A DESCRIPTIVE RETROSPECTIVE RECORD REVIEW OF PAEDIATRIC PATIENTS WITH INTRACARDIAC THROMBI ASSOCIATED WITH DILATED CARDIOMYOPATHY AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Paediatrics

Johannesburg, 2014
DECLARATION

I, Deksha Faye Morar declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Deksha Faye Morar

On 3rd day of September, 2015
ABSTRACT

INTRODUCTION

Intracardiac thrombi associated with dilated cardiomyopathy in paediatric patients can be a source of significant morbidity and mortality. This study looked at the prevalence, risk factors and outcomes of children complicated by intracardiac thrombi, following a diagnosis of dilated cardiomyopathy at a tertiary centre.

METHODS

A retrospective review of all children, between the ages of 1 and 14 years, diagnosed with dilated cardiomyopathy from August 1983 to July 2011 were assessed using the paediatric cardiology database at Chris Hani Baragwanath Academic Hospital. The study population comprised of 303 children.

RESULTS

The prevalence of intracardiac thrombi in the children with dilated cardiomyopathy was 13.2% (40 children). The majority were located in the left ventricle (80%). The children who developed intracardiac thrombi had a lower fractional shortening compared to the group without intracardiac thrombi (p≤0.05). 20 of these children (6.6%) had evidence of embolization (15/20 to the central nervous system). 52 of the 303 children were HIV positive (17.2%). There was no statistically significant association between HIV status and the development of intracardiac thrombi (p = 0.19). The overall mortality was 8.9%. 12 of the 27 deaths occurred in the intracardiac thrombi group showing that the children with intracardiac thrombi had a poorer outcome (p≤0.05).
CONCLUSION

Intracardiac thrombi is a common occurrence in paediatric patients with dilated cardiomyopathy. There is a significant relationship between the development of intracardiac thrombi and a poor fractional shortening. Patients with echocardiographic evidence of intracardiac thrombi have a worse outcome.
DEDICATION

To my husband Zane and my parents Pravin and Susiela, for their unending love, patience, support and encouragement,

my son Rylan, who brings so much joy to my life,

my siblings Lauren and Darren, for their love and support.

And in memory of my grandparents.
ACKNOWLEDGEMENTS

I would like to extend my thanks and appreciation to:

- Professor AM Cilliers, my supervisor, for all her assistance and time provided during the planning and development of this research work, as well as for allowing me to use the information captured in the paediatric cardiology database.
- Dr S Omar and Mr P Hajison for all their expertise and time provided.
- To the many colleagues, for their assistance, guidance and constructive criticism, with special acknowledgement to Dr Y Atiya, Dr K Naidoo and Dr A Moodley.
- To my family, for all their love, support and encouragement.
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DEFINITIONS

- Dilated cardiomyopathy - characterized by dilatation of the left ventricle or both ventricles with impaired contraction\(^2\)

- Intracardiac thrombi - echocardiographic finding of an intra-cavitatory mass suggestive of a thrombus

- Systemic embolization - defined as the involvement of the central nervous system as evidenced by neurological impairment (stroke) or signs of peripheral ischaemia eg. pulselessness, gangrene of a limb
LIST OF ABBREVIATIONS

- CHBAH - Chris Hani Baragwanath Academic Hospital
- CXR – Chest x-ray
- DCMO - Dilated cardiomyopathy
- ECG – Electrocardiogram
- HIV - Human Immunodeficiency Virus
- IAS - Interatrial septum
- IQR – Inter-quartile range
- IVC - Inferior vena cava
- IVS - Interventricular septum
- LA – Left atrium
- LV – Left ventricle
- LVH – Left ventricular hypertrophy
- MNTH(S) - Month(s)
- RA – Right atrium
- RAH – Right atrial hypertrophy
- RV – Right ventricle
- SVC – Superior vena cava
- YR(S) - Year(s)
1 CHAPTER ONE - INTRODUCTION

The occurrence of an intracardiac thrombus in the setting of a dilated cardiomyopathy is a serious complication. The potential to embolize can be a significant source of morbidity and mortality. The objectives of this study were to evaluate the available data and assess the prevalence, associated risk factors and outcomes in children with dilated cardiomyopathy complicated by intracardiac thrombi.

1.1 Background and classification

Cardiomyopathy refers to a group of disorders affecting the myocardium and leading to cardiac dysfunction.

The European Society of Cardiology Working Group on Myocardial and Pericardial Diseases\(^1\) has recently re-classified Cardiomyopathies into five categories, namely:

1. Dilated cardiomyopathy
2. Hypertrophic cardiomyopathy
3. Restrictive cardiomyopathy
4. Arrhythmogenic right ventricular cardiomyopathy
5. Unclassified.

Dilated cardiomyopathy (DCMO) is the most common form of cardiomyopathy (90\%)\(^3,6,7\) and is characterized by cardiac dilatation and systolic dysfunction (decrease in myocardial contractility).\(^4,8,14,26\)
2 Dilated cardiomyopathy

- Enlargement of cardiac chambers
- Globular-shaped heart
- ↓ ventricular wall thickness
- ↓ contractility

Figures drawn by author

1.2 Epidemiology

The incidence of DCMO in children is 0.34-0.73/100000.\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\)). The advent and availability of echocardiography has made the diagnosis of intracardiac thrombi in children possible. Previous studies, although few and lacking data from Africa, have reported a frequency of intracardiac thrombi of 4-16\(^%\)\(^{14,15,17,20}\) in children with DCMO and an even higher incidence of 43-57\(^%\)\(^{14,20,21}\) in paediatric autopsy reports, with a male predominance.\(^{16,23}\) Embolism associated with intracardiac thrombi has a reported frequency of 2.5-27\(^%\)\(^{16,18,22}\) with larger emboli embolizing more frequently,\(^{16,25}\) and with the central nervous system more commonly involved.\(^{15,18}\)
## 1.3 Etiology

The causes of cardiomyopathy may be primary/idiopathic or secondary in etiology. The majority of cases (66%) of DCMO, are classified as idiopathic.\textsuperscript{3,4,8} Other etiological categories include:

- Infectious diseases (e.g. viral-Coxsackie virus, bacterial-Streptococcal)
- Deposition disorders (e.g. hemochromatosis)
- Drugs/toxins (e.g. chemotherapeutic agents, antiretroviral agents, lead)
- Electrolyte abnormalities (e.g. hypocalcemia)
- Endocrine disorders (e.g. pheochromocytoma, diabetes mellitus)
- Neuromuscular disorders (e.g. Duchenne muscular dystrophy).\textsuperscript{26}

## 1.4 Pathophysiology and classification of intracardiac thrombi

Impaired left ventricular systolic function, stasis of blood flow, dysrhythmias, a hypercoagulable state and abnormal endocardial surfaces, are all factors that have been implicated in the pathogenesis of thrombosis.\textsuperscript{14,15,17,20,21,22} In DCMO the large end-systolic ventricular volumes causes stasis of blood and this creates a favourable environment for the development of intracardiac thrombi.\textsuperscript{24} Thrombi can be found in one or more chambers, but the left ventricle (LV) is the chamber most commonly involved.\textsuperscript{14,16,18,21,22,24} This is followed by the right ventricle, right atrial appendage and left atrial appendage, the last three often occurring in association with LV thrombus.\textsuperscript{24}

Intracardiac thrombi can be classified according to location (Table 1).\textsuperscript{24}
Table 1  Intracardiac thrombi: classification by location

- **Atrial cavities**
  - Left atrium
    - Appendage only
    - Body only
      - “Ball” “massive”
    - Combination
  - Right atrium
    - Appendage only
    - Body only
    - Combination
    - “Migrating”
  - Left and right atria

- **Ventricular cavities**
  - Left ventricle
    - With aneurysm
    - Without aneurysm
  - Right ventricle
    - With aneurysm
    - Without aneurysm
    - “Migrating”
  - Left and right ventricles

- **Atrial and ventricular cavities**
Previously reported studies have found that intracardiac thrombi tend to develop during rapid deterioration of ventricular function.\textsuperscript{14} Falk and Günthard both reported a significantly lower fractional shortening (echocardiographic measure of ventricular systolic function) in the group with thrombo-embolism, and suggested that a fractional shortening of <15\% (normal is \geq 28\%) appeared to be a high risk factor in the paediatric population.\textsuperscript{15,18}

1.5 Diagnosis

Patients with DCMO present with cardiomegaly and may have features of cardiac failure (fatigue, dyspnea, orthopnea, tachycardia, pulmonary oedema, hepatomegaly, gallop rhythm) and a systolic murmur (secondary to mitral/tricuspid regurgitation) may be audible. The chest X-ray (CXR) shows evidence of cardiomegaly and possibly pulmonary congestion. Findings on the electrocardiogram (ECG) may include tachycardia, left ventricular/left atrial (LA) hypertrophy or atrial/ventricular arrhythmia. Echocardiography will demonstrate chamber enlargement with poor contractility (Fig. 2), a reduced shortening fraction and may show evidence of an intracardiac thrombus.\textsuperscript{26}

Although the gold standard for the diagnosis of intracardiac thrombi is direct visualization of the characteristic mass at operation or autopsy, two-dimensional trans-thoracic echocardiography has been shown to be both sensitive (92\%) and specific (88\%),\textsuperscript{11,12,15,17} and has an advantage of being a non-invasive tool. Despite having been shown to be superior, trans-esophageal echocardiography is limited by its need for general anesthesia in children and the difficulty of examining the cardiac apex, which is a common site for thrombi.\textsuperscript{13,15,17,20}
False negative echocardiographic detection can result in those thrombi that are recent and less echogenic, whereas false positive echocardiographic detection can be found in those cases where the contours of cardiac chambers are irregular.  

1.6 Complications and prognosis

The complications of dilated cardiomyopathy include:

- Cardiac failure
- Valvular regurgitation
- Pericardial/pleural effusions
- Arrhythmias
- Infective endocarditis
- Failure to thrive
- Thrombo-embolic phenomenon
- Shock
- Death.

DCMO has a very poor prognosis and progressive deterioration is evident in the majority of patients. Studies have reported a 5 year survival rate of 60-75%.  

Accompanied with its potential to embolize and subsequent vascular occlusion, intracardiac thrombosis, if present, is a potential source of significant morbidity and mortality. Manifestations of embolism include, neurological impairment (hemiplegia), myocardial ischaemia, pulmonary embolus, renal dysfunction, and limb involvement (necrosis).
Certain echocardiographic-histologic observations regarding risk of embolization have been made. Thrombi which are most likely to embolize are recent, mobile, less bright, protruding and/or pedunculated. Large thrombi which tend to have liquefied central cores also have a tendency to embolise.\textsuperscript{16,19,25}
2 CHAPTER TWO - METHODOLOGY

2.1 Aims

To determine the prevalence, risk factors and outcomes of children with dilated cardiomyopathy complicated by intracardiac thrombi.

2.2 Objectives

- To calculate the prevalence of intracardiac thrombi associated with DCMO in children at CHBAH
- To find risk factors associated with the development of intracardiac thrombi in paediatric patients with DCMO at CHBAH
- To look at the outcomes of children with intracardiac thrombi associated with DCMO, as compared to those without, at CHBAH

2.3 Study design

A descriptive retrospective record review.

2.4 Study site

Data was extracted from the computerized paediatric cardiology database at Chris Hani Baragwanath Academic Hospital.

2.5 Study period

Data from August 1983 to July 2011 was assessed.
2.6 Study population

- All children aged between 1 and 14 years, diagnosed with DCMO at Chris Hani Baragwanath Academic Hospital were entered onto the paediatric cardiology database and analysed. This group was then sub divided into 2 groups:
  
  A. Children with intracardiac thrombi
  
  B. Children without intracardiac thrombi

- Children < 1 year old were excluded as there were no cases of intracardiac thrombi in this age group on review of the data. Children > 14 years were excluded as this is the cut-off age for admission to the paediatric wards.

2.7 Sampling

2.7.1 Inclusion criteria

- The diagnostic criteria for dilated cardiomyopathy must have been met

- Confirmed intracardiac thrombi by two-dimensional echocardiography

2.7.2 Exclusion criteria

- Children < 1 year old and >14 years old

- Insufficient patient data on the database

2.8 Data instruments

Data was extracted from the paediatric cardiology database. The data was then entered onto a data collection sheet (Appendix A).
The data collection sheet included:

- **Demographic characteristics**
  - Date of birth and age at first presentation
  - Gender

- **Echocardiogram**
  - Date
  - Findings relating to ventricular function and the presence of an intracardiac thrombus

- **Follow-up details**
  - Complications related to the thrombus
  - Outcome

- **Associated medical conditions**

2.9 **Data collection**

Data was extracted from the paediatric cardiology database and entered onto a data collection sheet.

2.10 **Data management**

Data was coded and captured using Microsoft Excel 2007. Some variables needed to be defined before they could be analysed.

- The presence of an intracardiac thrombus was categorized into two groups, “yes” if there was echocardiographic evidence of a thrombus or “no” if there was no thrombus observed during echocardiography.

- Embolization was categorized into two groups, “yes” if there was systemic signs of embolization and “no” if systemic signs were absent.
• Mortality at discharge was categorized into two groups, “survivor” if patient survived to hospital discharge and “non-survivor” if patient demised during that hospital stay.

• Anticoagulation was categorized into two groups, “yes” if the children were on any anticoagulation treatment and “no” if no record of treatment was made.

• HIV status was categorized into two groups, “positive” if the child was confirmed positive and “unknown” if no record of status was made.

2.11 Data analysis

Data was imported into STATA version 12 for analysis.

For descriptive purposes, medians (together with interquartile range [IQR]) have been reported for all variables related to age and fractional shortening.

This study used chi square and fisher’s exact tests for all categorical variables. All statistical tests were two sided and a $P$ value of $\leq 0.05$ was considered statistically significant.

For the purpose of measuring possible risk factors, association statistical tests were conducted. The mi command was used to drop the missing values in the two variables with missing data (gender and fractional shortening), before testing the variable.

Summary of tests used (Table 2).
Table 2  Summary of statistical tests used

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dependent variable</th>
<th>Statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (discrete variable)</td>
<td>Intracardiac thrombus (binary variable)</td>
<td>Logistic regression</td>
</tr>
<tr>
<td>HIV status (binary variable)</td>
<td>Intracardiac thrombus (binary variable)</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Gender (categorical variable)</td>
<td>Intracardiac thrombus (binary variable)</td>
<td>Welch t-test</td>
</tr>
<tr>
<td>Fractional shortening (continuous variable)</td>
<td>Intracardiac thrombus (binary variable)</td>
<td>Logistic regression</td>
</tr>
<tr>
<td>Mortality (binary variable)</td>
<td>Intracardiac thrombus (binary variable)</td>
<td>Fisher exact</td>
</tr>
</tbody>
</table>

2.12 Finance

Due to the retrospective nature of this study, no funding was required.

2.13 Ethical considerations

Ethics approval for the purpose of retrospective analyses for publication, was granted to the Paediatric Cardiology Department at Chris Hani Baragwanath Academic Hospital (Ethics clearance number: Appendix C).

Ethics clearance was obtained from The Ethics Committee for Research on Human Subjects (Medical) at the University of the Witwatersrand (Ethics clearance number: Appendix B).

Permission for the study was also obtained from the Medical Advisory Committee at Chris Hani Baragwanath Hospital (Appendix D).

Confidentiality of patient’s records were maintained. No identifying data fields (name, hospital number) were included in the data collection sheet.
3 CHAPTER THREE - RESULTS

3.1 Descriptive analysis

3.1.1 Study sample

In order for the study to be adequately powered, a sample size of 298 was required. However, upon considering the missing data in some of the patient’s records, the sample size was inflated by 5%, increasing the sample size required to 305. 327 children with DCMO were identified in the paediatric cardiology database. Of these 24 patients were excluded thus reaching a final sample size of 303 (Children with DCMO and intracardiac thrombi [N=40], children with DCMO and no intracardiac thrombi [N=263]). (Table 3)
Table 3 Demographic data

<table>
<thead>
<tr>
<th></th>
<th>Child with DCMO and no intracardiac thrombus</th>
<th>Children with DCMO and intracardiac thrombus</th>
<th>All children with DCMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5yrs</td>
<td>132</td>
<td>17</td>
<td>149</td>
</tr>
<tr>
<td>5yrs 1mnth-10yrs</td>
<td>84</td>
<td>14</td>
<td>98</td>
</tr>
<tr>
<td>10yrs 1mnth- to 14yrs</td>
<td>47</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>TOTAL</td>
<td>263</td>
<td>40</td>
<td>303</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>137</td>
<td>25</td>
<td>162</td>
</tr>
<tr>
<td>Female</td>
<td>117</td>
<td>15</td>
<td>132</td>
</tr>
<tr>
<td>TOTAL</td>
<td>254</td>
<td>40</td>
<td>294</td>
</tr>
<tr>
<td>HIV</td>
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<tr>
<td>Unknown</td>
<td>215</td>
<td>36</td>
<td>251</td>
</tr>
<tr>
<td>Positive</td>
<td>48</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>TOTAL</td>
<td>263</td>
<td>40</td>
<td>303</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>248</td>
<td>28</td>
<td>276</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>15</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>TOTAL</td>
<td>263</td>
<td>40</td>
<td>303</td>
</tr>
<tr>
<td>Embolization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>No</td>
<td>252</td>
<td>31</td>
<td>283</td>
</tr>
<tr>
<td>TOTAL</td>
<td>263</td>
<td>40</td>
<td>303</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>194</td>
<td>35</td>
<td>229</td>
</tr>
<tr>
<td>No</td>
<td>69</td>
<td>5</td>
<td>74</td>
</tr>
<tr>
<td>TOTAL</td>
<td>263</td>
<td>40</td>
<td>303</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>No</td>
<td>258</td>
<td>16</td>
<td>274</td>
</tr>
<tr>
<td>TOTAL</td>
<td>263</td>
<td>40</td>
<td>303</td>
</tr>
</tbody>
</table>

There are two variables with missing values, gender with 9 missing values, and fractional shortening with 74 missing values.
3.1.2 Demographic data

3.1.2.1 Age

The age ranged from 1 year to 13.9 years, with the median age at time of presentation in the DCMO group of 5.4 years (IQR 2.8, 9) and 6.7 years (IQR 3.3, 9.5) in the intracardiac thrombi group.

![Figure 3 Age distribution in DCMO group](image)

![Figure 4 Age distribution in intracardiac thrombus group](image)
3.1.2.2 Gender

Males represented 53.4% (162) and females 43.6% (132) of the sample with 3% (9) missing data for gender. In the intracardiac thrombus group there were 25 males and 15 females (no missing data), with a male:female ratio of 1.67:1.

![Gender distribution](image)

Figure 5 Gender distribution

3.2 Prevalence of intracardiac thrombi in children with DCMO

Of the 303 children with DCMO, 40 children had echocardiographic evidence of an intracardiac thrombus which translated to a prevalence of 13.2% (Patient characteristics – Appendix E). The majority were located in the left ventricle (80%).
3.3 Risk factors associated with the development of intracardiac thrombi in children with dilated cardiomyopathy

3.3.1 Age

17 cases of intracardiac thrombi occurred in the 1-5 year age group. There was however, no statistically significant relationship between age and the development of intracardiac thrombi (p=0.39).

3.3.2 Gender

Being male or female did not increase the risk of developing intracardiac thrombi (p=0.31).

3.3.3 Fractional shortening

The median fractional shortening in the group with and without an intracardiac thrombus was 11% (IQR 7%, 19%) and 16.5% (IQR 12%, 22.8%) respectively (Table 4). There was a statistically significant difference in fractional shortening between the group that developed intracardiac thrombi and the group that did not. The development of intracardiac thrombi was significantly associated with a poor fractional shortening (p≤0.05).
Table 4 Fractional shortening (%) on echocardiography

<table>
<thead>
<tr>
<th></th>
<th>CHILDREN WITH INTRACARDIAC THROMBI</th>
<th>CHILDREN WITHOUT INTRACARDIAC THROMBI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>35</td>
<td>194</td>
</tr>
<tr>
<td>MEDIAN (IQR)</td>
<td>11% (7%, 19%)</td>
<td>16.5% (12%, 22.8%)</td>
</tr>
</tbody>
</table>

### 3.3.4 Associated conditions

52 children (17.2%) were HIV positive. There was no significant relationship between HIV positive patients and the development of an intracardiac thrombus (p=0.19).

### 3.3.5 Anticoagulation

24 children were reported as being on anticoagulation in the intracardiac thrombi group. Only 5 out of the 263 children without intracardiac thrombi were reported as being on anticoagulation.

### 3.4 Outcome of children with dilated cardiomyopathy complicated by intracardiac thrombi

#### 3.4.1 Embolization

20 children (6.6% of the study population) demonstrated systemic signs of embolization. 11 of these children did not demonstrate any intracardiac thrombi at the time of the echocardiograph. 15 of the children had emboli to the central nervous system (75%).
3.4.2 Mortality

There was a total of 27 deaths in the study population during the first admission. The overall mortality during the first admission was 8.9%. 12 of the deaths occurred in the intracardiac thrombi group. Children with intracardiac thrombi had a poorer outcome as compared to children without the intracardiac thrombi (p≤0.05) (Table 5). Only 3 deaths were associated with embolization.

Table 5 Outcome data

<table>
<thead>
<tr>
<th></th>
<th>CHILDREN WITH INTRACARDIAC THROMBI</th>
<th>CHILDREN WITHOUT INTRACARDIAC THROMBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolization</td>
<td>9 (22.5%)</td>
<td>11 (4.2%)</td>
</tr>
<tr>
<td>Survivor</td>
<td>28 (70%)</td>
<td>248 (94.3%)</td>
</tr>
<tr>
<td>Non-survivor</td>
<td>12 (30%)</td>
<td>15 (5.7%)</td>
</tr>
</tbody>
</table>
4 CHAPTER FOUR - DISCUSSION

One of the many complications of DCMO is the development of intracardiac thrombi. The potential for the intracardiac thrombi to embolize is a significant source of morbidity and mortality. Despite this, there is limited information on the prevalence, risk factors and outcomes associated with DCMO complicated by intracardiac thrombi. Studies to date have been small in terms of sample size and have provided no concrete evidence to enable targeted preventative management guidelines.

Our study sample included 303 DCMO patients, 40 of whom were complicated by the development of intracardiac thrombi, which to our knowledge, is one of the largest studies to date. Sample sizes of studies reviewed ranged from 25 in the Boston study, to 130 in the Swiss study, with limited data from Africa.

4.1 Demographic data

4.1.1 Age

The median age at diagnosis of DCMO was 5.4 years (IQR 2.8, 9). The DCMO children in this study presented at a much later age compared to the reviewed studies. In the earlier studies reviewed, children usually presented at around 2 years of age however these studies also included children under 1 year of age in their cohort of patients. The delayed presentation at the time of diagnosis, as compared to the other studies, may be attributed to the poor socio-economic status of the families in this study population, the long distances occasionally travelled to the tertiary centre, the delay in accessing healthcare services and the possible delay in referring the children to a tertiary centre.
The median age at diagnosis of intracardiac thrombi was 6.7 years (IQR 3.3, 9.5). This value is not vastly different from a value of 8.8 years reported by John et al in the Texan study.16

4.1.2 Gender

Overall, females and males were equally represented in the DCMO group with a ratio of 1:1.23. The 9 missing data did not significantly affect the ratio. The other studies that were reviewed demonstrated a male predominance.4,6,17

In the intracardiac thrombi group (no missing data for gender), the female to male ratio was 1:1.67. This value is similar to the Texan study which also revealed a male predominance with a ratio of 1:2.4.16

4.2 Prevalence of intracardiac thrombi in children with DCMO

The prevalence of intracardiac thrombi in patients with DCMO at CHBAH was 13.2%. This correlates well with the current literature which cites a value of between 4% and 16%.14,15,17,19,20 There is an even higher incidence in autopsy reports,14,15,17,20 however, this could not be confirmed as details regarding autopsy were not available. Most of intracardiac thrombi were located in the LV, this is consistent with the Korean, Texan and Japanese study.14,16,21
4.3 Risk factors associated with the development of intracardiac thrombi in children with dilated cardiomyopathy

4.3.1 Gender

Although our study showed a male predominance as in the Texan study\textsuperscript{16}, there was no statistically significant relationship between gender and the development of intracardiac thrombi (p=0.31).

4.3.2 Fractional shortening and anticoagulation

The median fractional shortening in the intracardiac thrombi group was 11\% (IQR 7\%, 19\%), and 16.5\% (IQR 12\%, 22.8\%) in the group without intracardiac thrombi.

Children presenting with intracardiac thrombi were found to have a significantly poorer fractional shortening compared to the group of children without intracardiac thrombi.

The significant relationship between a low FS and the development of intracardiac thrombi is a finding consistent with the Korean, Swiss and Boston studies.\textsuperscript{14,15,18} One of the treatment modalities of DCMO includes anticoagulants. This is to reduce the risk of emboli in high risk patients.\textsuperscript{15,26} From the information gathered children with a FS of <15\% are at high risk for the development of intracardiac thrombi, and despite there being a lack of evidence, a recommendation for prophylactic anticoagulation can be made in those children with poor cardiac function.

Children with an intracardiac thrombus were more likely to be on anticoagulation as treatment was initiated as soon as the intracardiac thrombi was diagnosed.
4.4 Outcomes

4.4.1 Embolization

6.6% of the study population showed systemic signs of embolization. This is not vastly different from the Boston study of 8.4%. Other studies have reported between 2.5-27\%\textsuperscript{19} with the Texan and Japanese study showing that 13% and 17.5\% of patients showed signs of embolization respectively.\textsuperscript{16,21} Embolization to the central nervous system was predominant (75\%), and this is in keeping with the Swiss and Boston study.\textsuperscript{15,18}

Some children who demonstrated signs of embolization did not show an intracardiac thrombus on echocardiography, and this could be due to the thrombus having embolized. If we assumed that the group that showed embolization without any visible intracardiac thrombi, had developed intracardiac thrombi at some point following their disease then this assumption would increase the prevalence of intracardiac thrombi in patients with DCMO to 16.8\%. This still correlates well with the current literature.\textsuperscript{14,15,17,19,20}

4.4.2 Mortality

Despite presenting at an older age, 91.1\% of the study population survived during the first admission (due to missing data, a follow-up period could not be established). The Egyptian (follow-up period 36.2 ±22.1 months), Saudi Arabian (followed-up period 34.7 ±23.2 months) and London study (follow-up period 19 months) showed that the older the age of presentation, the worse the prognosis.\textsuperscript{3,8,10} Studies have reported a 5 year survival rate of 60-75\% in patients with DCMO.\textsuperscript{4,5,10}
The mortality in the ICT group was 30%, which is slightly less than in the Texas and Toronto studies, which quoted a mortality of 39% and 37.5% respectively.\textsuperscript{16,17}

A significantly worse outcome was demonstrated in the intracardiac thrombi group. Other concomitant illnesses were not taken into consideration and this could have influenced the result.

### 4.5 Limitations

Limitations of the study are as follows:

1. It is representative of a single tertiary institution of a low socio-economic status.

2. The missing information from the database required adjustments to be made by statistical calculations.

3. Retrospective data analysis whereby we could only account for mortality rate at the time of first admission. A long term follow-up of these children with a more detailed analysis including the cause of mortality would be useful.

4. The use of two-dimensional transthoracic echocardiography to diagnose intracardiac thrombi has been found to be very sensitive and specific,\textsuperscript{11,12,15,17} however, it is operator dependant and there is the possibility of missed thrombi. Trans-oesophageal echocardiography, found to be more superior to transthoracic echocardiography,\textsuperscript{13,15,17,20} was not used.
5 CHAPTER FIVE - CONCLUSION

This study is one of the largest studies to date investigating intracardiac thrombi in patients with DCMO. The data presented in this study, despite its limitations, demonstrates a prevalence of intracardiac thrombi in patients with DCMO in keeping with the current literature. There is a significant relationship with the development of intracardiac thrombi and a poor fractional shortening. Patients with echocardiographic evidence of intracardiac thrombi have a worse outcome.
6  CHAPTER SIX - RECOMMENDATIONS

The need for regular follow-up and the commencement of prophylactic anticoagulation in patients with poor fractional shortening and their impact on outcome requires further trials. In particular, future prospective multicenter trials are required to assess the benefits of anticoagulation in the prevention of intracardiac thrombus in children with DCMO.
7 REFERENCES


26. Park MK. Pediatric Cardiology for Practitioners. 5th edition; 341-44.
APPENDIX A – Data collection sheet

DATA COLLECTION SHEET

A Descriptive Retrospective Record review of Paediatric patients with Intracardiac thrombi associated with dilated cardiomyopathy at CHBAH

| Case number |

Date of birth:

Gender:

Date of first presentation:

Age:

Features of Thrombi:

Date diagnosed:

| Number | Location | Shortening Fraction |

Follow-up:

| Date | Echocardiograph | Outcome |

Associated conditions:
APPENDIX B – Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R1409 Dr DF Moor

CLEARANCE CERTIFICATE
M110974

PROJECT
A Descriptive Retrospective Record Review of Paediatric Patients with Intracardiac Thrombi
Associated with Dilated Cardiomyopathy

INVESTIGATORS
Dr DF Moor

DEPARTMENT
Department of Paediatrics

DATE CONSIDERED
30/09/2011

DECISION OF THE COMMITTEE
Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08/03/2013

CHAIRPERSON (Professor P E Steyn Jones)

*Guidelines for written ‘informed consent’ attached where applicable

cc: Supervisor: Prof AM Cilliers

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY submitted to the Secretary at Room 10064, 10th Floor, Senate House, University. I/we fully understand the conditions under which I/we are authorized to carry out the above-mentioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedures as approved I/we undertake to submit the protocol to the Committee for a completion of a progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.
APPENDIX C - Ethics clearance certificate for paediatric cardiology database

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R 144/99 Cilliers

CLEARANCE CERTIFICATE

PROJECT
Request to Use the Paediatric Cardiology Patients Started in 1993 for Purpose of Retrospective Analyses for Publication (ref M028006)

INVESTIGATORS
Dr AM Cilliers

DEPARTMENT
School of Clinical Medicine

DATE CONSIDERED

DECISION OF THE COMMITTEE*
request for extension approved

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.04.10

CHAIRPERSON

(Professors PF Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor

DECLARATION OF INVESTIGATORS
To be completed in duplicate and ONE COPY returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/We are authorized to carry out the abovementioned research and I/We guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure an approved I/We undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES
APPENDIX D – Hospital permission letter

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH HOSPITAL
PERMISSION TO CONDUCT RESEARCH

Date: 07 September 2011

TITLE OF PROJECT: Evaluation of intracardiac thrombi in paediatric patients with dilated cardiomyopathy at Chris Hani Baragwanath Academic Hospital (CHBAH)

UNIVERSITY: Witwatersrand

Principal Investigator: Dr DF Morar

Department: Paediatrics

Supervisor (if relevant): Associate Professor AM Cilliers

Permission Head Department (where research conducted): Yes

Date of start of proposed study: October 2011

Date of completion of data collection: June 2012

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

Recommended
(On behalf of the MAC)

Date: 07 September 2011

Approved/Not Approved

Hospital Management

Date: 07 Sept 2011
APPENDIX E – Characteristics of children with intracardiac thrombi

<table>
<thead>
<tr>
<th>No.</th>
<th>AGE (at first presentation)</th>
<th>GENDER</th>
<th>SITE</th>
<th>FS (at time of thrombus)</th>
<th>EMBOLIZATION</th>
<th>OUTCOME (with discharge)</th>
<th>HIV STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 yr 1 mth</td>
<td>Male</td>
<td>LV</td>
<td>6%</td>
<td>Yes</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>1 yr 1 mth</td>
<td>Male</td>
<td>LA</td>
<td>20%</td>
<td>No</td>
<td>Survivor</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>1 yr 3 mths</td>
<td>Male</td>
<td>LV</td>
<td>Unknown</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>1 yr 10 mths</td>
<td>Male</td>
<td>LV</td>
<td>12%</td>
<td>Yes</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>1 yr 11 mths</td>
<td>Male</td>
<td>LV</td>
<td>24%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>2 yrs 1 mth</td>
<td>Male</td>
<td>LV</td>
<td>16%</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>3 yrs 1 mth</td>
<td>Male</td>
<td>LV</td>
<td>6%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>8</td>
<td>3 yrs 1 mth</td>
<td>Male</td>
<td>LV, IVS</td>
<td>8%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>3 yrs 2 mths</td>
<td>Female</td>
<td>LV</td>
<td>23%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>3 yrs 2 mths</td>
<td>Female</td>
<td>LV</td>
<td>10%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>11</td>
<td>3 yrs 3 mths</td>
<td>Male</td>
<td>LV, RV</td>
<td>Unknown</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>12</td>
<td>3 yrs 4 mths</td>
<td>Female</td>
<td>LV</td>
<td>11%</td>
<td>No</td>
<td>Survivor</td>
<td>Positive</td>
</tr>
<tr>
<td>13</td>
<td>3 yrs 6 mths</td>
<td>Male</td>
<td>LV, IVS</td>
<td>7%</td>
<td>Yes</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>3 yrs 6 mths</td>
<td>Male</td>
<td>LV</td>
<td>10%</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>4 yrs 4 mths</td>
<td>Male</td>
<td>LV</td>
<td>18%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>16</td>
<td>4 yrs 6 mths</td>
<td>Female</td>
<td>LV</td>
<td>9%</td>
<td>Yes</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>17</td>
<td>4 yrs 7 mths</td>
<td>Male</td>
<td>IVC/RA junction</td>
<td>14%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>18</td>
<td>5 yrs 7 mths</td>
<td>Male</td>
<td>LV</td>
<td>24%</td>
<td>No</td>
<td>Non-survivor</td>
<td>Positive</td>
</tr>
<tr>
<td>19</td>
<td>6 yrs 1 mth</td>
<td>Male</td>
<td>LV</td>
<td>2%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>20</td>
<td>6 yrs 3 mths</td>
<td>Female</td>
<td>IAS</td>
<td>14%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>21</td>
<td>6 yrs 9 mths</td>
<td>Female</td>
<td>LV</td>
<td>25%</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>22</td>
<td>7 yrs 2 mths</td>
<td>Male</td>
<td>LA</td>
<td>10%</td>
<td>Yes</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Age and Gender</td>
<td>Location</td>
<td>Proportion</td>
<td>Outcome</td>
<td>Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>----------------</td>
<td>----------</td>
<td>------------</td>
<td>---------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>7 yrs 5 months</td>
<td>Male</td>
<td>LV, RV</td>
<td>Unknown</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>24</td>
<td>7 yrs 9 months</td>
<td>Male</td>
<td>LV</td>
<td>Unknown</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>25</td>
<td>7 yrs 10 months</td>
<td>Male</td>
<td>LV, IVS</td>
<td>16%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>26</td>
<td>8 yrs 1 month</td>
<td>Female</td>
<td>LA</td>
<td>5%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>27</td>
<td>8 yrs 2 months</td>
<td>Female</td>
<td>LV, LA</td>
<td>6%</td>
<td>Yes</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>28</td>
<td>8 yrs 4 months</td>
<td>Female</td>
<td>LV</td>
<td>5%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>29</td>
<td>8 yrs 4 months</td>
<td>Male</td>
<td>Unknown</td>
<td>7%</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>30</td>
<td>8 yrs 10 months</td>
<td>Female</td>
<td>LV</td>
<td>12%</td>
<td>Yes</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>31</td>
<td>9 yrs 6 months</td>
<td>Female</td>
<td>LV</td>
<td>13%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>32</td>
<td>10 yrs 7 months</td>
<td>Female</td>
<td>RV</td>
<td>10%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>33</td>
<td>11 yrs 1 month</td>
<td>Female</td>
<td>LV</td>
<td>7%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>34</td>
<td>11 yrs 4 months</td>
<td>Male</td>
<td>LV</td>
<td>30%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>35</td>
<td>11 yrs 5 months</td>
<td>Female</td>
<td>Unknown</td>
<td>29%</td>
<td>Yes</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>36</td>
<td>11 yrs 10 months</td>
<td>Male</td>
<td>LV</td>
<td>4.5%</td>
<td>No</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>37</td>
<td>12 yrs 2 months</td>
<td>Male</td>
<td>LV</td>
<td>10%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>38</td>
<td>12 yrs 6 months</td>
<td>Male</td>
<td>LV, RV</td>
<td>Unknown</td>
<td>Yes</td>
<td>Non-survivor</td>
<td>Unknown</td>
</tr>
<tr>
<td>39</td>
<td>12 yrs 6 months</td>
<td>Female</td>
<td>SVC/RA junction</td>
<td>15%</td>
<td>No</td>
<td>Survivor</td>
<td>Positive</td>
</tr>
<tr>
<td>40</td>
<td>13 yrs 9 months</td>
<td>Male</td>
<td>LV</td>
<td>4%</td>
<td>No</td>
<td>Survivor</td>
<td>Unknown</td>
</tr>
</tbody>
</table>