener *et al.,* 1983). Stroke occurred in 4 (16.7%) of patients with SEC and in 9 (4.6%) of patients without SEC. The findings of this study suggest that SEC has a strong association with stroke in patients with DCMO (Kim and Park, 2009).

2.2.3.5 Warfarin as a predictor of thrombus

Since 1950, there have been arguments concerning the effectiveness of anticoagulation treatment for preventing the formation of thrombi and subsequently embolic events in high risk patients (Gowal, 2000-2001). Conflicting views was found in the literature regarding anticoagulation in DCMO

patients as a debate exists on the effects of anticoagulants on the risk of embolisation.

Anticoagulants prevent blood from clotting or they prolong the time taken for blood to clot. This reduces the possibility of thrombus, thus reducing thromboembolic episodes of cardiogenic origin (Gowal, 2000-2001). Warfarin is a coumarin anticoagulant and remains the drug of choice to control and prevent thromboembolic disorders (Sagar, Kumar, Shah, Bhatnagar, 2006). Many patients with intracardiac thrombi are prescribed warfarin to treat an existing thrombus, to prevent a thrombus from forming and/or to prevent a clot from embolising (Gowal, 2000-2001). However, warfarin may cause life-threatening bleeding. This medication has a complex dose-response relationship and patients treated with warfarin require close monitoring to avoid bleeding (Sagar *et al*., 2006). Warfarin therapy may also be dangerous because of its narrow therapeutic index and large inter-individual variability in patient response (Sagar *et al*., 2006). However, studies by Sagar *et al*. (2006), have indicated that warfarin has been shown to prevent 20 strokes for every bleeding episode associated with its use.

The goal of anticoagulant therapy is to administer the lowest possible dose of anticoagulant to prevent clot formation/expansion while avoiding complications (Sagar *et al*., 2006). For most indications, the dose is adjusted to maintain the patient's INR at 2 to 3 (Sagar *et al*., 2006). Interactions with other drugs, patient's nutritional status and gender must be considered (Sagar *et al*., 2006). At present there is no trial data to guide anticoagulant treatment in IDCMO, but warfarin is advised in patients with a history of thromboembolism or evidence of intracardiac thrombus (Elliott, 2000). Patients with more than moderate to severe systolic dysfunction should also be advised to take warfarin (Elliott, 2000).

Landefeld and Beyth (1993) summarized randomized trials producing estimates of the risk for bleeding during anticoagulant therapy. The average annual

frequencies of fatal, major, and minor bleeding during warfarin therapy were 0.6%, 3.0%, and 9.6%, respectively and these frequencies are approximately 5 times more than those expected without warfarin therapy (Landefeld and Beyth, 1993). The risk for bleeding is highest at the beginning of therapy. An individual patient's risk for major anticoagulant-related bleeding can be estimated on the basis of specific risk factors such as the intensity of the anticoagulant effect needed, the presence of serious comorbid diseases, older age and concurrent medicines (Landefeld and Beyth, 1993). Major bleeding most often affects the gastrointestinal tract, soft tissues and urinary tract. Intracranial bleeding is rare, but when it occurs it is frequently fatal (Landefeld and Beyth, 1993).

Studies against anticoagulation:

It has been recognised that thromboembolism is a frequent cause of death in patients with CHF (congestive heart failure), occurring in up to 30% of patients (Lip, 1996). Despite the high incidence, anticoagulant therapy has not been widely used as routine therapy in patients with cardiac impairment. Lip (1996), stated that long-term oral anticoagulation is sometimes used but does not have any proven benefit. This is because there has never been a controlled study of long-term anticoagulation among patients with CHF due to DCMO, showing its efficacy and defining its morbidity (Koniaris and Goldhaber, 1998). Gowal (2000-2001), stated that studies regarding anticoagulation have not been conclusive and that a attempt at a retrospective analysis of the effectiveness of anticoagulation by Sharma and co-workers (2000) had too few patients to draw significant conclusions (Sharma, McCullough, Philbin, Weaver, 2000).

Patients with CHF have a low embolic risk without anticoagulants. In large scale studies, the risk of thromboembolism in clinically stable patients has been low (1-3% per year) (Pepi *et al*., 2010). Even in those with very low LVEF and echocardiographic evidence of intracardiac thrombi, rates are sufficiently low for anticoagulation to be beneficial (Pepi *et al*., 2010). Tsevat *et al* (1989) reported that although the current recommendations for the treatment of DCMO include

long-term anticoagulation to reduce the possibility of systemic embolisation, there have been no clinical trials examining the effectiveness of anticoagulation in this sphere. Furthermore, the issue of quality of life associated with long-term warfarin therapy has not been considered (Tsevat, Eckman, McNutt, Pauker, 1989). Tsevat and colleagues (1989), examined the benefits and risks of long-term anticoagulation for DMCO patients between the ages of 35 and 75 and found that anticoagulant therapy increases quality-adjusted life expectancy by 76 to 128 days (dependent on the patient's age). However, when using sensitivity analysis, the outcome is dependent on the disadvantages associated with long-term warfarin therapy (Tsevat *et al*., 1989). Furthermore, anticoagulation exerts most of its benefit by preventing pulmonary embolisation, and not systemic embolisation. The authors concluded that long-term anticoagulant therapy imposes a lifestyle change and this needs to be addressed. The benefit may not outweigh the sacrifice for some patients (Tsevat *et al*., 1989).

Stratton (1989) stated that the correct therapy for patients with LV thrombus is unclear as the bleeding risk of anticoagulation may outweigh the risk of embolism (Stratton, 1989). Patients who were on long-term anticoagulation had a bleeding risk of 23%, a major bleeding risk of 4.7% and a fatal bleeding risk of 1%. The current practice at the University of Washington is that patients who have thrombi are not treated with warfarin unless they have suffered a previous embolus or unless thrombus protrusion and mobility suggest a high risk of embolisation (Stratton, 1989).

Studies for anticoagulation:

However, the benefits of anticoagulants in patients with DCMO have been reported in many studies, with a reduction in thromboembolic events or a resolution of thrombus on echocardiography (Lip, 1996). Despite the ambivalence regarding the incidence of cardioembolism and the efficacy of

warfarin, many authors recommend the routine use of anticoagulation for patients with HF, even in the absence of atrial fibrillation (AF), systemic embolism or LV thrombus (Baker and Wright, 1994).

Kelley and Minagar (2003) agreed that anticoagulation therapy has been found generally to be the most effective treatment in preventing cardiogenic embolism, but the level of anticoagulation needs to be optimized to reflect the risk-to-benefit ratio for each patient. Anticoagulation at an accepted dosage is associated with a 7 to 10 fold increased risk of intracranial haemorrhage, which translates to roughly 1% per year.

Takamoto *et al* (1985) studied 47 patients with confirmed LV thrombus in 30% of the 47 patients. Presence and absence of anticoagulation treatment was available in 39 of these patients. A significant difference was found in the incidence of thrombi between the patients who had received anticoagulation and those who had not. These results were similar to the findings of Keating and co-workers (Keating, Gross, Schlamowitz, Glassman, Mazur, Pitt, Miller, 1983; Takamoto *et al*., 1985).

Meltzer *et al* (1986) stated that anticoagulation treatment decreases the prevalence of embolisation in IDCMO and should be administered regardless of whether thrombus is detected (Meltzer, Visser, Fuster, 1986). Kyrle *et al* (1985) reported that thromboembolism occurred in 17 of 38 DCMO patients before starting oral anticoagulants, but no thromboembolic events occurred in these patients whilst on anticoagulants (Kyrle, Korninger, Gossinger, Glogar, Lechner, Niessner, 1985). In the study by Meltzer *et al* (1986), none of the patients with DCMO taking anticoagulants had a thromboembolic episode, compared to 14 thromboembolic events in the 104 patients who were not anticoagulated (Meltzer *et al*., 1986). Ciaccheri *et al* (1989) did a follow up study on patients with DCMO and LV thrombus, all of whom were anticoagulated. No patients suffered emboli (Ciaccheri, Castelli, Cecchi 1989).

To conclude, Koniaris and Goldhaber (1998) concluded that although certain groups of patients with CHF have obvious indications for chronic anticoagulation, (previous thromboembolic event, AF and the presence of LV thrombus), evidence from published reports do not demonstrate convincingly that the benefits of anticoagulation exceed the risks in other groups. Moreover, the fluctuating metabolic state of patients with DCMO may predispose to bleeding complications. Patients with DCMO often have a chronically low CO that may impair renal function. Furthermore, they often require many medications that may interact with warfarin.

2.2.3.6 Cardioembolism as a predictor of thrombus

Dilated CMO patients have an increased risk of developing intracardiac thrombus, secondary to stasis of blood (Crawford, 2002). Thrombus provides a substrate for thromboembolic events such as stroke and peripheral artery occlusion (Gowal, 2000-2001). Many predictors of LV thrombi in DCMO have been studied. Various studies stressed the importance of previous thromboembolism events as a predictor (Crawford, 2002). Cardioembolic strokes are very often more severe than other ischemic strokes, and are associated to a higher mortality (Benavente, Calleja, de la Vega, Garcia, Lahoz, 2010). Primary prevention of cardioembolic strokes from cardioembolic sources is essential due to cardioembolic strokes being largely preventable (Schneck, Lutsep, Xu, Hogan, 2011). Secondary prevention is also important because once stroke due to cardiac embolism has occurred; the likelihood of recurrence is relatively high for most cardioembolic sources (Schneck *et al*., 2011). A literature search using various search engines revealed that no studies found previous cardioembolism an independent predictor of LV thrombus in patients with IDCMO.

However, a vast amount of literature was found on the subject of left ventricular thrombus as a predictor for cardioembolism, although many conflicting views was found in this literature

2.2.3.7 Left ventricular thrombus as a predictor of cardioembolism

Patients with DCMO have multiple factors that predispose to LV thrombus and thromboembolic events and in recent literature, an increase in thromboembolic events have been reported in patients with DCMO. Table 3 indicates the factors that influence the likelihood of thromboembolism of intracardiac thrombi in patients with a low LVEF.

Table 2: Factors influencing the likelihood of thromboembolism of intracardiac thrombi in patients with cardiac dysfunction (Lip, 1996)

Mechanical factors, including structural abnormalities (e.g., aneurysm formation)
Flow abnormalities in a dilated ventricle with a low EF
Duration of thrombus – recently formed, poorly attached thrombus is more likely to embolise
The mobility and protrusion of intracardiac thrombus
Whether significant global hypokinesis is present
Rhythm abnormalities, especially AF
Valve disease
Abnormalities of haemostasis, suggesting a 'hypercoagulable' state

Although there are a high percentage of patients with DCMO that have intracardiac thrombi, the correlation of these findings with evidence of systemic embolism is still controversial and reports of the incidence of thromboembolic events in this population vary widely (Koniaris and Goldhaber, 1998). Table 4 summarises the incidence of cardioembolism in patients with CHF not receiving anticoagulants.

Table 3 A summary of studies regarding incidence of cardioembolism in patients with CHF (Baker and Wright, 1994)

Incidence of Arterial Thromboembolism in Patients With Congestive Heart Failure Not Receiving Anticoagulants*

Study	Study Years	Inclusion Criteria	No.	Age, y	Male, %	Mean EF	Atrial Fibrillation, %	Mean Follow-up, y	Arterial Thromboembolism	
									% of Patients	Incidence (per 100 Patient-years)
Massumi et al[1]	1960-1963	Idiopathic dilated cardiomyopathy	50	NR	80	NR	30	NR	8	NR
Fuster et al[2]	1960-1973	Idiopathic dilated cardiomyopathy	104	49	62	NR	23	11.0	18.0	3.5
Segal et al[3]	1961-1978	Idiopathic dilated cardiomyopathy	115	NR	62	NR	19	NR	12	NR
Hatle et al[4]	1962-1972	Signs of myocardial disease	106	NR	71	NR	36	NR	18.8	NR
Ciaccheri et al[5]	1980-1987	Idiopathic dilated cardiomyopathy, clinical CHF	126	54	75	0.30	12	3.5	4.5	1.4
Gottdiener et al[6]	NR	LV dilation and diffuse hypokinesis, no LV thrombus	58	56	100	NR	NR	2.0	10.0	5.3†
Roberts et al[7]	1959-1981	Chart review and autopsy study for cases of idiopathic dilated cardiomyopathy	131	45	72	NR	25	4.5	11.0‡	2.6†
Kyrle et al[8]	NR	CHF, cardiomegaly, or decrease fractional shortening on echocardiogram; referred to thrombosis service	38	49	89	NR	NR	1.1	42.0‡	42.4‡

Earlier autopsy studies report a very high frequency of thromboembolic events, ranging from 37 to 50%. In an autopsy study, Roberts and co-workers (1987) found a frequency of 11% of thromboembolic events in patients not taking warfarin and an incidence of 3 events per 100 patient-years (Roberts, Siegel, McManus, 1987; Baker and Wright, 1994).

In a retrospective study of 104 patients with nonischaemic DCMO, Meltzer and co-workers reported an 18% frequency of thromboembolic events in patients not taking warfarin and an incidence of 4 events per 100 patient-years (Meltzer *et al.*, 1986; Gowal, 2000-2001). Ciaccheri and co-workers, on the other hand, found a lower incidence than *Meltzer* and co-workers. Ciaccheri and co-workers also studied the association between intracavitary thrombosis and systemic embolism in 126 consecutive patients with IDCMO. Embolic events occurred in 12 patients (9.5%). Intracardiac thrombosis was detected at the onset of the study in 7 patients and detected in 5 more during follow up. The occurrence of new embolic

events in patients not taking anticoagulants was 1-4 events for every 100 patient-years. None of the patients with thrombi had embolic complications and none of those with embolic events had thrombi. This study reported that there were no statistically significant differences in the clinical and echocardiographic findings between the patients with embolic events and those without. Ciaccheri *et al* (1989) concluded that the presence of intracardiac thrombi detected by echocardiography is not predictive of systemic embolism in patients with IDCMO. Possible reasons are that the patients did not have severe DCMO or because the 2D echocardiography did not detect all the thrombi (Ciaccheri *et al*., 1989; Baker and Wright, 1994; Meltzer *et al*., 1986)

The studies by Massumi *et al* (1965), Segal *et al* (1978) and Hatle *et al* (1976) reported the percentage of patients, who had suffered an arterial embolism, but the mean follow-up period was not reported and the incidence of embolic events could not be calculated (Massumi, Rios, Gooch, Nutter, De Vita, Datlow, 1965; Segal, Stapleton, McClellan, Waller, Harvey, 1978; Hatle, Orjavik, Storstein, 1976).

Baker and Wright (1994) reviewed literature regarding the incidence of arterial thromboembolism in patients with HF not receiving anticoagulants. The incidence of arterial thromboembolism ranged from 0.9 to 5.5 events per 100 patient-years, with the largest studies reporting an incidence of 2.0% and 2.4%. Findings regarding the relationship between ventricular function and thromboembolic events were contradictory.

In Segal *et al* (1978) and Kyrle *et al's* (1985) studies, the risk of arterial thromboembolism was greater in patients with low LVEF, although the association was not significant. Segal *et al* (1978) separated study patients by their heart size on chest roentgenogram. Eleven percent of patients with trivial or mild cardiac enlargement suffered systemic emboli compared with 16% of those with moderate to severe enlargement (not significant). Kyrle *et al* (1985) used

echocardiography to investigate the association between arterial embolism and the severity of LV dysfunction. The risk of embolism for patients with severe, moderate or mild LV dysfunction was 67%, 47%, and 20%, respectively. Ciaccheri *et al* (1989) found that the 12 patients in their study who suffered arterial emboli had a mean LVEF of 24% compared with a mean EF of 30% for those without thromboembolic complications (Baker and Wright, 1994; Ciaccheri *et al*., 1989; Kyrle *et al*., 1985; Segal *et al*., 1978).

CHAPTER THREE: MATERIALS AND METHODS

3.1 Aims and objectives

The principle objective of this study was to determine the prevalence of LV thrombus in IDCMO patients using echocardiography. The predictors were divided into echocardiographic and clinical predictors. The proposed echocardiographic predictors of LV thrombus evaluated, were LVEF, degree of MR, LVEDD and the presence of SEC. The clinical predictors were the use of warfarin and past cardioembolic events.

3.2 Sample selection

From May 2009 to September 2010, 114 were referred to the CMO clinic at Chris Hani Baragwanath hospital, which is a referral clinic for patients with CMO. All patients underwent a clinical evaluation and a screening echocardiogram and were either accepted into the clinic or referred back to their referring doctor. All patients with DCMO were enrolled into the BADCMO registry, which is a prospective registry, looking at the 5 year clinical outcomes of patients with IDCMO. All patients who entered this registry were interviewed and informed about this study in their local language. If they fulfilled the inclusion and exclusion criteria (Table 5) and offered voluntary consent they were enrolled into the study. Seventy patients were accepted. Permission was obtained from the hospital superintendent and the study was approved by the local Ethnics Committee (University of the Witwatersrand) as well as the DUT ethics committee. The recruitment period was from May 2009 to September 2010. All patients were followed up at the CMO clinic after accepting to participate in this study.

Table 4: Inclusion and exclusion criteria of this study

Inclusion criteria
Age ≥ 18 and ≤ 80 years
LVEF < 45% and an end diastolic diameters (EDD) of 52 mm on echocardiography
Exclusion criteria
Significant organic valvular disease
History or evidence of ischaemic disease/CAD
Renal failure
Co-morbid cancer
HPT (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 100 mmHg)
HIV (human immune deficiency virus)
Pregnancy or any underlying cause for DCMO (known secondary forms of DCMO)

3.3 Study design

This was a prospective single centre descriptive study. It was a cross sectional study of 70 patients with IDCMO, presented at the cardiac clinic at Chris Hani Baragwanath Hospital in Gauteng.

3.4 Clinical assessment

All patients were subjected to a clinical examination and were interviewed by a medical officer to obtain a medical history. Medical history information included clinical characteristics such as the patient's current alcohol consumption, family history of cardiac disease, previous cardioembolism and transient ischaemic

attacks (TIA). The functional capacity of each patient was determined according to their NYHA classification.

The classification of previous cardioembolic events was made on the basis of medical records and personal interviews. Height and weight was obtained to calculate the body mass index (BMI) and body surface area (BSA). Information regarding the presence of anticoagulation treatment was available for all the patients. However, information regarding dose, duration and interruption of anticoagulation treatment was not uniformly obtained in this study.

3.5 Protocol

All patients underwent a clinical examination, a 12-lead electrocardiogram (ECG) and an echocardiographic assessment. All patients were interviewed by a medical officer to obtain a history of their medical information.

3.6 Electrocardiography

Twelve-lead electrocardiographic recordings were made using a Philips, Page Writer Trim II ECG Recorder. The ECG was done in the supine position according to current standard procedure. The 12-lead ECG was subjected to blinded coding according to published Minnesota criteria (Prineas, Crow, Blackburn, 1982) to document any clinical abnormalities relating to wave form abnormalities (e.g. changes indicative of LV hypertrophy), conduction (e.g. left bundle- branch block) and most importantly cardiac rhythm, for e.g. AF. Electrocardiography analysis is important to confirm the exclusion of any patients with ischaemic DCMO. Furthermore, arrhythmias will also impact on the technical aspect of echocardiography.

3.7 Echocardiographic assessment

All echocardiographic studies were performed by 2 operators according to the standardized research protocol at Chris Hani Baragwanath hospital (see Appendix C) on a Phillips Sonos 5500 IE 33 machine attached to a S-5-1 transducer (frequency transmitted – 1.7 MHz, frequency received – 314 MHz).

To obtain accurate linear measurements of the LV internal dimensions, recordings were made from the parasternal long axis acoustic window in end diastole. Direct 2D minor-axis dimensions were used. The upper limits of normal for the LVEDD was 52 mm. Ejection fraction was measured using modified Simpson's method in the 4 chamber apical view (Lang, Bierig, Devereux, Flachskampf, Foster, Pellikka, Picard, Roman, Seward, Shanewise, Solomon, Spencer, Sutton, Stewart, 2005). For optimum views, echocardiograms were performed with the patient in a partial left lateral decubitus position. All echocardiograms were then transferred to an Xclera workstation where offline measurements and analysis was conducted. A senior cardiologist reviewed all measurements done offline by the investigator and all results were then exported to an Excel database (Microsoft Excel 2003).

All echocardiographic measurements were made according to the American society of echocardiography (ASE) guidelines for chamber quantification (Lang *et al.*, 2005) and the valvular regurgitation guidelines (Zoghbi, Enriquez-Sarano, Foster, Grayburn, Kraft, Levine, Nihoyannopoulos, Otto, Quinones, Rakowski, Stewart, Waggoner and Weissman, 2003).

3.7.1 End diastolic dimension

To obtain accurate linear measurements of the LV's internal dimensions, recordings were made from the parasternal long-axis acoustic window (Figure 2). The EDD was measured at the level of the LV minor axis, approximately at the

mitral valve (MV) leaflet tips. These linear measurements were made directly from 2D images (Lang *et al*., 2005). The direct 2D minor-axis dimensions are smaller than the M-mode measurements with upper limits of LVEDD being 52 mm versus 55 mm. Left ventricular EDD was measured at the end of diastole. End diastole can be defined at the onset of the QRS complex, but is preferably defined as the frame after MV closure or the frame in the cardiac cycle in which the LV is at its largest (Lang *et al*., 2005).

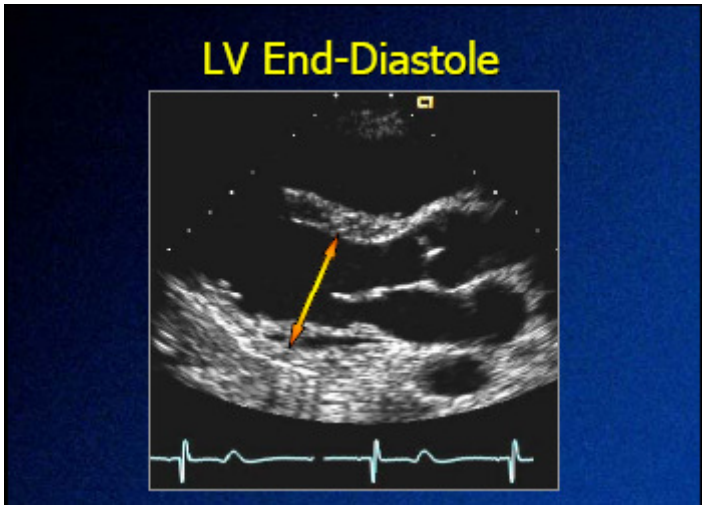

Figure 2 Measurement of EDD in long parasternal axis (Lang *et al*., 2005)

3.7.2 Left ventricular ejection fraction

In this study, EF was measured using modified Simpson's method in the 4 chamber apical view (Figure 3). Modified Simpsons' rule uses 2D measurements for volume calculation using biplane method of disks. This requires manual tracing of the endocardial border. It is recommended that the basal border of the LV cavity area be delineated by a straight line connecting the MV insertion at the lateral and septal borders of the annulus on the 4 chamber view (Figure 3). Measurements are made at the end of diastole and at the end of systole. End systole is best defined as the frame preceding MV opening or the time in the cardiac cycle in which the cardiac dimension is smallest (Lang *et al*., 2005). When tracing the LV, papillary muscles should be excluded. The LV is then

mathematically divided along its long axis into a series of disks of equal height. Individual disk volume is calculated as height multiplied by disk area where height is assumed to be the total length of the LV long axis divided by the number of disks. The surface area of each disk is determined from the diameter of the ventricle at that point. The ventricular volume is then represented by the total sum of the volume of each of the disks, which are equidistant from each other along the long axis of the LV (Senior and Bhatia, 2008).

Only patients with a LVEF < 45% were accepted in the study. Patients with an EF between 40% and 45% were considered to have mild LV dysfunction and an LVEF between 30% and 40% was described as moderate LV dysfunction. An EF less than 30% was considered severely depressed.

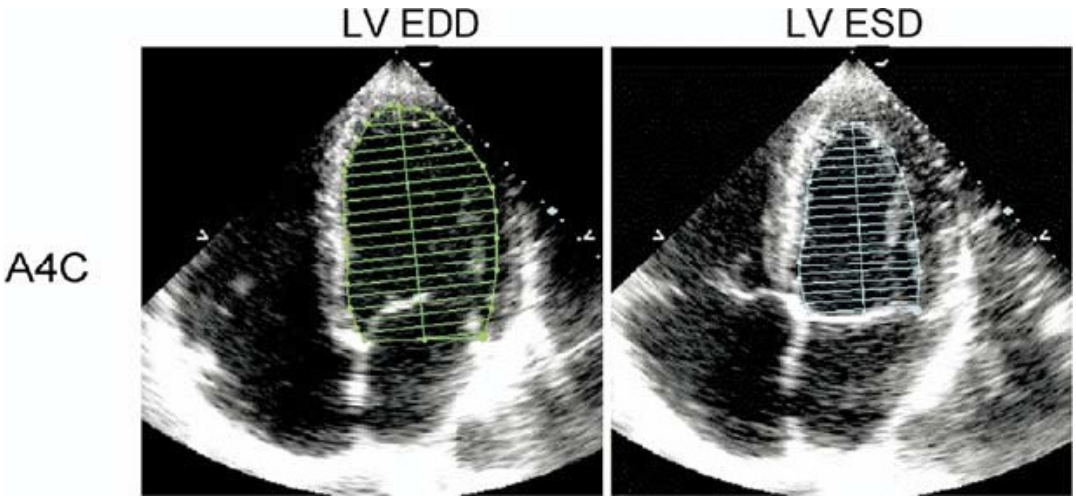

Figure 3 Modified Simpson's method of measuring EF (in apical 4 chamber views at end-systole and end-diastole) (Lang *et al*., 2005).

3.7.3 Mitral Regurgitation

The dilatation and remodeling of the LV will lead to mitral annular enlargement, which will cause the MV leaflets not to connect properly and consequently lead to functional MR (Nihoyannopoulos and Kisslo, 2009) (Figure 4). In patients with MR due to LV dilatation and 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). In functional MR, the leaflets are usually tethered by outward displacement of the LV walls and papillary muscles. This will occur with or without annular dilation (Zoghbi *et al*., 2003). In this study, colour Doppler evaluation of MR was used for the presence/absence of regurgitation and was semi quantitative for estimation of severity (Figure 4). Three grades of severity—mild, moderate, and severe—were identified, taking into account the width and depth of regurgitant jets from different views. Small, non-eccentric jets with an area < 4.0 cm^2 or < 20% of left atrial (LA) area were classified as trivial or mild MR. Moderate MR will have an area between 20% and 40 % of the LA area. Severe MR can be characterized with a large central MR jet (area > 40% of LA) or with a wall-hugging jet of any size, swirling in LA (Zoghbi *et al*., 2003; DeMaria, Sahn, Kisslo and Weyman, 1978)

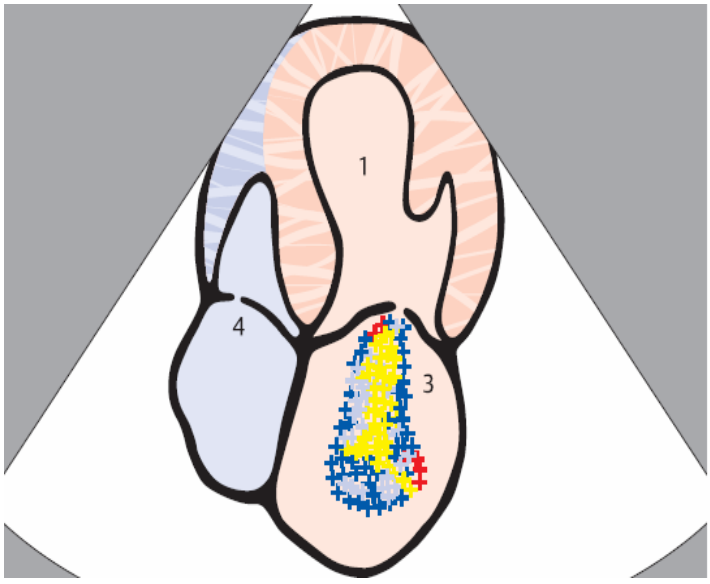

Figure 4 Mitral Regurgitation

Quantification was performed only on moderate and eccentric jets to confirm that severe MR was not misdiagnosed. Several studies have shown that the width of the VC is used in assessing the severity of MR. The vena contracta (VC) was evaluated. Measurement of the VC was done in the left parasternal view (Figure

5). In mild MR, the width of the VC was less than 0.3 cm and no or minimal flow convergence was present (Figure 6). Moderate MR had a VC width between 0.3 cm and 0.5 cm. In severe MR the VC width was more or equal than 0.7 cm with a large flow convergence (Figure 7) (Zoghbi *et al*., 2003).

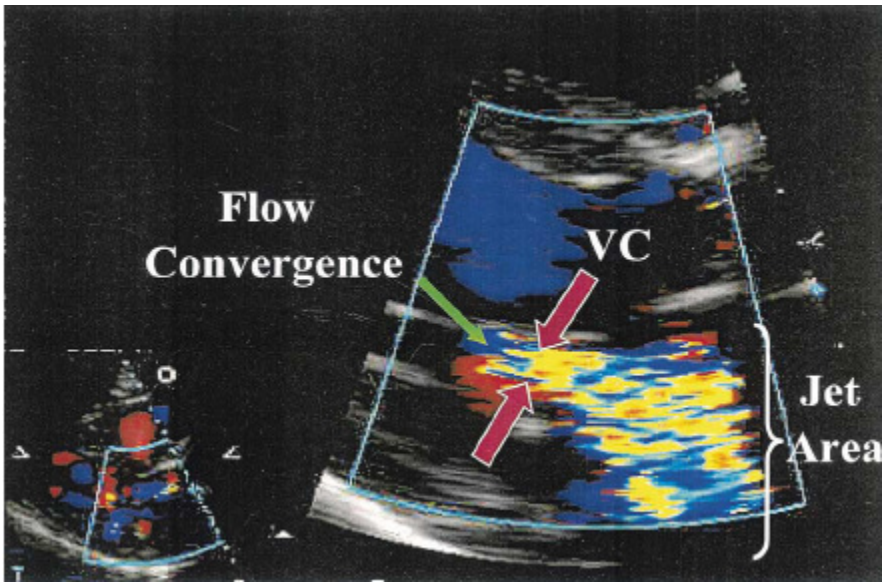

Figure 5 Colour flow recording of a MR jet obtained from a zoomed view in the parasternal long axis. The 3 components of the regurgitant jet are: flow convergence, VC and jet area in the LA. Measurement of the VC is shown between the red arrows (Zoghbi *et al*., 2003).

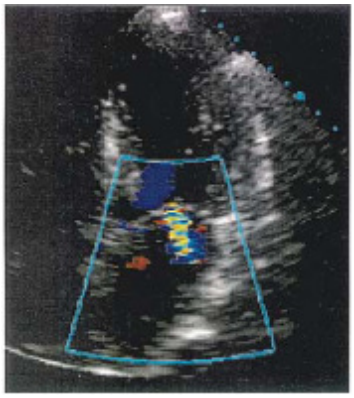

Figure 6 Mild central MR (no flow convergence, a small regurgitant jet area) (Zoghbi *et al*., 2003)

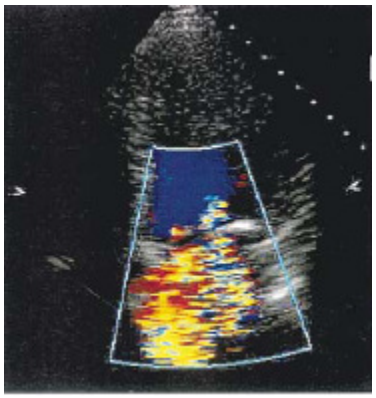

Figure 7 Severe central MR with a prominent flow convergence and a large regurgitant jet area (Zoghbi *et al*., 2003).

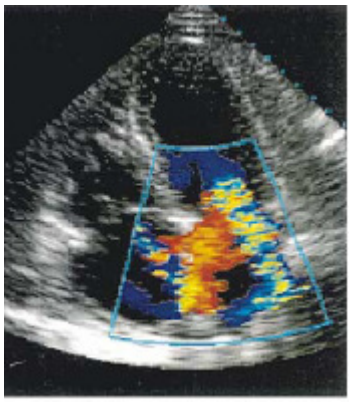

Figure 8 Severe eccentric MR (small jet area impinging on the wall of the LA but a large flow convergence and a wide VC) (Zoghbi *et al*., 2003).

The pattern of the continuous wave (CW) of the MR jet and the pulsed wave (PW) Doppler of the mitral inflow was assessed. If the PW Doppler displayed an "a" wave dominance it was considered unlikely that there was severe MR present.

In terms of the CW jet, the intensity and shape of the jet was used to assess the MR (Figure 9). The density of the CW Doppler signal is a qualitative index of MR severity. A dense signal that approaches the density of forward flow suggests significant MR, whereas a faint signal, with or without an incomplete envelope represents mild or trivial MR, presuming the recording is made through the VC (Zoghbi *et al*., 2003) (Figure 9).

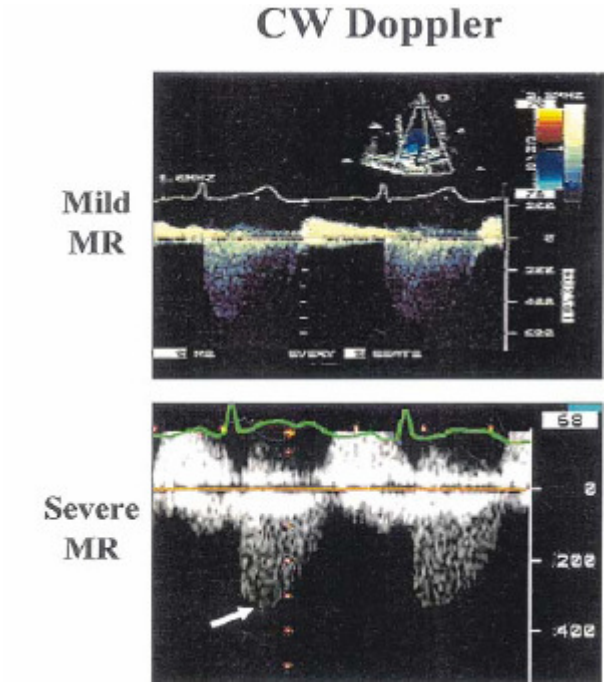

Figure 9 Continuous wave Doppler recordings. In mild MR, the MR jet has a soft density with a rounded contour. In severe MR, the jet is dense with a triangular jet (*arrow*) (Zoghbi *et al*., 2003).

3.7.4 Screening for thrombus

Left ventricular thrombus was defined as an echogenic mass with margins distinct from the ventricular endocardium. It also had to be easily distinguishable from other cardiac structures such as papillary muscles, chordae and trabeculations. It had to be seen in more than one view and had to be visible throughout the cardiac cycle (Chen *et al*., 2007). Classically, thrombi appear in 2D echo examination as dense intracavitary echoes and the apical 4 chamber view has been found to be the most useful view to diagnose LV thrombus (Choi *et al*., 2010). The most common location was the apex but right ventricular and multi chamber thrombi were also found (Figure 1 and Figure 10).

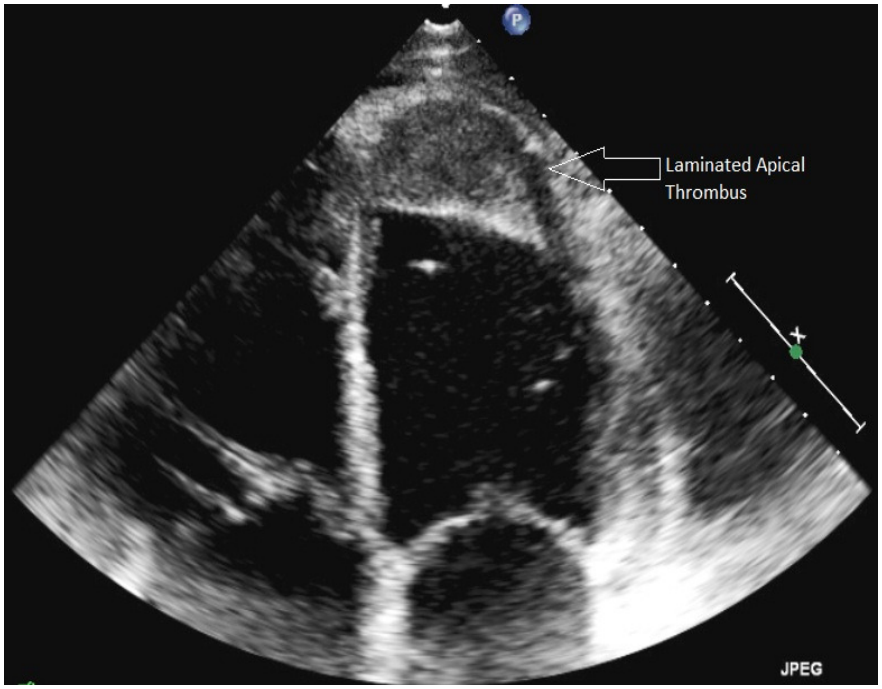

Figure 10 Laminated apical thrombus (Baragwanath Hospital, 2010)

Methods for detecting clot were:

- All short axis views (base, papillary level, apex) were analysed for the presence of thrombus
- Apical views (4 chamber, 5 chamber and 3 chamber), when available, were assessed for the presence of thrombus
- Zoom mode was employed in areas of concern and in the LV apex
- Operator also went off axis when viewing the LV

These techniques were employed to increase the sensitivity for the detection of thrombus.

3.7.5 Spontaneous echo contrast

Spontaneous echo contrast consists of dynamic, smoke-like echoes with a characteristic swirling motion (Figure 11). It is a manifestation of increased red blood cell aggregation seen in slow-flow states. The increased amplitude of

backscattered ultrasonic signals causes the typical smoke appearance (Weissman and Adelman, 2004). It is one of the various clinical manifestations of DCMO. It can be observed in TEE or transthoracic echocardiography (TTE), most often within the LA or LV. This phenomenon was first described by Feigenbaum in 1975, which has been observed under conditions of low blood flow velocity, such as dilated and dyskinetic segments of the LV. It is significantly associated with a history of embolism and LV thrombi (Kim and Park, 2009).

In the current study, the apical 4 chamber was used to detect SEC (Figure 11). It was diagnosed as the presence of smoke-like echodensities in the LV with a characteristic swirling motion that was distinct from white noise artifact. Gain settings were adjusted as required to distinguish SEC from echoes due to excessive gain. It was graded as mild or severe according to the following: Severe SEC occupied the entire ventricle and appeared very dense despite the low gain settings (Kim and Park, 2009).

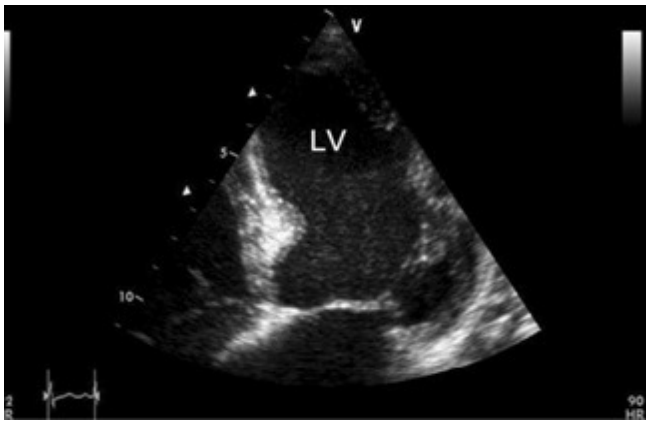

Figure 11 Diffuse SEC in LV in an apical 4 chamber in patient with DCMO (Kim and Park, 2009).

3.8 Statistical methods

The statistical significance of the data was assessed and evaluated by a biostatistician. 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 ± 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 were performed. A probability value less than 0.05 was considered statistically significant. Univariate logistic regression was performed for age, LVEF, severe MR and SEC to predict LV thrombus. Multiple logistic regressions were performed using the independent variables that showed significant odds ratio by Univariate analysis.

CHAPTER 4: RESULTS

4.1 Baseline characteristics

During the study period, 70 eligible Black African patients with IDCMO were enrolled with a mean age of 47.8 ± 13.8 years of which 55.7% were male. The baseline characteristics of this cohort are documented in Table 6. The majority of patients were classified as NYHA functional class II or III and were on optimal medical therapy which included an ace inhibitor and a beta blocker. The anticoagulation treatment in all the patients was warfarin. Previous cardioembolism was confirmed in 4.3% of the participants (Table 5).

Table 5: Baseline characteristics of total patients, n = 70

Variable	
Age*, (years)	47.8 ± 13.8
Sex, (male) n (%)	39 (55.7)
NYHA, n (%)	
I	26 (37.1)
II	31 (44.3)
III	13 (18.6)
BMI* (kg/m^2)	27.1 ± 5.8
Previous cardioembolism, n (%)	3 (4.3)
Warfarin, n (%)	16 (22.9)

* mean ± standard deviation

4.2 Echocardiographic measurements

The echocardiographic parameters included LV thrombus, LVEF, MR, LVEDD, and SEC (Table 6).

Table 6: Echocardiographic parameters, n = 70

Variable	
LV thrombus, n (%)	13 (18.6)
LVEF*, (%)	24.1 ± 10.2
MR, n (%)	
NIL	9 (12.9)
MILD	21 (30)
MOD	26 (37.2)
SEVERE	14 (20)
LVEDD*, (mm)	62.5 ± 6.9
SEC, n (%)	20 (28.6)

* mean ± standard deviation

Spontaneous echo contrast (SEC) was present in 20 patients (28.6%) (Table 6). All of the patients had significant LV remodeling. The mean LVEDD was 62.5 mm and the mean LVEF in all the participants was 24.1% (Table 6). Thirty three percent of the patients had a moderate LV dysfunction and 67% of patients had severe LV dysfunction (Figure 12).

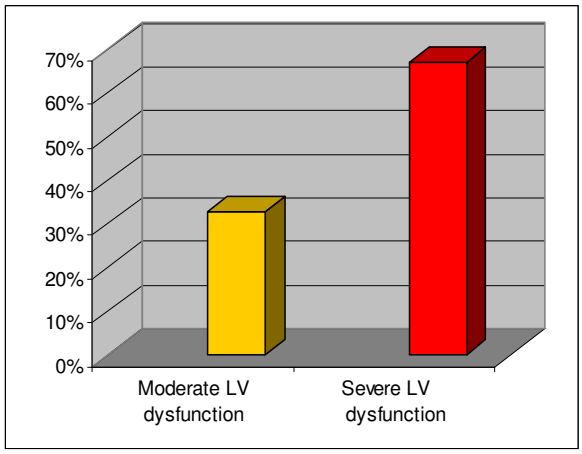

Figure 12 Degrees of LVEF dysfunction in patients with IDCMO

Nine patients had no or trivial MR, 21 patients presented with mild MR, 14 showed severe MR and most 26 (37.1%) had moderate MR (Figure 13).

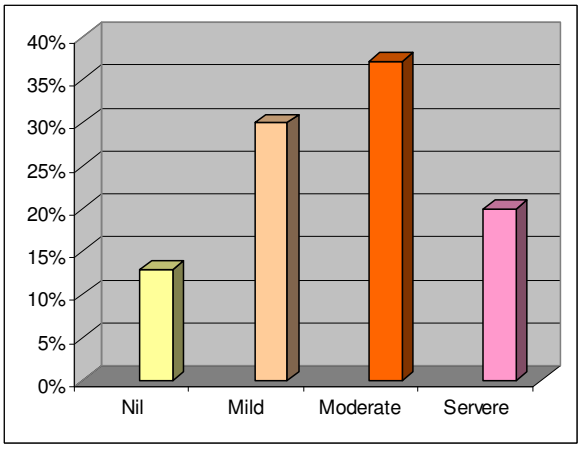

Figure 13 Degrees of MR in the patients with IDCMO

Cardiac thrombus was noted at presentation in 13/70 (18.6%, 95% CI 0.186 +_ 0.09) of IDCMO patients (Figure 14). Three of the thrombi were laminated whilst the rest were pedunculated. The most common location of LV thrombus was in the apex (11 - 84.6%). Two cases were found in the mid cavity. Left ventricular thrombus was present in 4 of the 16 patients who were receiving anticoagulation.

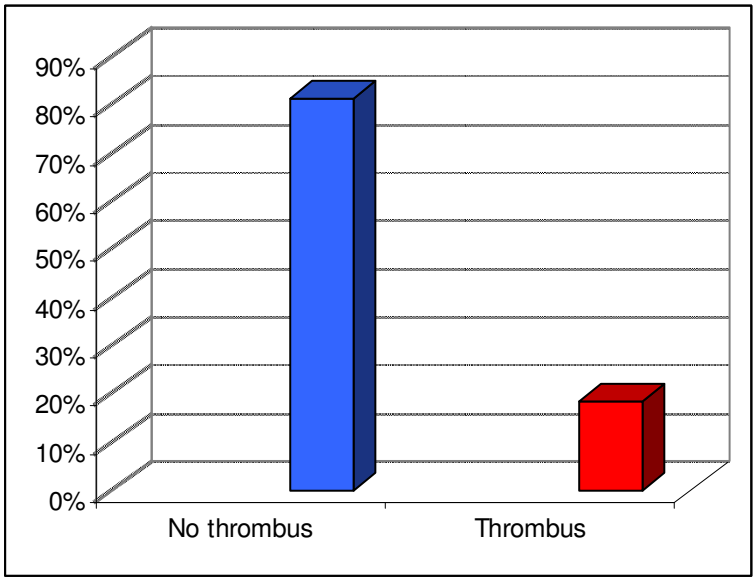

Figure 14 Percentage of thrombus in patients with IDCMO

Table 8 shows the differences in the characteristics between the patients with thrombus and patients without thrombus. When analyzing the differences between the 2 groups of patients, there was a significant association between the LVEF in the patients with thrombus and the patients without thrombus ($p = 0.03$).

Table 7: Characteristics of patients with thrombus and patients without thrombus

Variables	With thrombus n = 13	Without thrombus n = 57	P Value
Age*, (years)	37.7 ± 14.3	50.1 ± 12.7	0.005
Sex, (male) n (%)	6 (46)	33 (58)	0.54
BMI*,(Kg/m²)	28.0 ± 5.07	26.9 ± 5.9	0.45
Previous cardioembolism, n (%)	0 (0)	3 (5.3)	1
NYHA, n (%)			
I	7(54)	19 (33)	
II	5 (38)	26 (46)	0.31
III	1 (8)	12 (21)	
Warfarin, n (%)	4 (31)	12 (21)	0.48
Ejection fraction* %	19.6 ± 10.5	26.8 ± 8.9	0.02
LVEDD* (mm)	62.5 ± 8.9	62.5 ± 6.4	0.67
MR, n (%)			
NIL	5 (38)	4 (7)	
MILD	3 (23)	18 (32)	0.05
MOD	3 (23)	23 (40)	
SEVERE	2 (15)	12 (21)	
SEC, n (%)	6 (46.2)	14 (24.6)	0.17

* mean ± standard deviation

There was a significant association between age and thrombus (p = 0.005) and a borderline association between MR and thrombus (p = 0.05). Reflecting on the differences in characteristics, patients with thrombus were more likely to be younger, have lower LVEF and have MR. No differences were noted in sex, BMI, previous cardioembolism, NYHA, warfarin, LVEDD and SEC between patients with or without thrombus.

In the univariate logistic regression analysis, age was an independent predictor of LV thrombus formation with an unadjusted odds ratio of 0.92 (95% CI: 0.86 – 0.98, p = 0.006) (Table 8). Left ventricular EF was also an independent predictor with an unadjusted odds ratio of 0.92, (95% CI: 0.86 – 0.99, p = 0.03) (Table 8). Mitral regurgitation was graded as nil, mild, moderate or severe. In univariate logistic regression analysis and multivariate logistic regression analysis, severe MR was a variable (Table 8).

Table 8: Univariate logistic regression of prevalence of LV thrombus

Variable	Odds ratio unadjusted	95 %, CI	P Value
Age, years	0.92	0.86 – 0.98	0.006
LVEF	0.92	0.86 – 0.99	0.03
Severe MR	0.68	0.13 – 3.50	0.65
SEC	2.63	0.76 – 9.15	0.12

When multivariate logistic regression analysis was applied to the data, age was the only independent predictor for the prevalence of LV thrombus, with an adjusted odds ratio of 0.93, (95% CI: 0.87 – 0.99, p value = 0.03). Hence, for each unit increase in age, the probability of having a LV thrombus is reduced by 8%. The association between LVEF and LV thrombus was borderline significant (p = 0.05) with an adjusted odds ratio of 0.92 and a 95% confidence interval of 0.84 -1.00 (Table 9).

Table 9: Multivariate logistic regression of prevalence of LV thrombus

Variable	Odds ratio Adjusted	95 %, CI	P Value
Age (years)	0.93	0.87 – 0.99	0.03
LVEF,%	0.92	0.84 -1.00	0.05
Severe MR	0.64	0.30 – 1.36	0.24
SPEC	1.05	0.24 – 4.56	0.95

CHAPTER 5: DISCUSSION

Left ventricular thrombus formation is generally associated with diseases that involve both the endocardium and myocardium. The most common cause, worldwide, of LV thrombus is IHD. In IDCMO, the mechanisms of thrombus formation are thought to be due to impaired contractility, poor CO and abnormal flow patterns within the LV, all of which lead to stasis and subsequently predispose to thrombus formation (Baker and Wright, 1994). The consequences of thrombus formation are cardioembolism which causes clinical scenarios such as stroke and acute limb ischaemia. These clinical scenarios cause considerable morbidity and mortality in patients who already suffer from varying degrees of HF (Baker and Wright, 1994).

Echocardiography is quick, noninvasive, relatively inexpensive and is able to visualize the heart. It helps rule out known causes of DCMO such as valvular heart disease, HPT and IHD (Mahon *et al*., 2002). Echocardiographically, DCMO is characterized by global ventricular dilatation and systolic dysfunction with normal LV wall thickness. Diagnosis is made with 2D echocardiography (Maron, Towbin, Thiene, Antzelevitch, Corrado, Arnett, Moss, Seidman, Young, 2006) and 2D echocardiography has been confirmed to be a very valuable tool in the detection of LV thrombi (Choi *et al*., 2010).

The LV's internal dimensions, particularly the EDD were obtained by using 2D linear measurements from the parasternal long-axis acoustic window. Use of 2D linear dimensions overcomes the common problem of oblique parasternal images resulting in the overestimation of the LV cavity measured in M-mode (Lang *et al*., 2005).

There are several methods of measuring EF in echocardiography. In this study, EF was measured using modified Simpson's method in the 4 chamber apical view. Left ventricular EF is the decrease of LV volume in end-systole compared

with end-diastole, expressed as a percentage. It is the SV divided by the end-diastolic volume (Weissman and Adelman, 2004). The limitation related to EF is that it is not a true marker of LV contractility. Ejection fraction is load dependent which means that it is affected by preload and afterload. Both are important parameters in DCMO.

There are several limitations to using the Modified Simpson's rule. The first limitation might be the inability to technically obtain a good 2D image. Secondly in any view, foreshortening of the ventricular apex due to technical factors will result in an inaccurate assessment of the LVEF and most often an overestimation of the EF. If there is asymmetry of the LV or a systolic wall motion abnormality, a single-plane view will have reduced accuracy (Lang *et al*., 2005). In this instance, a biplane determination of volume will increase accuracy and is recommended by the ASE. When using apical views myocardial dropout is always a possible problem (Lang *et al*., 2005). The use of tissue harmonic imaging (THI) and contrast echocardiography can decrease but not always remove this problem. To eliminate this problem, the transducer must be at the true apex and the cursor must be through the centre of the LV. There are several clues that help determine whether the transducer is at the true apex (Lang *et al*., 2005). In the normal ventricle, the apex does not move from apex to base and it is the thinnest part of the LV. Furthermore, there may be difficulty in tracing the ventricular wall in end-systole and end-diastole due to trabeculation of the altered geometry of the LV due to remodeling (Lang *et al*., 2005).

The two other common ways of measuring EF is M-mode and direct 2D (Teichholz or Quinones).

By definition, an M-mode approach provides information regarding size and contractility along a single line. A limitation of M-mode is that one needs to visualize the entire LV and to ensure that one is truly perpendicular to the long axis of the LV (Senior and Bhatia, 2008). One of the most obvious limitations is

that many forms of heart disease will result in regional wall abnormalities. M-mode may either underestimate the severity of dysfunction if only a normal region is analysed or overestimate the abnormality if the M-mode beam travels through the wall motion abnormality (Senior and Bhatia, 2008). Due to LV remodeling and the LV being a spherical shape it is not always possible to have the cursor perpendicular to the LV walls. Therefore, using M-mode to measure LVEF was not a viable choice (Senior and Bhatia, 2008).

The previously used Teichholz or Quinones methods of calculating LVEF from LV linear dimensions may result in inaccuracies as a result of the geometric assumptions that are required to convert linear measurement to a 3D volume. Therefore, the use of linear measurements to calculate LVEF is not recommended for this study (Lang *et al*., 2005).

The limitation regarding the EF measurement in our study was that EF was only measured in one plane due to image acquisition of 2 chamber views not always being technically possible. However, using the 4 chamber only, to accurately measure EF using modified Simpsons' is acceptable because all the patients in this study had global hypokinesia. If a ventricle is contracting symmetrically, the 4 or 2 chamber view will reflect the true ventricular volume. Measuring EF using the modified Simpsons methods remains the current standard (Lang *et al*., 2005).

The limitations for the method we used for detecting clots were:

a) A high frequency probe such as a linear probe could have been used to more accurately detect apical clots.
b) Three Dimensional (3D) Echocardiography is more sensitive and superior to 2D echocardiography for assessing LV thrombus.
c) Intravenous contrast agents were not used. These agents have improved imaging capabilities for thrombus detection, providing improvements in both anatomical and tissue characterization approaches. It is useful for defining apical masses by differentiating

clots from apical trabeculations, apical hypertrophy, false tendons and artifacts (Chinitz, Mendoza, Kim and Weinsaft, 2009).

d) It is difficult to define or exclude thrombus if the apex is foreshortened

The main findings of the present study, was that the prevalence of LV thrombus in patients with IDCMO was 18.6%, using transthoracic echocardiography. When using univariate logistic regression, the only independent predictors of LV thrombus formation was LVEF and age. However, when multivariate logistic regression analysis was applied to the data, the only predictor with a significant association was age. The association between LVEF and LV thrombus was borderline significant.

The results of the present study need to be interpreted in the context of the study's limitations. The major limitation of this study relates to its design and sample size. This single centre cross sectional study is limited by the fact that the prevalence of LV clots may be an underestimation of the true burden of LV clot formation in patients with IDCMO. Observation on this cohort was made on a once off basis, which could have resulted in a false negative outcome. Patients with IDCMO are continuously predisposed to the development of thrombus and thus may developed thrombus at any point. Left ventricular thrombi may have become present during follow-up visits or may have disappeared in some patients. Having a study applied at serial observations over time would be better suited to detect thrombus formation and thus a prospective/cohort type study geared towards calculating the incidence, may provide a more accurate assessment of LV thrombus formation. In addition, a larger sample would have been more representative and may have resulted in LVEF becoming a more statistically significant predictor of LV clot formation using multivariate analysis.

The present study found that the prevalence of LV thrombus in patients with IDCMO was 18.6%. Regarding the prevalence of LV thrombus, the results concur with some previous studies performed in patients with IDCMO. Yokota *et*

al (1989) documented that 27.5% of their patients had LV thrombus. However, the present study was not compatible with other studies that found a greater proportion of patients with thrombus i.e. Gottdiener *et al* (1983) – 36%, Coats *et al* (1992) – 44 %. Discrepancies in the prevalence of LV thrombus may relate to patient's factors, differences in medical therapy which does alter heamodynamics and neurohumoral factors, which in turn may influence thrombus predisposition; and imaging technique (Sharma *et al*., 2000).

In this study, echocardiography was used for the diagnosis of LV thrombus. Whilst this imaging technique is perhaps the most appropriate technique to evaluate IDCMO patients because of its availability, cost and portability; it is important to note that the sensitivity of 2D echocardiography for the detection of LV thrombus varies between 77 and 95% with a specificity of 86-93% (Armstrong and Ryan, 2009). This may be because of technical issues relating to either the operators' skill and experience or the limited near field resolution when imaging the apex with conventional transthoracic probes. A further limitation is that small clots may not have been detected, especially those that were less than 5 mm in size (Chen *et al*., 2007). In addition, patient factors such as obesity and COPD result in 15-20% of patients being unsuitable for adequate imaging. In this study patients were excluded if they could not be adequately imaged with echocardiography and this could have led to an underestimation of thrombus burden. A further limitation of this study is that contrast was not used. Contrast echocardiography enhances images in technically difficult subjects and improves the detection of thrombi especially in the LV apex (Pepi *et al*., 2010). A final limitation of echocardiography is its inability to reflect thrombus activity, that is, whether or not ongoing thrombogenesis is present (Lip, 1996). Other limitations pertaining to this study were that the sample study of 70 patients was limited for an epidemiological study and too small for logistic regression. This was a preliminary prospective prevalence study. Unfortunately the duration and dosage of warfarin therapy was difficult to accurately ascertain in more than 50% of the patients due to patient factors such as poor patient records. The unavailability of

the information regarding dose, duration and interruption of anticoagulation treatment, can be regarded as a limitation.

In the present study the proposed echocardiographic predictors of LV thrombus evaluated were LVEF, the degree of MR, LVEDD and the presence of SEC. The clinical predictors were the use of warfarin and past cardioembolic events.

In this study, 2 statistically significant variables were found to differ between patients with thrombus and those without thrombus. Patients with thrombus were more likely to be younger and have a lower LVEF.

However, as mentioned earlier, after applying univariate and subsequently multivariate analysis, only age emerged as an independent predictor of thrombus formation. The reason for this is not clear. We postulate that perhaps younger patients have differences in the pathophysiology of their disease such as a greater smoldering inflammatory component which may, therefore, predispose them to thrombus formation. For example the presence of IL-6 may be important in the formation of LV clot in cases of LV dysfunction (Sosin *et al*., 2003).

In the present study, LVEF emerged after multivariate analysis as a borderline predictor of LV clot formation ($p= 0.05$). As mentioned, perhaps if this study population was greater, LVEF may have very well emerged as a predictor of LV thrombus formation. This relationship has been explored by other investigators over the last 18 years. Yokota and co-workers (1989) found that patients with a cardiac thrombus had a lower EF than patients without a thrombus (25% vs. 39 %, $P<0.001$). Coats *et al* (1992) reported similar results. However, 2 further studies related to this issue by Katz and colleagues (1993) and Stratton (1989) found no relationship between LV thrombus and LVEF or NYHA class (Katz, Marantz, Biasucci, Jondeau, Lee, Brennan, LeJemtel, 1993; Stratton, 1989). Thus there is no clear consensus that LVEF is a predictor of thrombus formation at this stage.

In the present study, LVEF was used as a surrogate for a marker of LV contractility. However, low contractility, low CO and abnormal flow, all predispose to clot formation (Lip, 1996), (Nihoyahhopoulus and Kisslo, 2009). The latter 2 variables were not assessed and it may be that all 3 factors are necessary for clot formation. Mural thrombi may be more related to flow abnormalities than contractility. Maze, Kotler and Parry (1989) studied 20 patients with thrombi and 20 DCMO patients without mural thrombus. Their findings were that the inflow and systolic flow velocity at the ventricular apex was markedly lower in those with thrombi. The authors proposed that LV thrombi may result from segmental wall motion abnormalities or atypical flow through the LV rather than simply stasis due to global LV dysfunction (Lip, 1996).

Severe MR was not a predictor for LV thrombus in this study when univariate and multivariate analysis was applied to the data ($p = 0.24$). However, several studies described an association between MR and LV thrombus (Blondheim *et al*., 1991; Kalaria *et al*., 1985). Blondheim *et al* (1991), found that patients with HF and MR had higher flow velocities and less LV thrombi than those without MR. This particular echocardiographic study performed in patients with DCMO reported a 5.5 times lower incidence of LV thrombus in patients with severe MR than in patients without severe MR. When comparing the degree of MR between patients with LV thrombus and patients without, Kalaria *et al* (1985) found that although the presence of any degree of MR was similar between the 2 groups, severe MR was found only in patients with no evidence of LV thrombus. In both studies there was a strong association between MR and LV thrombus. However, univariate and multivariate analysis was not used in these studies to analyse the strength of the association.

In terms of SEC, the presence of SEC was thought to predispose patients to LV thrombus. However, no relationship was found between SEC and LV thrombus in this study or in any other literature reviewed. Gottdiener *et al* (1983) did suggest that SEC had a strong association with stroke in patients with DCMO (Kim and

Park, 2009). However, there is no conclusive evidence that SEC is a predictor of thrombus formation.

CHAPTER 6: CONCLUSION AND FUTURE WORK

Heart failure caused by cardiomyopathies remains a major cause of cardiovascular morbidity and mortality. The prevalence of HF continues to increase and it remains a major public health threat causing the overall annual healthcare expenditure to increase. While a new diagnosis of HF is associated with substantial risk of death within one year, the institution of appropriately guided pharmacologic treatment has led to substantial reductions in cardiovascular mortality. Identification of potential candidates for such treatment can be facilitated through use of echocardiography (Wood and Picard, 2004).

Systemic embolism is a life-threatening complication in patients with DCMO and thromboembolism is a frequent cause of death in patients with CHF, occurring in up to 30% of patients. Anticoagulation may reduce the risk of embolism, but there is controversy about the necessity of routine anticoagulation in all DCMO patients (Ciaccheri *et al*., 1989). In this study we found the prevalence of LV thrombus in patients with IDCMO was found to be 18.6%. After multivariate analysis, age was a significant predictor of LV clot formation. Left ventricular EF may be a possible predictor of LV thrombus but needs to be further investigated in a study with a larger population. This study is the first study in South Africa to attempt to address issues relating to LV clot formation in patients with IDCMO and has added some insight into the issues of anticoagulation in this population despite its limitations relating to study design.

Many investigators have called for a prospective, randomized clinical trial; to assess the risks and benefits of long-term anticoagulation in patients with DCMO. In South Africa, what is needed is a study on patients with DCMO; to collect observational data on the incidence of LV clot detected on serial echocardiography, the rate of embolic events and bleeding complications among patients with and without anticoagulation.

In this way, predictors of LV clot formation and cardioembolism can be determined.

This may provide the opportunity to formulate a model which may be used to guide the clinician regarding the appropriate use of anticoagulation therapy in patients with IDCMO.

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APPENDIX A

LETTER OF INFORMATION AND CONSENT

Department of Biomedical and Clinical Technology
Faculty of Health Sciences
P O Box 1334, DURBAN, 4000

Title of the Research Study:

The use of echocardiography in predicting left ventricle thrombus in patients with idiopathic dilated cardiomyopathy (IDCMO) at the Chris Hani Baragwanath Hospital.

Principal Investigator:

Miss C. Ferreira Dos Santos, student in Master's Degree: Clinical Technology (Cardiology) at Durban University of Technology.

Brief Introduction and Purpose of the Study:

Idiopathic DCMO, 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 left ventricular thrombus in this disease, using echocardiography, and discover the predictors for left ventricular thrombus.

Outline of the Procedures:

This is a prospective follow-up study of 70 patients with IDCMO, presented at the cardiac clinic of the Chris Hani Baragwanath Hospital in Johannesburg. When you arrive, a cardiac doctor will take your medical history, examine you and

arrange for you to have an electrocardiogram, an echocardiogram (which is "heart scan") as well as blood tests. You will be required to sign a consent form to participate in this study.

Risks or Discomforts to the Subject:

There will be no risk to the participants, as all the tests being conducted for this study are recommended in all patients, presented to Chris Hani Baragwanath Hospital, with IDCMO and represent the best international standard of care.

Benefits:

The new information gained from the study will help to improve diagnosis and treatment of IDCMO. Idiopathic DCMO is a frequently encountered condition in the cardiac clinic at Chris Hani Baragwanath hospital.

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

The subject may be withdrawn from the study if they contain any elements of the exclusion criteria. These include patients with significant organic valvular disease, coronary artery disease (CAD), renal failure, co morbid cancer of/and hypertension (HPT), patients who have had a previous MI and patients with an underlying cause for DCMO (i.e. peripartum).

Remuneration:

There will be no remuneration given to the participant, except money for transport when necessary.

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.

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

Miss Claudia Dos Santos	Prof. Jamila Adam	Dr. Ferande Peters
Principal Investigator	Supervisor	Co-Supervisor
0741066617		

Statement of Agreement to Participate in the Research Study:

I,……(subject's full name) 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 to 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…

APPENDIX B

SAMPLE PERMISSION LETTER

Department of Health/Hospital Manager
Chris Hani Baragwanath Hospital
Gauteng

Dear Sir/Madam

REQUEST FOR PERMISSION TO CONDUCT STUDY

I am currently registered as a student at the Durban University of Technology in the department of Clinical Technology. I would like to embark on a research project towards a Masters Degree in Clinical Technology. I have a B Tech Degree in Clinical Technology (specialist category of cardiology).

The title of my project is: The use of echocardiography in predicting left ventricle thrombus in patients with idiopathic dilated cardiomyopathy (IDCMO) at the Chris Hani Baragwanath Hospital.

This study is not structured to alter the course of treatment in any way. I plan to commence the data collection process from May 2009 and complete the process by December 2009.

A cardiologist has offered me his support in supervising the project. I strongly believe that this study will benefit health care professionals in terms of expanding knowledge on IDCMO. There will be no additional cost to the patient or the hospital.

I hereby apply for permission to undertake this research using the patients from Chris Hani Baragwanath Hospital Echocardiography Laboratory.

My proposal has been reviewed by the Department of Clinical Technology and approved by the research committee of the Faculty of Health Science, at the Durban University of Technology.

My research proposal is attached for your perusal. Your support and permission to perform this study at Chris Hani Baragwanath Hospital will be greatly appreciated.

Yours sincerely
Miss Claudia Ferreira Dos Santos

APPENDIX C

Imaging protocol at the Echo lab at the Chris Hani Baragwanath Hospital

Long axis views

(Acquire 2D first then apply colour where relevant)

Parasternal long axis

1) Perform Colour Doppler across aortic valve
2) Perform colour Doppler across MV
3) Parasternal long axis in 2D (with measurements)
4) Parasternal long axis in M - mode (with measurements)
5) Right ventricular (RV) inflow view in 2D
6) Perform colour Doppler across tricuspid valve (TV)
7) CW across TV
8) RV outflow view in 2D
9) Perform colour Doppler across RV outflow view

Short axis views

(Acquire 2D first then apply colour where relevant)

Aortic level

1) Colour across right ventricular outflow tract (RVOT) and main pulmonary artery (MPA)
2) CW across RVOT
3) PW in RVOT below acceleration (closing click)
4) Perform colour Doppler across aortic valve
4) Perform colour Doppler across TV
5) CW across TV
6) Base-mitral leaflets (speckle tracking view, frame rate > 50)
7) Papillary muscles in 2D (speckle tracking view, frame rate > 50)
8) Apex in 2D (speckle tracking view, frame rate > 50)

Apical 4 chamber (no apical foreshortening)

1) Acquire 2D view (ensuring the apex is not foreshortened)

2) Focus on LV (speckle tracking view, frame rate > 50)

3) Focus on RV (speckle tracking view, frame rate > 50)

4) Perform colour Doppler of MV

5) CW across MV

6) PW across MV (with measurements)

7) Perform tissue Doppler of medial mitral annulus (with measurements)

8) Perform tissue Doppler imaging (TDI) of lateral mitral annulus (with measurements)

9) Perform colour Doppler of TV

10) CW across TV (with measurement)

11) PW across the tips of TV leaflets

12) Perform TDI of lateral tricuspid annulus (with measurement)

13) Perform tricuspid annular plane systolic excursion (TAPSE) of lateral tricuspid annulus using M - mode.

14) Perform colour Doppler across interatrial septum.

15) Perform colour Doppler across aortic valve.

16) CW across aortic valve

17) PW on left ventricular outflow tract (LVOT) below acceleration point (blood pressure to be recorded)

<u>Apical 2 chamber</u>

1) Acquire 2D view

2) Perform colour Doppler on MV

<u>Apical 3 chamber</u>

1) Acquire 2D view

2) Perform colour Doppler on MV

3) 2D of aortic valve

4) CW across aortic valve.

<u>Subcostal view</u>

1) Visualize interatrial septum
2) Visualize inferior vena cava (IVC) in 2D
3) Visualize the IVC in M – Mode and measure

Suprasternal view

1) Acquire 2D view

DR F Peters
Directors of the Echo lab