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Peripartum cardiomyopathy: risk factor profile, familial aggregation, prognostic indicators and treatment

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TITLE: Peripartum Cardiomyopathy: Risk factor profile, familial aggregation, prognostic indicators and treatment

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YEAR OF SUMBISSION: 2013

DECLARATION

I, Dr. Kemilembe B. Tibazarwa, declare that this work is my own work. Where appropriate, I also acknowledge the contribution of others to this work in the respective Statements of Originality

This work is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: Dr. K. B. Tibazarwa_____

Date: _____ day of _____ [month], 2013

PREFACE

The contents of this PhD thesis are focussed on a grave form of heart failure in women that occurs most commonly within the first two months after delivery, leaving many young mothers who survive the initial episode morbidly ill for the rest of their lives. This condition is called peripartum cardiomyopathy (PPCM). Whilst studying the disease (PPCM), it was often necessary to make comparisons to its closest simulant, non-ischaemic dilated cardiomyopathy, with a special focus on the clinical, biochemical and genetic risk factors, which were used to inform a small trial of a new treatment modality for this condition.

This PhD in Cardiovascular Medicine was done as a 50% collaboration between the University of Cape Town and the University of the Witwatersrand.

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The journey has been long and extremely difficult. But if it can add just one stream to the rivers of scientific knowledge that my continent needs to blossom, it will all have been worth it.

ABSTRACT

Introduction: Peripartum cardiomyopathy (PPCM) is a form of unexplained heart failure associated with pregnancy that leads to considerable morbidity and mortality. Most patients present with acute postpartum heart failure that otherwise resembles dilated cardiomyopathy (DCM). Little is understood about the aetiopathogenesis of PPCM, including the genetic contribution; or its treatment. I hereby report on a comprehensive collection of studies that begins with a study of familial DCM in PPCM, which incorporated genetic screening for mutations in the Lamin-A gene (LMNA), known for their virulence in familial DCM, to assess their role in the development of PPCM. I then proceeded to identify risk factors and prognostic indicators for PPCM, including those identifiable through the electrocardiogram (ECG). Finally, given the shortage of evidence for a treatment modality specific to PPCM, a trial of the use of Bromocriptine in the treatment of PPCM was conducted.

Methods: Consenting prevalent and incident PPCM patients seen at two tertiary hospitals across South Africa, were recruited, and systematic analyses done of their full clinical profiles. A small subset of patients recruited immediately post-partum underwent a trial of Bromocriptine therapy. Another subset of PPCM patients had their respective first degree relatives undergo full clinical screening for DCM.

Results and Conclusion: Our findings support the notion that over a third of PPCM cases may form part of the spectrum of familial DCM. Routine family screening may be as much merited in PPCM as it is in DCM. The ECG appears to be a useful adjunctive tool in both screening and prognostication in resource-poor settings. Further assessment of the prognostication of PPCM suggests that increased LVESD, lower BMI and lower serum cholesterol at baseline may be independent predictors of poor outcome in patients with PPCM, while older age and smaller LVESD at baseline appear to be independently associated with a higher chance of LV recovery. In the trial reported herein, the addition of Bromocriptine to standard heart failure therapy appeared to improve left ventricular ejection fraction and a composite clinical outcome in women with acute severe PPCM.

ACRONYMS

	Clinical terminology
AV	Atrio-ventricular
BMI	Body mass index
CVD	Cardiovascular disease
DCM	Dilated cardiomyopathy
FDCM	Familial dilated cardiomyopathy
HF	Heart failure
HT	Hypertension
IDCM	Idiopathic dilated cardiomyopathy
LA	Left atrium
LV	Left ventricle (or left ventricular)
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
NYHA	New York Heart Association (functional class)
PPCM	Peripartum cardiomyopathy
PPCM-Br	PPCM patients randomised to the group receiving standard of care
PPCM-Std	PPCM patients randomised to the group receiving Bromocriptine therapy
	Genetic abbreviations
GWAS	Genome-Wide Association Studies
LMNA	Lamin A gene
MYH6	α-Myosin Heavy Chain
MYH7	β-Myosin Heavy Chain
PSEN2	Presenelin 2
SCN5A	Sodium Channel Voltage-Gated Type V α-Subunit
SNP	Single nucleotide polymorphism
TNNC1	Cardiac Troponin C
TNNT2	Cardiac Troponin T
	Metric and laboratory-based abbreviations
ml	millilitre
ms	millisecond
ng	nanogram
µl	microlitre
rpm	rates per minute (centrifuge)
	Abbreviated public sources of reference
NCBI	National Center for Biotechnology Information
NCBI BLAST	National Center for Biotechnology Information Basic Local Alignment Search Tool

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SIGNIFICANT WORKS TOWARDS PHD

A. Paper publications relevant to PhD[1]

1. Ntyintyane L, Stewart SS, Wilkinson D, Becker A, **Tibazarwa K**, Sliwa K. Incident and prevalent cases of heart disease presenting to a tertiary hospital in South Africa: Initial results from the Heart of Soweto Study. *S Afr Med J*. 2006 (October); 96 (10): 1020-1021. *Peer-reviewed* **IF 1.676**

2. **Tibazarwa KB**, Ntyintyane L, Stewart S, Wilkinson D, Sliwa K. Cardiovascular screening and hypertension in an African population: Heart awareness day in Soweto. *CVJA*. 2007 (May/June). Supplementum; 18 (3): S29, S31*Peer-reviewed* **IF 0.708**

3. **Tibazarwa K**, Ntyintyane L, Sliwa K, Gerntholtz T, Wilkinson D, Stewart S. A time-bomb of cardiovascular risk factors in South Africa: Results from the Heart of Soweto Study "Heart Awareness Days". *Int J Cardiol*. 2008; 20;132(2):233-9. *Peer-reviewed* **IF 6.802**

4. **Tibazarwa K**, Ntyintyane L, Sliwa K, Gerntholtz T, Wilkinson D, Stewart S. Profile and high prevalence of cardiovascular risk factors in an urban community: Heart awareness days in Soweto – 2007 Update. *S Afr Med J* 2007: 97 (11): 1106. [Abstract] *Peer-reviewed* **IF 1.676**

5. Sliwa K, Wilkinson D, Hansen C, Ntyinyane L, **Tibazarwa K**, Becker A, Stewart S. A broad spectrum of heart disease and risk factors in a black urban population in South Africa: Results from The Heart of Soweto Study Clinical Registry. ***Lancet.*** 2008 (15 March); 371: 915-22. *Peer-reviewed* **IF 33.633**

6. **Tibazarwa K**, Ntyintyane L, Sliwa K, Wilkinson D, Gerntholtz T, Stewart S. Profile and high prevalence of cardiovascular risk factors in an urban Black African population. *EQUINET Capacity Building Paper*, 2008 (June). University of the Witwatersrand, University of Queensland, Baker Heart Research Institute, and EQUINET: Harare.www.equinetafrica.org

7. Sliwa K, Forster O, **Tibazarwa K**, Libhaber E, Becker A, Yip A, Hilfiker-Kleiner D. Long-term outcome of peripartum cardiomyopathy in a population with high seropositivity for Human Immunodeficiency Virus. *Int J Cardiol.* 2011 Mar 3; 147(2):202-8. Epub 2009 Sep 13.*Peer-reviewed* **IF6.802**

8. Sliwa K, **Tibazarwa K**, Hilfiker-Kleiner D. Management of peripartum cardiomyopathy. *Curr Heart Fail Rep*. 2008 Dec; 5(4):238-44. *Peer-reviewed* **IF**

9. **Tibazarwa K**, Sliwa K. Peripartum cardiomyopathy in Africa: Challenges in diagnosis, prognosis and therapy. *Prog Cardiovasc Dis*. 2010 Jan-Feb;52(4):317-25. *Peer-reviewed* **IF 4.841**

[1] **IF** = Impact Factor

10. Sliwa K, Blauwet L, **Tibazarwa K**, Libhaber E, Smedema JP, Becker A, McMurray J, Yamac H, Labidi S, Struhman I, Hilfiker-Kleiner D. Evaluation of Bromocriptine in the treatment of acute severe peripartum cardiomyopathy: A proof-of-concept pilot study. *Circulation*. 2010 Apr 6;121(13):1465-73. *Peer-reviewed* **IF 14.429**

11. **Tibazarwa K**, Lee G, Mayosi BM, Carrington M, Stewart S, Sliwa K. The 12-Lead ECG in peripartum cardiomyopathy. *Cardiovasc J Afr*. 2012 Feb 16;23:1-8. doi: 10.5830/CVJA-2012-006. *Peer-reviewed* **IF 0.767**

12. Blauwet LA, Libhaber E, Forster O, **Tibazarwa K**, Mebazaa A, Hilfiker-Kleiner D, Sliwa K. Predictors of outcome in 176 South African patients with peripartum cardiomyopathy. *Heart*. 2013 (Mar); 99(5): 308-13. [Epub ahead of print 31 Oct 2012] *Peer-reviewed* **IF 4.223**

13. **Tibazarwa K**, Sliwa K, Wonkam A, Mayosi BM. Peripartum Cardiomyopathy and Familial Dilated Cardiomyopathy: A Tale of Two Cases. Cardiovascular Journal of Africa. 2013; 25(5): pp. e4-e7 *Peer-reviewed* **IF 0.708**

B. Conference presentations and publications relevant to PhD

1. May 2007. *Pan-African Society of Cardiology (PASCAR)*; Kenya. **Poster.**
   "Profile and high prevalence of cardiovascular risk factors in an urban Black African population: Heart awareness days in Soweto".

2. May 2007. *Southern African Hypertension Society (SAHS)*; Johannesburg. **Oral.**
   "Cardiovascular screening and hypertension in an urban African population: Heart awareness days in Soweto".

3. June 2007. *Public Health Association of Southern Africa (PHASA) – AFRIHEALTH Conference*; Pretoria. **Oral.**
   "Profile and high prevalence of cardiovascular risk factors in an urban Black African population: Heart awareness days in Soweto".

4. November 2007. *South African Heart Association (SAHA);* Sun City. **Poster.**
   "Profile and high prevalence of cardiovascular risk factors in an urban Black African population: Update on heart awareness days in Soweto".

5. December 2007. *Union for African Population Studies (UAPS)*; Tanzania. **Oral**.
   "Profile and high prevalence of cardiovascular risk factors in an urban Black African population: Heart awareness days in Soweto".

6. May 2008. World Congress of Cardiology; Argentina. **Oral.**
   "Profile and high prevalence of cardiovascular risk factors in an urban Black African population: Heart awareness days in Soweto".

7. June 2008. *UAPS*; Cape Town. **Oral.**
   "Profile and high prevalence of cardiovascular risk factors in an urban Black African population: 'Heart awareness' 2007 Update".

8. October 2008. *South African Heart Association (SAHA)*; Durban. **Oral.**
   "ECG characteristics in peripartum cardiomyopathy".

9. May 2009. *Heart Failure Association of Europe (HFA, under ESC)*; France. **Poster.**
   "ECG characteristics in peripartum cardiomyopathy".

10. August 2009. *European Society of Cardiology (ESC)*; Spain.
    a) "Delayed mortality in peripartum cardiomyopathy indicates need for long-term follow-up". **Oral.**
    b) "ECG characteristics in peripartum cardiomyopathy". **Poster.**

11. October 2009. *South African Heart Association (SAHA)*; Sun City. **Poster.**
    "Delayed mortality in peripartum cardiomyopathy indicates need for long-term follow-up".

12. August 2010. *South African Heart Association (SAHA)*; Sun City. **Oral.**
    "The genetics of peripartum cardiomyopathy".

13. December 2010. *South African Society for Cardiovascular Research (SASCAR)* and *British Society for Cardiovascular Research (BSCR)*; Joint Workshop. Hatter Cardiovascular Institute; London. **Oral.**
    "Peripartum cardiomyopathy: challenges in diagnosis, prognosis and therapy".

14. October 2011. *South African Heart Association (SAHA)*; East London (South Africa). **Oral.**
    "Familial aggregation of dilated cardiomyopathy in patients with post-partum cardiomyopathy. **Winner (conjoint) – Best Oral Presentation [Heart Failure].**

C. Training workshops/courses relevant to PhD

1. Cardiac Clinic (UCT). Intensive training in clinical echocardiography. January - March 2006.

2. Wits Health Consortium. Good Clinical Practice – Update. October 2006.

3. Joint UCT/NIH Training Workshop. Genetic Epidemiology. June 2007.

4. Heart Failure Society of South Africa (HeFSSA). Echocardiography Course. 2007.

5. Medical School of Hannover (DGF/NRF Research Cooperation Programme).

   Molecular Cardiology (Benchwork and Research). July 2010.

6. SAHA-based Mayo Clinic Group (Sun City). Echocardiography Workshop. August 2010.

7. Hatter Institute (London). SASCAR-BSCR Workshop. December 2010.

   (Applied Molecular Cardiology and Imaging).

8. Hatter Institute (Cape Town). Cardiogenetics; May - September 2011.

9. PASCAR (Uganda). Echocardiography Workshop. May 2011.

10. SAHA-based Mayo Clinic Group (East London). Echocardiography Workshop. October 2011.

1. INTRODUCTION

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1.1.2. Heart failure in South Africa

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1.1.4.8 Challenges to improving on the diagnosis and prognosis of PPCM in Africa

1.2. Management of peripartum cardiomyopathy (published review)

1.3. Problem statement and rationale

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1.5. Objectives

1.1. Literature Review

1.1.1 Cardiovascular disease in Africa

Historically, sub-Saharan African societies have fought a long and difficult battle against malnourishment and infectious disease, as the major cause of morbidity and mortality (Bradshaw et al, 2003; Steyn et al, 2006). The impact of globalisation and growing economies has had the additional influence of Westernising at least parts of the health profiles of these African countries (Tibazarwa et al, 2008). However, despite sporadic observations of a rise in the burden of non-communicable disease in these societies, there remains a paucity of data to describe the emergence and impact of cardiovascular disease (CVD) in low to middle-income countries.

A recent report on the largest township in South Africa (Soweto) helped to address this gap by providing novel and systematic data on the cardiovascular profiles of its population. The report highlights how, despite a sustained epidemic of HIV/AIDS epidemic (responsible for 41% and 64% of deaths for men and women aged 15 - 44 years, respectively), coronary artery disease, hypertensive heart disease and stroke already account for more than a third of deaths in those aged above 65 years (Sliwa et al, 2008[a]).

Apart from patients with a primary diagnosis of hypertension, most cases represented late clinical presentation, with established heart disease with more than one cause. Overall, the four most common diagnoses were: hypertension, heart failure, valvular heart disease and coronary artery disease. Overall, rheumatic valvular heart disease, the cardiomyopathies and tuberculous pericardial effusion combined, accounted for 40% of these newly diagnosed cases. On presentation, most patients had evidence of advanced and complex disease (Sliwa et al, 2008[a]). In all diagnostic groups, the rate of common risk factors for cardiovascular disease was very high; overall, only 13% had no risk factors, whereas 59% had several risk factors (Sliwa et al, 2008[a]).

The study provides preliminary evidence to show the effect of epidemiological transition in this population, which face many threats to their present and future cardiac health, including a combination of infectious and non-communicable forms of heart disease and late clinical presentations. This mirrors the findings of its sister-study, a large-scale community-based survey and awareness campaign that showed that, contrary to popular belief, common risk factors for atherosclerotic heart disease are highly prevalent in the urban Black African population of Soweto and resemble the proportions seen in Western societies, where all forms of CVD (and most particularly, coronary heart disease) has reached epidemic proportions (Tibazarwa et al, 2008).

1.1.2 Heart Failure in Africa: A South African study representative of Africa

Historically, heart failure in tropical African countries has been attributed to infective aetiologies of the poor, including: rheumatic heart disease, endocardial myofibrosis, tuberculous pericarditis, cardiomyopathy (Abengowe, 1979; Antony, 2000; Mayosi, 2007,) and anaemia-induced heart failure in areas where malaria and tuberculosis are endemic (Brown et al, 1975; Korner, 1980). The last few decades, however, have shown hypertension rise to take the lead in causing heart failure in Sub-Saharan Africa (Amoah et al, 2000, Sliwa et al, 2005, Mayosi, 2007). Still, heart failure and CVD from the region remains grossly under-reported, with only two countries (Nigeria and South Africa) accounting for the majority of Medline publications from the region.

Being the first systematic study to describe the epidemiological profile of cardiovascular disease in sub-Saharan Africa in such great clinical detail, the Heart of Soweto Study might be considered representative of many other African nations (Sliwa et al, 2008). Its strengths include it being the largest such study to have attempted to do so in a predominantly disadvantaged society that nevertheless has access to the commercial aspects of industrialisation. In this study, the most frequent primary diagnosis was heart failure. In comparison to men, proportionately fewer women

were diagnosed with heart failure [OR 0·89, 0·79–0·99]. In absolute terms, however, 112 more women than men were diagnosed with heart failure. Of the cases of heart failure seen in this Soweto study: a quarter had a mixed underlying aetiology; over a third had developed valvular dysfunction; 8% had a primary diagnosis of valve disease. The three most common forms of heart failure were the dilated cardiomyopathies (35%), which included: peripartum cardiomyopathy; heart failure second to hypertensive heart disease (33%); and right heart failure (27%), which was commonly associated with underlying cor pulmonale. Overall, half the patients with heart failure had moderate to severe systolic dysfunction and just over a quarter had impaired diastolic function. Mean left ventricular ejection fraction was: 34% in those with idiopathic dilated cardiomyopathy; and 39% in those with ischaemic cardiomyopathy. Patients with heart failure related to underlying hypertensive heart disease and valvular disease were most likely to have impaired diastolic function. Almost all ECGs in patients diagnosed with heart failure had some form of abnormality, with 16% patients having ECG evidence of left ventricular hypertrophy.

1.1.3 A focus on dilated cardiomyopathy

Having been characterised historically as a group of various forms of heart failure of "no apparent cause", the cardiomyopathies pose the greatest challenge of all the cardiovascular diseases in Africa, because of: their greater prevalence in impoverished communities; the difficulty in diagnosis, which often requires specialised cardiological investigation that is lacking in resource-poor environments; the lack of access to effective interventions, such as heart transplantation; and the high mortality associated with these often irreversible disorders of heart muscle (Sliwa et al, 2005). Nowadays, cardiomyopathies are defined as diseases of the myocardium associated with cardiac dysfunction (Richardson et al, 1996). They are classified into: dilated cardiomyopathy (DCM); hypertrophic cardiomyopathy (HCM); restrictive cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy (ARVC); and unclassified cardiomyopathies (Sliwa et al, 2005).

Idiopathic DCM (IDCM) is one form of DCM, comprising a clinical syndrome of heart failure characterised by impaired systolic function and left ventricular dilatation in the absence of an identifiable cause (Akinkugbe et al, 1991). IDCM occurs at any age (but remains more common in the third and fourth decades of life) and men are affected twice as commonly as women (Sliwa et al, 2005). In South Africa and Uganda, DCM accounts: for up to 17% of all cardiac conditions encountered at autopsy; and in many parts of Africa, for 17% to 48% of patients who are hospitalised for heart failure (Sliwa et al, 2005). In the West, up to one-fifth of IDCM patients will have familial DCM (FDCM), whereby, i.e. 15-25% of first degree relatives demonstrate IDCM at some time in their life (McKenna et al, 1997).

Table 1. Profile of cardiovascular disease in Soweto

	All (n=1593)	Hypertension (n=310)	Heart failure (n=704)	Valve disease (n=268)	CAD (n=165)	Other (n=146)
Sociodemographic profile						
Age (years)	52·8 (17·1)	58·3 (15·3)	55·1 (16·2)	45·7 (18·2)	56·7 (12·4)	38·8 (16·6)
Black African	1359 (85%)	265 (86%)	640 (91%)	243 (91%)	77 (47%)	134 (92%)
Women	939 (59%)	199 (64%)	409 (58%)	179 (67%)	68 (41%)	84 (58%)
No or standard education	416 (26%)	76 (26%)	204 (31%)	69 (27%)	29 (21%)	38 (27%)
Live in Soweto	842 (53%)	169 (55%)	418 (59%)	126 (47%)	42 (25%)	87 (60%)
Years living in Soweto	41 (27–50)	46 (35–54)	43 (30–52)	36 (20–50)	44 (40–55)	28 (17–39)
Risk factor profile						
Positive family history	405 (25%)	67 (22%)	168 (24%)	75 (28%)	60 (36%)	35 (24%)
Hypercholesterolaemia*	159 (22%)	54 (38%)	45 (17%)	16 (21%)	37 (35%)	7 (20%)
History of smoking	661 (41%)	112 (36%)	327 (46%)	84 (31%)	84 (51%)	54 (37%)
Risk factors						
None	209 (13%)	0	71 (10%)	78 (29%)	8 (5%)	52 (36%)
One	451 (28%)	72 (23%)	203 (29%)	77 (29%)	40 (24%)	59 (40%)
More than one	933 (59%)	238 (77%)	430 (61%)	113 (42%)	117 (71%)	35 (24%)
Clinical presentation						
NYHA class III or IV	486 (31%)	84 (27%)	255 (36%)	63 (24%)	32 (19%)	52 (36%)
Heart rate (min)	86 (21·5)	82 (19·2)	90 (20·3)	83 (18·3)	77 (19·2)	97 (37·6)
Systolic BP (mm Hg)	130 (27·1)	144 (29·0)	129 (26·1)	123 (24·4)	124 (27·1)	120 (23·4)
Diastolic BP (mm Hg)	73 (16·6)	78 (16·8)	75 (16·7)	68 (15·0)	70 (13·5)	71 (17·3)
Angina pectoris/chest pain	451 (28%)	89 (29%)	182 (26%)	70 (26%)	82 (50%)	28 (19%)
Oedema (pulmonary/peripheral)	494 (31%)	78 (25%)	275 (39%)	75 (28%)	35 (21%)	31 (21%)
Co-morbidity						
Renal dysfunction†	115 (10%)	23 (10%)	51 (10%)	20 (8%)	16 (11%)	5 (5%)
Anaemia‡	156 (13%)	30 (12%)	64 (11%)	22 (12%)	7 (6%)	33 (28%)
Diabetes	165 (10%)	41 (13%)	66 (9%)	13 (5%)	35 (21%)	10 (7%)
HIV positive	74 (5%)	4 (1%)	35 (5%)	10 (4%)	2 (1%)	23 (16%)
ECG profile§						
Sinus rhythm	1321 (92%)	267 (98%)	574 (90%)	222 (90%)	140 (98%)	118 (93%)
Atrial fibrillation	102 (7%)	12 (4%)	48 (8%)	32 (13%)	4 (3%)	6 (5%)
Arrhythmia	487 (34%)	79 (29%)	252 (40%)	74 (30%)	31 (22%)	51 (40%)
Bundle block	127 (9%)	11 (4%)	76 (12%)	23 (9%)	11 (8%)	6 (4%)
Echocardiographic profile§						
Mean LVEF	53·0 (17·4)	65·0 (10·8)	45·7 (18·3)	57·1 (13·4)	51·6 (15·9)	61·8 (8·8)
Systolic heart failure¶	415 (29%)	0	341 (52%)	37 (14%)	37 (31%)	0
Preserved heart failure¶	373 (26%)	0	316 (48%)	35 (13%)	22 (18%)	0

Data are number (%), mean (SD), or median (IQR). CAD=coronary artery disease. NYHA=New York Heart Association. BP=blood pressure. LVEF=left ventricular ejection fraction. ECG=electrocardiogram. *Hypercholesterolaemia defined as fasting total cholesterol serum concentration greater than 5·5 mmol/L (clinical data collected in 728 cases). †Renal dysfunction defined as a serum creatinine concentration greater than 160 µmol/L (clinical data in 1182 cases). ‡Anaemia defined as haemoglobin concentration less than 110 g/L in men and less than 100 g/L in women (clinical data in 1185 cases). §Echocardiographic data were available in 1431 and 1433 cases, respectively. ¶Systolic or preserved (diastolic) heart failure defined by the presence or absence of a left ventricular ejection fraction of 45% or less (measured on presentation to the cardiology unit) when clinical symptoms or signs of heart failure were present.

Table: Sociodemographic and clinical profile according to primary diagnosis

[Extracted from Sliwa et al, 2008[a]]

1.1.4 Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) has previously been considered a variant of DCM, although current criteria do not mandate the presence of a dilated left ventricle (Sliwa et al, 2010). PPCM is defined as per Lampert and Lang's (1995) modification of Demakis et al's definition (1971), i.e.: the development of new heart failure in the last month of pregnancy or within the first five months post-partum, in the absence of any other determinable cause for cardiac failure and in the absence of demonstrable heart disease prior to the last month of pregnancy; and bearing echo-cardiographical evidence of left ventricular systolic dysfunction (Ladwig et al, 1997). Restriction to this particular puerperal period serves to exclude pre-existing causes of cardiomyopathy that may be exacerbated by pregnancy, rather than arise as a result of pregnancy (Ladwig et al, 1997; Pearson et al, 2000). The vast majority of cases present within the first four months post-partum (Ladwig et al, 1997; Fett et al, 2003; Sliwa et al, 2006[a]), with only 10% presenting in the last month ante-partum (Ladwig et al, 1997; Sliwa et al, 2006[a]).

1.1.4.1 The epidemiology of Peripartum Cardiomyopathy

The incidence reportedly varies from 1 in 3000 - 4000 deliveries in Western societies (Satpathy et al, 2008) to 1 in 1000 in developing societies (Sliwa et al, 2006[b]), with the highest incidence of 1 in 300 live births being reported in Haiti (Fett et al, 2005). The apparent rise in incidence across all geographical borders is most likely due to improved awareness and diagnostic measures (Satpathy et al, 2008). In a large African centre, PPCM was seen in 1.5% of all patients with heart failure attending the centre during one year (Stewart et al, 2008). While studies in the USA show PPCM to occur more in women of African descent and those aged above 30 years (Ventura, 1991), PPCM has been reported across the world and across all ages and parities (Ladwig et al, 1997; Fett et al, 2003). The younger age of PPCM patients in developing nations (Fett et al, 2003; Sliwa et al, 2006[b]) may

reflect the younger age of the bulk of reproductive activity in developing nations. Multiple gestation within the index pregnancy has been implicated in causing PPCM in 7-10% of women (Veille et al, 1984), while multi-parity is a more widely documented predisposing factor to the development of PPCM (Sliwa et al, 2006[b]; Satpathy et al, 2008). However, recent studies have suggested that the effect of multi-parity is far less significant in the development of PPCM (Fett et al, 2005). PPCM also appears to occur more commonly in women who breastfeed for longer (Watkins et al, 2005).

PPCM is an important cause of mortality and chronic, debilitating morbidity that affects relatively young women in the reproductive age group. It is the second most-common aetiology of cardiomyopathy-related cardiac transplant in women in the United States (Habli et al, 1994); hence it poses a considerable burden on the health, economic and other social sectors of society.

1.1.4.2 The diagnosis of PPCM

The diagnosis of apparently unexplained heart failure is based on symptoms and clinical findings in combination with appropriate investigations, such as electro-cardiography, chest radiograph, biomarkers and echocardiography. PPCM is a diagnosis of exclusion. However, there is no agreement on the exclusion of pre-eclampsia. Unfortunately, the inclusion of patients with varying degrees of gestational hypertension, in the index as well as prior pregnancies, has contributed greatly to the discrepancy in reported characteristics of PPCM. This may also form the basis for the difference in the puerperal time of presentation. Studies comprising greater proportions of patients with pre-eclampsia, and of greater severity, tend to have far greater concentrations of PPCM cases presenting in the last month of pregnancy (Sliwa et al, 2006[a]; Duran et al, 2008; Sliwa et al, 2011). In contrast, studies that have attempted to minimize the inclusion of patients with pre-eclampsia to milder forms show a clear post-partum peak in the presentation of PPCM, with reported onset of symptoms most commonly being 2-62 days post-partum (Satpathy et al, 2008; Fett et al, 2005).

Symptoms of PPCM

PPCM often presents with acute onset of heart failure. The presentation, with reduced cardiac output, tissue hypo-perfusion, increase in the pulmonary capillary wedge pressure and tissue congestion, is often life-threatening and requires urgent treatment. Most patients report severe shortness of breath of the order NYHA-FC III – IV (Sliwa et al, 2008[a]), presenting with: lower limb swelling; some with right upper quadrant pain; as well as other symptoms of acute heart failure.

Signs of PPCM

Most patients will manifest grade III – IV functional class by being overtly tachypnoeic in the clinic or hospital room. Systematic clinical assessment of the peripheral circulation, venous filling and peripheral temperature are important. Most patients (Lee, 1991) have a mild resting tachycardia (Tibazarwa et al, 2010). Blood pressure averages are usually normal, with larger prospective studies reporting mean systolic and diastolic blood pressure of 113±19mmHg and 75±12mmHg, respectively (Sliwa et al, 2011). Bedside examination often suggests a dilated cardiomyopathy in the lateral and/or downward displacement of the apex, with dyskinetic apex and sometimes palpable gallop rhythm (Talley et al, 2006). Arterial blood gas and pulse oximetry are important in a first assessment of the severity of respiratory insufficiency.

Complications of PPCM

Thromboembolic complications are common (Lee, 1991; Liakakos et al, 2009; Dresang et al, 2008). Often these will manifest in the form of pulmonary embolism and stroke, usually resulting from embolised mural thrombi in the dilated myopathic chambers of the heart. Rarely, this has culminated in embolic retinal artery occlusion that caused acute onset of unilateral blindness in the patient with PPCM (Liakakos et al, 2009). Bearing in mind that pregnancy itself potentiates a state of hyper-coagulability (Dresang et al, 2008), the added risk in PPCM is a major concern. Although anti-coagulation has been recommended in PPCM patients with left ventricular ejection fractions of less

than 35% (Lata et al, 2009), there remains no systematic data to support this practice for PPCM or for other forms of left ventricular dysfunction in sinus rhythm (Hirsh et al, 2003). As with other forms of cardiomyopathy, arrhythmias are a common complication of PPCM and are further described below.

Routine biochemical tests

The full blood count is usually normal (given that significant anaemia has been excluded as a separate potential cause of heart failure), with normal electrolytes and bio-markers of renal function. In advanced cases, congestive cardiac failure will cause renal insufficiency and a pre-renal biochemical profile. Most patients have normal liver function tests. In PPCM patients with abnormal liver function tests, this often represents the acutely congested liver; and manifests as raised canalicular enzymes, with only slightly raised transaminases. While older studies suggested micro-nutrient deficiency could play a role in the development of PPCM (Ventura, 1991), many of these were smaller descriptive studies. Since then, a comparative study on a larger series of PPCM patients has shown micro-nutrient deficiencies not to differ significantly between cases and controls (Fett et al, 2003). The micro-nutrients included selenium, vitamins A-, B12-, C-, and E-, as well as beta-carotene (Fett et al, 2003). Hence these tests are no longer considered necessary in the diagnostic work-up of patients with PPCM.

To date, many centres in developing countries have considered HIV serology to be an important baseline investigation, as HIV-positivity formed an exclusion criteria for clinical studies in the face of HIV-associated cardiomyopathy bearing clinical resemblance to PPCM. However, novel data report that patterns of left ventricular function and mortality were similar between PPCM patients with and without HIV co-infection (Sliwa et al, 2011).

Urine samples need to be assessed for albumin and other proteinuria, as an essential means of excluding pre-eclampsia. While a proteinuria presence helps to confirm the diagnosis of pre-eclampsia, its absence does not exclude it.

The electrocardiogram in PPCM

The vast majority of patients present in sinus rhythm (Elkayam et al, 2001), although little else has been reported on the occurrence of other common electrocardiographic abnormalities in PPCM. Arrhythmias in PPCM occur as with cardiomyopathies and heart failure in general (Tibazarwa et al, 2009) and include: atrial fibrillation, frequent premature ventricular systoles, ventricular tachy-arrhythmias, and bundle branch block (Lamparter et al, 2007) - the latter occurring more frequently among chronic cases (Duran et al, 2008). While ventricular arrhythmias have been reported in up-to one-fifth of patients thought to have PPCM (Diao et al, 2004), one of the few comparative studies showed the more life-threatening complex ventricular arrhythmias to occur almost as often in PPCM (60%) as in its closest variant, idiopathic dilated cardiomyopathy (76% of patients) (O'Connell et al, 1986). Another study suggests that subsequent pregnancy in PPCM patients might result in deterioration of ventricular arrhythmias through various mechanisms, including triggering premature ventricular extra systoles as the cardiomyopathy worsens in subsequent pregnancy (Yamada et al, 2009). This arrhythmic deterioration is thought to either precede (and hence facilitate) further decompensation of heart failure, or else to be triggered by already worsening left ventricular dysfunction in asymptomatic patients (Yamada et al, 2009). Furthermore, they suggest that ventricular arrhythmias occurring in the acute phase of PPCM are likely to improve with left ventricular recovery, whereas those in patients not recovering will more likely require intervention (Yamada et al, 2009).

Radiological findings in PPCM

Chest Roentgenogram

Typically, the chest x-ray will show cardiomegaly, pulmonary congestion (including upper lobe diversion and Kerley-B lines) and, occasionally, right-sided pleural effusion, in keeping with more severe congestive cardiac failure.

Echocardiography

Echocardiography has become the mainstay for definitive diagnosis of PPCM. Diagnosis requires echocardiographic evidence of left ventricular systolic dysfunction (ejection fraction < 45%) (Sliwa et al, 2008[b]). Echocardiography allows for visual estimations of global and regional cardiac chamber function to assess systolic and diastolic function, thrombotic complications of PPCM, as well as to exclude other organic heart disease. While most reports document elevated left ventricular end-diastolic diameters (LVEDD) in PPCM (averaging 6cm in most studies), not all patients will present with dilated left ventricles. Hence the current definition of PPCM does not mandate the presence of left ventricular dilatation.

Magnetic Resonance Imaging (MRI)

Over the last few years, MRI has received increasingly favourable attention in the evaluation of patients with PPCM. This is due to the ability to elicit the presence of myocardial fibrosis using late enhancement imaging in cardiac MRI with a marker of the persistence of left ventricular dysfunction (32). Given the poor understanding of the pathophysiology of PPCM and the conflicting data on myocarditis as the causative process, there has been hope that cardiac MRI would also help to clarify pathogenetic mechanisms. Further attributes of cardiac MRI are its ability to assess myocardial kinesia and ejection fraction, and view the shapes, size and contents of the cardiac chambers through the use of cine cardiac MRI (Marmursztejn et al, 2009). One study of over 1000 consecutive patients with heart failure assessed eight women considered to have PPCM, yet found: no specific pattern of PPCM on cardiac MRI; no late enhancement; and no difference in MRI features between patients recovering within the first two years and those who failed to recover systolic function

(Mouquet et al, 2008). However, the PPCM sample size was small, making more research mandatory.

Cardiac Catheterisation

As with other forms of heart failure, in patients with PPCM cardiac catheterisation and angiography remains the gold standard for the determination of systolic function. Yet few systematic reports of PPCM have conducted haemodynamic studies; those existing having shown decreased cardiac output and high filling pressure, but normal coronary arteriograms (Ventura, 1991).

1.1.4.3 The immunology of PPCM

Increasingly, studies have suggested myocarditis to be a key pathogenetic process in the development of PPCM (O'Connell et al, 1986; Melvin et al, 1982; Midei et al, 1990; Sanderson et al, 1979). Endomyocardial biopsies have strongly supported this theory (O'Connell et al, 1986), as has the demonstrable clinical and histological improvement of PPCM patients on immuno-suppressive therapy (O'Connell et al, 1986), such as prednisone and azathioprine (Melvin et al, 1982). The specific aetiology of the underlying myocarditis remains to be confirmed. For many years, the enhanced suppressor cell activity during pregnancy was thought to predispose pregnant women exposed to cardiotropic viruses to more severe forms of viral myocarditis (O'Connell et al, 1986). Common pathogens implicated include Coxsackie and encephalo-myelocarditis viruses (O'Connell et al, 1986), as well as Parvovirus B 19 (Kuhl et al, 2005). Adenovirus, HSV-6, EBV, and CMV DNA have been isolated in endomyocardial biopsies of PPCM patients (Ramaraj et al, 2009). However, myocarditis could simply reflect the immune response from any other form of myocardial damage.

In essence, the molecular components of the inflammatory process in PPCM have been found to be very similar to that of idiopathic dilated cardiomyopathy, with elevated tumour necrosis factor alpha

(TNF-) and C-reactive protein (CRP) and (in particular) persistently raised leukocyte cytokines despite treatment (Watkins et al, 2009).

The above-mentioned aetiology is not restricted to PPCM, but may form the basis of a variety of dilated cardiomyopathies. First, the prevalence of myocardial inflammation in PPCM appears to be similar to that of age-matched patients with idiopathic dilated cardiomyopathy (Rizeq et al, 1994) and has thus far failed to predict outcome in PPCM (Felker et al, 2000). Secondly, viral clearing has been associated with clinical improvement in both PPCM and idiopathic dilated cardiomyopathy (Sliwa et al, 2006[b]). Unique to PPCM, however, are certain immune activation processes, such as the finding of elevated levels of the apoptotic marker Fas/Apo-1, which predicts mortality (Sliwa et al, 2006[a]) and is considered causative (Sliwa et al, 2006[b]). Class G3 immunoglobulins (Lamparter et al, 2007; Wairraich et al, 2005), which act against cardiac myosin (Sliwa et al, 2006[b]), bear the sub-class IgG3. This IgG3s sub-class has pro-inflammatory characteristics and may be associated with higher NYHA-FC at presentation (Wairraich et al, 2005). While idiopathic dilated cardiomyopathy demonstrates highly selective up-regulation of the IgG3s sub-class of G3 immunoglobulins, the humoral response in PPCM is not sub-class-restricted, with class G and all sub-class immunoglobulins being raised in PPCM (Wairraich et al, 2005). Sliwa et al identified increased plasma levels of the inflammatory cytokine tumour necrosis factor (TNF) α, C-reactive protein and a plasma marker of apoptosis, Fas/Apo-1 in a large population of newly diagnosed patients with PPCM (2006[a] and 2006[b]). Furthermore, C-reactive protein levels on presentation demonstrate linear correlations with left ventricular end-diastolic, end-systolic diameters and, inversely, with left ventricular ejection fraction (Sliwa et al, 2006[a]). Given the ethnic variations in serum levels of C-reactive protein, it was therefore proposed that an increase in the intensity of an inflammatory response could be one of the many factors contributing to the development of PPCM (Sliwa et al, 2006[b]).

Ground-breaking data on the pathogenesis of PPCM emerged in recent reports of enhanced oxidative stress in a mouse model for PPCM (i.e. mice with a cardiac-specific deletion for signal

transducer and activator of transcription-3 [STAT 3]) being the trigger for activation of cathepsin D. Cathepsin D is a ubiquitous lysosomal-enzyme that subsequently cleaves serum prolactin into its anti-angiogenic and pro-apoptotic 16-kDa form(Hilfiker-Kleiner et al, 2007[a]).The presence of this shorter aberrant form of prolactin was associated with endothelial inflammation, impaired cardiomyocyte metabolism, reduced myocardial contraction and increased apoptosis. This suggested that oxidative stress, inflammation and prolactin maybe inter-connected and responsible for initiating PPCM. Similar evidence of increased oxidative stress, enhanced cathepsin D activity and increased prolactin cleavage has been shown in patients with acute PPCM (Hilfiker-Kleiner et al, 2007[a]), who had higher levels of circulating serum 16-kDa prolactin. This led this research group to consider new treatment options in PPCM by using Bromocriptine to block prolactin further upstream.

1.1.4.4 The genetics of PPCM

Only a few studies have assessed the genetics of peripartum cardiomyopathy (Ventura, 1991; Pierce et al, 1963), with the occurrence of PPCM in twins having been reported by Constanzo-Nordin et al (Constanzo-Nordin et al, 1989). Most recently, two studies conducted in Western societies demonstrated familial disease and went further to suggest that: a sub-set of PPCM patients may in fact be familial IDCM (FDCM) presenting in pregnancy (Van Spaendonck et al, 2010; Morales et al, 2010); while a smaller sub-set may be due to sporadic mutations (Morales et al, 2010). This was after their demonstration of genetic mutations similar to those found in FDCM among their recruited PPCM patients. Specifically, mutations found in patients with familial disease: were on TNNC1 of the troponin C gene (Van Spaendonck et al, 2010), as well as MYH7, SCN5A and PSEN2 (Morales et al, 2010); while MYH6 and TNNT2 mutations were found in patients with sporadic disease (Morales et al, 2010). Interestingly, the Lamin A/C mutation (considered the most virulent among patients with FDCM, due its phenotype of aggressive heart failure, arrhythmia and high mortality (Taylor et al,

2003), was not found in either of these PPCM studies. However, the small sample sizes and retrospective nature of identifying PPCM patients may have limited the spectrum of PPCM patients recruited for genetic studies - one study recruited patients from known families with FDCM. For example, PPCM patients bearing the LMNA/C mutation may have died before the onset of their study period.

Polymerase chain reaction testing has been recommended in assessing the role of cardiotropic viruses in inflammatory cardiomyopathies such as PPCM; and not just in endomyocardial biopsy tissue, but possibly also in the study of peripheral blood samples, particularly for IgM detection during the viraemic phase (Fett et al, 2008[a]).

Persistent microchimerism has been implicated in the aetiopathogenesis of PPCM (Ansari et al, 2002). This is the presence of foetal cells in maternal circulation, which can be investigated through the demonstration of foetal male chromosomal DNA in maternal plasma within a narrow period from term pregnancy to a few days post-partum (Fett et al, 2003). This test remains to be validated in the evaluation of PPCM. However, high levels of foetal microchimerism in mono-nuclear cells has been found in PPCM patients bearing high titres of auto antibodies; these levels of foetal microchimerism being significantly higher than in control non-PPCM mothers during the third trimester of pregnancy, at term, and in the first week post-partum (Ansari et al). Most of these auto-antibodies happen to target human cardiac tissue proteins of 37kD, 35KD and 25kD (Ramaraj et al, 2009; Lamparter et al, 2007), leading to auto-immune myocarditis (Sliwa et al, 2006[b]; Lamparter et al, 2007). This emphasises the need to facilitate detection tools for foetal microchimerism.

The pro-apoptotic gene Nix or Bnip3 has been considered a possible precipitant of apoptosis in PPCM and heart failure in vitro (Hilfiker-Kleiner et al, 2008). Up-regulation of Bnip3: was also observed in postpartum ventricular tissue of mice with a cardiomyocyte-specific deletion of the signal transducer and activator of transcriptin-3 (STAT3, STAT3-KO mice); and was associated with a high degree of myocardial apoptosis (Hilfiker-Kleiner et al, 2007[a]).

1.1.4.5 Prognosis

Local data (Johannesburg)

Our research unit studied a large cohort of PPCM patients and described a pro-inflammatory response in PPCM patients with: elevated plasma levels of TNF-alpha, Fas-Apo-1, Interleukin-6 (IL-6) (Sliwa et al, 2002); and a positive correlation between C-reactive protein (CRP) levels, left ventricular (LV) end-diastolic and end-systolic diameters at the time of diagnosis (Sliwa et al, 2006[a]). A potential causative effect of a cascade involving enhanced oxidative stress, subsequent activation of cathepsin D and cleavage of serum prolactin in an anti-antigenic, pro-apoptotic and pro-inflammatory 16-kDa form on the development of PPCM was later postulated by members of the collaborative research group (Hilfiker-Kleiner et al, 2007[a]; Tabruyn et al, 2007). Moreover, they recently reported a positive correlation of this cascade in PPCM patients who failed to recover within a six-month follow-up (Forster et al, 2008), suggesting that oxidative stress, inflammation and prolactin may all be inter-connected in a vicious cycle of events responsible for initiating and progressing PPCM.

The first prospective report of the long-term outcome of a large series of PPCM patients in Africa was also conducted by the same research team; it provided much needed data on the "natural history" of PPCM patients who received only standard heart failure treatment. At baseline, this cohort had a mean age of 30±7 years; with one-third being primigravid women and a similar proportion being co-infected with HIV. Almost 90% of patients presented with: NYHA functional class III-IV; the mean left ventricular ejection fraction (LVEF) was 30±9%. The two-year mortality rate was 28%. Contrary to what most other Western studies have reported, only a minority of these (10%) died by six months. Interestingly, the novel finding of this study was not only the continuous high mortality of PPCM patients occurring beyond six months independent of HIV infection and subsequent pregnancy, but also the high number of patients who delayed or failed to recover their ejection fractions, with the earliest evidence of recovery being at 18 months. Of patients still enrolled at 6 months, 20% died over the remaining 18-month period, despite functional recovery.

Mean LVEF of surviving patients was: 44±11% at six-months, 46±13% at 12-month follow-up and 50±14% at 24-month follow-up [see Figure 1]. This finding strongly encourages the need for long-term clinical follow-up and management of women with PPCM.

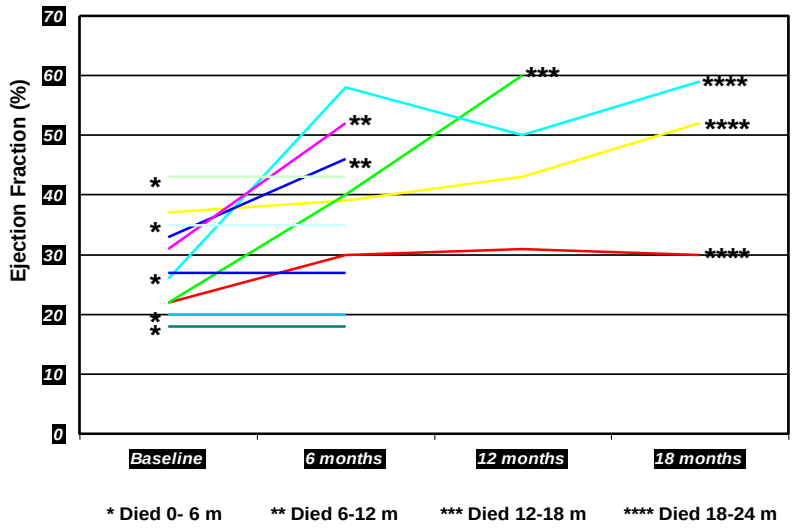


Figure 1: Trend in %LVEF with time in PPCM;

By point in time of death.

This graph of mortality among the 11 HIV-negative PPCM patients illustrates that even among patients who recovered their ejection fraction within six months, the risk of mortality persists well beyond six months of follow-up. From this graph, it appears neither baseline EF, six-month EF, nor the degree of change in EF within the first six months can predict the point in time of death.

[Extracted with permission from Sliwa et al, Int J Cardiol. 2011 Mar 3;147(2):202-8]

1.1.4.6 Summary of global data on prognosis of PPCM

Recovery from PPCM has often been limited to achievement of left ventricular ejection fraction above 50% (Fett et al, 2005 and 2009[a]), while the term "full recovery" in PPCM has been considered to be achievement of both NYHA-FC I and left ventricular ejection fraction above 50% (Fett et al, 2005; Duran et al, 2008).

Historically, most studies have suggested that full recovery of left ventricular function occurs in up-to 50% of patients (Pearson et al, 2000; Elkayam et al, 2001; O'Connell et al, 1986; Forster et al, 2008). Larger and more recent prospective studies of patients from lower and middle-income cohorts suggest; only a quarter will fully recover by the end of the first six months (Fett et al, 2005; Duran et al, 2008); while 10-15% will die by six months (Sliwa et al, 2006[a] and 2009). *Long-term* prospective outcome studies have shown overall recovery in a quarter of all PPCM patients, the vast

majority of these being achieved only 18 - 24 months after diagnosis (Sliwa et al, 2011; Forster et al, 2008). Long-term *overall* mortality rates in Haiti, Turkey and South Africa are estimated at 15% (Fett et al, 2005) to 30% (Duran et al, 2008; Sliwa et al, 2009[a]), with average death occurring: at 54±41 months in one study (Duran et al, 2008); but within the first couple of months in another study (Fett et al, 2005). This is markedly higher than the mortality rates of 0 - 6% (Lamparter et al, 2007; Brar et al, 2007; Mielniczuk et al, 2006; Felker et al, 2000) and 9% (Elkayam et al, 2001) reported in the United States. Interestingly, two of these United States studies demonstrate low mortality rates of 0% (Lamparter et al, 2007) and 6% (Felker et al, 2000), despite the high prevalence of myocarditis within their PPCM cohorts (of 50% (Felker et al, 2000) and 29% (Lamparter et al, 2007), respectively). Felker et al's cohort from the United States further showed PPCM to have a far better prognosis than all other forms of cardiomyopathy (2000).

Earlier studies consistently showed a greater chance of survival in patients with higher ejection fractions and smaller left ventricular end-diastolic diameters at baseline (Sliwa et al, 2006[a]; O'Connell et al, 1986). The suggested cut-off values for left ventricular dimensions that predict a favourable outcome at six months after first presentation are: >27% for the ejection fraction; and ≤5.5cm for the end-diastolic diameter (Duran et al, 2008). Strikingly, recent data imply that the impact of *baseline and six-month* left ventricular dimensions and function in predicting outcome falls away among chronic PPCM patients, i.e. those who failed to recover fully by six months (Fett et al, 2005 and 2009[a]). These long-term outcome studies present a consistent message that the natural history of PPCM goes far beyond what the six-month prognoses were suggesting in earlier years. They show that while a minority of only 25% of PPCM patients will recover, the vast majority of these will only do so from 18 to 24 months onwards.

Perhaps inclusion criteria that strictly excludes pre-existing cardiovascular disease (such as pre-eclampsia) applied in some of the more recent prospective studies of PPCM has facilitated this revelation, which further strengthens the theory that the higher rates of rapid recovery in earlier

studies could possibly be attributed to reversible effects of gestational hypertension. However, it may remain true that inherent differences in socio-genetic predisposition of PPCM patients in the United States (Elkayam et al, 2001; Felker et al, 2000) and in less developed societies (Sliwa et al, 2009[a]; Fett et al, 2005; Duran et al, 2008) account for the better prognosis in the former group.

Consistent among studies of PPCM is the high risk of relapse with subsequent pregnancy (Elkayam et al, 2001; Sliwa et al, 2004), with remarkable levels of mortality post-partum, alongside a strong association between TNF-α and deteriorating left ventricular function (Sliwa et al, 2004). A recent publication by Forster at al (2008) in an African cohort showed that a significantly higher baseline NT-proBNP and failure to decrease oxLDL, IFN-gamma and prolactin were all associated with poor outcome in patients with newly diagnosed PPCM; this suggests a potential role of these factors in the pathophysiology of PPCM and allows for further exploration of target substances for monitoring and treatment programmes.

1.1.4.7 Therapy in PPCM

So far, medical management and therapy of patients with PPCM has been similar to other forms of heart failure, with detailed reviews having been attempted (Sliwa et al, 2008[b]).

Administration of diuretics is indicated in the presence of symptoms secondary to fluid retention, whereas ionotropic agents are recommended in the presence of peripheral hypo-perfusion (particularly hypotension and decreased renal function). Temporary mechanical circulatory assistance should be used in patients with acute heart failure who are not responding to conventional therapy. Generally favourable outcomes have been attributed to the young age of recipients and to the relatively short duration of heart failure, resulting in minimal end-organ damage. Conventional pharmacological therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (and, if haemo-dynamically stable, beta-adrenergic blockers) are

effective in the treatment of PPCM. Because of the potential hazardous effects on the foetus, hydralazine (with or without additional nitrates) should replace ACE-inhibitor use during pregnancy. Digitalis, an inotropic agent, is also safe during pregnancy and may help to maximize contractility and rate control. However, its use requires close monitoring of the patient, which may prove difficult in low-resource environments.

Cardiac transplantation has been performed successfully in PPCM patients. Given the potentially inflammatory nature of PPCM with up-regulated inflammatory cytokines, such as TNF-alpha, IL6 and Fas-Apo-1, there may be a role for immuno-modulatory therapy. A prospective study of 59 consecutive women reporting with PPCM reported a significant reduction in TNF-alpha and improved outcome in patients receiving the immuno-modulating agent pentoxifylline in addition to conventional therapy (that included ACE-inhibitors and beta-blockers) (Sliwa et al, 2002).

However, further research into the pathogenetic mechanisms of PPCM by Hilfiker-Kleiner et al (2007[a]) revealed the co-existence of systemic oxidative stress and significantly higher prolactin levels in patients with PPCM; this supports the notion of the previously published concept that oxidative stress-mediated prolactin cleavage into its detrimental 16kDa form is crucial for the initiation of PPCM and subsequently for the release of inflammatory cytokines. This suggests that inhibition of prolactin with Bromocriptine may prevent a prolonged inflammatory response via activation and perpetuation of the inflammatory cascade. A recent pilot study in newly diagnosed PPCM patients suggested that this process can be ameliorated or even abolished by administering the prolactin inhibitor Bromocriptine (Sliwa et al, 2009[b]).

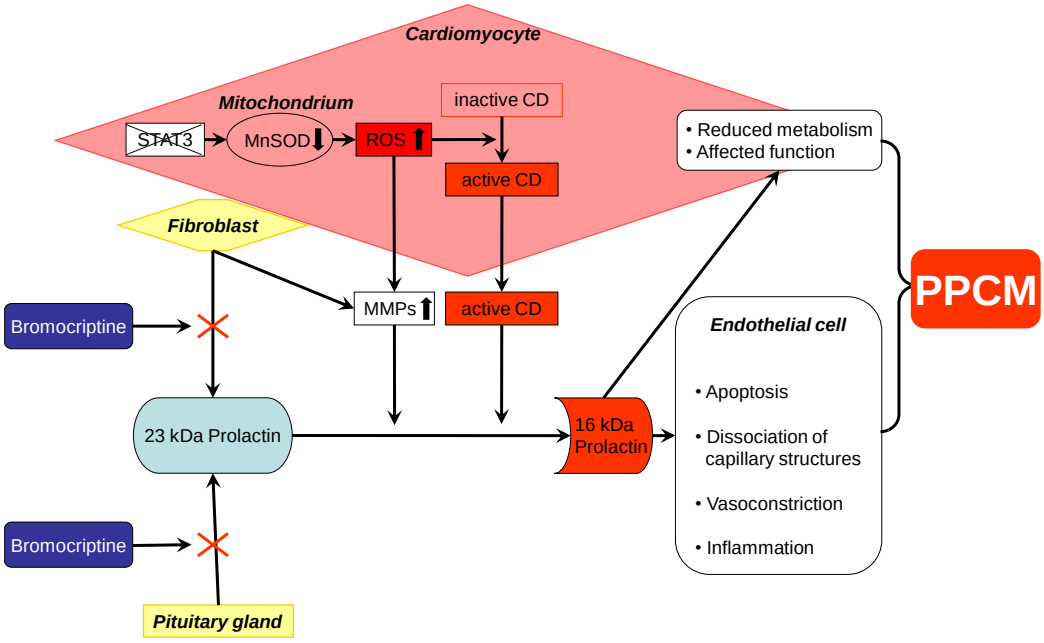


Figure 2: Development of peripartum cardiomyopathy in the mouse model: The STAT3-oxidative stress-cathepsin D-16 kDa cascade.

By knocking out STAT 3 in the cardiomyocyte, the expression of the oxygen radical scavenger manganese sodium dismutase (MnSOD) is attenuated. As a consequence, reactive oxygen species (ROS) accumulate and promote the release of matrix metalloproteinases (MMPs) and the production of active cathepsin-D (CD) from the cardiomyocyte. Prolactin is produced by the pituitary gland and cardiac fibroblasts. CD and MMPs cleave this 23kDa full-length form into its 16kDa form. In cardiomyocytes, this leads to affected function and endothelial cells react with vaso-constriction, apoptosis, inflammation and dissociation of capillary structures, which display peripartum cardiomyopathy. The blockage of systemic and local prolactin release by Bromocriptine prevents the generation of 16 kDa prolactin, thereby preventing this fragment's detrimental effects on endothelial cells and cardiomyocytes.

[Extracted with author's permission from Selle et al, 2009.]

1.1.4.8 Challenges to improving the diagnosis and prognosis of PPCM in Africa

The lack of uniformity in case definitions of PPCM may result from clinicians differing in opinion about what constitutes an alternative cause of heart failure in patients evaluated for the diagnosis of PPCM; and it is also fuelled by the shortage of large studies for this rare disease. Confounding the issue are studies comparing PPCM patients with various levels of gestational hypertension to those who are hypertension naïve.

In an attempt to address this deficit, the American College of Cardiology (ACC) guidelines now classifies PPCM as an entity on its own (Maron et al, 2006), while the European Society of Cardiology (ESC) has taken active measures towards this process (Sliwa et al, 2010). To benefit from the success

in recognizing PPCM as a disease on its own, awareness of PPCM must be raised amongst clinicians and across societies, as this has been shown to contribute significantly to delayed diagnosis and under-reporting of PPCM (Sliwa et al, 2008[b]; Deneux-Tharaux, 2005). This will have a great impact in developing societies, where levels of awareness of cardiovascular disease are disproportionately lower than the actual prevalence of cardiovascular disease (Sliwa et al, 2008[a]) and particularly so in Africa (Tibazarwa et al, 2008) - and more so in the case of PPCM.

The plight of poverty-related infectious disease has over-ridden many African countries' ability to pay sufficient attention to heart failure. Despite the greatest burden of heart failure in Africa caused by two infectious disease, rheumatic heart disease and tuberculous pericarditis (Sliwa et al, 2005), inequitable access to facilities permitting the definitive diagnosis and management of these patients has contributed to the paucity of research data on the epidemiology of the many various forms of heart failure in sub-Saharan Africa. To date, no population-based epidemiological studies on PPCM in Africa have been published (Mayosi, 2007). Like idiopathic dilated cardiomyopathy, PPCM is a diagnosis of exclusion. To confirm that the case fits the definition, Lampert et al (2005) mandate the use of sophisticated echocardiography. The exhaustive requirements for serological tests, imaging and, in more mature women, cardiac catheterization to exclude coronary artery disease, falls beyond the capacity of most tertiary health centres in sub-Saharan Africa. Patients in rural areas continue to suffer grossly inequitable access to health facilities capable of even the most basic of these investigations. Recently, however, joint efforts to increase global awareness of the burden of cardiac disease in Africa has, to some extent, facilitated access to practical solutions, such as partially-subsidized portable echocardiography equipment and regional sharing of laboratory services for the rarer disease tests.

Across the world, a major challenge to clinicians remains the gross overlap between clinical features of PPCM and the dyspnoea, fatigue and pedal oedema of normal pregnancy (Tibazarwa et al, 2010; Sliwa et al, 2008[b]; Lata et al, 2009; Abboud et al, 2007). In this regard, recent studies have suggested

adoption of the ECG as a simple screening tool for PPCM (or at least for heart failure) in women presenting peripartum with symptoms and signs resembling those of PPCM, particularly shortness of breath and fatigue.

Globally, the gap in available data on PPCM remains vast and the shortage of long-term outcome studies is also evident. We are only aware of seven long-term outcome studies (Fett et al, 2005; Habli et al, 2008; Duran et al, 2008; Sliwa et al, 2009[a]; Elkayam et al, 2001; Amos et al, 2006; Fett et al, 2009), two of which were retrospective in nature (Habli et al, 2008; Amos et al, 2006). Much of the gaps in the literature should be overcome with new research into the aetiology of PPCM and also by the creation and use of registries (Damasceno et al, 2007).

1.2 Management of PPCM – A Published Review

Management of Peripartum Cardiomyopathy

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Peripartum cardiomyopathy (PPCM) is a form of heart failure that occurs in women within 1 month of predelivery and 5 months postdelivery. Echocardiography demonstrates features of cardiomyopathy with impaired ejection fraction; global dilatation and thinned-out walls are sometimes present. The symptoms and signs of PPCM are similar to those in patients with idiopathic dilated cardiomyopathy. The acute form of PPCM is a clinical syndrome, with reduced cardiac output, tissue hypoperfusion, and increase in the pulmonary capillary wedge pressure. Monitoring of the patient with the acute form of PPCM should be initiated as soon as possible. The types and levels of monitoring required for an individual patient vary widely depending on the severity of the cardiac decompensation and response to initial therapy. The syndrome carries a high morbidity and mortality, and diagnosis is often delayed. This review summarizes recent data charting the incidence, recent advances in the understanding of the pathophysiology of PPCM, and outlines the current treatment options available.

Introduction

Peripartum cardiomyopathy (PPCM) is defined as a disorder of unknown pathogenesis, in which left ventricular dysfunction and symptoms of heart failure are present and occur between the last month of pregnancy and the first 5 months postpartum. By definition, PPCM occurs in the absence of an identifiable cause of heart failure and in the absence of recognizable heart disease prior to the last month of pregnancy [1,2•]. Some authors go beyond this defined time frame to include patients diagnosed with heart failure as early as 3 months of pregnancy [3•]. Diagnosis requires echocardiographic evidence of left ventricular systolic dysfunction (ejection fraction < 45%) [4]. Heart failure that occurs in earlier pregnancy may be caused by previously unsuspected familial or other forms of cardiomyopathy that (unmasked by the hemodynamic and hormonal stress of pregnancy) forms a different entity. Diagnosis of PPCM should be established by ruling out other causes of perinatal heart failure, such as infectious diseases, metabolic disorders, and ischemic or valvular heart disease. Complications of late pregnancy that may have similar symptoms and signs to PPCM include pre-eclampsia, amniotic or pulmonary embolism, hemolysis, elevated liver enzymes, and low platelets [5].

The American College of Cardiology (ACC) guidelines classify PPCM as an entity of its own [6]. However, in the recently published European Society of Cardiology classification [7], PPCM is not listed as a specific disease and is placed under the category of "unclassified cardiomyopathies." The more recently described cardiomyopathies, such as left ventricular noncompaction and Takotsubo cardiomyopathy, for which little of their pathogenesis is known, have been listed as "unclassified cardiomyopathies" [7], which promote ongoing interest and research into these conditions. Because gynecologists, physicians, and cardiologists have little awareness of PPCM, the condition is not diagnosed quickly and often leads to unnecessary morbidity and mortality. A recent publication by Deneux-Tharaux et al. [8] highlights the underreporting of pregnancy-related mortality in the United States and Europe. The study clearly shows the limitations of maternal mortality statistics based on the International Classification of Diseases cause of death codes.

Epidemiology of PPCM

PPCM is most common in women of African descent [2•,9], but it has been reported in all major ethnic populations. The incidence varies from 1:100 to 1:10,000 between geographic regions. Due to diagnostic limitations, including limited access to echocardiography, the incidence in some areas may be overestimated.

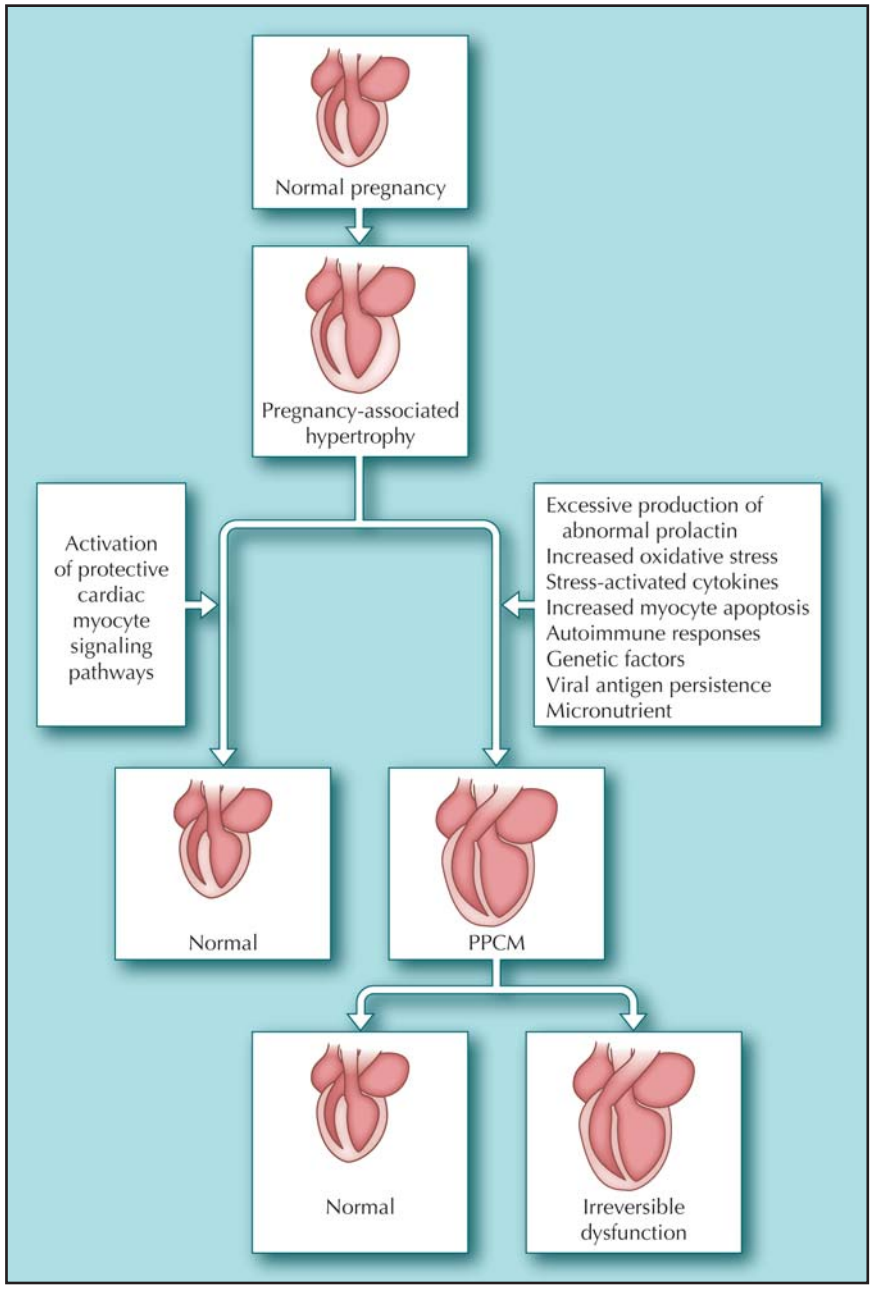


Figure 1. Proposed mechanism that possibly contributes to pathogenesis of peripartum cardiomyopathy (PPCM).

Etiology and Pathogenesis

There is considerable controversy regarding the etiology of human PPCM, but a number of recent publications have contributed to better understanding of its pathogenesis [10,11•,12,13]. A number of mechanisms have been proposed in the development of PPCM, including nutritional deficiencies, genetic disorders, viral or autoimmune etiologies, hormonal imbalances, volume overload, alcohol, physiologic stress of pregnancy (Fig. 1), and unmasking of latent idiopathic dilated cardiomyopathy (DCMO) [2•]. However, none of these mechanisms have been confirmed in detailed investigations or prospective studies [14]. The rare incidence of PPCM and the paucity of relevant animal models have limited guided research and understanding of the pathogenic mechanisms involved. Several authors have suggested that multiparity may be a risk factor for PPCM. However, a study by Elkayam et al. [3•] does not support this theory within their cohort in the United States because almost 40% of the cases occurred in association with a first pregnancy and more than 50% within the first two pregnancies.

Clinical Presentation and Diagnosis

Features of a normal pregnancy include an expansion of blood volume, an increase in metabolic demands, relative anemia, and changes in vascular resistance that are associated with mild ventricular dilatation and an increase in cardiac output. These physiologic changes are due to an increase in preload and heart rate accompanied by a

decrease in afterload. Decompensation of patients with subclinical valvular, ischemic, or myopathic heart disease usually occurs during the second or third trimester of pregnancy. The onset of PPCM can be easily missed because many symptoms and signs of pregnancy and postpregnancy stages are similar to those of early congestive heart failure (CHF) (eg, dyspnea, abdominal discomfort, and fatigue) [15]. Elkayam et al. [3•] reported that 7% of their patients in the United States were diagnosed within 1 month before delivery, whereas 75% were diagnosed during the first month postpartum, the remainder having fulfilled criteria for PPCM *before* the last 1 month of pregnancy. In contrast, patients in South Africa and Haiti developed symptoms almost exclusively within the postpartum period [16,17]. The symptoms and signs are similar to those in patients with idiopathic DCMO. Echocardiography usually demonstrates features of DCMO with impaired ejection fraction, often global dilatation, and sometimes thinned-out walls.

PPCM often presents with acute onset of heart failure (AHF). The presentation, with reduced cardiac output, tissue hypoperfusion, increase in the pulmonary capillary wedge pressure, and tissue congestion, is often life threatening and requires urgent treatment. The diagnosis of AHF is based on symptoms and clinical findings in combination with appropriate investigations, such as electrocardiography, chest radiograph, biomarkers, and echocardiography. Systematic clinical assessment of the peripheral circulation, venous filling, and peripheral temperature are important. Right ventricular filling in decompensated heart failure may be evaluated from the central jugular venous pressure. Caution is necessary in the interpretation of raised measures of central jugular venous pressure in AHF, as it may be a reflection of decreased venous compliance together with decreased right ventricular compliance [18]. Left-sided cardiac filling pressure is assessed by chest auscultation, with the presence of wet rales in the lung fields usually indicative of raised pressure. The confirmation, classification of severity, and clinical follow-up of pulmonary congestion and pleural effusions should be done using chest radiograph. Cardiac palpation and auscultation for ventricular and atrial gallop rhythms (S_3, S_4) and an electrocardiogram should be performed.

Chest radiograph and other imaging modalities should be conducted early for all patients with AHF to evaluate pre-existing chest or cardiac conditions and to assess pulmonary congestion. They are used for confirmation of the diagnosis and monitoring response to therapy. Chest radiograph allows the differential diagnosis of left-sided heart failure from inflammatory or infectious lung disease. A chest CT scan with or without contrast angiography and scintigraphy may be used to clarify pulmonary pathology and diagnose major pulmonary embolism [18].

A number of laboratory tests should be used in all patients with PPCM presenting with AHF: full blood count, urea and electrolytes, C-reactive protein (CRP), blood glucose, D-dimer, creatine kinase-MB (CKMB), and cardiac troponin T (cTnT). In severe heart failure, international normalized ratio (INR) and arterial blood gas should also be performed. Transaminases, urinalysis, and plasma B-type natriuretic peptide (BNP) or N-terminal pro–B-type natriuretic peptide (NTproBNP) can be considered. Arterial blood gas analysis allows assessment of oxygenation (pO_2), respiratory adequacy (pCO_2), acid base balance (pH), and base deficit, and should be performed in all patients with severe heart failure. Noninvasive measurement with pulse oximetry and end-tidal carbon dioxide (E_TCO_2) can often replace arterial blood gas analysis, but not in very low output vasoconstricted shock states [19]. BNP is released from the cardiac ventricles in response to increased wall stretch and volume overload and has been used to exclude or identify CHF in patients. NTproBNP has been found to be elevated in patients with PPCM presenting with AHF [12].

Echocardiography is an essential tool for evaluating the functional and structural changes underlying or associated with AHF. The most important measurement of ventricular function is the left ventricular ejection fraction for distinguishing patients with cardiac systolic dysfunction from those with preserved systolic function. Echocardiography with Doppler imaging should be used to evaluate and monitor regional and global left and right ventricular function, valvular structure and function, possible pericardial pathology, and mechanical complications. We have observed that patients with severe functional mitral regurgitation at presentation have a lower chance of full recovery of LV function (Sliwa, unpublished data). Appropriate echocardiographic Doppler study can also estimate pulmonary artery pressures and may help to detect the presence of pulmonary embolus.

Monitoring of Patients With Newly Diagnosed PPCM

Monitoring of the patient presenting with AHF should be initiated as soon as possible. The extent and means in which to monitor for an individual patient vary widely depending on the severity of the cardiac decompensation and the response to initial therapy. However, we observed that because of their young age our patients often appear relatively well at first glance despite low cardiac output and marked tachycardia. Many women request inappropriate early discharge due to social pressures, including caring for their newborn, which may lead to rapid readmission or possible death (Sliwa, unpublished data).

Current Theories on the Pathogenetic Mechanisms in PPCM

Over the past decade, accumulating evidence has suggested distinct pathogenetic mechanisms for PPCM, which may differ from those of other forms of DCMO. Apoptotic events—systemically and in the myocardium—appear to

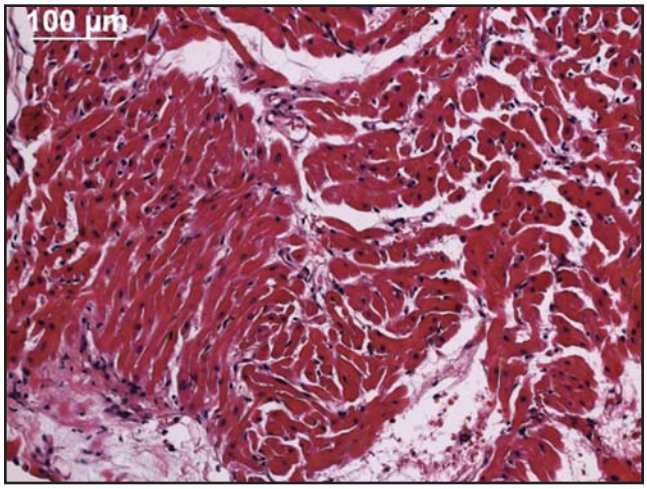


Figure 2. Left ventricular biopsy from a patient with acute peripartum cardiomyopathy. Formalin and paraffin-embedded tissue was stained with hematoxylin and eosin (H&E). No significant infiltrations are visible.

be causally associated with PPCM. In this regard, transgenic mice with cardiac-restricted over-expression of Gαq exhibit a lethal PPCM accompanied by strongly enhanced apoptosis [10]. Reduction in cardiac apoptosis by caspase inhibition through administration of the polycaspase inhibitor IDN-1965 improved left ventricular function and survival in pregnant Gαq mice, suggesting that cardiac apoptosis plays a causal role in the pathogenesis of cardiomyopathy [10].

The apoptosis signaling surface receptor Fas/Apo-1 is known to trigger cell death in a variety of cell types. Patients with PPCM had significantly higher plasma levels of Fas/Apo-1 compared with healthy volunteers [16]. Elevated plasma levels of tumor necrosis factor (TNF)-α have also been found in a cohort of 100 patients with PPCM. Elevated TNF-α has also been implicated in the pathogenesis of idiopathic DCMO [20•].

There is evidence suggesting the role of viral illness or an autoimmune etiology in the development of PPCM [21–24], with histologic samples of myocardial tissue having shown inflammatory infiltrates similar to that of myocarditis. Biopsies from PPCM patients often do not show inflammatory infiltrates (Fig. 2). Furthermore, a high prevalence of viral genomes were detected in endomyocardial biopsy (EMB) specimens of PPCM patients in 8 of 26 PPCM patients, and in 10 of 33 control subjects (30.3%) [21]. Viruses identified (parvovirus B19 [PVB19], human herpesvirus 6 [HHV-6], human herpesvirus 5 [HCMV], and EMBs) have been related to inflammatory cardiomyopathy, but also exist at high prevalence in healthy populations [21]. Similar results were presented by Rizeq et al. [24], whose retrospective review of EMB specimens from 34 PPCM patients showed a comparable incidence of myocarditis (8.8%) to that found in age- and sex-matched patients undergoing transplantation for idiopathic DCMO (idiopathic cardiomyopathy: 9.1%). Thus, the role of EMB remains controversial and is likely to be clinically useful only if performed early in the course of the disease.

Recently, we discovered increased serum levels of oxidized low-density lipoprotein (oxLDL), indicative of enhanced systemic oxidative stress together with significantly higher prolactin levels and increased activation of the prolactin-cleaving protease cathepsin D [11•,12] among PPCM patients compared with healthy nursing- and pregnancy-matched control women. Moreover, we detected substantial amounts of cleaved 16-kDa prolactin in some PPCM patients, but not in healthy nursing mothers [11•].

In a mouse model for PPCM that lacked the signal transducer and activator of transcription 3 (STAT3) in cardiac myocytes, we were able to demonstrate that increased oxidative stress is responsible for the activation of cathepsin D and the subsequent cleaving of prolactin in a 16-kDa fragment. Furthermore, we showed that the 16-kDa prolactin has detrimental effects on the maternal heart by impairing the cardiac microvasculature and the cardiac myocyte metabolism, all of which appear to be largely responsible for the development of PPCM in mice [11•]. Bromocriptine is a dopamine D_2 receptor antagonist that is known to efficiently block prolactin release from pituitary glands in humans [25] and mice [26] and is widely used in stopping lactation in women who cannot or do not want to nurse. Bromocriptine prevented PPCM in mice [11•]. This observation supports a crucial role of prolactin, namely its 16-kDa form in prolactin for PPCM, and supports previous studies viewing prolactin as a potential factor in the pathogenesis of PPCM [27].

In a recent study, the kinetics of a set of biomarkers associated with cardiac function, oxidative stress, apoptosis, inflammation, remodeling, and pregnancy were monitored at 6-month follow-up of PPCM patients, comparing biomarkers between patients who improved clinically versus those who did not [12]. This study revealed that among all markers analyzed, only the kinetics of NTproBNP, oxLDL, and interferon-γ (IFN-γ) correlated significantly with nonimprovement in there being a positive correlation. Moreover, NTproBNP correlated positively with oxLDL, IFN-γ, and prolactin. Thus, the kinetics of NTproBNP in correlation with the kinetics of more disease-specific markers (oxLDL, IFN-γ, and prolactin) may serve to distinguish patients with poor prognosis from those who may recover [12]. However, the role of each of these factors in disease progression is still unclear and needs further clinical and experimental analysis.

Current Therapeutic Approaches Towards Heart Failure in PPCM

Treatment is directed toward symptomatic relief and improvement of cardiac function, similar to other forms of heart failure treatment. The maintenance of blood oxygen saturation within the normal range (95%–98%) is important to maximize oxygen delivery to the tissues and tissue

oxygenation, thus helping to prevent end-organ dysfunction and multiple organ failure. This is best achieved by first ensuring that there is a patent airway and then administering an increase in fraction of inspired oxygen (FiO_2). Endotracheal intubation is indicated if these measures fail to improve tissue oxygenation. The use of continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV) in acute cardiogenic pulmonary edema is associated with a significant reduction in the need for tracheal intubation and mechanical ventilation [28]. Respiratory muscle fatigue is the most frequent reason for endotracheal intubation and mechanical ventilation in AHF. It may be diagnosed by decreasing respiratory rate associated with hypercapnia and a confused state of mind. Invasive mechanical ventilation should only be used if acute respiratory failure does not respond to vasodilators, oxygen therapy, and/or CPAP or NIPPV [18,29].

Administration of diuretics is indicated in the presence of symptoms secondary to fluid retention. Ionotropic agents are indicated in the presence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary edema refractory to diuretics and vasodilators.

Temporary mechanical circulatory assistance may be indicated in patients with AHF who are not responding to conventional therapy and where there is reasonable potential for myocardial recovery, for use as a bridge to heart transplantation, or interventions that may result in significant recovery of heart function. These include an intra-aortic balloon pump and a left ventricular assist device [19].

Cardiac transplantation has been successfully performed in PPCM patients. Favorable outcomes have been attributed to the young age of the recipients and to the relatively short duration of heart failure, resulting in minimal end-organ damage. However, there are reports of increased transplant rejection [30]. In view of the success of transplantation in these young and otherwise healthy mothers, aggressive temporary life support measures, such as cardiopulmonary bypass or a left ventricular assist device, have been encouraged until a transplant becomes available [31].

Coexistence of systemic oxidative stress and significantly higher prolactin levels in patients with acute PPCM supports the notion of our previously published concept that oxidative stress-mediated prolactin cleavage into its detrimental 16-kDa form is crucial for the initiation of PPCM. A recent pilot study suggests that this process can be ameliorated or even abolished by bromocriptine, an inhibitor of the detrimental prolactin [11•,32]. In this light, trials assessing the therapeutic effects of prolactin blockade with bromocriptine have begun in PPCM patients. A few case reports suggest that the addition of bromocriptine to standard therapy of heart failure may be beneficial in patients with acute onset of PPCM [11•,32].

In patients with stable heart failure, β-blockers and angiotensin-converting enzyme (ACE) inhibitors should be initiated when the patient has stabilized after the acute episode (usually after 4 days). ACE inhibitors should be titrated up to dosages shown to be effective in the large controlled trials of heart failure and not towards symptomatic improvement alone. ACE inhibitors are contraindicated during pregnancy because of teratogenicity, but should be considered a mainstay of treatment for PPCM after delivery.

β-blockers, preferably carvedilol, should be considered for treatment of all patients with heart failure, unless there is a contraindication. β-blocker therapy reduces hospitalization, improves the New York Heart Association (NYHA) functional class, and leads to smaller proportions of patients whose heart failure worsens [29]. The initial dose should be small and increased slowly and progressively to the target dose used in the large clinical trials. Aldosterone receptor antagonists are recommended in addition to ACE inhibitors, β-blockers, and diuretics in advanced heart failure (NYHA III–IV) with systolic dysfunction to improve survival and morbidity. Angiotensin II receptor blockers (ARBs) can be used as an alternative to ACE inhibition in symptomatic patients who are intolerant to ACE inhibitors to improve morbidity and mortality. Digoxin therapy is associated with an increased risk of death from any cause among women, but not men, with heart failure and depressed left ventricular systolic function [33]. Retrospective analysis of data from the Digitalis Investigation Group (DIG) trial indicates a beneficial effect of digoxin on morbidity and no excess mortality in women at serum concentrations from 0.5 to 0.9 ng/mL, whereas serum concentrations of 1.2 ng/mL or greater appear harmful [34].

Thromboembolic phenomena have been reported frequently in PPCM patients. Pregnant patients are at increased risk of thromboembolic complications due to the hypercoagulable state of late pregnancy that may persist for up to 6 weeks postpartum. Left ventricular systolic dysfunction resulting in blood stasis additionally predisposes to formation of left ventricular, pulmonary, and cerebral thromboemboli. During the last weeks of pregnancy, low-molecular weight heparin is the agent of choice, whereas warfarin is preferred postpartum in patients with low ejection fraction (< 30 %) [18].

Appropriate birth control measures are recommended for patients with enlarged hearts. Oral contraceptives should be avoided because of the risk of increasing the incidence of thromboembolism.

Prognosis and Subsequent Pregnancy

Echocardiography is an important diagnostic tool in PPCM and may provide significant prognostic information with regard to recovery of cardiac function [35•]. A fractional shortening value of less than 20% and a left ventricular end-diastolic dimension of more than 6 cm at the time of diagnosis are associated with a threefold or higher risk for persistent left ventricular dysfunction [4].

In a cohort of 100 patients from South Africa, a mortality of 15% within a 6-month period was reported. Baseline plasma levels of Fas/Apo-1 and NYHA functional class were identified as independent predictors of death [2•]. Compared with other forms of cardiomyopathy (n = 1230), patients with PPCM (n = 51) demonstrate better survival [36]. In a study from Haiti, the ratio of PPCM deaths for the 5-year period was 47.1 per 100,000 births, and the mortality rate was 15.3% during a mean follow-up period of 2.2 years. Only 28% of patients who were observed for at least 6 months regained normal left ventricular function [37].

One of the most common issues for women surviving an episode of PPCM is whether it is safe to become pregnant again. If a subsequent pregnancy occurs, it should be managed in close collaboration between the obstetrician and attending physician or cardiologist. Most authors agree that PPCM patients with persistent left ventricular dilatation and dysfunction are at high risk for complications and death should they become pregnant again [38].

In contrast, the issue of whether patients with PPCM and recovered left ventricular function can safely undergo a subsequent pregnancy remains controversial. Elkayam et al. [39] conducted a record review among members of the ACC in the United States and one hospital in South Africa and described the outcome of 60 subsequent pregnancies in 44 women with a history of PPCM. Among the first subsequent pregnancies in the 44 women, 28 occurred among women in whom left ventricular function had returned to normal (group 1) and 16 occurred in women with persistent left ventricular dysfunction (group 2). The pregnancies were associated with a reduction in mean left ventricular ejection fraction in each group; 19% of PPCM patients with sustained impaired systolic function, who then conceived their first subsequent pregnancy, eventually died [39]. Although the likelihood of maternal death seems to be very low in women who recovered their left ventricular function before a subsequent pregnancy, a reduction in left ventricular ejection fraction and symptomatic heart failure will occur in the majority of PPCM patients in subsequent pregnancies.

However, pilot data of bromocriptine trials are promising. Twelve patients who suffered from PPCM in a previous pregnancy presented with a subsequent pregnancy and therefore had a high risk for developing the disease again [11•]. Six patients obtained bromocriptine immediately after delivery, in addition to standard therapy for heart failure, and all of them had an uneventful postpregnancy follow-up. In contrast, all patients (n = 6) in the group who obtained only standard therapy suffered from recurrence of PPCM, three of whom subsequently died. Since this pilot, another four patients have had similar positive outcome on bromocriptine, and further efforts to clarify its efficacy in preventing recurrence of PPCM continue to be encouraging (Sliwa, unpublished data).

Conclusions

PPCM is a common disorder in some geographic regions and possibly goes unrecognized in others. Defining this disorder as an entity of its own may be justifiable given the recent discovery of an oxidative stress cathepsin D 16-kDa prolactin cascade in experimental and human PPCM serving as a specific pathophysiologic mechanism that may provide the rationale for a specific therapeutic intervention. Bromocriptine, a drug blocking the release of prolactin systemically and locally, has been used for many years in women to stop lactation, and now needs to be tested in randomized trials to treat women with PPCM. Systematic prospective data collection is required as well as international cardiac registries to study the etiology and different pathogenic mechanisms of PPCM, including potential genetic and lifestyle aspects. Furthermore, attempts to establish specific biomarker profiles and diagnostic tests are warranted for risk stratification and prevention of PPCM.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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1.3 Problem Statement and Rationale

Peripartum cardiomyopathy (PPCM) is a severe form of heart failure affecting women of child-bearing age. In a single centre study offering optimal PPCM management, as many as 15% of patients died and only 23% achieved full recovery (Sliwa et al, 2006[a]). While the loss of maternal life or functionality bears the most obvious consequences for both the individual and society, the repercussions on the young infant remain as a deepening scar over a broader period of time. This indicates that PPCM is a disease of public health concern, with the majority of survivors requiring prolonged and often repeated inpatient care for heart failure.

1.3.1 PPCM: A diagnostic dilemma – the need for a rapid screening tool

Despite recent efforts to increase recognition of PPCM, it often remains undetected – particularly in resource-poor environments. Definitive diagnosis and subsequent management requires a high index of suspicion and, usually, referral to a tertiary centre with the capacity to perform echo-cardiographic studies alongside specialist cardiologic and neo-natal care services. Anecdotal evidence suggests that many women who initially present with signs and symptoms of heart failure indicative of PPCM are concluded to suffer non-specific symptoms of the puerperal period and are not adequately investigated, which leads to their deterioration. This clearly represents a preventable component of PPCM-related morbidity and mortality.

Patients who have experienced an episode of PPCM are at a very high risk of relapse in further pregnancies (Elkayam et al, 2001; Sliwa et al, 2004), even those patients who recovered left ventricular function after the first pregnancy (Sliwa et al, 2008[b]). Therefore, early diagnosis of PPCM is important to limit the high risk of morbidity and mortality induced by subsequent pregnancy.

Until specific aetiologies can be identified and tested for, PPCM remains a diagnosis of exclusion. Women in their peripartum period suspected of having PPCM are thus required to undergo rigorous investigation; a task that is costly and laborious for the patient and health care provider. For this reason, prompt use of simpler screening tools for this form of heart failure could help limit the number of women eligible to undergo the full series of expensive investigations. The challenge in resource-poor environments is to provide relatively easy, cheap and reliable investigative tools for potentially fatal but rare conditions not easily diagnosed (Stewart et al, 2009; Tibazarwa et al, 2010). In the case of PPCM, it is unlikely, for example that every pregnancy in sub-Saharan Africa will trigger an echo-cardiograph (even if confined to those with advanced symptoms of heart failure). Although screening with (point-of-care derived) brain natriuretic peptide levels may offer a means for detecting elevated atrial pressures secondary to systolic dysfunction (particularly given the age of those affected [Sliwa et al, 2008[b]; Cardarelli et al, 2003; Martin-Du Pan et al, 2003), there are technical issues and the cost remains prohibitive. It is within this context that we regard the electro-cardiogram (ECG) to be a relatively cheap and effective tool for diagnosis and treatment of many forms of heart disease, including heart failure. In a resource-poor environment, the cost-effectiveness of ECG screening, automated software for detecting abnormalities and portability of findings for evaluation at a central point makes ECG an attractive option for detecting PPCM.

To date, in the literature, the nature, frequency and evolution of ECG abnormalities in PPCM is not well defined and limited to small studies. There is also a lack of data on ECG characteristics of PPCM patients in Africa, as well as data on what characterises a normal ECG in African societies. Should ECG abnormalities prove to be common in women with PPCM, this would provide a strong basis for further studies examining the utility of ECG screening in a larger cohort of pregnant women in the sub-Saharan Africa context.

1.3.2 Shortage of data on the natural history of PPCM

Across the world, there is a dire shortage of data on the natural history of PPCM. Short-term studies have yielded conflicting data on the pattern of recovery in PPCM within the first six months of diagnosis, while long-term studies of PPCM remain few in number. Less than ten accessible Anglophonic publications on the long-term outcome of PPCM have been identified. Of these, three were of relatively compromised quality by being retrospective in nature and *no* studies reported the long-term outcome of PPCM in Africa. Amidst these studies on the short and long-term outcome of PPCM, there is considerable variation in baseline clinical entry criteria for patients recruited. This has further weakened the ability to come to consensus on some of the clinical patterns that have been observed. The study of PPCM in an African setting is further complicated by the high prevalence of communicable disease, for which the concomitant presence of some infections (no matter how subtle their clinical manifestation) may confound the diagnosis of PPCM. This could occur, for example, through the overlapping symptomatology with that of PPCM, or through objective demonstration of reduced systolic function in persons with systemic infections that might lead to the mis-classification of PPCM. No other disease could pose a greater threat to such confounding than infection with the HIV virus, where the virus itself, the persistent inflammatory state that it places the body in and the plethora of opportunistic infections that it invites through the state of immunodeficiency of AIDS has meant that HIV co-infected persons have been excluded from being diagnosed with PPCM. As yet, however, there is no systematic data on the impact of HIV infection on PPCM.

1.3.3 No clinical trials published on the medical management of PPCM

With the exception of Pentoxyfillene, which has only been studied in a small series of patients (Sliwa et al, 2002; Batchelder et al, 2005), no clinical trials on the pharmacological management of PPCM

have been published. This is almost entirely attributed to a lack of insight into the aetiopathogenetic mechanisms leading to the development of PPCM. However, recent reports show that enhanced oxidative stress in a mouse model for PPCM (mice with a cardiac specific deletion for signal transducer and activator of transcription-3, STAT3-KO) triggers the activation of cathepsin D, a ubiquitous lysosomal enzyme that subsequently cleaves serum prolactin into its anti-angiogenic and pro-apoptotic 16-kDa form (Hilfiker-Kleiner et al, 2007[a]). The subsequent co-existence of the triad of oxidative stress, endothelial inflammation and prolactin seen in these mice was also documented in patients with acute PPCM (Brar et al, 2007); thereby strengthening suggestions that they may be inter-connected and responsible for initiating PPCM.

Blockage of prolactin with the dopamine-2D agonist Bromocriptine prevented onset of PPCM in mice and in 12 women at high risk of this condition identified through documented PPCM in a previous pregnancy (Hilfiker-Kleiner et al, 2007[a]). A number of case reports further describe seemingly beneficial effects from the addition of Bromocriptine to standard heart failure therapy in patients with acute PPCM (Forster et al, 2008; Hilfiker-Kleiner, 2007[b]; Jahns et al, 2008). While these preliminary results for the beneficial effects of Bromocriptine treatment in patients with acute PPCM are promising, concerns have been raised regarding the risk of thrombotic complications. These include cerebral vascular incident and myocardial infarction related to Bromocriptine therapy (Hopp et al, 1996; Loewe et al, 1998; Dutt et al, 1998; Fett, 2008[b]) and the consequences for the children of these patients, as the mothers are unable to breast-feed (Fett et al, 2008[b]). This presented an urgent need for the systematic evaluation of the effectiveness of Bromocriptine as a medical therapy in the treatment of patients with PPCM.

1.3.4 No systematic study of familial component to PPCM

Non-systematic studies have revealed siblings of PCM patients demonstrating left ventricular dilatation and left ventricular dysfunction. Even more striking, however, is that PCM appears to share similar predisposing factors and clinical features with non-ischaemic idiopathic dilated cardiomyopathy (IDCM); hence our partial concern that they may be different manifestations of the same disease. If this were true, the prevalence of FDCM in families of PPCM patients might even resemble that of FDCM (this being as high as 30% - 48% when screening of asymptomatic relatives is included (Ghosh et al, 2011; Mahon et al al, 2005).

In this doctoral report, the researcher addressed this question by first investigating whether there is evidence of increased familial occurrence of DCM in patients with PCM. Thereafter, the researchers proceeded to evaluate the presence of one of the most virulent genetic mutations known to FDCM amongst PPCM patients in the study, namely the Lamin A/C gene.

1.4 Objectives

The objectives of this doctoral thesis are as follows:

[1] To determine the role of genetics in the aetio-pathogenesis of PPCM.

Specifically:

a. To measure the prevalence of DCM, left ventricular enlargement and depressed fractional shortening among first degree relatives of patients with PPCM.

b. To determine if the prevalence of DCM among first degree relatives of PPCM patients is independent of the socio-environmental conditions within families screened.

c. To determine the prevalence of potentially pathogenic mutations along the Lamin A/C gene in patients with PPCM.

[2] To provide the first systematic descriptive study of ECG characteristics in PPCM, and thereby determine any characteristics typical to PPCM (to inform us of the electro-physiological causes and/or consequences of PPCM) and their possible application in clinical detection and monitoring.

Specifically:

a. To assess the prevalence of 12-lead ECG abnormalities in newly diagnosed South African women with PPCM at baseline and at six-months follow-up.

b. For PPCM patients who had six-month follow-up data, to identify any association between 12-lead ECG characteristics at baseline and at six-months with echocardiographic LV systolic dysfunction.

[3] To conduct the first randomised control trial of Bromocriptine therapy in humans; this is the first drug thought to be uniquely beneficial to PPCM of all the dilated cardiomyopathies. Specifically:

a. To assess the efficacy of Bromocriptine on recovery of LV function, symptom status and other clinical measures in PPCM patients presenting within the first month post-partum with new onset symptomatic PPCM and a left ventricular ejection fraction (LVEF) less than 35%.

b. To assess the clinical safety of Bromocriptine on young infants of patients with PPCM over the six-month follow-up period.

2. METHODOLOGY

2.1 GENERAL METHODS

2.2 METHODS SPECIFIC TO SUB-STUDY ON THE GENETICS OF PPCM

2.2.1 SUB-STUDY ON FAMILIAL AGGREGATION OF IDCM IN PCM

2.2.2 SUB-STUDY ON THE PREVALENCE OF POTENTIALLY PATHOGENIC MUTATIONS ON THE LAMIN A/C GENE AMONG PPCM PATIENTS

2.3 METHODS SPECIFIC TO SUB-STUDY OF ECG CHARACTERISTICS IN PPCM

2.4 METHODS SPECIFIC TO SUB-STUDY OF BROMOCRIPTINE THERAPY IN PPCM

2.1 General Methodology

Prior to commencement of this study, ethical approval was obtained from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand, Johannesburg, South Africa (***PRC 990409***) as well as the Research Ethics Committee (REC) of the University of Cape Town (***REC.REF: 309/2006***). The study complies with the Declaration of Helsinki. All patients and controls gave written informed consent before being enrolled into the study.

Study Period

The study was conducted over a two-year period between 2006 and 2007. All PPCM cases (prevalent and incident) were recruited during this study period. However, some components of the family screening exercise had to continue well into 2008 and 2010.

Study Site

The study was conducted at two tertiary health care institutions in South Africa, namely Chris Hani Baragwaneth Hospital in Soweto, Johannesburg (a teaching hospital of the University of the Witwatersrand) and Groote Schuur Hospital in Cape Town (a teaching hospital of the University of Cape Town).

Despite Chris Hani Baragwaneth Hospital being the sole accessible tertiary medical facility for the vast community of Soweto, the apparent under-detection of PPCM necessitated me to take active measures to raise awareness about PPCM and the call to refer patients suspected of having PPCM at both study sites. Therefore, patients were referred from local clinics, secondary hospitals, private GPs and from within the Departments of Medicine and Obstetrics at Chris Hani Baragwaneth Hospital.

PPCM patients

Consenting patients with a provisional diagnosis of PPCM underwent thorough medical interview and examination and were investigated to confirm the diagnosis. Thus, all patients had routine blood tests, as per the requirements to confirm the diagnosis, as well as a 12-lead ECG and echocardiography. Patients requiring additional investigation to exclude potential differential diagnoses had these done (as indicated) for that specific case.

Any history of pre-eclampsia and mode of delivery were obtained from the patient and confirmed by examining the obstetric card carried by each patient. The history of the onset of symptoms and signs were recorded at first presentation at the Cardiac Clinic at Chris Hani Baragwaneth Hospital (baseline) and after a follow-up period of 6-months (6-month visit), patients enrolled in the long-term outcome sub-study were assessed again at 12-months (12-month visit) and 24 months (24-month visit). Clinical assessment, echocardiography, and, where relevant for that sub-study in question, blood analyses were performed at baseline and at each of those visits.

It must be noted that although all new patients presenting within the study period were approached for consent to join each sub-study, the ECG and familial screening study also targeted prevalent PPCM cases, including those that had been discharged from the clinic's care.

A physician, who was provided with the clinical data, but blinded to the study protocol and unaware of the results of the laboratory tests, evaluated the New York Heart Association Functional Class (NYHA FC) of each patient during baseline and follow-up visits.

Heart rate and systolic and diastolic blood pressure were measured non-invasively with a Critikon Dinamap Vital Signs Monitor 1846 and calculated as mean values from five serial readings. Measurements were made after a 30-minute resting period in a seated position with two-minute intervals between successive measurements.

ECG data

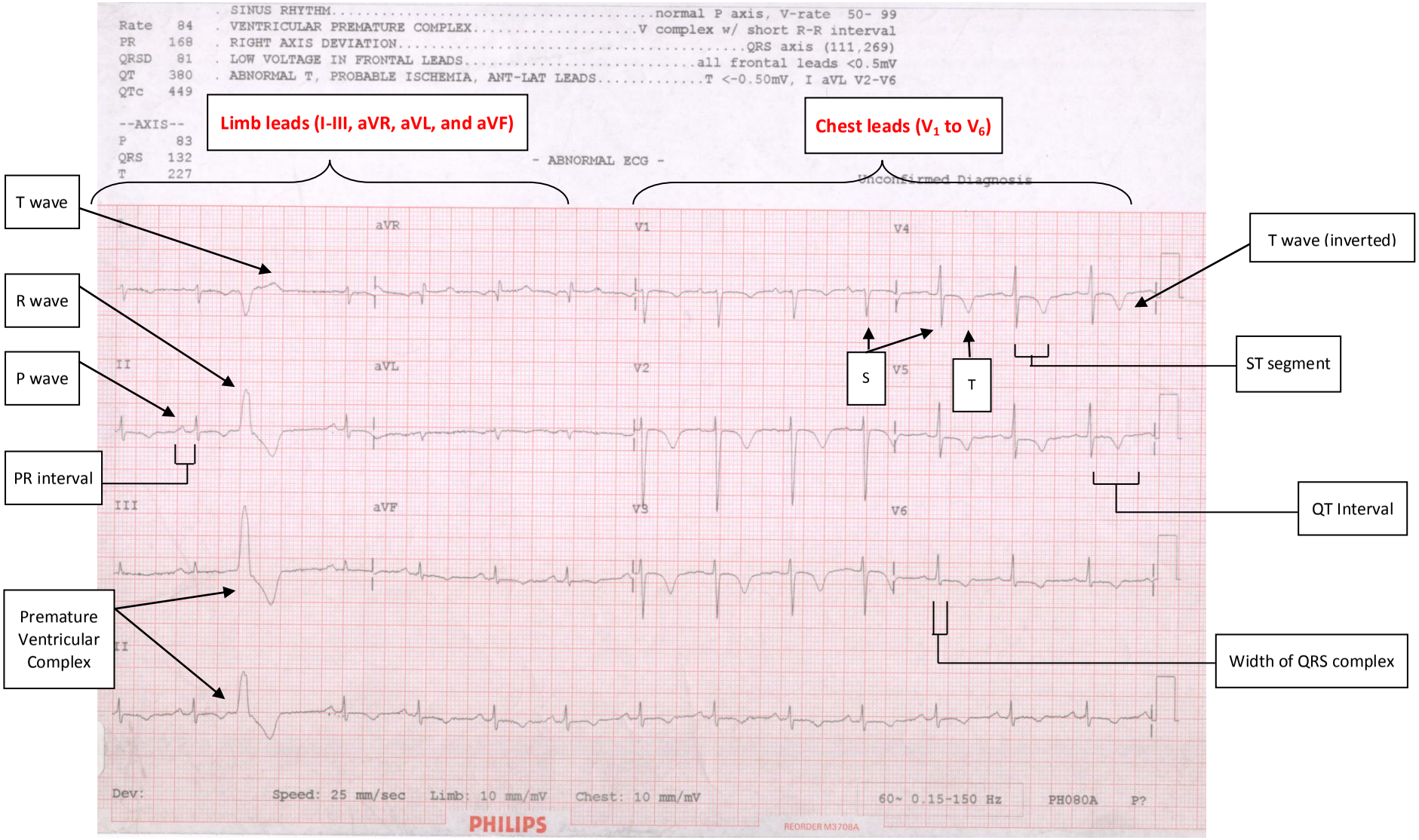
At baseline, a simultaneous 12-lead electro-cardiogram (ECG) was recorded at a paper speed of 25 mm/s and an amplitude of 10mV/mm on a digital ECG recorder (Philips). The ECGs were analysed by one of the investigators (KT) and validated by another (KS) using standard methods of ECG reading and interpretation [see **Figure 3.**] QRS duration was calculated using the standard leads from start to end of the QRS complex, and the longest QRS was considered (Iacoviello et al, 2007; Baye's et al, 1993). The QT interval and the QT interval corrected for heart rate using Bazett's formula (known asQTc) were calculated in all chest leads (V_1 to V_6) from the onset of the QRS complex to the end of the T-wave (Suwaricz, 1995) (at the point at which it returned to the iso-electric line) (Iacoviello et al, 2007; Statters et al, 1994). Prolonged QRS was defined as a QRS width of 110 milliseconds (ms) and prolonged QTc as a QTc interval of greater than 470ms; prolonged PR was defined as a PR interval greater than 220ms. For the sub-study on the ECG characteristics of PPCM, an additional analysis of ECGs was done using the Minnesota Code [see **Section 2.3** below].

Echocardiographic studies, assessment of New York Heart Association (NYHA) functional class and non-invasive blood pressure measurements

Echocardiographic examinations were taped on video and a portable hard-drive device and stored at the respective research unit for that study site; the purpose for storage was for further reference, audit purposes and to enable repeat blinded analysis by a single operator. All studies were performed and interpreted by the same operators who were blinded to the protocol (AY[1] and AB[2] at Chris Hani Baragwaneth hospital; the resident echo-cardiographer at Groote Schuur Hospital). For purposes of standardisation and research storage, all echoes were reviewed by two of the investigators (KT[3] and KS[4]), the latter of whom was first blinded to the results of the diagnostic

[1] **AY:** Dr Anthony Yip
[2] **AB:** Dr Anthony Becker
[3] **KT;** Dr. Kemi Tibazarwa
[4] **KS;** Prof. Karen Sliwa

Figure 3. An Example of an ECG in a PPCM Patient



echoes above. There was a high level of concordance between the echocardiographic card reports at the two phases described above. Standard methods of 2D-doppler transthoracic echocardiography were adopted according to the American Society of Echocardiography (ASE) guidelines (Sahn et al, 1978). LV systolic dysfunction was defined by echocardiographic documentation of left ventricular ejection fraction (LVEF) of ≤45%. Two-dimensional targeted M-mode echocardiography with Doppler colour flow mapping was performed using an echocardiography machine attached to a 2.5 or 3.5 MHz transducer.

At Chris Hani Baragwaneth Hospital, either a Hewlett Packard Sonos 5500 (Philips, Bothell, Washington) or a VIVID-e (General Electric Company, Fairfield, Connecticut, USA) echo machine was used. At Groote Schuur Hospital a General Electric Vivid-3 machine was used. All measurements, including systolic and diastolic left ventricular dimensions, valve dimensions and Doppler parameters were measured according to the ASE guideline (Sahn et al, 1978). Measurements of left ventricular dimensions and function were determined using an average of ≥ 3 beats. [See **Figure 4.**]

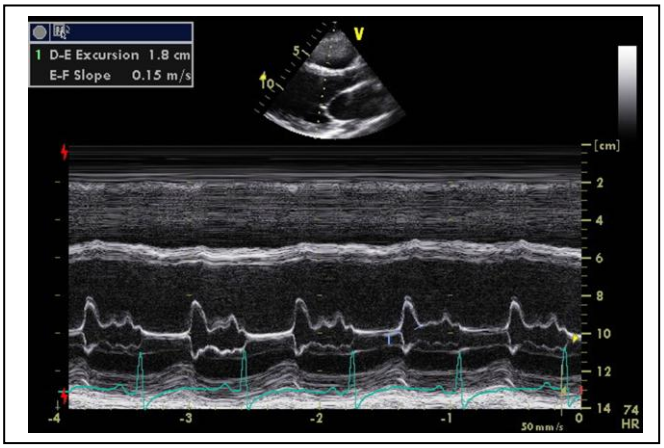
Having followed the processes described above on first presentation, the following inclusion and exclusion criteria were applied to each patient before finalising recruitment:

Inclusion criteria

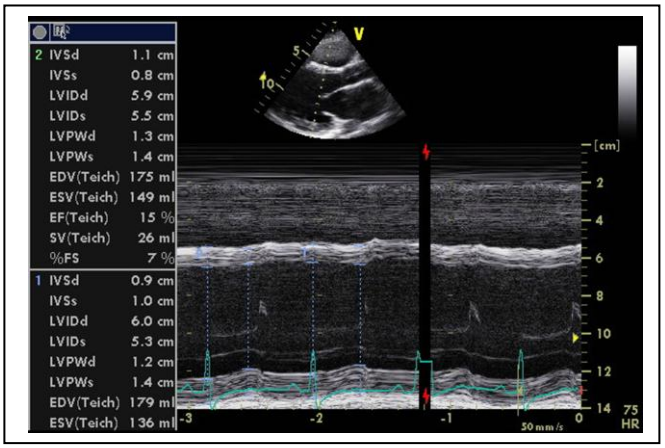
1) Symptoms of congestive heart failure that developed in the last month of pregnancy or during the first five months post-partum.
2) No other identifiable cause for heart failure, such as: current or past severe hypertension, current or past ischaemic heart disease (IHD), rheumatic valvular disease, mitral valve prolapse, significant aortic valve disease, congenital heart disease, metabolic disorders (including diabetes mellitus), severe anaemia, or HIV infection.
3) LVEF <45% by transthoracic echocardiography.

Figure 4. Examples of echocardiographic images obtained from a patient with PPCM

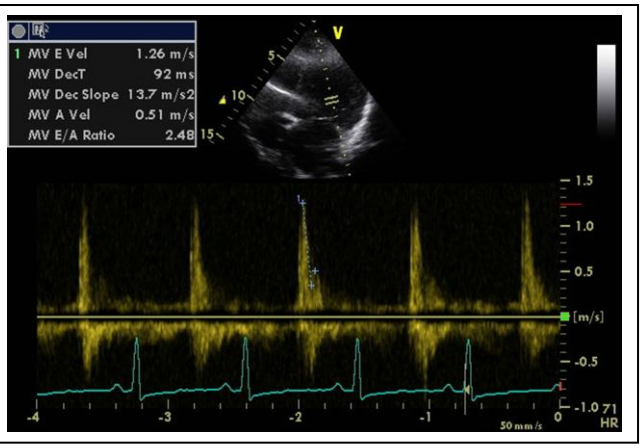
a. Dilated LV & LA, hypokinetic septum, no organic MV



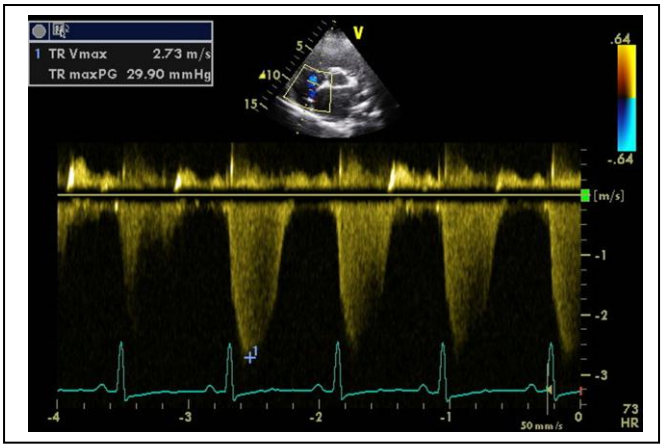
b. Severely reduced fractional shortening on repeated measures.



c. 4-Chamber view; Dilated LV, LA and RA. Normal MV inflow.



d. Functional TR with mild PHT (after adding patient's JVP reading).



LVL Left ventricle | **LA:** Left atrium | **RA:** Right atrium | **MVL** Mitral valve |**TR:** Tricuspid regurgitation; **PHT:** Pulmonary hypertension; **JVP:** Jugular Venous Pressure

Exclusion criteria

1) Systolic blood pressure >160 mmHg or <95 mmHg or diastolic >105 mmHg.
2) Clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers, such as: sepsis, autoimmune disease or being HIV positive.
3) Significant liver disease (defined as liver transaminase levels greater than two times the upper limit of normal).
4) History of psychiatric disorders.

5) Impaired renal function (defined as urea and/or serum creatinine greater than 1.5 times the upper limit of normal).
6) Rapid atrial fibrillation at the time of first diagnosis of PPCM.
7) Any clinical condition that, according to the investigators, precluded inclusion in the study (such as malignancy).

The key inclusion and exclusion criteria have been summarised in **Table 2** below.

Table 2. Summary of key inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Age $\geq$ 16 and $\leq$ 40 years	Significant organic valvular heart disease
Symptomatic CHF*	Systolic BP>160mmHg and/or diastolic BP>100mmHg
No other identifiable cause for heart failure	Severe anaemia (haemoglobin concentration <9gm/dL)
Left ventricular EF$\leq$45% by trans-thoracic echocardiography	Other clinical conditions accounting for raised inflammatory markers#
	Rapid atrial fibrillation at the time of first diagnosis

*****Symptoms of congestive heart failure (CHF) that developed in the last month of pregnancy or during the first five months post-partum

BP: Blood pressure. **#NB:** For purposes of this study, this meant HIV-seropositivity was considered an exclusion factor.

Medical management of PPCM patients

Following the initial screening and baseline visits, monthly out-patient visits were scheduled for clinical assessment and evaluation of medication compliance. All patients received treatment with the diuretic Furosemide and the angiotensin-converting enzyme (ACE) inhibitor Enalapril. Patients with an LVEF <25% or LV thrombus received anti-coagulation therapy using Warfarin for six months. Carvedilol was added after resolution of acute heart failure. Enalapril and Carvedilol doses were

titrated upward, as tolerated, during the first four weeks after diagnosis (as long as systolic blood pressure was ≥ 100 mmHg or symptoms, such as dizziness, did not occur) and then remained unchanged throughout the remainder of the six month study period**.** For patients who stabilized quickly on treatment, Furosemide doses were gradually decreased, as indicated, according to clinical assessment during the six-month study period.

Statistical analysis

The primary data collection instrument was the proposed Cardiomyopathy Registry for Sub-Saharan Africa (SSA), as developed by Mayosi et al from the University of Cape Town (unpublished). Data from hard copies of the Cardiomyopathy Registry were captured on its identical electronic registry database in Access format (using Microsoft Office Access 2007). Preliminary data analysis was begun by exporting encoded data from the Access database into Excel for reference purposes. Final cleaning and statistical analysis was done using Version 8 of the STATA software (STATA Corp., 2003), while ECG data were analysed using the SAS Version 9.1 statistical program (SAS, Cary, NC, USA). Descriptive summary results were expressed as "mean (standard deviation)" or "median [inter-quartile range]". Wilcoxon Scores (Rank Sums) were used for comparison between patients for continuous measurement. When data were non-normally distributed, log transformation was performed of all variables at baseline across the comparison groups for that sub-study. Comparison between groups and within groups of categorical variables were analysed using the Chi-square test and McNemar test or Mantel-Haenszel Test for repeated measurements. Subsequently multivariate analysis of variance (MANOVA) within groups (for time) and between groups was performed. Significance was assumed at a two-tailed value of $p < 0.05$.

Finally, a pre-specified combined end-point of poor outcome was created in an attempt to improve the chances of detecting associations of smaller effect. This end-point variable was defined as: death; NYHA functional class III/IV; or LVEF <35% at six months.

2.2 Methods Specific to Sub-Study on the Genetics of PPCM

The study design for this sub-study was cross-sectional in nature. During the study period, all prevalent PPCM patients known to the two hospitals were sought out and requested to participate in the study. In addition, all patients newly diagnosed with PPCM during the study period were requested to participate in the study.

2.2.1 Methods specific to sub-study on familial aggregation of DCM in PPCM

Only first degree relatives (aged 17 years or above) of consenting patients were approached telephonically or through the index case for enrolment into the study. In the event of positive findings amongst screened adult relatives, the screening exercise was expanded to include younger relatives and, where necessary, more distant relatives. Consenting relatives underwent the same clinical procedure of interview, examination, 12-lead ECG and echocardiography.

All family members were: assessed and their echocardiography done by KT; and reviewed by another expert echo-cardiographer blinded to the study protocol (A.B. in Soweto and J.S. in Cape Town). All relatives found to have any abnormality on initial screening were then requested to undergo blood tests for baseline screening of common cardiovascular risk factors, as per the recommendations of Fatkin et al (Fatkin et al, 2006). Relatives with any abnormality found during the assessment were referred as appropriate for correct management and treatment.

While patient and relative data were uploaded onto the main database described above (unique codes being applied to identify members of the same family and to separate patients from relatives screened), qualitative and more descriptive details of the family trees were uploaded onto Cyrillic software [Version 2.1].

2.2.2 Methods specific to sub-study on the prevalence of potentially pathogenic mutations on the Lamin A/C gene among PPCM patients

Overview

Genetic screening for mutation on the Lamin A/C gene (LMNA) was successfully conducted in 38 PPCM patients, alongside two separate pairs of controls matched for sex and ethnicity. These controls were randomly selected from a pool of apparently healthy controls, who had been recruited for such purposes by the Cardio-Genetics Laboratory of the University of Cape Town. Mutations were detected by genomic DNA screening assay; variants were confirmed by direct sequencing.

Standardisation of DNA

During the study period, peripheral venous blood samples were obtained using conventional methods. From these, DNA was extracted and purified using the GentraPuregene Blood Kit (Quiagen Catalogue No. 158422). While this DNA was stored, any remaining buffy coat and whole blood samples were also stored, in case more DNA would need to be extracted in the future. However, given that most of the blood samples and stored DNA were at least 3 years old by the time of this analysis, it was important to re-assess the concentrations of all DNA samples stored. This was done using the Qubit[5]dsDNA Broad Range (BR) Assay Kit and its respective protocol (Invitrogen, 2006). [See **Figure 5**]. DNA concentrations yielded from this process were used to calculate appropriate volumes of distilled water needed for standardised working samples, each containing 50ng of DNA.

Figure 5 The Qubit Fluorometer and its reagents



[5]The various Qubit Assay kits were previously known as "Quanti-iT™" Assay kits.

PCR primer design

Twelve exons were identified for the LMNA gene, each complete with the appropriate flanking regions. Larger exons were broken into two sub-components (e.g. exon 7 was broken into exons 7.1 and 7.2), bringing the total number of exon components to 18. To locate these exons on the samples, 18 primers needed to be developed. These were designed as follows:

1. The LMNA gene sequence was obtained from Ensembl and NCBI genome browsers.
2. Primers were chosen with reference to annotated sequences, then analysed with web-based tools in order to determine the optimal primer sequences for amplification of the gene (IDT OligoAnalyzer and NCBI BLAST).
3. Amplicons were restricted to between 250 and 300 base pairs in size, as increased amplicon length would have led to decreased resolution and sensitivity with HRMA.
4. Predicted melting patterns of amplicons were checked using POLAND (Sterger, 1994).

PCR primer optimisation

On arrival, all ordered primers were diluted in a 1 x TE buffer, tested with control DNA samples; their subsequent high resolution melt reaction was optimised by running them through the Rotor-Gene analysis described above. Of the 18 primers that were ordered (to complement the 12 exons and their sub-components), six failed this initial trial run and further resisted adjustments to annealing temperatures. Hence, for these six primers, the Type-iT Kit had to be used to *simultaneously* optimise *and* amplify those six exons/exon-components.

DNA amplification and screening

All 18 exons/exon-components, with their respective flanking regions, were: amplified using these primers using the local laboratory protocol [**Table 3**]; screened for mutations using the Corbett Rotor-Gene 6000 High-Resolution Melting curve Analysis (HRMA) [see **Figure 6**]. Amplicons with abnormal melt curves were then sequenced.

Sequencing and identification of mutations

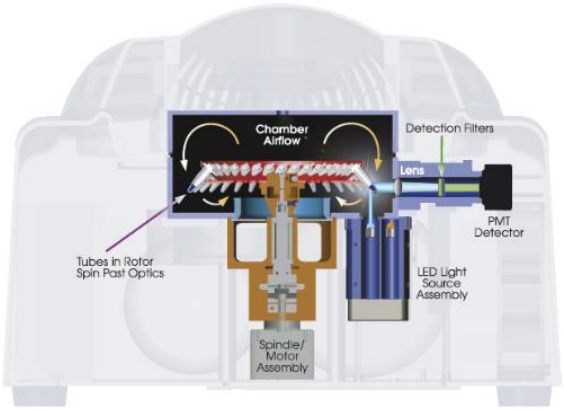
Amplicons were: purified using local laboratory protocol [**Table 4**] in a Labnet Multigene Thermocycler (from Labnet International Incorporated); then sequenced in both forward and reverse directions on an AB13100 sequencer. Sequences were analysed using bio-informatics tools, including tools for: protein production (Polyphen, SIFT), secondary structure prediction, RNA prediction, as well as alignment tools.

Figure 6. QIAGEN Rotor-Gene Q (Corbett Rotor-Gene 6000); Pure detection.

a. Rotor-Gene Q



b. Cross-section of the Rotor-Gene Q



The Rotor-Gene Q is an innovative real-time cycler that enables high-precision real-time PCR due to its unique rotary design. In its High Resolution Melt Analysis (HRMA), the resulting "Melt Curve Analysis" plot shows the first derivative (dF/dT) of the raw melting data. By default, the sign of the first derivative is inverted, showing the DNA melting points as positive maxima. Peak characteristics (i.e. peak temperature value, width) of known genotypes can be used to define "Peak Bins". These "Peak Bins" enable automatic identification of particular genotypes.

Table 3. Details of the DNA amplification and screening process

a. List of reagents mixed for DNA amplification

REAGENT (Stock Concentration)	Volume in Solution (per DNA sample)
Forward primer (20µM)	0.5 µl
Reverse primer (20µM)	0.5 µl
dNTPs (20µM)	1 µl
GoTaq polymerase (5U/µl)	0.1 µl
GoTaqFlexiBuffer (5x)	5 µl
$MgCl_2$ (25mM)	3 µl
DNA (50 ng/µl)	1 µl
EvaGreen dye	1 µl
Distilled water	12.9 µl
TOTAL	**25µl**

b. Rotor-gene cycling reaction conditions

Condition	Temperature (Time)	
Initial denaturation	95°C – 10 seconds	
Denaturation	95°C – 5 seconds	50 cycles
Primer annealing	55°C – 10 seconds	
Template elongation	72°C – 10 seconds	
High Resolution Melt (HRM)	72°C – 95°C (0.1°C increments)	

Table 4. Protocol applied for amplicon purification and DNA sequencing

I. AMPLICON CLEANSING AND PURIFICATION			
Reagents added (Volume in stock)	**Volume added (per sample of DNA)**	**Reaction conditions**	
Exonuclease I (20 000U/ml)	0.1 µl	37°C – 1 hour	
Shrimp alkaline phosphatase [SAP] (1U/ml)	1 µl	75°C – 15 minutes	
Amplicon product	5 µl	4°C – 15 minutes	
Distilled water	13.9		
TOTAL	**20µl**		
II. SEQUENCING			
Reagents added	**Volume added (per sample of DNA)**	**Reaction conditions**	
Primer (respective to that amplicon product)	2 µl		
Terminator mix	2 µl		
Buffer	4 µl		
Amplicon product	3 µl		
Distilled water	9 µl		
TOTAL	**20µl**		
Sequencing process			
Initial denaturation		95°C – 5 minutes	
Denaturation		96°C – 30 minutes	25 cycles
Primer annealing		50°C – 15 minutes	
Template Elongation		60°C – 4 minutes	

2.3 Methods Specific to Sub-Study of ECG Characteristics in PPCM

The study design used here was a bi-directional cohort study. For prevalent cases the researchers looked retrospectively at the baseline and six-month follow-up ECG. For all other new cases that presented during the study period, baseline and follow-up ECGs were assessed prospectively. The retrograde component formed a considerable minority of the final analysis.

A 12-lead resting ECG was performed by a trained technician and analysed by a reviewer blinded to all clinical data (GL[6]) using a standardised approach to ECG interpretation entitled the Minnesota Code Classification system (Prineas et al, 1982) [see **Appendix 3c**]. The code allows systematic classification of Q and QS patterns, axis deviation, R waves, ST depression and elevation and T wave changes along with conduction abnormalities in both atria and ventricles (Prineas et al, 1982; Blackburn et al, 1960). The abnormalities detected by the Minnesota Code were categorised into

[6]**GLL** Geraldine Lee

major abnormalities and minor variations from the "normal" 12-lead ECG, using the classification system previously applied by De Bacquer et al (1998). Separate analyses for ST segment depression, arrhythmia or AV block, bundle branch block and left axis deviation were also performed. Major abnormalities were thus defined as those with: Q waves; ST segment depression; T wave inversion; complete or second degree AV block; complete left or right bundle branch block; frequent premature beats; atrial fibrillation; flutter. Minor abnormalities were defined as: borderline Q waves; left or right axis deviation; high amplitude R waves; border-line ST segment depression; T-wave flattening and low QRS voltage [See **Table 5**].

Table 5. Minnesota Code major and minor ECG criteria

[Adapted from Lee et al, 2008]

Major ECG criteria	Minor ECG criteria
Q-wave abnormalities	Borderline Q-waves
ST-segment depression	Left or right axis deviation
T-wave inversion	High amplitude R-waves
2^{o} or 3^{o} AV-block	Borderline ST-depression
Complete LBBB or RBBB	T-wave flattening
	Low QRS voltage

***LBBB:** Left Bundle Branch Block; **RBBB:** Right Bundle Branch Block

2.4 Methods Specific to Sub-Study of Bromocriptine Therapy in PPCM

The study design of the Bromocriptine sub-study was purely that of a clinical randomised controlled trial. It was conducted in the 12-month period between January 2007 and January 2008. Only newly diagnosed PPCM patients were approached for inclusion in the study; this being done within 24 hours of first diagnosis. Only women who had delivered recently (within the past month) could be included. For the purposes of this Phase II trial, the researchers had to be able to prove therapeutic efficacy of Bromocriptine in at least those with more severe forms of PPCM (i.e. those who stand to benefit the most). Hence the third difference to the diagnostic criteria described above was that patients were included only if the echocardiographic ejection fraction at presentation was equal to or less than 35%.

The 10 patients randomised to standard therapy (PPCM-Std group) were treated as outlined in the General Methods section above. The 10 patients randomised to standard therapy plus Bromocriptine (PPCM-Br) received Bromocriptine 2.5 twice daily for two weeks, followed by 2.5 mg daily for six weeks in addition to standard heart failure therapy.

Cardiac MRI (CMR) was performed for 4 - 6 weeks post-diagnosis in patients receiving Bromocriptine to detect possible mural thrombi. Studies were performed using a 1.5 Tesla MRI scanner (General Electric, Milwaukee, Wisconsin, USA) with a cardiac-dedicated phased-array coil. The CMR studies were ECG triggered by standard software. Studies consisted of steady-state-free precession (SSFP) and spin echo (SE). Short axis, transverse and coronal views were obtained. SSFP sequences were performed to assess regional wall motion abnormalities and LVEF. Slice thickness was 8mm, no gap, matrix 256 × 256, FOV 400mm, voxel size 1.6mm × 1.6 mm × 8mm. The total time required for the investigation was 30 - 45 minutes. Gadolinium enhancement was not studied. Ventricular parameters were assessed in a standard manner by one observer using commercially available software (CAAS MRV, Pie Medial Imaging, Maastricht, Netherlands). The CMR studies were assessed by two independent experienced observers who determined the presence or absence of intra-cavitary thrombi.

For all patients recruited, eight millilitres of blood was withdrawn from an ante-cubital vein and collected in pre-chilled tubes containing ethylenediaminetetraacetic acid (EDTA) or clot activator and mixed rapidly. Plasma or serum was separated by centrifugation at 2500 rpm for seven minutes within 10 minutes of collection. Aliquots were stored at minus -80 degrees Celsius for possible future analysis. High sensitivity C-reactive protein (hsCRP) was measured as per standard laboratory techniques. In addition, prolactin, NT-proBNP, full blood count, liver function and serum creatinine were also measured. Serum levels of 16kDa prolactin were measured by immuno-precipitation, followed by Western blotting. Cathepsin D activity was assayed with the Sensolyte 520 cathepsin D assay kit (MoBiTec).

Given that this was the first controlled clinical study on the effects of Bromocriptine in PPCM, and that our PPCM patients presented early in the post-partum period, it was important to attempt some systematic evaluation of the consequences of not breast-feeding on the young infants. Standard growth monitoring charts issued by the South African Department of Health and maintained by primary physicians were obtained for purposes of evaluating the newborn children of mothers included in this study. These charts listed the weight of each child at birth and at regular intervals to six months and beyond. Weights were plotted on World Health Organization (WHO) weight-for-age Child Growth Standard charts for girls and boys (WHO).

3. RESULTS

Over the three-year period in which the doctorate research was conducted, and during the preceding ten months spent in training and in preparation for the work that would form the contents of this thesis, over a hundred patients with PPCM were studied; and a considerable number that were initially suspected of having PPCM, but were later given other primary diagnoses. Of those PPCM patients found eligible for any of the sub-studies in question: 78 were included in the final ECG characterisation of PPCM; 10 were randomised alongside 10 controls to assess the efficacy of Bromocriptine therapy; and 51 were approached for the study of familial aggregation of IDCM in PPCM. In a minority of cases, and only where there were no clinical or ethical contra-indications, some patients were enrolled in more than one sub-study.

3.1 Overview of PPCM; the Experience in Africa and in Comparison with the World

"Peripartum Cardiomyopathy in Africa: Challenges in diagnosis, prognosis and therapy"

3.2 Results of the Familial Aggregation Sub-Study

3.2.1 Case series and commentary:

"Familial Dilated Cardiomyopathy in Peripartum Cardiomyopathy: A tale of two cases"

3.2.2 Full report on the family screening study:

"One-third of PPCM cases may be Familial Dilated Cardiomyopathy"

3.2.3 A report on our screening of PPCM patients for Lamin A/C mutations:

3.3 Results of the ECG Sub-Study:

"The 12-Lead ECG in Peripartum Cardiomyopathy"

3.4 Results of Sub-Study on the Use of Bromocriptine in Peripartum Cardiomyopathy:

"Evaluation of Bromocriptine in the treatment of acute severe Peripartum Cardiomyopathy: A proof-of-concept pilot study"

3.5 Results on the Study of the Predictors of Outcome in Peripartum Cardiomyopathy:

"Predictors of outcome in 176 South African patients with Peripartum Cardiomyopathy"

NB. Except for section 3.2.2 and 3.2.3, figures and tables in the results section are numbered according to their respective published article.

3.1 Overview of PPCM; The Experience in Africa and in Comparison to the World

"Peripartum Cardiomyopathy in Africa: challenges in diagnosis, prognosis and therapy"

***Tibazarwa K**, Sliwa K*

[Prog Cardiovasc Dis. 2010 Jan-Feb; 52(4):317-25]

This publication was important for this doctorate .The article was written at a time when many new theories had emerged regarding the causes and outcome patterns of PPCM (eg. Elkayam et al, 2001; O'Connell et al, 1986 versus Fett, 2005; and so forth); but where it remained unclear how these merged with the older theories (eg. Falase et al, 1985).

The article was also written to address what seemed to be an increasing divide on the diagnostic approach towards PPCM; initially between Western Societies and developing societies. However, the article also served to highlight that the increased research efforts into PPCM across the two hemispheres had actually narrowed the differences in the clinical pictures seen; hence allowing for similar diagnostic approaches to be used to improve research and clinical practice.

The article formed a comprehensive review on the diagnosis and management of PPCM, as well as on the challenges faced in Africa and across the world in managing such a disease diagnosed mainly by exclusion of other underlying causes.

Article Title:

Peripartum Cardiomyopathy in Africa: Challenges in diagnosis, prognosis, and therapy

Statement of Originality

NAME	**RESPONSIBILITY**
Kemi Tibazarwa **University of the Witwatersrand**	Conceived and designed the research Acquired the data Analysed and interpreted the data Performed statistical analysis where necessary Drafted the manuscript
Karen Sliwa University of the Witwatersrand	Conceived the research Supervised the research Drafted the manuscript
Candidate: I declare that this work is wholly my own, except where acknowledged as being the work of others (as listed above). I also acknowledge the contribution of others (as listed above) to this work in this Statement of Originality.	**Principle Advisor:** I hereby certify that all co-authors have provided their consent for inclusion of the paper in the thesis, and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.
Signed: Dr Kemi Tibazarwa (January 2013)	**Signed:** Professor Karen Sliwa (January 2013)

Progress in Cardiovascular Diseases 52 (2010) 317–325
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Peripartum Cardiomyopathy in Africa: Challenges in Diagnosis, Prognosis, and Therapy

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Abstract Peripartum cardiomyopathy (PPCM) is a form of heart failure affecting women of childbearing age, which can be associated with considerable mortality and chronic debilitating disease. Most patients present with acute postpartal heart failure that resembles the clinical presentation of idiopathic dilated cardiomyopathy. Historically, patients with PPCM have shown high rates of rapid recovery, with 6-month recovery rates averaging at 50%. However, recent prospective long-term follow-up of patients with PPCM in developing societies suggest recovery occurring only well into the second year after diagnosis, and recovery is poorly predicted by baseline left ventricular function. Beyond any potentially inherent factors contributing to poorer outcomes of patients with PPCM in developing societies, prognosis in these settings will continue to lag behind as the challenges faced to optimizing diagnosis remain immense. New insights into the role of inflammatory, apoptotic, and other genetic pathways may improve prognosis through the early detection and more targeted treatment of PPCM. (Prog Cardiovasc Dis 2010;52:317-325)
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Keywords: Peripartum cardiomyopathy; Africa; Heart failure; Women; Challenges; Diagnosis; Prognosis; Review

Peripartum cardiomyopathy (PPCM) is a clinical syndrome comprising reduced cardiac output that leads to tissue hypoperfusion and increased pulmonary capillary wedge pressure.[1] Peripartum cardiomyopathy is defined as per the modification by Lampert and Lang[2] of the definition given by Demakis et al[3]; this is the development of heart failure in the last month of pregnancy or within the first 5 months postpartum, in the absence of any other determinable cause for cardiac failure and in the absence of demonstrable heart disease before the last month of pregnancy, and bears echocardiographic evidence of left ventricular systolic dysfunction.[4] Restriction to this particular puerperal period serves to rule out preexisting causes of cardiomyopathy that may be exacerbated by pregnancy rather than arising as a result of pregnancy.[4,5] Most cases present within the first 4 months postpartum,[4,6,7] with only 10% presenting in the last month antepartum.[4,7]

The incidence reportedly varies from 1 in 3000 to 4000 deliveries in Western societies[8] to 1 in 1000 in developing societies,[7] with the highest incidence of 1 in 300 live births being reported in Haiti.[9] The apparent rise in the incidence across all geographic borders is most likely due to the improved awareness and diagnostic measures.[8] In a large African center, PPCM formed 1.5% of all patients with heart failure attending the center during the space of 1 year.[10]

Although studies in the United States show PPCM to occur more in women of African descent and those older than 30 years,[11] PPCM has been reported across the world,

Statement of Conflict of Interest: see page 323.

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Abbreviations and Acronyms

NYHA-FC = New York Heart Association functional class

PPCM = peripartum cardiomyopathy

TNF-α = tumornecrosis factor α

across all ages, and parities.[4,6] The younger age of patients with PPCM in developing nations[6,7] may reflect the younger age of the bulk of reproductive activity in developing nations. Multiple gestation within the index pregnancy has been implicated toward causing PPCM in 7% to 10%,[12] whereas multiparity is a more widely documented predisposing factor to the development of PPCM.[8,13] However, recent studies have suggested that the effect of multiparity is far less significant in the development of PPCM.[9] Peripartum cardiomyopathy also appears to occur more commonly in women who breast-feed for longer.[14]

Peripartum cardiomyopathy is an important cause of mortality and chronic debilitating morbidity, affecting relatively young women in the reproductive age group. It is the second most common etiology of cardiomyopathy-related cardiac transplant in women in the United States[15] and hence poses a considerable burden on the health, economic, and other social sectors of society.

Diagnosis

Peripartum cardiomyopathy is a diagnosis of exclusion. However, there is no agreement on the exclusion of preeclampsia. Unfortunately, the inclusion of patients with varying degrees of gestational hypertension, in the index as well as prior pregnancies, has contributed greatly to the discrepancy in reported characteristics of PPCM. This may also form the basis for the difference in the puerperal time of presentation. Studies comprising greater proportions of patients with preeclampsia, and of greater severity, tend to have far greater concentrations of PPCM cases presenting in the last month of pregnancy.[7,16,17] In contrast, studies with smaller proportions of patients with preeclampsia tend to document a postpartum peak in the presentation of PPCM, with reported onset of symptoms most commonly being 2 to 62 days postpartum.[8,9,18]

Important differential diagnoses are the common complications of late pregnancy, whose presentation may mimic that of PPCM and include preeclampsia, amniotic or pulmonary embolism, HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count occurring in association with preeclampsia),[19] and anemia-induced puerperal heart failure. Perhaps the most important of these is the first, as patients with preeclampsia have often been included amid patients considered to have PPCM, whereas others have included women with hypertension without documenting the presence of proteinuria or edema.

Symptoms

Most patients report severe shortness of breath of the order New York Heart Association functional class (NYHA-FC) III to IV,[20] presenting with lower limb swelling, some with right upper quadrant pain as well as other symptoms of acute heart failure (Fig 1).

Signs

Most patients will manifest the grades III to IV functional class by being overtly tachypneic in the clinic or hospital room (Fig 1). Most patients[21] have a mild resting tachycardia.[18] Blood pressure averages are usually normal, with larger prospective studies reporting mean systolic and diastolic blood pressures of 116 ± 20 mm Hg and 76 ± 14 mm Hg, respectively.[18] Bedside examination often suggests a dilated cardiomyopathy in the lateral and/or downward displacement of the apex, with dyskinetic apex, and sometimes palpable gallop rhythm.[22]

Arterial blood gas and pulse oximetry are important in a first assessment of the severity of respiratory insufficiency.

Complications

Thromboembolic complications are common.[21,23,24] Often these will manifest in the form of pulmonary embolism and stroke; these usually result from embolized mural thrombi in the dilated myopathic chambers of the heart. Rarely, this has culminated in embolic retinal artery occlusion that caused immediate onset of unilateral blindness in the patient with PPCM.[23] Bearing in mind that pregnancy itself potentiates a state of hypercoagulability,[24] the added risk in PPCM is a major concern. Although anticoagulation has been recommended in patients with PPCM with left ventricular ejection fractions of less than 35%,[25] there remains no systematic data to support this practice for PPCM or for other forms of left ventricular dysfunction in sinus rhythm.[26]

As with other forms of cardiomyopathy, arrhythmias are a common complication of PPCM and are further described later.

Routine biochemical tests

The full blood count is usually normal (given that significant anemia has been ruled out as a separate potential cause of heart failure), with normal electrolytes and biomarkers of renal function. In advanced cases, congestive cardiac failure will cause renal insufficiency and a prerenal biochemical profile. Most patients have normal liver function tests and, if raised, represent the acutely congested liver through raised canalicular enzyme levels, with only slightly raised transaminase levels.

Although older studies had suggested micronutrient deficiency could play a role in the development of PPCM,[11] many of these were smaller descriptive studies.

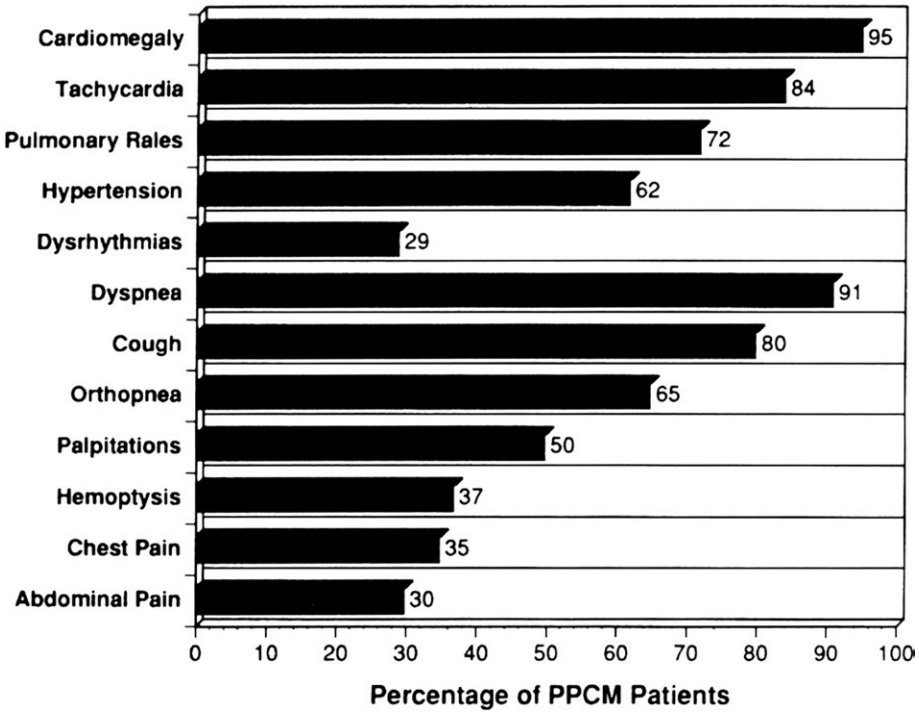


Fig. 1. Clinical characteristics of peripartum cardiomyopathy (PPCM). Reprinted with permission.[21]

Since then, a comparative study on a larger series of patients with PPCM has shown micronutrient deficiencies not to differ significantly between cases and controls.[6] These included selenium and vitamins A, B_{12}, C, and E as well as betacarotene.[6] Hence, these tests are no longer considered necessary in the workup of patients with PPCM.

To date, many centers in developing countries have considered HIV serology to be an important baseline investigation, as HIV positivity formed an exclusion criteria for clinical studies in the face of HIV-associated cardiomyopathy bearing clinical resemblance to PPCM. However, novel data report that patterns of left ventricular function and mortality were similar between patients with PPCM with and without HIV coinfection.[17]

Urine samples need to be assessed for albumin and other proteinuria, as an essential means of ruling out preeclampsia. Although such proteinuria presence helps to confirm the diagnosis of preeclampsia, its absence does not rule it out.

Electrocardiogram

Most patients present in sinus rhythm,[18,27] with nonspecific ST-segment and T-wave abnormalities that resolve for most patients within the first 6 months of treatment.[18]

Arrhythmias in PPCM occur as with cardiomyopathies and heart failure in general[18] and include atrial fibrillation, frequent premature ventricular systoles, ventricular tachyarrhythmias, and bundle branch block,[28] the later occurring more frequently among long-term cases.[16]

Although ventricular arrhythmias have been reported in up to one fifth of patients thought to have PPCM,[29] one of the few comparative studies showed the more life-threatening complex ventricular arrhythmias to occur almost as often in PPCM (60%) as in its closest variant, idiopathic dilated cardiomyopathy (76% of patients).[30] Another study suggests that subsequent pregnancy in patients with PPCM might result in deterioration of ventricular arrhythmias, through various mechanisms including triggering premature ventricular extrasystoles as the cardiomyopathy worsens in subsequent pregnancy.[31] This arrhythmic deterioration is thought to either precede and hence facilitate decompensation of heart failure or else be triggered by already worsening left ventricular dysfunction in asymptomatic patients.[31] Furthermore, they suggest that ventricular arrhythmias occurring in the acute phase of PPCM are likely to improve with left ventricular recovery, whereas those in patients not recovering will more likely require intervention.[31]

Radiologic

Chest roentgenogram

Typically, the chest x-ray will show cardiomegaly, pulmonary congestion (including upper lobe diversion and Kerly-B lines), and occasionally, right-sided pleural effusion in keeping with more severe congestive cardiac failure.

Echocardiography

Echocardiography has become the mainstay for the definitive diagnosis of PPCM. Diagnosis requires

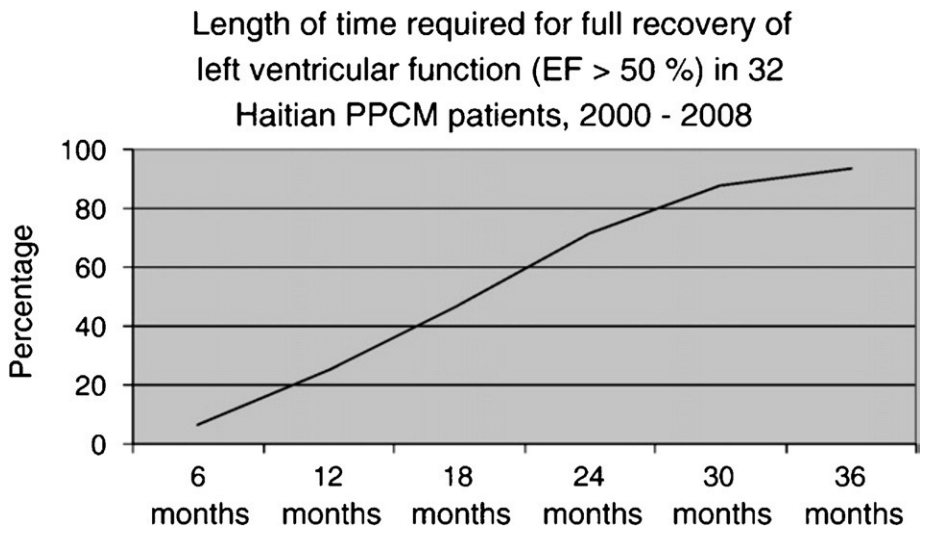


Fig. 2. Progression from shortest to longest time required for left ventricular systolic function recovery in peripartum cardiomyopathy. Reprinted with permission.[48]

echocardiographic evidence of left ventricular systolic dysfunction (ejection fraction < 45%).[1] Echocardiography allows for visual estimations of global and regional cardiac chamber function to assess systolic and diastolic functions and thrombotic complications of PPCM as well as to rule out other organic heart disease. Although most reports document elevated left ventricular end-diastolic diameters in PPCM, averaging 6 cm in most studies, not all patients will present with dilated left ventricles; hence, the current definition of PPCM does not mandate the presence of left ventricular dilatation.

Magnetic resonance imaging

For the last few years, MRI has received increasingly favorable attention in the evaluation of patients with PPCM. This is due to the ability to elicit the presence of myocardial fibrosis using late enhancement imaging in cardiac MRI, a marker of the persistence of left ventricular dysfunction.[32] Given the poor understanding of the pathophysiology of PPCM and the conflicting data on myocarditis as the causative process, there has been hope that cardiac MRI would also help to clarify the pathogenetic mechanisms. Further attributes of cardiac MRI are its ability to assess myocardial kinesia and ejection fraction and view the shapes, sizes, and contents of the cardiac chambers through the use of cine cardiac MRI.[32] One study of more than 1000 consecutive patients with heart failure assessed 8 women considered to have PPCM yet found no specific pattern of PPCM on cardiac MRI, no late enhancement, and no difference in MRI features between patients recovering within the first 2 years and those who failed to recover systolic function.[33] However, the PPCM sample size was small making more research mandatory.

Cardiac catheterization

As with other forms of heart failure, cardiac catheterization and angiography remain the gold standard for determination of systolic function. Yet, few systematic reports of PPCM have conducted hemodynamic studies; those existing having shown decreased cardiac output and high filling pressures but normal coronary arteriograms (Fig 2).[11]

Immunohistochemistry

Increasingly, studies have suggested myocarditis to be a key pathogenetic process in the development of PPCM.[30,34-36] Endomyocardial biopsies have strongly supported this theory,[30] as has the demonstrable clinical and histologic improvement of patients with PPCM on immunosuppressive therapy[30] such as prednisone and azathioprine.[34]

The specific etiology of the underlying myocarditis remains to be confirmed. For many years, the enhanced suppressor cell activity during pregnancy was thought to predispose pregnant women exposed to cardiotropic viruses to more severe forms of viral myocarditis.[30] Common pathogens implicated include Coxsackie and encephalomyelocarditis viruses[30] as well as Parvovirus B 19.[37] Adenovirus, human simplex virus 6, Epstein-Barr virus, and cytomegalovirus DNA have been isolated in endomyocardial biopsies of patients with PPCM.[38] However, myocarditis could simply reflect the immune response from any other form of myocardial damage. In essence, the molecular components of the inflammatory process in PPCM has been found to be very similar to that of idiopathic dilated cardiomyopathy, with elevated tumor necrosis factor α (TNF-α) and C-reactive protein levels

and, in particular, persistently raised leukocyte cytokine levels despite treatment.[14]

The aforementioned etiology is not restricted to PPCM but may form the basis for a variety of the dilated cardiomyopathies. For one, the prevalence of myocardial inflammation in PPCM appears to be similar to that of age-matched patients with idiopathic dilated cardiomyopathy[39] and has so far failed to predict outcome in PPCM.[40] Secondly, viral clearing has been associated with clinical improvement in both PPCM and idiopathic dilated cardiomyopathy.[13]

Unique to PPCM, however, are certain immune activation processes, such as the additional finding of elevated levels of the apoptotic marker Fas/Apo-1 that predicts mortality[7] and is considered causative.[13] Class G3 immunoglobulins,[28,41] which act against cardiac myosin,[13] bear the subclass IgG3. This IgG3s subclass bears pro-inflammatory characteristics and may be associated with higher NYHA-FC at presentation.[41] Although idiopathic dilated cardiomyopathy demonstrates highly selective up-regulation of the IgG3s subclass of G3 immunoglobulins, the humoral response in PPCM is not subclass restricted, with class G and all subclass immunoglobulins being raised in PPCM.[41] Sliwa et al[7,13] identified increased plasma levels of the inflammatory cytokine TNF-α, C-reactive protein, and a plasma marker of apoptosis, Fas/Apo-1, in a large population of newly diagnosed patients with PPCM. Furthermore, C-reactive protein levels on presentation demonstrate linear correlations with left ventricular end-diastolic and end-systolic diameters and, inversely, with left ventricular ejection fraction.[7] Given the ethnic variations in serum levels of C-reactive protein, it was hence proposed that an increase in the intensity of an inflammatory response could be one of the many factors contributing to the development of PPCM.[13]

Groundbreaking data into the pathogenesis of PPCM have implicated prolactin cleavage to play a key role.[42] Recent findings showed that a 16-kDa fragment of prolactin may induce myocardial damage[42] offering new treatment options in PPCM by blocking prolactin with bromocriptine.

Genetics

Only few studies have assessed the genetics of peripartum cardiomyopathy,[11,43] with the occurrence in twins of PPCM having been reported by Constanzo-Nordin and O'Connell.[44]

Polymerase chain reaction testing has been recommended in assessing the role of cardiotropic viruses in inflammatory cardiomyopathies such as PPCM, not just in endomyocardial biopsy tissue but possibly also in the study of peripheral blood samples, particularly for IgM detection during the viremic phase.[45]

Persistent microchimerism has been implicated in the etiopathogenesis of PPCM.[46] This is the presence of fetal cells in maternal circulation and suggests possible cross-reactivity of any antibodies generated by the mother in response to the circulating paternal antigen, irrespective of the sex of the fetus.[6] Unfortunately, current methods of fetal cell detection are limited to the demonstration of Y-chromosomal DNA, hence, relying on detection of fetal male chromosomal DNA in maternal plasma within a narrow period from term pregnancy to a few days postpartum.[6] This test remains to be validated in the evaluation of PPCM. However, high levels of fetal microchimerism in mononuclear cells has been found in patients with PPCM bearing high titers of autoantibodies; these levels of fetal microchimerism are significantly higher than that in control non-PPCM mothers during the third trimester of pregnancy, at term, and in the first week postpartum.[46] Most of these autoantibodies happen to be against human cardiac tissue proteins of 37, 35, and 25 kD,[28,38] leading to autoimmune myocarditis[13,28] and thereby emphasizing the need to facilitate detection tools for fetal microchimerism.

Another possible precipitant of apoptosis in PPCM and heart failure in vitro is the proapoptotic pathway resulting from overexpression of the 2 gene proteins Nix and BNi*p*3.[47] Up-regulation of BNi*p*3 was also observed in postpartum ventricular tissue of mice with a cardiomyocyte-specific deletion of the signal transducer and activator of transcriptin-3 (STAT3, STAT3-KO mice) and was associated with a high degree of myocardial apoptosis.[42] However, this is yet to be confirmed in humans.

Prognosis

Recovery from PPCM has often been limited to achievement of left ventricular ejection fraction more than 50%,[9,48] whereas the term "full recovery" in PPCM has been considered to be achievement of both NYHA-FC I and left ventricular ejection fraction more than 50%.[9,16]

Historically, most studies have suggested that full recovery of left ventricular function occurs in up to 50% of patients.[5,27,30,49] Larger and more recent prospective studies of patients from lower- and middle-income cohorts suggest only a quarter will fully recover by the end of the first 6 months,[9,16] whereas 10% to 15% would die by 6 months.[7,17] Long-term prospective outcome studies have shown overall recovery in a quarter of all patients with PPCM, most of these are achieved only 18 to 24 months after diagnosis (Fig 2).[17,48] Long-term overall mortality rates in Haiti, Turkey, and South Africa are estimated at 15%[9] to 30%,[16,17] with average death occurring at 54 ± 41 months in one study[16] but within the first couple of months in another study.[9] This is markedly higher than the mortality rates of 0% to 6%[28,40,50,51] and 9%[27] reported in the United States. Interestingly, two of these US studies demonstrate low mortality rates, one of 0% mortality,[28] and the other a 5-year

risk of death of 6%,[40] despite the high prevalence of myocarditis within their PPCM cohorts of 50%[40] and 29%,[28] respectively. The cohort by Felker et al[40] from the United States further showed PPCM to bear far better prognosis than all other forms of cardiomyopathy.

Earlier studies consistently showed greater chance of survival in patients with higher ejection fractions and smaller left ventricular end-diastolic diameters at baseline.[7,30] Suggested left ventricular cutoff values predicting favorable outcomes at 6 months after first presentation are higher than 27% for the ejection fraction and 5.5 cm or less for the end-diastolic diameter.[16] Strikingly, recent data imply that the impact of baseline and 6-month left ventricular dimensions and functions in predicting outcome falls away among long-term patients with PPCM, that is, those who failed to recover fully by 6 months.[9,48] These long-term outcome studies present the unified message that the natural history of PPCM goes far beyond what our 6-month prognoses were suggesting in earlier years. They show that although a minority of only 25% of PPCM will recover, most will only do so from 18 to 24 months onward.

Perhaps inclusion criteria that strictly excludes preexisting cardiovascular disease such as preeclampsia applied in some of the more recent prospective studies of PPCM has facilitated this revelation, which further strengthens the theory that the higher rates of rapid recovery in earlier studies could possibly be attributed to the reversible effects of gestational hypertension. However, it may remain true that inherent differences in the sociogenetic predispositions of patients with PPCM between the United States[27,40] and less developed societies[9,16,17] account for the better prognosis in the former group.

Consistent among studies of PPCM is the high risk of relapse with subsequent pregnancy,[27,52] with remarkable levels of mortality postpartum, alongside a strong association between TNF-α and deteriorating left ventricular function.[52]

A recent publication by Forster at al[49] in an African cohort showed that significantly higher baseline N-terminal pro-B-type natriuretic peptide, failure to decrease oxidized low-density lipoprotein, interferon γ, and prolactin were all associated with poor outcome in patients with newly diagnosed PPCM, suggesting a potential role of these factors in the pathophysiology of PPCM and allowing further exploration of target substances for monitoring and treatment programs.

Therapy

Medical management and therapy of patients with PPCM is similar to other forms of heart failure and has been reviewed in detail.[1]

Administration of diuretics is indicated in the presence of symptoms secondary to fluid retention, whereas ionotropic agents are recommended in the presence of peripheral hypoperfusion (particularly hypotension, decreased renal function). Temporary mechanical circulatory assistance should be used in patients with acute heart failure who are not responding to conventional therapy. Generally favorable outcomes have been attributed to the young age of recipients and to the relatively short duration of heart failure, resulting in minimal end-organ damage. Conventional pharmacologic therapy with angiotensin-converting enzyme inhibitor or angiotensin receptor blockers and, if hemodynamically stable, β-adrenergic blockade are effective in the treatment of PPCM. Because of the potential hazardous effects on the fetus, hydralazine (with or without additional nitrates) should replace angiotensin-converting enzyme inhibitor use during pregnancy. Digitalis, an ionotropic agent, is also safe during pregnancy and may help to maximize contractility and rate control. However, its use requires close monitoring of the patient, which may prove difficult in low-resource environments. Cardiac transplantation has been performed successfully in patients with PPCM.

Given the potentially inflammatory nature of PPCM with up-regulated inflammatory cytokines as TNF-α, interleukin 6, and Fas-Apo-1, there may be a role for immunomodulatory therapy. A prospective study of 59 consecutive women with PPCM reported a significant reduction in TNF-α and improved outcome in patients receiving the immunomodulating agent pentoxifylline in additional to conventional therapy that included angiotensin-converting enzyme inhibitors and β-blockers.[53]

However, further research into the pathomechanisms of PPCM by Hilfiker-Kleiner et al[42] revealed the coexistence of systemic oxidative stress and significantly higher prolactin levels in patients with PPCM; this supports the notion of the previously published concept that oxidative stress-mediated prolactin cleavage into its detrimental 16-kDa form is crucial for the initiation of PPCM and subsequent release of inflammatory cytokines. This suggests that inhibition of prolactin with bromocriptine may prevent a prolonged inflammatory response via activation and perpetuation of the inflammatory cascade. A recent pilot study in newly diagnosed patients with PPCM suggested that this process can be ameliorated or even abolished by administering the prolactin inhibitor bromocryptine.[54,55]

Challenges to improving diagnosis and prognosis in Africa

The lack of uniformity in case definitions of PPCM may result from clinicians differing in opinion about what constitutes an alternative cause of heart failure in patients evaluated for the diagnosis of PPCM, and it is fuelled also by the shortage of large studies for this rare disease.

Confounding the issue are studies comparing patients with PPCM with various levels of gestational hypertension from those who are hypertension naive.

In an attempt to address this deficit, the American College of Cardiology guidelines now classifies PPCM as an entity of its own,[1] whereas the European Society of Cardiology has taken active measures toward this process.[56] To benefit from this success of recognizing PPCM as a disease of its own, awareness of PPCM must be raised among clinicians and across societies, as this has been shown to contribute significantly to delayed diagnosis and underreporting of PPCM.[1,57] This will make a great impact in developing societies, where levels of awareness on cardiovascular disease are disproportionately lower than the actual prevalence of cardiovascular disease,[20] particularly so in Africa[58] and more so for PPCM.

The plight against poverty-related infectious disease has overridden many African countries' ability to pay sufficient attention to heart failure. Despite the greatest burden of heart failure in Africa caused by 2 infectious diseases, rheumatic heart disease and tuberculous pericarditis,[59] inequitable access to facilities permitting the definitive diagnosis and management of these patients have contributed to the paucity of research data on the epidemiology of the many various forms of heart failure in sub-Saharan Africa. To date, no population-based epidemiologic studies on PPCM from Africa have been published.[60] Like idiopathic dilated cardiomyopathy, PPCM is a diagnosis of exclusion. To confirm that the case fits the definition as per Lampert et al[2] mandates the use of sophisticated echocardiography. The exhaustive requirements for serologic tests, imaging, and, in more mature women, cardiac catheterization to rule out coronary artery disease falls beyond the capacity of most tertiary health centers in sub-Saharan Africa. Patients in rural areas continue to have grossly inequitable access to health facilities capable of even the most basic of these investigations. Recently, however, joint efforts to increase global awareness of the burden of cardiac disease in Africa has, to some extent, facilitated access to practical solutions, such as partially subsidized portable echocardiography equipment, and regional sharing of laboratory services for the more rare disease tests.

Across the world, a major challenge to clinicians remains the gross overlap between the clinical features of PPCM and the dyspnea, fatigue, and pedal edema of normal pregnancy.[18,25,61] In this regard, recent studies have suggested that electrocardiogram be used as a simple screening tool for heart failure in women presenting peripartum with the aforementioned symptoms, whereas women with abnormal electrocardiograms would merit further investigations for PPCM.[18]

Globally, the gap in available data on PPCM remains vast, and the shortage of long-term outcome studies is also evident. We are only aware of 7 long-term outcome studies,[9,15-17,27,48,62] 2 of which were retrospective in nature.[15,62] Much of this should be overcome with new research into the etiology of PPCM and also by the creation and use of registries.[63]

Summary

Peripartum cardiomyopathy is a form of heart failure often with a more devastating outcome in developing societies. We have highlighted important theories on the pathogenesis of PPCM, which have already served to shed light on agents such as bromocriptine and potent antiinflammatory agents that are currently being evaluated in clinical trials. However, practical challenges in the diagnosis and prognosis of PPCM remain, specifically so in resource-poor settings. Contributing to these challenges is the lack of consensus regarding etiologic mechanism and clinical criteria permissible for PPCM. We would like to emphasize, again, the need for concerted efforts and population-based data, as per a registry, to overcome the statistical barriers in evaluating the epidemiologic characteristics of PPCM.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

Acknowledgments

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3.2 Results of the Familial Aggregation Sub-Study

3.2.1 Case series and commentary:

"Familial Dilated Cardiomyopathy in Peripartum Cardiomyopathy: a tale of two cases"

***Tibazarwa K**, Sliwa K,Wonkam A,Mayosi BM*

[Cardiovascular Journal of Africa. 2013; 25(5): pp. e4-e7]

This paper singles out just two of a series of cases of PPCM that were found to have relatives with FDCM. The paper discusses the implications of these findings and compares how the findings relate to recent data that emerged from two studies in developed societies.

Being framed as a letter to the editor, the article presents a detailed debate on the existing evidence of some PPCM cases being FDCM manifesting post-partum; it proceeds to outline a number of thought-provoking recommendations.

This paper was important for this PhD in that it maps out current theories and debates that are a major aspect of the research, i.e. addressing the genetic contribution to PPCM - at both clinical and molecular level. Despite being restricted to the length-limits of a case report publication, the manuscript forms a platform onto which the authors could do an in-depth review of the various concepts published on the genetics of PPCM and synthesise suggestions in terms of approaching the genetics of PPCM going forward.

Article Title:

Familial Dilated Cardiomyopathy in Peripartum Cardiomyopathy: A tale of two cases

Statement of Originality

NAME	**RESPONISIBILITY**
Kemi Tibazarwa **University of the Witwatersrand**	Conceived and designed the research Acquired the data Analysed and interpreted the data Performed statistical analysis Drafted the manuscript
Karen Sliwa University of the Witwatersrand	Conceived and designed the research Acquired the data Assisted in arranging funding Supervised the research Drafted the manuscript
Ambroise Wonkam University of Cape Town	Acquired the data Analysed and interpreted the data Drafted the manuscript
Bongani Mayosi University of Cape Town	Conceived and designed the research Acquired the data Assisted in arranging funding Supervised the research Drafted the manuscript
Candidate: I declare that this work is wholly my own, except where acknowledged as being the work of others (as listed above). I also acknowledge the contribution of others (as listed above) to this work in this Statement of Originality.	**Principle Advisor:** I hereby certify that all co-authors have provided their consent for inclusion of the paper in the thesis, and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.
Signed: Dr Kemi Tibazarwa (January 2013)	**Signed:** Professor Karen Sliwa (January 2013)

Case Report

Peripartum cardiomyopathy and familial dilated cardiomyopathy: a tale of two cases

K TIBAZARWA, K SLIWA, A WONKAM, BM MAYOSI

Abstract

Peripartum cardiomyopathy (PPCM) is a form of pregnancy-related heart failure that is associated with considerable morbidity and mortality. Most patients present with acute postpartal heart failure that otherwise resembles the clinical presentation of dilated cardiomyopathy (DCM). There is increasing recognition that PPCM may be due to genetic factors in a significant proportion of cases. There is evidence that at least 7% of cases of PPCM may be part of the spectrum of familial DCM. We report on two cases of PPCM, with relatives demonstrating familial DCM, both patients displaying autosomal dominant patterns of inheritance, and showing severe cardiomyopathy among proband and affected relatives. Family screening for familial DCM should be indicated in all cases of unexplained PPCM.

Keywords: peripartum cardiomyopathy, genetics, familial dilated cardiomyopathy, Africa

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DOI: 10.5830/CVJA-2013-027

Peripartum cardiomyopathy (PPCM) causes heart failure in women of child-bearing age. We describe two African patients with PPCM, diagnosed according to standard criteria,[1] who underwent comprehensive screening of first-degree relatives and were found to have familial disease. Informed consent was obtained from both patients and the study protocol conformed to the ethical guidelines of the 2008 Declaration of Helsinki as reflected in *a priori* approval by the human research ethics committee of the University of Cape Town.

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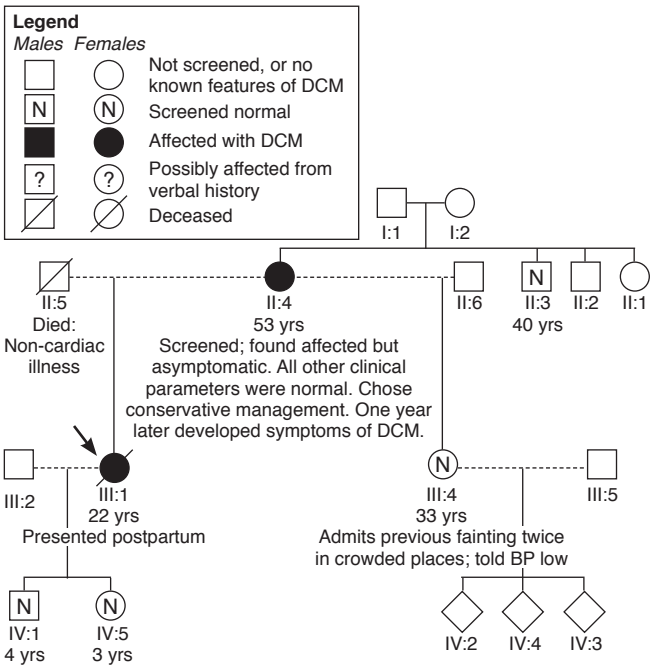
Case report 1

A 22-year-old mother of two presented 27 days postpartum with one week of symptoms and was diagnosed with PPCM. Despite treatment, she died at home within six months. Family screening found her mother to have asymptomatic dilated cardiomyopathy (DCM) (Fig. 1).

After opting for conservative management, the mother developed symptomatic DCM a year later, presenting in florid heart failure. Cardiac catheterisation and other investigations excluded coronary artery disease (CAD). The index case's half-sister admitted to a history of dizziness, low blood pressure and occasional fainting episodes in crowds but had no echocardiographic evidence of DCM.

Case report 2

A 23-year-old mother of two presented two months postpartum with PPCM. Family history revealed an unspecified heart condition in her mother, who died shortly after a cerebrovascular accident at age 60 years (Fig. 2). Her sister apparently developed heart failure four years after her first delivery at 19



NB. Dotted lines imply partners that never married

Fig. 1. Pedigree of index case (arrowed) with peripartum cardiomyopathy with familial disease (Family I). (DCM, dilated cardiomyopathy)

years of age and deteriorated after the birth of her second child 10 years later. This sister soon suffered a stroke and died one year after the second childbirth.

Active family screening revealed symptomatic DCM in her 39-year-old brother, without CAD; and asymptomatic left ventricular (LV) systolic dysfunction in her 22-year-old sister. Screening one elder sister showed Wolf-Parkinson-White syndrome.

These two cases of PPCM have at least one family member with DCM, and therefore meet the definition of familial cardiomyopathy.[2] The presentation in both cases is compatible with autosomal dominant inheritance.

PPCM and idiopathic DCM

The distinction of PPCM from idiopathic DCM may be difficult because both conditions are characterised by LV dysfunction with no apparent cause. Indeed, some investigators have proposed that PPCM may simply be idiopathic DCM manifesting in late pregnancy, this being a time when the haemodynamic changes of pregnancy could overwhelm the heart.[3] Along this hypothesis, increased preload leads to LV dilatation and cardiac insufficiency, a theory partly supported by earlier studies in which a number of cases presented in the last month antepartum or immediately postpartum.

However, such theory is not supported by studies showing that PPCM with no gestational hypertension present on average at two months postpartum,[4-6] having developed symptoms within two months postpartum.[6,7] By this time, these haemodynamic changes of pregnancy would have ceased.[4] However, cohorts with predominantly postpartum-onset PPCM display prognoses similar to those of idiopathic DCM, with far slower recovery than in PPCM phenotypes with predominantly gestational hypertension.[1,7]

Even though most women with asymptomatic or mildly symptomatic idiopathic DCM tolerate pregnancy uneventfully,[8] as with other pre-existing heart disease, any subclinical cardiomyopathy may be associated with the worsening of symptoms in the second trimester of pregnancy when the haemodynamic stress on the heart is maximal.[4] However, recent attempts to broaden the traditional gestational period defining PPCM[6] have renewed the controversy. Clear consensus on case definition is vital before clinical and epidemiological patterns can be reliably described.

Studies show 20–50% of all idiopathic DCM cases to have familial disease.[9-11] Although women have been shown in some studies to be equally affected as men,[9,12] more studies suggest a male predominance.[10] However, less than a handful of studies report on the incidence and outcomes of pregnancy in women with familial DCM.[8] To the best of our knowledge, no study has systematically investigated all immediate relatives of PPCM patients to ascertain the prevalence of familial DCM among these patients.

PPCM and familial DCM

There have been several reports of familial disease in PPCM.[1,13,14] Two Western studies and one South African case series suggest that a subset of PPCM patients may be part of the spectrum of familial DCM presenting in the peripartum period.[10,14,15] Surprisingly, PPCM patients in each of these two Western studies almost uniformly presented postpartum, with only one case in each study presenting within the last six weeks of term pregnancy (i.e. only one to two weeks from the

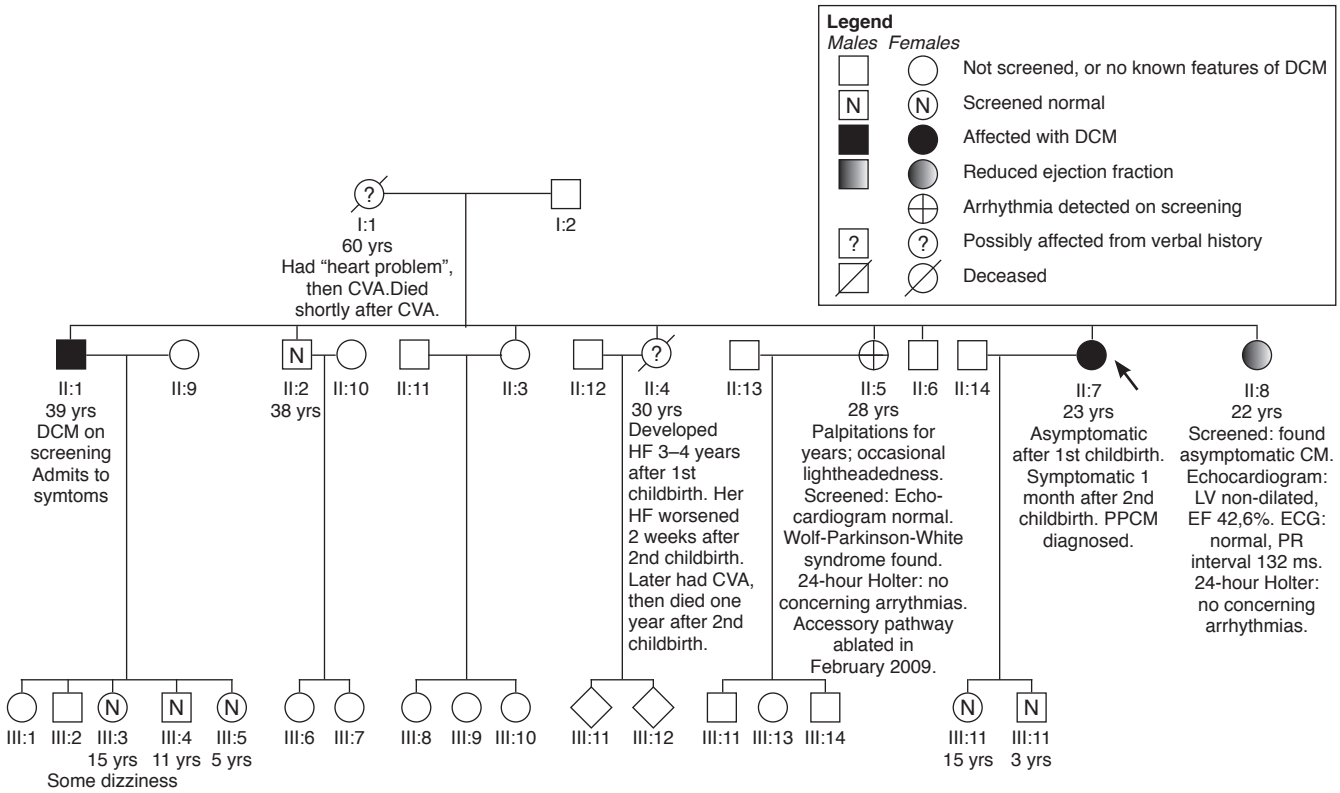


Fig. 2. Pedigree of index case (arrowed) with peripartum cardiomyopathy with familial disease (Family II).

traditionally defined time of onset of PPCM).[14,15] These studies were weakened by their exclusion of patients who recovered LV function within the first year, thereby cutting out 25–50% of the spectrum of PPCM patients and favouring the possibility that only FDCM phenotypes were retained, as the latter rarely recover LV function.

Nonetheless, these findings raise two pertinent questions. First, other than postulations of late-pregnancy oxidative stress triggering the PPCM phenotype, how did these putative familial DCM cases surpass the expected time of presentation for pre-existing heart disease in the second trimester? Second, could the genetic polymorphisms or mutations identified so far in PPCM cases with familial disease be a co-incidental finding, while the real culprits for PPCM phenotypes lie in other genetic mutations inadequately sought for beyond those known to cause familial DCM?

Familial DCM manifests in an age-dependent manner with incomplete disease penetrance.[9] Therefore, in the absence of long-term, population-based studies, answering our second question will remain a challenge. As heterogeneous as familial DCM is, over 40 defective genes have been associated with inherited DCM, although they account for a minority of familial DCM cases.[16]

Genome-wide association studies (GWAS) may succeed in identifying pathogenic mutations for PPCM. The only known attempt at GWAS in PPCM patients was done in Utah,[17] and revealed 10 single-nucleotide polymorphisms (SNPs) that may play a role in the pathogenesis of PPCM.[17] Of these, one SNP (located on chromosome 12) demonstrated genome-wide significance for PPCM, likely triggering disease through abnormal immune modulation.[17] The strength of the study lies in its efforts to exclude patients with co-morbidities that would confound the diagnosis of PPCM, and for screening a variety of controls, including post-menopausal controls,[17] to enable discovery of PPCM-associated loci relevant to the at-risk population of pregnant/potentially pregnant females.[17] Furthermore, the authors went as far as to describe 30 other SNPs which appeared to predict the absence of PPCM,[17] suggesting a route for the exploration of protective mechanisms to PPCM.

Recent advances favouring PPCM as an independent disease shows *in vitro* and *in vivo* evidence of an abnormal 16-kDa prolactin pathway intertwined with oxidative stress.[18] However, given that oxidative stress, together with signal transducer and activation of transcription factor-3 (STAT-3) depletion, as implicated in this model may be common to most forms of severe heart failure, including idiopathic DCM,[19] the only component to this pathway that might remain unique to PPCM is that fuelling production of the 16-kDa fragment of prolactin. However, linking this abnormal prolactin pathway exclusively to PPCM would require proof of its absence in women with familial DCM, including relatives who subsequently fall pregnant and deteriorate.

Despite the GWAS described above[17] having failed to find any SNP or other variation on the STAT-3 gene to account for PPCM, it introduced the possibility of an association between polymorphic variations (SNPs) on the STAT-5 gene and PPCM. This is important because STAT-5 is a known culprit in idiopathic DCM,[19] making the thought of it playing a role in the development of PPCM an interesting possibility.

Novel data further suggest that imbalances between cardiac pro-angiogenic factors PGC-1α and vascular endothelial growth factor (VEGF), and anti-angiogenic factors such as the VEGF inhibitor soluble Flt1 may result in PPCM, and that this association is more profound in the presence of gestational hypertension and multiple pregnancy.[20] If indeed these mechanisms become validated, it would be essential to establish any genetic bases for these abnormalities.

Conclusion

There are several lessons to be learned from this detailed family study of two cases with PPCM. First, we emphasise the need for family screening of PPCM and idiopathic DCM patients,[10] with long-term follow up of screened persons, particularly of females of child-bearing age. There is a need for well-structured incidence studies of PPCM and idiopathic DCM, with baseline echocardiograms of primary relatives (irrespective of symptoms), pre-pregnancy echocardiography of all women being followed up (irrespective of underlying co-morbidities), and follow up with echocardiography every two to five years.[21] This exercise could mould routine practice, given the high prevalence of familial DCM, its lethal course, and the suggested benefits of treating asymptomatic relatives with LV dysfunction.[11]

Aside from the GWAS reported several years ago,[17] the search for genetic abnormalities in PPCM has remained narrowed towards screening for mutations (or SNPs) associated with familial DCM. It would be recommended to expand on the reported GWAS by testing the clinical impact of the SNPs already suspected to be associated with PPCM.[17] Furthermore, in the hope of identifying new SNPs accountable for PPCM through target-gene search or GWAS, it may be logical to start comparing genotypes of extreme phenotypic presentations of both PPCM and idiopathic DCM (i.e. mild versus severe) within and across their respective diagnostic groups.

In addition, in the search for PPCM-specific genetic abnormalities, the co-existence of the abnormal 16-kDa prolactin cascade would need to be evaluated in familial DCM patients who deteriorate in pregnancy, and the genetic abnormalities programming this abnormal pathway further explored. Lastly, next-generation sequencing (NGS) is a recently developed, massively parallel, large-scale sequencing technology that has been used for rapid gene cloning and mutation detection. Taking advantage of the larger size of families in Africa, NGS with exome selection could be used to identify the causative genes and to improve both genetic and clinical delineation of DCM and PPCM.

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3.2.1 Full report on the family screening study:

"One-third of PPCM cases may be Familial Dilated Cardiomyopathy"

***Tibazarwa K**, Sliwa K, Wonkam A, Boulle A, Mayosi BM*

[Presented at the Annual SAHA Congress – October 2011]

This study was novel in it being the first large series of PPCM patients to undergo detailed systematic family screening of eligible first degree relatives for the presence of familial DCM. Our findings support the notion that over a third of PPCM cases bear familial DCM; a proportion similar to the prevalence of familial DCM amongst so-called idiopathic DCM patients. This in turn supports the notion that at least this sub-set of PPCM patients may form part of the spectrum of familial DCM.

The study was also novel in its attempt to compare the prevalence of familial DCM amongst PPCM patients with that in women presenting with pregnancy-associated heart failure in the context of current or prior history of hypertension. Interestingly, we demonstrate the latter group of women to also be at risk of familial disease - albeit at a far lower risk than PPCM patients.

Through this study, we were able to recommend with confidence that routine family screening may be as merited in PPCM as it is in DCM.

"One-third of PPCM cases may be Familial Dilated Cardiomyopathy"

Rationalé

Non-systematic studies have revealed that siblings of PCM patients demonstrate left ventricular dilatation and left ventricular dysfunction. Furthermore, despite a number of scientific contributions towards understanding possible predisposing factors for PPCM, its clinical resemblance to idiopathic DCM remains undeniable, including recent revelations that PPCM cases defined strictly as per the standard diagnostic criteria (Sliwa et al, 2010) may follow a similar natural history to idiopathic DCM. In our continued efforts to evaluate how the two can be clinically differentiated, we assessed familial occurrence of DCM in patients with PPCM in an attempt to compare it with that known for idiopathic DCM.

Results

A total of 51 families of un-related PPCM patients were approached for family screening [**Figure 7**]. However, over half of these family screening attempts failed for a variety of reasons, ranging from reluctance to come to hospital to pre-entry exclusion of first degree relatives on the basis of concomitant disease, such as hypertension, diabetes, HIV infection and so forth.

For purposes of this paper, detailed analysis of PPCM patients (i.e. probands) was restricted to the 18 families with at least one first degree relative eligible and successfully screened for the presence of DCM. From these 18 probands, a total of 44 relatives were successfully screened, giving a mean of 2.4 relatives screened per proband. 43% of screened relatives were male, without there being any statistically significant difference in the proportion of female relatives compared to males.

Tables 6 to 8 show the demographic and clinical profiles for PPCM cases and for all relatives, including echocardiographic findings [**Table 8**]. The mean age of probands was 28 years (± 7 years); the group of relatives did not differ significantly in age from the group of probands (median age 24 years, IQR 18-34 years; p= 0.3).

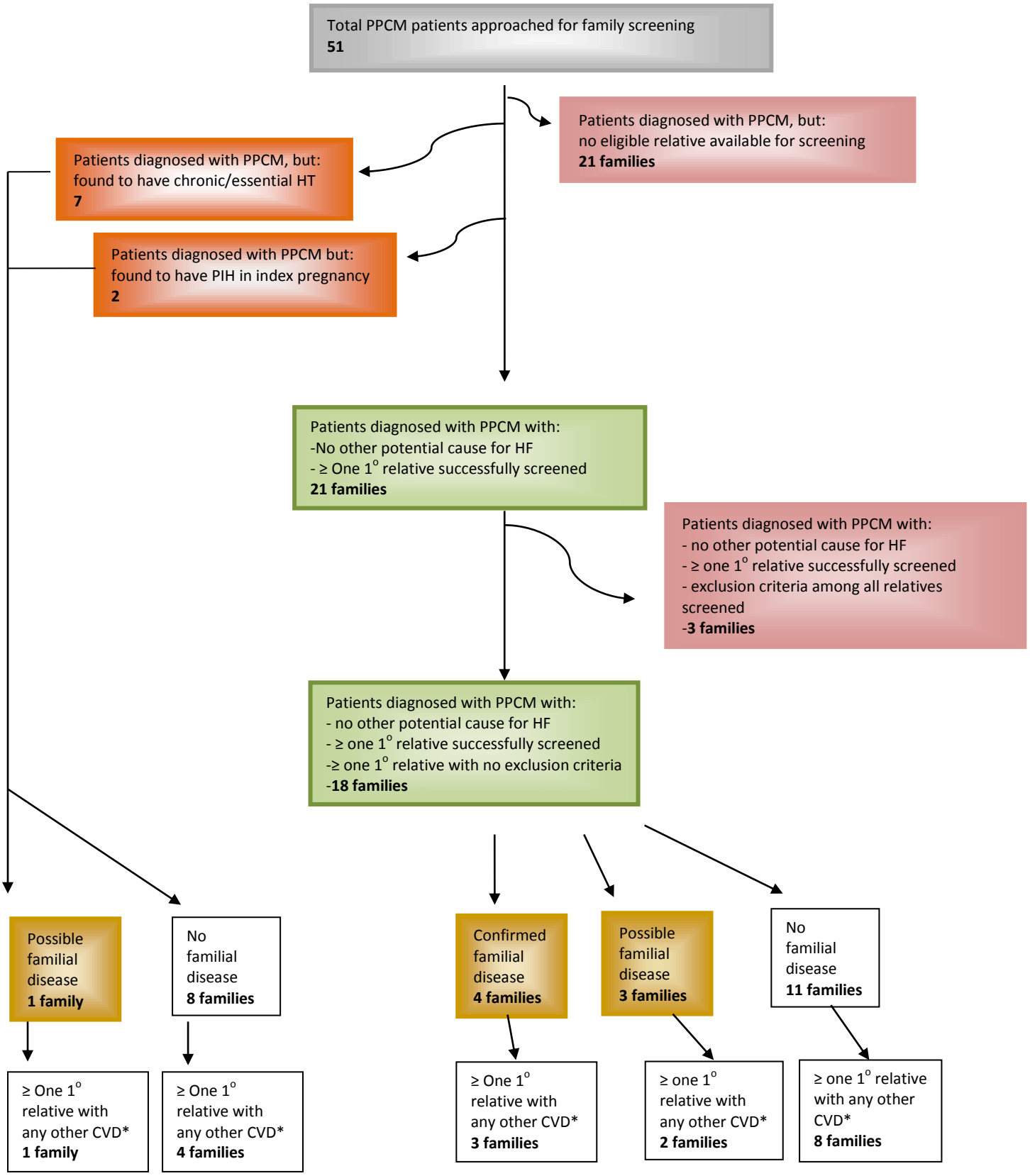
Of the 18 probands: a total of 4 probands (22%) had at least one relative with definite echocardiographic evidence of DCM, rendering them positive for familial disease; a further 3 (16%) had at least one relative with possible DCM, rendering them possible bearers of familial disease [see **Figure 7**]. In these families with definite and possible familial disease, we cannot preclude the potential for an underlying genetic cause for development of the PPCM phenotype in the proband, as would be required to fulfil it being a diagnosis of exclusion; hence we consider these cases to be familial DCM.NB: This brings the total prevalence of familial dilated cardiomyopathy amongst first degree relatives of PPCM patients to 39%.

Relatives across the three different categories of being affected did not differ from each other significantly in their demographic and basic clinical profile. Both autosomal dominant and autosomal recessive patterns of inheritance were seen amongst the families of patients with PPCM [**Figure 8**].

Interestingly, one of the patients presenting with PPCM and manifesting hypertensive heart failure in pregnancy (HHFP, i.e. pregnancy-associated heart failure with current or prior history of hypertension) also demonstrated possible familial disease (HHHP). This was in the form of autosomal dominant pattern of inheritance.

A full list of pedigrees for families of patients screened can be seen in section 7 of the Appendix section at the very end of this thesis.

Figure 7. Flowchart illustrating participant flow from recruitment to diagnosis



CVD Cardiovascular Disease; **HT** Hypertension; **HF** Heart Failure; **PIH** Pregnancy-Induced Hypertension

*Relatives known or found to have other CVD during the active screening process included ones with HT (the vast majority), rheumatic heart disease, type II diabetes mellitus, and heart disease due to other underlying conditions

Table 6.Bio-demographic profile of PPCM probands and their first degree relatives screened

	PROBANDS	1ST DEGREE RELATIVES	
		All Relatives	p
Age (years)	28 ± 7	24 (IQR 18-34)	0.339
Parity	1.5 (IQR 1-2)	1 ± 1.7#	**0.007**
BMI (kg/m²)	27 ± 6	28 ± 7	0.625
Pulse rate	97 ± 18	70 ± 11	**<0.001**
Blood pressure			
• **Mean systolic (mmHg)**	105 ± 15	118 ± 13	**0.003**
• **Mean diastolic (mmHg)**	68 ± 7	75 ± 8	**0.006**

*Standard deviation (± SD); Inter-quartile range (IQR) #Applies to female relatives only

Table 7. Heart failure symptomatology in screened first degree relatives of PPCM patients

Symptom	Prevalence among probands	Prevalence among 1st degree relatives	p
Dyspnoea (NYHA FC II or greater)	100%	2%	**<0.001**
Dizziness	31%	3%	0.240
Palpitations	44%	6%	0.099
Chest pain	25%	10%	0.809
Lower limb swelling	56%	0%	**0.001**
Other (eg. Abdominal pain)	56%	0%	-

NYHA FC II – New York Heart Association Functional Class II

Table 8a.Echo-cardiographic characteristics of PPCM patients in comparison with their relatives

Echocardiographic measurement	Proband	1st Degree Relatives	p
LVISd (cm)	0.9 (IQR 0.8-1.1)	0.9 ± 0.2	1.000
LVEDd (cm)	6.2 ± 0.7	4.8 ± 0.4	**<0.001**
LVPWd (cm)	0.95 (IQR 0.7-1.1)	0.9 ± 0.2	0.712
LVISs (cm)	1.1 (IQR 0.9-1.4)	1.3 ± 0.3	0.108
LVEDs (cm)	5.0 ± 0.7	3.2 ± 0.4	**<0.001**
LVPWs (cm)	1.3 (IQR 1-1.2)	1.4 ± 0.4	
Fractional shortening (%)	19 ± 8	34 ± 6	**<0.001**
Ejection fraction (%)	33 ± 14	61 ± 9	**<0.001**
Mitral valve area (cm^2)	3.7 ± 1.5	3.3 ± 0.8	0.410
Pressure half time (cm/s)	101 ± 73	76 ± 16	0.105
Deceleration time (cm/s)	205 (IQR 134-676)	247 (IQR 216-310)	0.710
Aortic root (cm)	2.4 ± 0.5	2.6 ± 0.4	0.19
Left atrial diameter (cm)	3.9 ± 0.9	3.3 ± 0.7	0.02
Mild-severe valve regurgitation **(% of sub-group population)** • **Mitral** • **Tricuspid**	63% 44%	3% 16%	**<0.001** **0.040**
Dilated right-sided chamber(s), **[% of population]**	6%	6%	0.543
Raised right ventricular systolic pressure **(% of population)**	63%	0%	0.063

LVISD - Left ventricular septal width in diastole; **LVEDd** – Left ventricular end-diastolic diameter; **LVPWD** - Left ventricular posterior wall width in diastole; **LVISs** – Left ventricular septal width in systole; **LVEDs** Left ventricular end-systolic diameter; **LVPWs** – Left ventricular posterior wall width in systole.

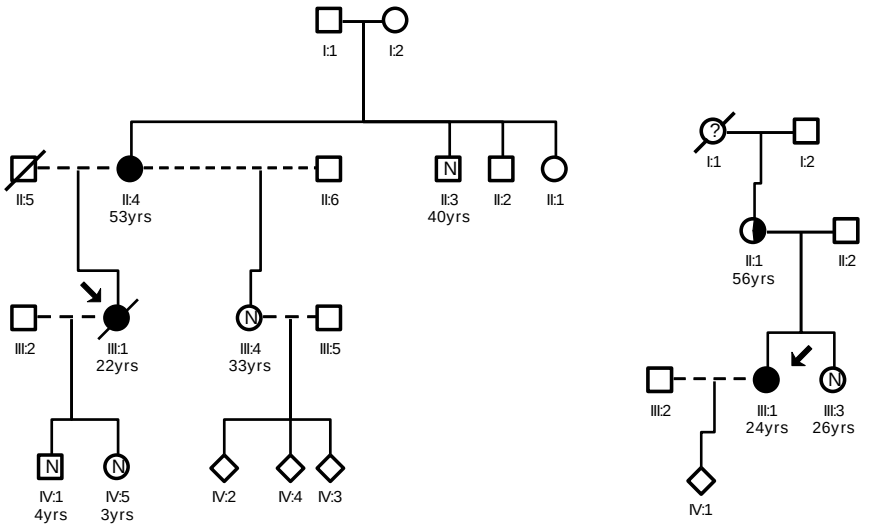
Table 8b.Summary of key abnormal echo findings among first degree relatives of PPCM patients

Echo-cardiographic measurement	Proband	Relatives	
Dilated LV in diastole	100%	19%	**<0.001**
Dilated LA in diastole	25%	13%	0.186
Reduced ejection fraction	81%	6%	**<0.001**
Mitral regurgitation	63%	3%	**<0.001**
Tricuspid regurgitation	44%	16%	**0.040**

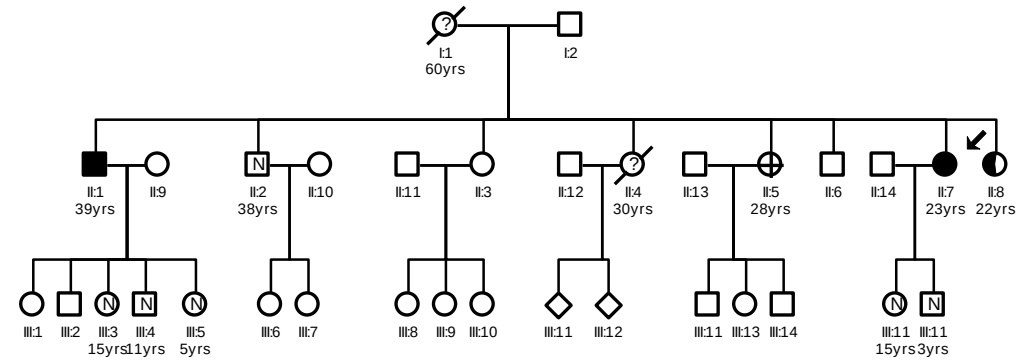
[LV Left ventricle; **LA** Left atrium]

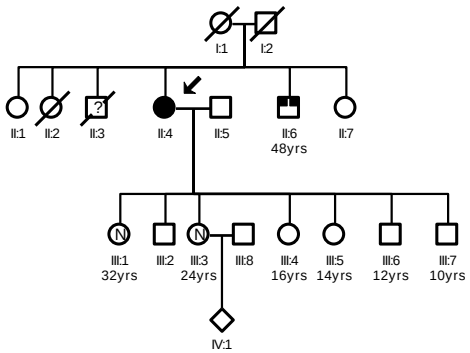
Figure 8. Pedigrees where relatives of PPCM probands screened positive for DCM

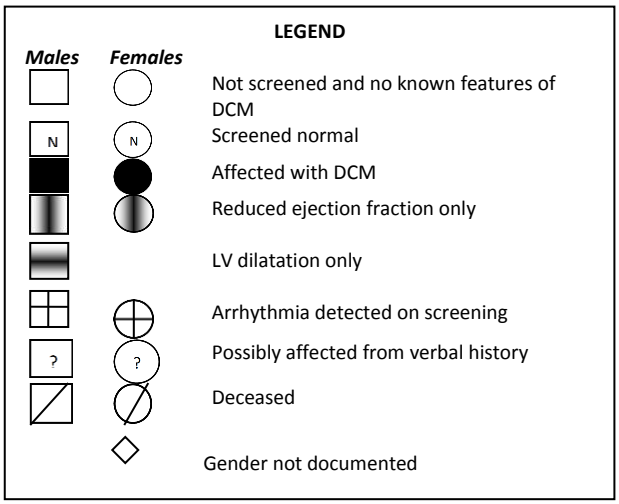
2a. Two families suggesting autosomal dominant pattern of inheritance



2b. Two families suggesting autosomal recessive pattern of inheritance







3.2.2 A report on our screening of PPCM patients for Lamin A/C mutations:

This sub-study addressed a specific component of the genetic aetiology of PPCM; it sought to establish the prevalence of one of the most notorious genetic mutations associated with its clinical simulant familial DCM. This concerns the Lamin A gene (LMNA), which codes for the Lamin A and C proteins found in muscular tissue. A number of LMNA mutations are known to be associated with more aggressive clinical presentations of DCM due to the increased occurrence of deadly arrhythmias, heart failure and higher mortality. These three disease outcomes are common in PPCM patients of this study, although so far there hasn't been any clear clinical parameter that could predict which patients would be likely to do worse. Thus, we postulated that patients doing worse in this regard may bear an underlying genetic predisposition to doing worse, such as harmful mutations to the Lamin A/C gene.

Despite two recent studies, one from the Netherlands (Van Spaendonck et al, 2010) and the other from USA (Morales et al, 2010) having attempted to screen their PPCM patients for this mutation, this study remains the first to systematically screen a large number of prospectively recruited PPCM patients with the primary intention of genetic analysis. Although our results differed from those from Western societies, as indicated above (Van Spaendonck et al, 2010; Morales et al, 2010), in that we did find Lamin A/C abnormalities to be prevalent in our PPCM patients, all were well-documented SNPs, with the vast majority reported to be non-pathogenic.

Our experiment failed to demonstrate any novel mutation on the LMNA gene. However, given that the only other genetic abnormality of pathologic potential in PPCM was found on a different chromosome using Genome Wide Association Studies in the United States, our study remain the first to perform a systematic exon-sequencing of the LMNA gene in a statistically significant number of PPCM patients. Our sample size was not particularly small. Yet a larger sample size may have helped to overcome any under-estimation of the occurrence of pathogenic Lamin A/C mutations amongst the PPCM patients.

A report on our screening of PPCM patients for Lamin A/C mutations

The Lamin A Gene (LMNA)

The Lamin A/C gene codes for both the Lamin A and Lamin C proteins. We refer to the portions encoding for Lamin A as LMNA [see **Figure 9** below].

Figure 9. The Lamin A Gene (LMNA) and its constituent exons

[Adapted from Parks et al, 2008; and Perrot et al, 2009]



The LMNA gene is shown (LMNA). The Lamin A protein is coded by exons 1−12 and has a total of 664 amino acids in length. Lamin C is coded by exons 1−9 and an alternatively spliced exon 10, and is 572 amino acids long. White boxes are coding, while grey-shaded boxes are un-translated regions. Lamin A protein results from alternative splicing that adds exons 11 and 12 and removes the Lamin-C-specific portion of exon 10 (the latter being shown as the upper of the two boxes marked exon 10).

Screening for LMNA mutations in PPCM patients

Genetic screening for mutation on the Lamin A/C gene (LMNA) was successfully conducted in 38 PPCM patients alongside two separate pairs of controls matched for sex and ethnicity, as described in the methods section above.

I. Bio-demographic profile of PPCM probands

Table 9 shows the bio-demographic profile of the 38 PPCM patients recruited. None of the patients had hypertension or raised blood pressure on presentation.

Table 9. Bio-demographic profile of the 38 PPCM patients

	Proband
Age (years)	28 ± 7
Parity	1.5 (IQR 1-2)
Of African Descent	95%
BMI (kg/m^2)	27 ± 6
Pulse Rate	96 ± 18
Blood Pressure • Mean systolic (mmHg) • Mean diastolic (mmHg)	 104 ± 16 68 ± 7

II. Results of genetic screening for mutation to the Lamin A/C gene

As per the methods, primers were designed to cover all the exonic region of the LMNA gene, but parts of the intron on either side of the exon were included. 12 exons were identified for the LMNA gene, each complete with the appropriate flanking regions.

As many runs of the amplification process were done as was deemed necessary to ensure the best possible result in amplified material. Sequencing analyses were performed on all amplified tracings where high-resolution melt analysis curves suggested the presence of a possible variation. PPCM patients demonstrated abnormalities in 6 of the 12 exons [see **Table 10**], most of which were within the intronic region of that exon.

Amidst these 6 exons, a total of 9 mutations were observed; 78% of which were intronic, 22% synonymous. All of the 7 intronic changes were known SNPs [see **Figure 10**]. Of the two synonymous variations, one was reported by dbSNP to be non-pathogenic, whilst the other remained untested; according to both dbSNP and 1000 genomes databases. Still, the fact that both are polymorphisms makes the likelihood of the untested one being non-pathogenic very high.

Of marked importance, however, is the absence of any novel mutation amidst our PPCM patients.

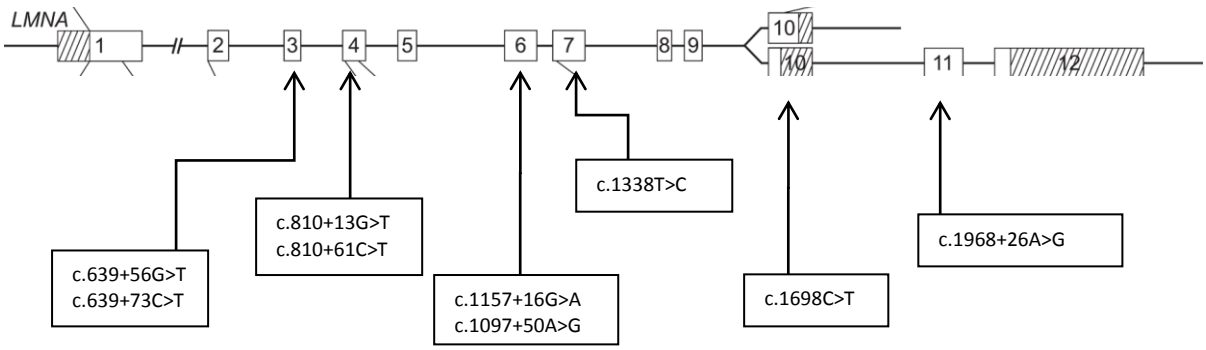
Table 10. Sequencing analysis for mutations in Lamin A/C gene in PPCM patients

Location	No. of Patients with Mutations	Nucleotide change	Amino acid change	Mutation type	Documented in Literature	Pathogenic*
Exon 3	10 Heterozygous/6 Homozygous	c.639+56G>T	-	Intronic	dbSNP: rs11264442	No (dbSNP, Mutation Taster)
	13 Heterozygous/2 Homozygous	c.639+73C>T	-	Intronic	dbSNP: rs11264443	Untested (1000 Genomes)
Intron 4	13 Heterozygous/1 Homozygous	c.810+13G>T	-	Intronic	dbSNP: rs11264444	No
	13 Heterozygous/1 Homozygous	c.810+61C>T	-	Intronic	dbSNP: rs11264445	No
Intron 6	3 Homozygous/14 Heterozygous	c.1157+16G>A	-	Intronic	dbSNP: rs534807	No (dbSNP, Mutation Taster)
	8 Heterozygous	c.1097+50A>G	-	Intronic	dbSNP: rs16837198	No
Exon 7	6 Heterozygous	c.1338T>C	p.D446	Synonymous	dbSNP: rs505058	No (dbSNP), Untested (1000 Genomes)
Exon 10	1 Heterozygous	c.1698C>T	p.H566	Synonymous	dbSNP: rs4641 HGMD-PUBLIC: CM003892	Untested (1000 Genomes)
Intron 11	2 Heterozygous	c.1968+26A>G	-	Intronic	dbSNP: rs80264244	Untested

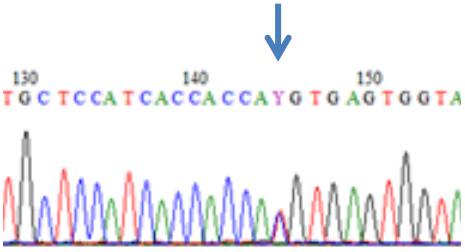
*****The pathogenicity of the given abnormality was determined by searching relevant published genetic databases, namely: Ensemble NCBI dbSNP, Human Gene Dabatabase (HGMD), Mutation Taster and 1000 Genomes.

Figure 10. Illustrated: localisation of the variations in the Lamin A gene found in patients with Peripartum Cardiomyopathy

[Adapted from Parks et al, 2008; and Perrot et al, 2009]



A. Locations of the SNP variations are shown below the respective intron/exon.



B. Sequencing electropherogram showing heterozygosity for one of the known SNPs seen on the LMNA gene in PPCM patients

3.3 Results of the ECG Sub-Study

"The 12-lead ECG in Peripartum Cardiomyopathy"

***Tibazarwa K**, Lee G, Mayosi BM, Carrington M, Stewart S, Sliwa K*

[Cardiovasc J Afr. 2012 Feb 16;23:1-8. doi: 10.5830/CVJA-2012-006]

Presented at SAHA Annual Congress in Durban (October 2008)

Presented at: HFA (ESC) in Nice, France (May 2009); ESC Congress in Barcelona, Spain (August 2009); ICEPS in Athens, Greece (December 2011)

This study was original in that it provided the first large series of PPCM patients that were systematically assessed for the ECG characteristics of PPCM at baseline and, where possible, at six months after commencement of treatment.

Here, we showed that while the ECG in PPCM did not appear to bear characteristics unique to PPCM, it appeared useful as a screening tool for clinicians to tease out peripartal women with some form of heart failure from those without any heart disease.

Article Title:

The 12-lead ECG in Peripartum Cardiomyopathy

Statement of Originality

NAME	**RESPONSIBILITY**
Kemi Tibazarwa **University of the Witwatersrand**	Conceived and designed the research Acquired the data Analysed and interpreted the data Performed statistical analysis Drafted the manuscript
Geraldine Lee Baker Heart Institute	Analysed and interpreted the data
Bongani Mayosi University of Cape Town	Conceived and designed the research Acquired the data Assisted in arranging funding Drafted the manuscript
Melinda Carrington Baker Heart Institute	Analysed and interpreted the data Designed the database that housed the data
Simon Stewart Baker Heart Institute	Drafted the manuscript Supervised initial data analysis and interpretion
Karen Sliwa University of the Witwatersrand	Conceived and designed the research Acquired the data Assisted in arranging funding Supervised the research Drafted the manuscript
Candidate: I declare that this work is wholly my own, except where acknowledged as being the work of others (as listed above). I also acknowledge the contribution of others (as listed above) to this work in this Statement of Originality.	**Principle Advisor:** I hereby certify that all co-authors have provided their consent for inclusion of the paper in the thesis, and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.
Signed: Dr Kemi Tibazarwa (January 2013)	**Signed:** Professor Karen Sliwa (January 2013)

Cardiovascular Topics

The 12-lead ECG in peripartum cardiomyopathy

KEMI TIBAZARWA, GERALDINE LEE, BONGANI MAYOSI, MELINDA CARRINGTON, SIMON STEWART, KAREN SLIWA

Abstract

Background: **The value of the 12-lead electrocardiogram (ECG) to provide prognostic information in the deadly and disabling syndrome peripartum cardiomyopathy (PPCM) is unknown.**

Aims: **To determine the prevalence of major and minor ECG abnormalities in PPCM patients at the time of diagnosis, and to establish whether there are ECG correlates of persistent left ventricular dysfunction and/or clinical stability at six months of follow up, where available.**

Methods: **Twelve-lead ECGs were performed at the point of diagnosis on 78 consecutive women presenting with PPCM to two tertiary centres in South Africa and 44 cases (56%) at the six-month follow up. Blinded Minnesota coding identified major ECG abnormalities and minor ECG changes.**

Results: **The cohort mainly comprised young women of black African ancestry (90%) [mean age 29 ± 7 years and median body mass index 24.3 (IQR: 22.7–27.5) kg/m^2]. The majority of cases (n = 70; 90%) presented in sinus rhythm (mean heart rate 100 ± 21 beats/min). At baseline, at least one ECG abnormality/variant was detected in 96% of cases. Major ECG abnormalities and minor changes were detected in 49% (95% CI: 37–60%) and 62% (95% CI: 51–74%) of cases, respectively; the most common being T-wave changes (59%), p-wave abnormality (29%) and QRS-axis deviation (25%).**

Of the 44 cases (56%) reviewed at six months, normalisation of the 12-lead ECG occurred in 25%; the most labile ECG features being heart rate (mean reduction of 27 beats/min; $p < 0.001$) and abnormal QRS axis (36 vs 14%; $p = 0.014$). On an adjusted basis, major T-wave abnormalities on the baseline 12-lead ECG were associated with lower left ventricular ejection fraction (LVEF) at baseline (average of –9%, 95% CI: –1 to –16; $p = 0.03$) and at six months (–12%; 95% CI: –4 to –24; $p = 0.006$). Similarly, baseline ST-segment elevation was also associated with lower LVEF at six months (–25%; 95% CI: –0.7 to –50; $p = 0.04$).

Conclusions: **In this unique study, we found that almost all women suffering from PPCM had an 'abnormal' 12-lead ECG. Pending more definitive studies, the ECG appears to be a useful adjunctive tool in both screening and prognostication in resource-poor settings.**

Keywords: peripartum cardiomyopathy, ECG, baseline, follow up, comparative study, South Africa

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Peripartum cardiomyopathy (PPCM) is a form of heart failure (HF) with poorly understood aetiology, occurring between the last trimester of pregnancy and up to the first five to six months postpartum.[1,2] Despite an early definition,[3] later modified by Pearson and colleagues,[4] there is no consensus regarding PPCM as a single entity among the leading cardiology societies.[5] The European Society of Cardiology recently declared PPCM a distinct disease entity,[1] although it may take time before wider awareness of PPCM facilitates more timely diagnosis and proactive treatment. This is unfortunate given that PPCM causes left ventricular (LV) dysfunction, is more common in particular populations (e.g. African women[6]) and is associated with poor clinical outcomes and survival rates.[7,8]

Some studies suggest the incidence of PPCM is one in 3 000 live births. However, one African study found it to be one in 1 000 live births.[9] There is also a very high risk of relapse in subsequent pregnancies,[10,11] even following full recovery of LV function after the first pregnancy.[6] Therefore, early and definitive diagnosis of PPCM is essential to limit the high risk of morbidity and mortality in both current and subsequent pregnancies.

Definitive diagnosis and subsequent management of PPCM requires a high index of suspicion. It also usually requires referral to a tertiary centre for echocardiographic studies and specialist cardiological management. Anecdotal evidence suggests that many women who initially present with signs and symptoms indicative of PPCM are diagnosed with 'non-specific symptoms of the puerperal period'. The misdiagnosis of PPCM (often leading to clinical deterioration and in some instances death) represents a clear target for early intervention and prevention. Until

specific aetiologies are identified, PPCM remains a diagnosis of exclusion.

Women in their peripartum period suspected with PPCM require rigorous investigation; a costly and laborious process for the patient and healthcare provider. This is particularly difficult in a resource-poor environment. Although screening with (point-of-care derived) brain natriuretic peptide (BNP) levels may offer a means of detecting elevated atrial pressures secondary to systolic dysfunction (particularly given the age of those affected[6,12,13]), for example, technical and cost issues remain that prohibit their use. In settings such as sub-Saharan Africa where resources are scarce but the incidence of PPCM is high, the advantages of finding alternative screening tools for this condition that truncate the need for more extensive investigations, while being simple and inexpensive to apply, are abundantly clear.[2,14]

Although there is a paucity of electrocardiographic data specifically relating to PPCM, an 'abnormal' 12-lead electrocardiogram (ECG) is common in individuals with HF syndrome, with common anomalies including supraventricular arrhythmias, bundle branch block, and sinus bradycardia.[15] Given the above, we undertook a prospective, pilot study of the 12-lead ECG in a consecutive cohort of newly diagnosed women with PPCM in South Africa. Specifically, the primary aim of this study was to describe the baseline ECG characteristics in PPCM patients, noting the type and prevalence of major and minor ECG abnormalities. We also sought to analyse six-month follow-up ECGs (where available) of PPCM patients to determine potential ECG correlates of persistent LV dysfunction and/or clinical stability, where possible, as repeat ECGs are not part of the routine follow up of PPCM patients.

Methods

Consecutive patients presenting with *de novo* PPCM to two tertiary centres in South Africa (Chris Hani Baragwanath Hospital, Johannesburg, and Groote Schuur Hospital, Cape Town) between January 2003 and August 2008 were studied. Patients were referred from primary and secondary health facilities, as well as internally from other departments. Only patients aged ≥ 17 years who fulfilled the diagnostic criteria for PPCM[4] were considered eligible for the study. For recruitment, previously described[16] inclusion and exclusion criteria had to be met.

Ethical approval was obtained from each of the local ethical committees of the universities of Cape Town and the Witwatersrand, respectively, prior to the commencement of the study. This study complied with all the requirements of the Declaration of Helsinki. All patients were offered treatment and follow up as per the local standard of tertiary care.

A total of 78 women presenting with PPCM were studied. Of these, 56% had follow-up ECG data and were included in the comparative study analyses. Of those patients who had not had six-month ECGs (n = 34), three patients died (3.9%). Importantly, patients with repeat six-month ECG data did not differ significantly with respect to baseline heart rate, NYHA functional class, and left ventricular ejection fraction (LVEF) from the remaining cohort.

All patients with the provisional diagnosis of PPCM underwent a thorough medical interview and examination, and were investigated to confirm the diagnosis at baseline. All patients had a 12-lead ECG and echocardiography. Additional investigations were performed on a case-by-case basis. Data were captured on standardised case report forms.

A 12-lead resting ECG was performed by a trained technician and analysed by a reviewer blinded to all clinical data (GL), using the Minnesota code classification system.[17] The code allows systematic classification of Q and QS patterns, axis deviation, R waves, ST depression and elevation, T-wave changes, along with conduction abnormalities in both atria and ventricles.[17,18] The abnormalities detected by the Minnesota code were pooled into major abnormalities and minor variations from the 'normal' 12-lead ECG using the classification system previously applied by de Bacquer and colleagues[19] (Table 1). Separate analyses for ST-segment depression, arrhythmia or atrio-ventricular (AV) block, bundle branch block and left-axis deviation were also performed.

Standard methods for two-dimensional Doppler transthoracic echocardiography were applied as per the American Society of Echocardiography guidelines.[20] LV systolic dysfunction was defined by echocardiographic documentation of left ventricular ejection fraction (LVEF) ≤ 45%. All studies were saved onto

TABLE 1. MAJOR ABNORMALITIES AND MINOR 12-LEAD ECG VARIATIONS BASED ON MINNESOTA CODING

Major ECG abnormality	*Minor ECG variations*
Q-wave abnormalities	Borderline Q waves
ST-segment depression	Left- or right-axis deviation
T-wave inversion	High-amplitude R waves
2° or 3° AV block	Borderline ST-segment depression
Complete LBBB or RBBB	T-wave flattening
Frequent premature atrial or ventricular beats	Low QRS voltage
Atrial fibrillation or flutter	

AV = atrio-ventricular; LBBB = left bundle branch block; RBBB = right bundle branch block. (Adapted from de Bacquer *et al*., 1998).[19]

TABLE 2. BASELINE CLINICAL AND DEMOGRAPHIC PROFILE

Socio-demographic profile	
Mean age (years)	29 ± 7*
Proportion black African (%)	90
Obstetric profile	
Median parity	2 (IQR 1–3)**
Median postpartum period at presentation (days)	18 (IQR 6–30)**
Clinical presentation	
Proportion with New York Heart Association functional class III or IV (%)	64
Median body mass index (kg/m²)	24.3 (IQR 22.7–27.5)**
Mean pulse rate	99 ± 19*
Blood pressure (mmHg)	
Mean systolic	116 ± 20*
Mean diastolic	76 ± 14*
2D Doppler echocardiography	
Median intra-ventricular septal thickness in diastole (cm)	0.9 (IQR 0.8–1.1)**
Mean left ventricular end-diastolic diameter (cm)	5.8 ± 0.7*
Mean ejection fraction (%)	30.5 ± 9*

*Standard deviation (± SD); **interquartile range (IQR).

hard-drive facilities, and a random sample of these was reviewed by a cardiologist blinded to the clinical details of these patients, to confirm the accuracy of parameters describing cardiac structure and function.

Statistical analyses

All data analyses were performed with STATA-8.[21] For numerical variables, we report on the mean [standard deviation (SD)] for normally distributed variables, and median [inter-quartile range (IQR)] for non-parametric variables. Comparison between baseline and follow-up ECGs was done using paired *t*-tests for normally distributed numerical variables, Mann-Whitney/Wilcoxon signed rank tests for non-parametric paired numerical variables, and chi-squared tests for categorical variables and proportions. Multivariate analysis was conducted using linear and logistic regression for numerical and categorical outcome variables, respectively.

Results

Table 2 summarises the clinical and demographic profiles of the 78 women with *de novo* PPCM, 10 of whom experienced a first-ever detected episode of mildly raised blood pressure at some stage during the index pregnancy. The case report and Fig. 1 describe such a typical case.

Interestingly, no patients under the age of 17 years presented to either study unit and 90% of patients included were young women of African ancestry. Of the 10% that were of non-black African ethnicity, almost all were of mixed ancestry, with only one Caucasian patient. The majority of respondents were normotensive and experienced onset of symptoms in the postpartum period (median 18 days, IQR 6–30 days). However, 8% of respondents reported the onset of symptoms prepartum, of which only two were hypertensive (one mild and the other with moderate hypertension, defined as per standard protocol).[22-24]

Table 3 summarises baseline ECG abnormalities/variations from normal ($n = 78$). The majority of cases (90%) were in sinus rhythm, although mean heart rate was markedly elevated, with 45% of cases in sinus tachycardia (defined as those ≥ 100 beats/min, given that our patients' maximum heart rate was 134 beats/min). Only three patients (4%) had completely normal ECGs; excluding those with an elevated heart rate, this increased to nine patients (12%). Overall, 49% (95% CI: 37–60) of cases had a major Minnesota ECG abnormality detected, while 62% (95% CI: 51–74) had a minor ECG variant. A combined total of 63 (81%; 95% CI: 70–89%) cases had one or both forms of abnormality detected on their 12-lead ECG. Of the major abnormalities, major T-wave anomalies (38%), followed by abnormal QRS axis (26%) were the most common (Fig. 2). T-wave anomalies were also the most common of all documented ECG abnormalities overall (59%), followed by atrial abnormalities (29%).

Univariate analysis showed no association between LV systolic function and baseline ECG readings. However, on adjustment for age, functional class, echocardiographic LV dimensions, and all the other ECG parameters listed in Table 3, major T-wave abnormalities correlated negatively with left ventricular systolic dysfunction. The presence of major T-wave changes was associated with a clinically relevant 9% (95% CI: 1–16; $p = 0.03\%$) reduction in LVEF compared to those without T-wave changes.

At six months, a number of clinical parameters had improved

Case report: the ECG in PPCM

Our patient presented to hospital one week after giving birth through spontaneous vaginal delivery, reporting a five-week history of shortness of breath equivalent to New York Heart Association functional class II, two-pillow orthopnoea associated with cough, bilateral leg swelling, and mild dizziness. On further interrogation, there was a positive family history of sudden 'unexplained' death of her grandmother. Our patient denied any consumption of alcohol or tobacco products.

Clinical examination revealed central and peripheral signs of fluid overload. The pulse rate was 92 beats per minute, this being weak, with occasional irregularities suggestive of ventricular extrasystoles. Her blood pressure was 97/72 mmHg, her apex beat displaced laterally, and the abdominal examination proved there to be tender hepatomegaly. Positive findings on cardiac auscultation included a loud, split, second heart sound, and systolic murmur best heard over the mitral and tricuspid areas. Chest auscultation revealed bilateral basal crepitations.

Chest X-ray demonstrated four-chamber cardiomegaly and pulmonary congestion, while her ECG abnormalities included right-axis deviation, with poor R-wave progression and diffuse T-wave inversion (Fig. 1a). Echocardiography showed dilated cardiac chambers, markedly reduced systolic ventricular function (EF 35%), moderate to severe functional mitral regurgitation, trace tricuspid regurgitation, and a small clear pericardial effusion. Tissue Doppler imaging revealed no further evidence of diastolic dysfunction.

Further tests permitted the exclusion of other common causes of dilated cardiomyopathy, as well as important differential diagnoses. The working diagnosis remained that of peripartum cardiomyopathy.

The patient was started on carvedilol, enalapril, spirinolactone and furosemide. Given the high risk for thromboembolic phenomena presented with the ejection fraction of 35% and below, she was started on warfarin. Despite being seen several times in between, six weeks later she continued to manifest the subtle arrhythmia of moderate-frequency ventricular extrasystoles, with suboptimal heart rate control; hence digoxin was introduced.

Following regular follow-up visits, after six months she reported that she was well, without any heart-failure symptoms. Her blood pressure had normalised to 113/64 mmHg and heart rate to 58 beats/min, while the pulse rhythm remained irregular as if with ventricular extrasystoles (now at low frequency). The mitral regurgitation murmur had diminished to grade 1. On ECG, the axis had now normalised, and although there remained diffusely inverted T-waves, their depths had improved, and this inversion normalised in limb lead I. The patient now qualified for left ventricular hypertrophy by voltage criteria using this same lead I (Fig. 1b). Echocardiography showed persistent but improved LV dilatation, minimal functional tricuspid and mitral regurgitation, with improvement of LV systolic function to an EF of 49%.

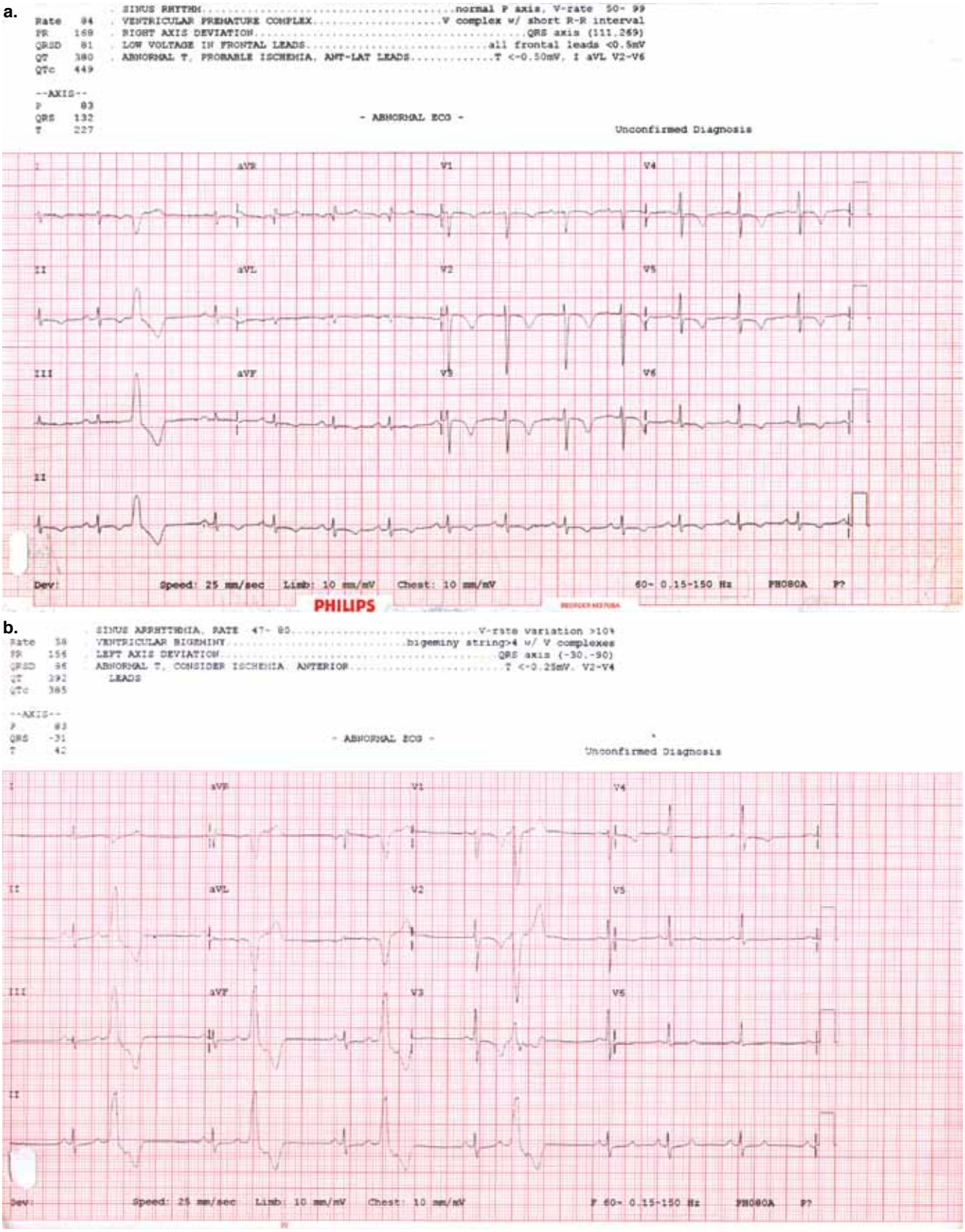


Fig. 1. A typical ECG in PPCM at baseline (a) and after six months (b).

in surviving cases subjected to study follow up ($n = 44$) (Table 4). Overall, 55% had no residual evidence of LV systolic dysfunction ($p < 0.001$), although 10% still reported functional impairment (NYHA class II or more). Overall, 25% of this sub-set of cases had a normal 12-lead ECG at six months.

According to univariate analyses, no difference between

TABLE 3. 12-LEAD ECG AT BASELINE IN 78 PPCM PATIENTS

	ECG characteristic	*No. (%) (n = 78)*
Rate and rhythm	Mean heart rate (beats/min) ± SD	100 ± 21
	Proportion in sinus rhythm	70 (90%; 95% CI: 81–95)
	Proportion with sinus tachycardia	35 (45%; 95% CI: 34–57)
	Proportion with arrhythmias	
	• premature ventricular complex	3 (4%; 95% CI: 0.8–11)
	• supraventricular tachycardia	1 (1%; 95% CI: 0.03–7)
	• sinus arrhythmias	4 (5%; 95% CI: 1–13)
Axis	QRS axis	
	• abnormal	20 (26%; 95% CI: 16–37)
	• left axis	9 (12%; 95% CI: 5–21)
	• right axis	8 (10%; 95% CI: 5–19)
	• indeterminate	3 (4%; 95% CI: 0.8–11)
Conduction	PR interval > 220 ms	1 (1%; 95% CI: 0.04–7)
	Proportion with bundle branch block (BBB)	9 (12%; 95% CI: 5–21)*
	• left BBB	4 (5%; 95% CI: 1–13)
	• right BBB	1 (1%; 95% CI: 0.03–7)
	Proportion with prolonged QTc (> 470 ms)	4 (5%; 95% CI 1–13)
Repolarisation	Proportion with T-wave abnormalities	46 (59%; 95% CI: 47–70)**
	• major	30 (38%; 95% CI: 28–50)
	• minor	24 (31%; 95% CI: 21–42)
	Proportion with ST-segment changes	
	• major ST-segment changes	1 (1%; 95% CI: 0.03–7)
	• minor ST-segment changes	3 (4%; 95% CI: 0.8–11)
	• ST-segment elevation	1 (1%; 95% CI: 0.03–7)
Hypertrophy	Proportion with left ventricular hypertrophy [Defined by Minnesota codes III_1 and (IV_{1-3} or V_{1-3})]	7 (9%; 95% CI: 4–18)
Atria	Proportion with atrial abnormalities	23 (29%; 95% CI: 20–41)**
	• left atrium	8 (10%; 95% CI: 5–19)
	• right atrium	11 (14%; 95% CI: 7–24)
	• bi-atrial	4 (5%; 95% CI: 1–13)

*This sum exceeds that of individual BBB as some patients manifested incomplete BBB (either left or right).
**This sum exceeds that of individual sub-categories as some patients manifested features of each sub-category.

'clinically stable/responded to treatment' (i.e. recovered LV function) versus non-responders (persistent LV dysfunction) were found in respect of any ECG parameter. However, on an adjusted basis, major T-wave changes and major ST-segment depression found on the baseline 12-lead ECG subsequently correlated with persistently impaired systolic function at six months. Specifically, the presence of major T-wave changes at baseline was associated with a markedly lower LVEF at six months (–12%, 95% CI: –4 to –21; $p = 0.006$) compared to those without T-wave changes at baseline. In addition, ST-segment elevation at baseline was associated with an even greater reduction in LVEF at six months (–25%, 95% CI: –0.7 to –50; $p = 0.044$) compared to those without this ECG pattern at baseline.

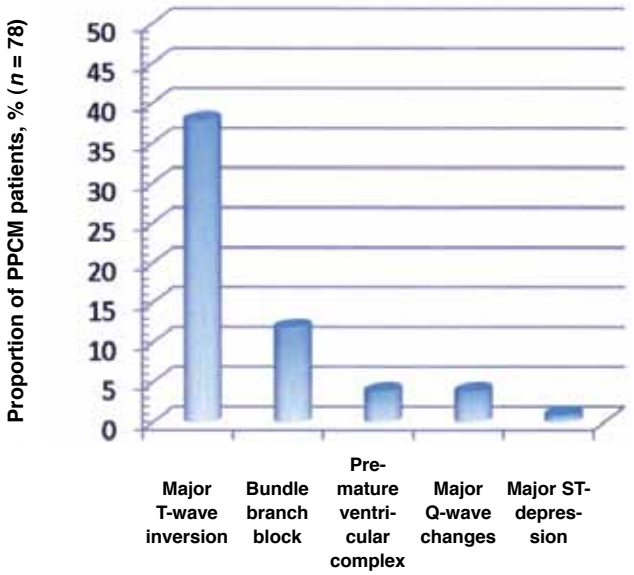


Fig. 2. Prevalence of Minnesota major criteria at baseline in 78 PPCM patients.

Discussion

To the best of our knowledge, this is the first study to systematically describe the 12-lead ECG in *de novo* cases of PPCM. Our main aim was to examine the potential utility of the 12-lead ECG (a relatively inexpensive and easy-to-apply diagnostic tool) in detecting underlying LV dysfunction in confirmed cases of *de novo* PPCM in African women. This would require a high underlying level of ECG abnormalities in such a cohort in order to discriminate against (presumably) more normal 12-lead ECGs in African women experiencing healthier pregnancies.

Of the 78 cases studied, 49% demonstrated major ECG abnormalities, usually associated with significant underlying cardiac pathology, while 62% demonstrated one or more forms of minor variation/abnormality, potentially indicative of the same. We also attempted to examine whether the 12-lead ECG is a useful tool for discriminating between those cases who respond to treatment (by the resolution of initially observed ECG

TABLE 4. COMPARING BASELINE AND SIX-MONTH ECG CHARACTERISTICS IN 44 PPCM PATIENTS WITH FOLLOW-UP DATA

		Baseline % of population	*6-month follow up % of population*	p-*value*
Rate and rhythm	Mean heart rate (beats/min) ± SD	104 ± 18	77 ± 14	< 0.001
	Proportion in sinus rhythm	84 (95% CI: 70–93)	66 (95% CI: 50–80)	0.049
	Proportion with sinus tachycardia	48 (95% CI: 32–63)	7 (95% CI: 1–19)	< 0.001
	Proportion with arrhythmias			
	• premature ventricular complex	2 (95% CI: 0.06–12)	2 (95% CI: 0.06–12)	1.0
	• sinus arrhythmias	7 (95% CI: 1–19)	27(95% CI: 15–43)	0.011
Axis	Proportion with QRS axis being:			
	• abnormal	36 (95% CI: 22–52)	14(95% CI: 5–27)	0.014
	• left axis	18 (95% CI: 8–33)	7 (95% CI: 1–19)	0.107
	• right axis	11 (95% CI: 4–25)	5 (95% CI: 0.6–15)	0.237
	• indeterminate	7 (95% CI: 1–19)	2 (95% CI: 0.06–12)	0.306
Conduction	Proportion with bundle branch block (BBB)	20 (95% CI: 10–35)*	18 (95% CI: 8–33)	0.787
	• left BBB	9 (95% CI: 3–22)	9 (95% CI: 3–22)	1.0
	• right BBB	2 (95% CI: 0.06–12)	2 (95% CI: 0.06–12)	1.0
Repolarisation	Proportion with T-wave abnormalities	45 (95% CI: 30–61)**	27(95% CI: 15–43)	0.123
	• major	30 (95% CI: 17–45)	34 (95% CI: 20–50)	0.647
	• minor	16 (95% CI: 7–30)	9 (95% CI: 3–22)	0.334
	Proportion with ST-segment changes			
	• major ST changes	0	0	–
	• minor ST changes	2 (95% CI: 0.06–12)	0	0.315
	• ST-segment elevation	2 (95% CI: 0.06–12)	0	0.315
Hypertrophy	Proportion with left ventricular hypertrophy [Defined by Minnesota Codes III_1 and (IV_{1-3} or V_{1-3})]	7 (95% CI: 1–19)	7 (95% CI: 1–19)	1.0
Atria	Proportion with atrial abnormalities	20 (95% CI: 10–35)**	9 (95% CI: 3–22)	0.133
	• left atrium	5 (95% CI: 0.6–15)	2 (95% CI: 0.06–12)	0.557
	• right atrium	9 (95% CI: 3–22)	7 (95% CI: 1–19)	0.694
	• bi-atrial	7 (95% CI: 1–19)	0	0.078

*This sum exceeds that of individual BBB as some patients manifested incomplete BBB (either left or right).
**This sum exceeds that of individual sub-categories as some patients manifested features of each sub-category.

abnormalities) and those who had persistent LV dysfunction. In this respect, we found that the presence of two major abnormalities (T-wave inversion and ST-segment depression) and a third Minnesota code criterion not listed as one of the major or minor criteria (ST-segment elevation) found on the baseline 12-lead ECG correlated with persistently poor LV systolic function at six months. T-wave inversion also correlated with LV systolic function at baseline.

Typically, LV systolic functional recovery in PPCM is a slow and drawn-out process that enters the second year of treatment.[2] On this basis, while LVEF in those patients subjected to six-month follow up improved overall, just under half still had defined impaired LV dysfunction, and this represents a major therapeutic target for treatment. Therefore, long-term follow up using the ECG in PPCM might well show ECG reversal to normality as late as 18 months after first diagnosis, as our long-term echocardiographic data suggest.[8] Moreover, we have identified potentially useful markers (i.e. major T-wave inversion and/or ST-segment depression on the 12-lead ECG) as simple but important prognostic markers that might trigger more intensive/aggressive treatment and follow up in PPCM cases.

Our findings and the overall utility of the 12-lead ECG in this clinical setting require careful interpretation when fundamental investigations such as echocardiography remain inaccessible to most hospitals and patients in sub-Saharan Africa. Serum levels of NT-proBNP are known to strongly predict the degree of heart failure,[12] yet this test is still not available in most referral hospitals in Africa where PPCM is prevalent. Surprisingly, because of vast differences in sensitivity and specificity in detecting HF, it has been suggested that the overall cost-effectiveness of measuring serum NT-proBNP becomes comparable to that of screening for HF using the 12-lead ECG alone,[25,26] due mainly to the relatively low specificity of the 12-lead ECG.[26]

The scarcity of the serum NT-proBNP test in our setting almost mandates using something as inexpensive and easy as the 12-lead ECG to screen for PPCM, even if its sensitivity and specificity prove to be imperfect. These data will be particularly useful if (after comparing ECG patterns in healthy African women, derived from the Heart of Soweto cohort[27]) the 12-lead ECG has the potential to be applied as a 'rule-out' test (i.e. high specificity to identify all truly negative for PPCM cases). Unfortunately, the ability to combine 12-lead ECG with typical symptoms of HF (to increase its accuracy in detecting PPCM) is confounded by their parallel presence in the late stages of pregnancy (but not typically post-partum).

As indicated, our data suggest that baseline major T-wave abnormalities were associated with poorer LV systolic function at baseline, and, alongside baseline ST-segment depression, they were also associated with persistent LV systolic dysfunction in the short to medium term (i.e. six months). In Western countries, major ST-segment depression and T-wave abnormalities are often regarded as indications of myocardial ischaemia, bearing consistent prognostic significance for cardiovascular disease mortality across prospective studies, especially for men.[28]

We remain wary of the fact that gender differences in ECG findings often show women to have a higher prevalence of

ST-segment depression or T-wave changes, such as to question the true significance of any association between ST-segment depression and T-wave abnormalities with coronary heart disease (CHD) mortality in women.[28] However, we are greatly reassured by the number of large, population-based studies that show major ST-depression to be the most predictive ECG characteristic of cardiovascular disease (CVD) and CHD mortality, lending an average two-fold risk of CVD and CHD mortality, and, as with our study, predicting these outcomes from their mere presence at baseline.[19]

Studies reporting on the ECG in prognostication of PPCM remain scarce, with two from Nigeria suggesting it to be a weak predictor of recovery and long-term prognosis in PPCM.[29,30] However these studies did not use echocardiography to confirm the diagnosis of PPCM,[30] and had a greater proportion of patients with hypertension than those without.[29,30] Given recent insight that patients with the PPCM phenotype who present with hypertension appear to follow a different natural history to those without,[2] any comparisons between data from PPCM patients with hypertension with those without hypertension should be interpreted with great caution.

Systematic reports of ECG abnormalities associated with idiopathic dilated cardiomyopathy (IDCM), which bears some resemblance to PPCM, are few. One such study of IDCM reported that the ECG was found to be normal in up to 25% of affected relatives of IDCM patients (who by definition suffer from familial DCM), although these were not all newly diagnosed IDCM cases.[31] Hence, as in our study, an overwhelming majority had abnormal ECGs.

It remains fair to say that the shortage of studies systematically reporting on the prevalence of ECG anomalies in PPCM may account for most for our inability to corroborate our findings with other available evidence, yet no reports contradict our findings. Overall, therefore, our data can only suggest that the 12-lead ECG in PPCM may be sensitive to underlying LV dysfunction and/or that it can serve as a marker of more extensive cardiac insult early in the disease process.

Lastly, we note that the 1% prevalence of first-degree heart block, usually not considered to bear any significant risk to adverse CVD outcome, except for its association with lamin A/C mutation in familial DCM, may in our PPCM cohort merely reflect the 1–2% prevalence in normal young adults.[32] However, after recent reports implicating this so-called benign form of heart block in the general population with increased risk of atrial fibrillation and adverse CVD outcome 20 years down the line,[32] and suggestions that post-exercise measurements of PR intervals may be more prognostic within five-year follow-up periods than resting ECG PR intervals,[32] it would be useful to revise the prognostic implications of first-degree heart block post exercise in patients with underlying myocardial disease and congestive cardiac failure as in PPCM.

Furthermore, evaluation of this conduction disorder may be of particular importance in PPCM, in view of several reports of first-degree AV block being among one of the earliest signs of lamin A/C mutation, which in turn commonly leads to a phenotype of apparently unexplained DCM.[33] It is worth considering that the prognostic implications behind each of the criteria for major and minor ECG abnormalities/variants derived from the Minnesota code appear more applicable in the screening of high-risk persons only,[34] as in this clinical context.

This pilot study has a number of limitations that require comment. Firstly, the Minnesota code may not be sufficiently validated for the detection of heart disease in pregnant women. Moreover, the 'normal' 12-lead ECG in African women is yet to be definitively described. Whether the combined presence (81% of cases) of major abnormalities and minor variations is sufficient to support further investigation of the 12-lead ECG as a screening tool (particularly when there are few data to describe the 'normal' 12-lead ECG in pregnant and non-pregnant African women), is open to debate.

In determining the sensitivity of ECG changes over time, relative to underlying LV dysfunction, we had valid data for only 56% of the cohort. Although our PPCM patients who did not have follow-up ECGs did not differ in clinical and echocardiographic outcome from those with follow-up data, the possibility that the former group may have been clinically worse off than those with six-month data cannot be excluded, given that greater proportions of the former manifested minor T-wave anomalies, and that their left ventricular diameters and BMI at baseline appeared greater than those who had six-month ECGs. However, in light of the lower prevalence of QRS-axis deviation and bundle branch block among the former group, interpretation of the similarity of patients with and without follow up with regard to ECG characteristics becomes speculative.

Further data are required to better characterise the 12-lead ECG as a marker of LV dysfunction in this specific clinical (and ethnic) context, before any firm recommendations can be made in respect of obtaining a 12-lead ECG at the conclusion of each pregnancy in sub-Saharan Africa.

Conclusions

Despite a number of limitations, this still represents a unique study that will prove to be invaluable in determining the future role of the 12-lead ECG as an inexpensive and simple 'rule-out' screening tool for PPCM, and perhaps an important tool for increasing the intensity of subsequent treatment and management. Overall, we found the majority (96%) of PPCM patients presented with 'abnormal' 12-lead ECGs, which improved significantly to 75% after the first six months of treatment. Over 80% of patients displayed either major abnormalities or minor variations using the Minnesota code. Of these, sinus tachycardia and QRS-axis deviation were most likely to be attenuated after six months. Even though these ECG abnormalities were mostly non-specific and similar to those of other dilated cardiomyopathies, our study further suggests the ECG to be useful in simple monitoring of clinical progress during treatment and prognostication.

Specifically, the baseline presence of major T-wave and ST-segment abnormalities in the context of PPCM patients may place these patients at similar risk of adverse outcomes to those with myocardial ischaemia. More definitive studies are required to determine if this simple and relatively inexpensive tool will prove to be of particular clinical use in the setting of PPCM. Any progress in this regard will be welcome, given the persistently poor health outcomes associated with PPCM in resource-poor settings.

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3.4 Results of the Sub-Study on Bromocriptine Therapy in PPCM

"Evaluation of Bromocriptine in the treatment of acute severe Peripartum Cardiomyopathy: a proof-of-concept pilot study"

*Sliwa K, Blauwet L, **Tibazarwa K**, Libhaber E, Smedema JP, Becker A, McMurray J, Yamac H, Labidi S, Struhman I, Hilfiker-Kleiner D*

[Circulation. 2010 Apr 6;121(13):1465-73.]

Recent experiments by a group of scientists in Germany showed that in a mouse model of PPCM, Bromocriptine appeared to prevent the development of PPCM in mice at risk (Hilfiker-Kleiner et al, 2007: *Cell*).'Mice at risk' in this case were considered to be those with increased levels of the detrimental 16 kilo-Dalton prolactin (16kDa), which has been implicated in the pathogenesis of PPCM (Selle et al, 2009: Future Cardiol).

Based on these findings, we conducted a proof of concept study, which formed the first ever randomised controlled trial of therapeutic use of the dopamine-antagonist Bromocriptine in the medical treatment of humans with PPCM. The study compared 10 newly diagnosed PPCM patients that were randomised to receive Bromocriptine therapy in addition to standard heart failure therapy, to another 10 newly diagnosed patients who received standard heart failure therapy alone.

Although the study may have been relatively small, there was clear evidence of the beneficial effects of adding Bromocriptine to standard heart failure therapy, based on the improvements seen in both the quality and quantity of life. Beyond the clinical effects on the patient (mother), this study went

further to evaluate the potential for harm of Bromocriptine therapy on the biometric measurements of growth of young infants of PPCM mothers. It proved that with careful counselling, mothers who do not breastfeed because of the Bromocriptine therapy could still raise healthy babies.

This study had a major clinical impact, being the basis on which the European Society of Cardiology developed guidelines for the management of PPCM.

Article Title:

Evaluation of Bromocriptine in the treatment of acute severe peripartum cardiomyopathy: A proof-of-concept pilot study.

Statement of Originality

NAME	**RESPONSIBILITY**
Lori Blauwet Mayo Clinic (USA)	Acquired the data Analysed and interpreted the data Drafted the manuscript
Karen Sliwa University of the Witwatersrand	Conceived and designed the research Acquired the data Assisted in arranging funding Supervised the research Analysed and interpreted the data Drafted the manuscript
Kemi Tibazarwa **University of the Witwatersrand**	Acquired the data Analysed and interpreted the data Performed statistical analysis Drafted the manuscript
Elena Libhaber University of the Witwatersrand	Analysed the data Performed statistical analysis
Jan Pieter Smedema Netcare N1 City Hospital	Acquired the data Drafted the manuscript
Anthony Becker University of the Witwatersrand	Acquired the data Drafted the manuscript
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H Yamac Hannover Medical School (Germany)	Acquired the data Analysed and interpreted the data
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I Struhman GIGA-R (Belgium)	Acquired the data Drafted the manuscript
Denise Hilfiker-Kleiner Hannover Medical School (Germany)	Conceived and designed the research Acquired the data Assisted in arranging funding Supervised the research Drafted the manuscript
Candidate: I declare that this work is wholly my own, except where acknowledged as being the work of others (as listed above). I also acknowledge the contribution of others (as listed above) to this work in this Statement of Originality.	**Principle Advisor:** I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis, and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.
Signed: Dr Kemi Tibazarwa (January 2013)	**Signed:** Professor Karen Sliwa (January 2013)

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Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy

A Proof-of-Concept Pilot Study

Karen Sliwa, MD, PhD; Lori Blauwet, MD; Kemi Tibazarwa, MD; Elena Libhaber, PhD; Jan-Peter Smedema, MD, MMed(Int); Anthony Becker, MD; John McMurray, MD, FESC; Hatice Yamac, MD; Saida Labidi, MSc; Ingrid Struman, PhD; Denise Hilfiker-Kleiner, PhD

Background—Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease that occurs in previously healthy women. We identified prolactin, mainly its 16-kDa angiostatic and proapoptotic form, as a key factor in PPCM pathophysiology. Previous reports suggest that bromocriptine may have beneficial effects in women with acute onset of PPCM.

Methods and Results—A prospective, single-center, randomized, open-label, proof-of-concept pilot study of women with newly diagnosed PPCM receiving standard care (PPCM-Std; n=10) versus standard care plus bromocriptine for 8 weeks (PPCM-Br, n=10) was conducted. Because mothers receiving bromocriptine could not breast-feed, the 6-month outcome of their children (n=21) was studied as a secondary end point. Blinded clinical, hemodynamic, and echocardiographic assessments were performed at baseline and 6 months after diagnosis. Cardiac magnetic resonance imaging was performed 4 to 6 weeks after diagnosis in PPCM-Br patients. There were no significant differences in baseline characteristics, including serum 16-kDa prolactin levels and cathepsin D activity, between the 2 study groups. PPCM-Br patients displayed greater recovery of left ventricular ejection fraction (27% to 58%; $P=0.012$) compared with PPCM-Std patients (27% to 36%) at 6 months. One patient in the PPCM-Br group died compared with 4 patients in the PPCM-Std group. Significantly fewer PPCM-Br patients (n=1, 10%) experienced the composite end point of poor outcome defined as death, New York Heart Association functional class III/IV, or left ventricular ejection fraction <35% at 6 months compared with the PPCM-Std patients (n=8, 80%; $P=0.006$). Cardiac magnetic resonance imaging revealed no intracavitary thrombi. Infants of mothers in both groups showed normal growth and survival.

Conclusions—In this trial, the addition of bromocriptine to standard heart failure therapy appeared to improve left ventricular ejection fraction and a composite clinical outcome in women with acute severe PPCM, although the number of patients studied was small and the results cannot be considered definitive. Larger-scale multicenter and blinded studies are in progress to test this strategy more robustly. **(*Circulation*. 2010;121:1465-1473.)**

Key Words: cardiomyopathy ■ heart failure ■ hormones ■ parturition ■ pregnancy

Peripartum cardiomyopathy (PPCM) is characterized by new onset of heart failure between 1 month before and 5 months after delivery in previously healthy women.[1] The clinical presentation and management of PPCM and its outcome have been reviewed recently.[1,2] Only 23% to 54% of patients show recovery of cardiac function within 6 months.[3–6] Investigation of a large cohort of PPCM patients demonstrated that this condition is associated with a proinflammatory response, as evidenced by elevated plasma levels of tumor necrosis factor-α, Fas-Apo-1, interleukin-6, and C-reactive protein (CRP).[5,7,8]

Editorial see p 1463
Clinical Perspective on p 1473

We recently reported that enhanced oxidative stress in a mouse model for PPCM (mice with a cardiac-specific deletion for signal transducer and activator of transcription-3) triggers the activation of cathepsin D, a ubiquitous lysosomal

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This study is a proof-of-concept study and was initiated before the new Declaration of Helsinki 2008 was published. Therefore, it has not been registered as a clinical trial on a publicly accessible Web site.

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Table 1. Baseline Characteristics, Treatment, and 6-Month Results for 20 PPCM Patients

Patient	Group	Age, y	Parity, n	Symptom Onset Postpartum, d	Carvedilol Dose, mg BID	Enalapril Dose, mg/d	Furosemide Dose, mg/d	Aldactone Dose, mg/d
1	PPCM-Std	23	2	25	6.25	10	80	25
4	PPCM-Std	21	2	18	12.5	10	80	25
5	PPCM-Std	22	1	20	6.25	5	80	25
9	PPCM-Std	46	3	21	12.5	10	120	50
10	PPCM-Std	24	2	26	25	10	80	25
12	PPCM-Std	21	1	26	6.25	5	80	0
13	PPCM-Std	24	1	22	25	10	80	25
16	PPCM-Std	44	6	28	12.5	5	80	0
17	PPCM-Std	18	1	12	6.25	5	80	0
20	PPCM-Std	38	3	7	12.5	10	80	25
2	PPCM-Br	22	2	8	6.25	5	80	25
3	PPCM-Br	38	3	14	6.25	5	80	12.5
6	PPCM-Br	24	1	26	12.5	5	80	25
7	PPCM-Br	22	2	7	6.25	5	80	25
8	PPCM-Br	18	2	24	6.25	5	80	25
11	PPCM-Br	24	2	7	6.25	10	120	25
14	PPCM-Br	23	1	4	25	5	80	50
15	PPCM-Br	28	1	30	25	5	80	25
18	PPCM-Br	22	1	2	6.25	5	80	25
19	PPCM-Br	18	1	3	12.5	5	120	0

LVEDD indicates LV end-diastolic diameter; CHF, congestive heart failure; and NR, not reported.

enzyme that subsequently cleaves serum prolactin into its antiangiogenic and proapoptotic 16-kDa form.[9] This is associated with endothelial inflammation, impaired cardiomyocyte metabolism, and reduced myocardial contraction, suggesting that oxidative stress, inflammation, and prolactin may be interconnected and responsible for initiating PPCM.

Similarly, we found evidence for increased oxidative stress, enhanced cathepsin D activity, and increased prolactin cleavage in patients with acute PPCM.[9] More recently, we documented a close correlation between N-terminal brain natriuretic peptide (NT-proBNP; a marker of ventricular wall stress and heart failure), prolactin, and markers of oxidative stress (oxidized low-density lipoprotein) and inflammation (interferon-γ), further supporting the detrimental role of the oxidative stress–prolactin axis.[10]

Importantly, blockade of prolactin with the dopamine-2D agonist bromocriptine prevented the onset of PPCM in mice and in 6 women at high risk of this condition as a result of documented PPCM in a previous pregnancy.[9] Several case reports have also described seemingly beneficial effects from the addition of bromocriptine to standard heart failure therapy in patients with acute PPCM.[9,11,12] Although these preliminary results suggesting beneficial effects of bromocriptine treatment in patients with acute PPCM appear promising, concerns have been raised about the risk of thrombotic complications, including cerebral vascular incident and myocardial infarction, related to bromocriptine therapy[13–16] and the consequences for the children of these patients because the mothers are unable to breast-feed.[17]

The present work summarizes data from the first randomized study to assess the efficacy of bromocriptine on recovery of left ventricular (LV) function, symptom status, and other clinical measures in patients presenting within the first month postpartum with new-onset symptomatic PPCM and an LV ejection fraction (LVEF) <35%. The progress of the newborn children over the 6-month follow-up period was also studied. All open-label efficacy assessments were made by independent blinded investigators.

Methods

Study Design and Patient Recruitment

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa, and complies with the Declaration of Helsinki. All patients and control subjects gave written informed consent before study entry. Twenty consenting consecutive patients diagnosed with PPCM and fulfilling the inclusion criteria were enrolled in the study. All patients were included and randomized with a computer-generated randomization list within 24 hours of diagnosis.

The study was conducted at the Chris Hani Baragwanath Hospital. Patients were referred from local clinics, secondary hospitals, and the Department of Obstetrics at the Chris Hani Baragwanath Hospital. History of preexisting cardiac symptoms and signs, occurrence of preeclampsia, and mode of delivery were obtained from the patient and confirmed by examination of the obstetric card carried by each patient. Symptoms and signs were recorded during first presentation at the cardiac unit at the Chris Hani Baragwanath Hospital (baseline) and after a follow-up period of 6 months. Clinical assessment, echocardiography, and blood analysis were performed at baseline and at 6 months. Cardiac magnetic resonance imaging (MRI) was obtained 4 to 6 weeks after diagnosis in patients receiving bromocriptine.

Inclusion criteria were symptoms of congestive heart failure that developed in the last month of pregnancy or during the first month postpartum, no other identifiable cause for heart failure, and LVEF

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Table 1. Continued

Prolactin at Baseline, μg/L	Prolactin at 6 mo, μg/L	NYHA Class at Baseline	NYHA Class at 6 mo	LVEDD at Baseline, mm	LVEDD at 6 mo, mm	LVEF at Baseline, %	LVEF at 6 mo, %	Prespecified End Point of Poor Outcome
54	60	III	III	46	43	33	40	Yes
11	NR	II	NR	61	NR	28	NR	Yes (died 1 mo after baseline of sudden death)
9	NR	IV	NR	65	NR	18	NR	Yes (died 1 mo after baseline of CHF)
16	16	IV	III	62	60	24	22	Yes
50	48	II	II	60	62	19	24	Yes
50	9	II	I	59	52	34	50	No
5	NR	II	NR	62	NR	34	NR	Yes (died 3 mo after baseline of CHF)
233	7	III	III	57	43	32	44	Yes
52	NR	IV	NR	59	NR	14	NR	Yes (died on index admission)
30	8	II	II	60	74	32	37	No
135	8	IV	I	33	44	34	58	No
122	6	II	I	65	59	29	37	No
22	7	II	I	68	65	30	62	No
56	7	II	I	54	51	27	72	No
4	6	II	I	56	48	30	56	No
91	25	III	I	63	51	30	58	No
55	8	IV	I	55	47	33	60	No
18	13	II	I	49	34	32	75	No
NR	NR	III	NR	55	NR	18	NR	Yes (died on index admission)
5	12	III	I	54	56	8	48	No

<35% by transthoracic echocardiography. Exclusion criteria were systolic blood pressure >160 or <95 mm Hg or diastolic >105 mm Hg; clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers such as sepsis, autoimmune disease, or HIV positivity; significant liver disease (defined as liver transaminase levels >2 times the upper limit of normal); history of peptic ulcer disease; history of psychiatric disorders; impaired renal function (defined as urea and/or creatinine >1.5 times the upper limit of normal); and any clinical condition that, according to the investigators, precluded inclusion in the study such as ischemic heart disease or malignancy.

All patients received treatment with the diuretic furosemide and the angiotensin-converting enzyme (ACE) inhibitor enalapril. Patients with an LVEF <25% or LV thrombus received anticoagulation therapy with warfarin for 6 months. Carvedilol was added after resolution of overt heart failure. Enalapril and carvedilol doses were titrated upward as tolerated during the first 4 weeks after diagnosis and then remained unchanged throughout the remainder of the 6-month study period. Furosemide dose was decreased as indicated according to clinical assessment during the 6-month study period. The 10 patients randomized to standard therapy (PPCM-Std group) were treated as outlined above. The 10 patients randomized to standard therapy plus bromocriptine (PPCM-Br) received bromocriptine 2.5 twice daily for 2 weeks followed by 2.5 mg daily for 6 weeks in addition to standard heart failure therapy. After the initial screening and baseline visits, monthly outpatient visits were scheduled for clinical assessment and evaluation of medication compliance.

Echocardiography, Cardiac MRI, Assessment of New York Heart Association Functional Class, and Noninvasive Blood Pressure Measurements

Patients were diagnosed by specialist physicians and cardiologists working at the Chris Hani Baragwanath Hospital. Patients were included in this trial within 24 hours after diagnosis once the diagnosis was confirmed by a cardiologist (K.S.), who repeated the echocardiography. Two-dimensional and targeted M-mode echocardiography with Doppler color-flow mapping was performed with either a Hewlett Packard Sonos 5500 (Royal Philips Electronics, Amsterdam, the Netherlands) or a VIVID i (General Electric Company, Fairfield, Conn) echocardiography machine. Systolic and diastolic LV dimensions were measured according to the American Society of Echocardiography guidelines.[18] Measurements of LV dimensions and function were determined by use of the average of ≥3 cycles. Mitral effective regurgitant orifice area and Doppler parameters of diastolic function were measured according to American Society of Echocardiography guidelines.[19,20] Echocardiography was recorded on video or a compact disk and stored within the Soweto Cardiovascular Research Unit Division for further reference, audit purposes, and repeat blinded analysis by a single operator.

Cardiac MRI was performed 4 to 6 weeks after diagnosis in patients receiving bromocriptine to detect possible mural thrombi. Studies were performed with a 1.5-T MRI scanner (General Electric, Milwaukee, Wis) with a cardiac-dedicated phased-array coil. The cardiac MRI studies were ECG triggered by standard software. Studies consisted of steady-state free precession and spin echo. Short-axis, transverse, and coronal views were obtained. Steady-state free-precession sequences were performed to assess regional wall motion abnormalities and LVEF. Slice thickness was 8 mm with no gap, 256×256 matrix, 400-mm field of view, and 1.6×1.6×8-mm voxel size. The total time required for the investigation was 30 to 45 minutes. Gadolinium enhancement was not studied. Ventricular parameters were assessed in a standard manner by 1 observer using commercially available software (CAAS MRV, Pie Medial Imaging, Maastricht, the Netherlands). The cardiac MRI studies were assessed by 2 independent experienced observers who determined the presence or absence of intracavitary thrombi.

New York Heart Association (NYHA) functional class of each patient at baseline and follow-up visits was evaluated by a physician who was provided clinical data but was blinded to treatment allocation and was unaware of the results of the laboratory tests. Heart rate and systolic and diastolic blood pressures were measured noninvasively with a Critikon Dinamap Vital Signs Monitor 1846

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and calculated as mean values from 5 readings. Measurements were made after a 30-minute resting period in patients in the sitting position with 2-minute intervals between successive measurements.

Research-Specific Blood Tests

Blood (8 mL) was withdrawn from an antecubital vein, collected in prechilled tubes containing EDTA acid or clot activator, and mixed rapidly. Plasma or serum was separated by centrifugation at 2500 rpm for 7 minutes within 10 minutes of collection. Aliquots were stored at −80°C for possible future analysis. High-sensitivity CRP (hsCRP) was measured as described previously.[5,7,8] In addition, prolactin, NT-proBNP, full blood count, liver function, and creatinine were measured. Serum levels of 16-kDa prolactin were measured by immunoprecipitation followed by Western blotting. Cathepsin D activity was assayed with the Sensolyte 520 Cathepsin D Assay Kit (MoBiTec) as previously described.[9]

Analysis of Outcome

The prespecified combined end point of poor outcome was defined as death, NYHA functional class III/IV, or LVEF <35% at 6 months as previously described.[8]

Assessment of Children

Standard growth monitoring charts issued by the South African Department of Health and maintained by primary physicians were obtained for the newborn children of mothers included in this study. These charts listed the weight of each child at birth and at regular intervals to 6 months and beyond. Weights were plotted on World Health Organization weight-for-age Child Growth Standard charts for girls and boys.[21,22]

Statistical Analysis

Data were analyzed with the SAS version 9.1 statistical program (SAS Institute Inc, Cary, NC). Results are expressed as mean±SD or median (range). Comparison between groups at baseline and within groups (baseline to 6 months) of class variables was analyzed by χ^2 test or the Fisher exact test when adequate. NT-proBNP data were log transformed. To assess differences between the 2 treatment groups, we analyzed mean changes (baseline to 6 months) in all continuous variables with a *t* test or an exact Wilcoxon 2-sample test when distribution was not normal. For within-group comparisons, a paired *t* test or a sign test when distribution was not normal was performed. Significance was assumed at a 2-sided value of $P<0.05$.

Results

Baseline Characteristics and Treatment

Ninety-three patients with suspected PPCM were screened to recruit 20 consecutive patients with confirmed PPCM who were HIV negative and presented within 1 month postpartum. As depicted in Tables 1 and 2, the baseline characteristics of patients in the PPCM-Br and PPCM-Std groups were similar in terms of age, parity, NYHA functional class, systolic and diastolic blood pressures, heart rate, LV end-diastolic and end-systolic dimensions, and LVEF. Median prolactin and median NT-proBNP levels were comparable, whereas serum levels of 16-kDa prolactin and cathepsin D activity were elevated to a similar degree in all patients (Figure 1).

Treatment with standard heart failure medications was similar between the PPCM-Br and PPCM-Std groups (Table 1). Median dose of enalapril in the PPCM-Br group was 5 mg/d (range, 5 to 10 mg/d) and in the PPCM-Std group was 10 mg/d (range, 5 to 10 mg/d). Median dose of carvedilol in the PPCM-Br group was 6.25 mg twice daily (range, 6.25 to 25 mg) and in the PPCM-Std group was 12.5 mg twice daily (range, 6.25 to 25 mg). Median dose of furosemide at 6 months was 80 mg/d (range, 80 to 120 mg). All patients, including those with normalized LV systolic function, continued on medical therapy with ACE inhibitor and carvedilol during the 6-month study period. Cardiac transplantation or implantation of a LV assist device is not performed in state hospital patients in the Gauteng province of South Africa.

Table 2. Baseline Characteristics of PPCM-Br Versus PPCM-Std Patients

	PPCM-Br (n=10)*	PPCM-Std (n=10)*	*P*
Clinical parameters			
Age, y	24±6	28±10	0.60
Parity, n (range)	1.5 (1–3)	2 (1–6)	0.52
Systolic blood pressure, mm Hg	116±23	110±19	0.50
Diastolic blood pressure, mm Hg	70±16	76±18	0.45
Heart rate, bpm	102±13	108±15	0.34
NYHA functional class, n (%)			1.00
II	5 (50)	5 (50)	
III/IV	5 (50)	5 (50)	
Echocardiographic parameters			
LVEDD, mm	55±10	59±5	0.25
LVESD, mm	46±9	52±6	0.16
LVEF, %	27.2±8.1	26.9±7.6	0.87
Mitral regurgitation (grade)	2.1±0.6	1.9±0.6	0.70
Mitral ERO, cm^2	0.45±0.13	0.44±0.18	0.90
Laboratory parameters			
Hemoglobin, g/dL	13.0±2.2	11.8±1.9	0.22
Creatinine, μmol/L†	71 (6–109)	66 (5–96)	0.43
hsCRP, mg/L†	7.8 (1.1–58.0)	6.0 (4.0–115.3)	0.86
Prolactin, μg/L†	49.9 (3.8–135.0)	30.0 (5.1–233.0)	0.87
Log NT-proBNP	8.54±1.14	8.45±1.24	0.88

LVEDD indicates LV end-diastolic diameter; LVESD, LV end-systolic diameter; and ERO, effective regurgitant orifice.

*Values are mean±SD unless otherwise specified.

†Values are median (range).

Hemodynamic and Echocardiographic Parameters

Changes in systolic and diastolic blood pressures and heart rate from baseline to 6 months were not significantly different between the 2 treatment groups. In contrast, recovery of LVEF between baseline and 6 months was greater in the PPCM-Br group (31%) than in the PPCM-Std group (9%; $P=0.012$; Table 3 and Figure 2). Furthermore, the degree of mitral regurgitation significantly improved in the PPCM-Br group compared with the PPCM-Std group ($P=0.013$), as did several parameters of diastolic function (Table 3). No significant differences were observed in LV end-diastolic and end-systolic dimension change from baseline to 6 months between the 2 groups (Table 3).

NYHA Functional Class

All 9 surviving patients in the PPCM-Br group recovered to NYHA functional class I at 6 months. In contrast, all patients

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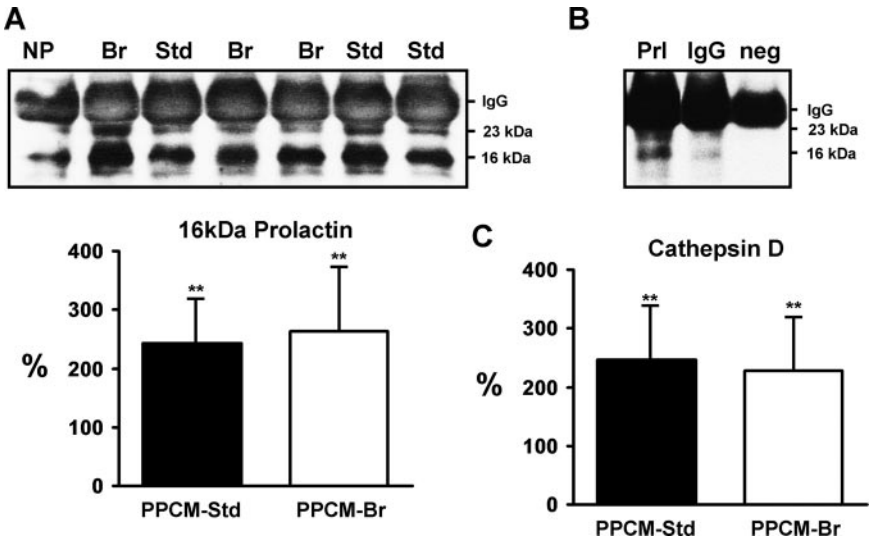


Figure 1. Analysis of prolactin subforms and cathepsin D activity in baseline serum probes from PPCM patients. A, Representative Western blot showing 16-kDa prolactin immunoprecipitated from serum probes of PPCM patients and from serum of a nulliparous (NP) control. Bar graph depicts 16-kDa prolactin serum levels in PPCM-Std (Std; n=7) and PPCM-Br (Br; n=8) vs the mean value of NP (n=3), which was set at 100% (**$P<0.01$ vs NP). B, The specificity of the immunoprecipitation (IP) was confirmed with anti-prolactin antibodies (Prl), nonspecific immunoglobulin G (IgG), and no antibody (neg) in a PPCM serum probe, followed by detection of 16-kDa prolactin by Western blot. C, Bar graph depicting cathepsin D activity in serum probes from PPCM patients (PPCM-Std, n=8; PPCM-Br, n=9) at baseline and in NP (n=7). Mean value of NP was set at 100% (**$P<0.01$ vs NP).

from the PPCM-Std group who survived 6 months were in NYHA functional class II (3 patients) or III (3 patients) (Tables 1 and 4).

Survival

The single patient who died in the PPCM-Br group presented in severe heart failure and survived only 7 days. All 9 remaining patients in the PPCM-Br group survived 6 months. Four patients in the PPCM-Std group died during the 6-month follow-up period: 1 died of heart failure during the index admission, 2 died of heart failure 4 to 12 weeks after diagnosis, and 1 experienced sudden cardiac death 1 month after baseline assessment.

Laboratory Parameters

There was a difference in change of log NT-proBNP levels from baseline to 6 months of borderline statistical significance in the PPCM-Br patients compared with the PPCM-Std patients ($P=0.05$), whereas the reductions in prolactin and hsCRP levels at 6 months were similar between the 2 groups (Table 5).

Table 3. Comparison of Hemodynamic and Echocardiographic Parameters in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

	PPCM-Br Baseline (n=10)*	PPCM-Br 6 Months (n=9)*	PPCM-Std Baseline (n=10)*	PPCM-Std 6 Months (n=6)*	P†
Clinical parameters					
Systolic blood pressure, mm Hg	116±23	118±13	110±19	115±9	0.78
Diastolic blood pressure, mm Hg	70±16	74±9	76±18	73±6	0.77
Heart rate, bpm	102±13	64±7	108±15	79±15	0.22
Echocardiographic parameters					
LVEDD, mm	55±10	51±9	59±5	56±12	0.50
LVESD, mm	46±9	34±10	52±6	45±11	0.18
LVEF, %	27±8	58±11	27±8	36±11	0.0007
Mitral regurgitation (grade)	2.1±0.6	0.22±0.44	1.9±0.6	1.5±1.0	0.0042
Mitral ERO, cm^2	0.45±0.13	0.11±0.03	0.44±0.18	0.34±0.18	0.02
Left atrial diameter, cm	3.54±0.25	3.36±0.53	3.83±0.62	3.93±0.83	0.25
Mitral E velocity, cm/s	86±19	66±24	89±23	85±24	0.53
Mitral A velocity, cm/s	32±7	48±19	33±6	45±12	0.80
Mitral E velocity/A velocity ratio	2.82±0.76	1.63±1.13	2.73±0.68	1.94±0.67	0.82
Deceleration time, ms	118±26	197±59	136±30	168±36	0.08
Mitral medial annular (E′) TDI velocity, cm/s	7.0±1.3	12.4±2.4	6.5±1.1	7.3±2.5	0.014
E/E′ (medial annular velocity)	12.5±3.0	5.4±2.5	14.0±4.6	12.4±4.6	0.08
Mitral lateral annular (E′) TDI velocity, cm/s	7.2±1.1	12.4±2.5	6.6±0.97	7.3±2.5	0.007
E/E′ (lateral annular velocity)	12.0±2.0	5.4±2.5	13.8±4.2	12.1±3.9	0.051

Abbreviations as in Table 2, plus TDI indicates tissue Doppler imaging.
*Values are mean±SD.
†Comparing the change from baseline to 6 months in PPCM-Br and PPCM-Std patients.

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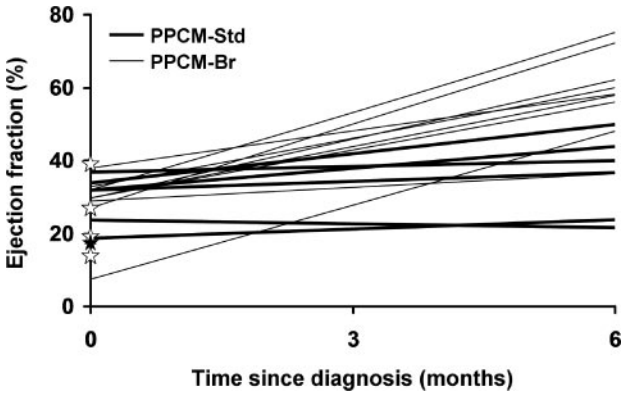


Figure 2. Change in LVEF from baseline to 6 months among survivors. Stars represent baseline LVEF for patients who died during the study period.

Combined Measure of Poor Outcome

The combined measure of poor outcome that included LVEF <35% (surviving PPCM-Br, 0 of 9 [0%] versus surviving PPCM-Std, 2 of 6 [33%]), NYHA functional class III/IV at 6 months (surviving PPCM-Br, 0 of 0 [0%] versus surviving PPCM-Std, 3 of 6 [50%]), or death within 6 months (PPCM-Br, 1 of 10 [10%] versus PPCM-Std, 4 of 10 [40%]) revealed that the PPCM-Br patients had better outcome than the PPCM-Std patients (P=0.006; Figure 3).

Thrombi and Thromboembolism

No adverse effects, including thromboembolism, were reported in either group. Cardiac MRI was performed at 4 to 6 weeks after diagnosis in 8 of the 10 patients in the PPCM-Br group to assess for thrombus formation. MRI results were not available for 1 patient who died before becoming stable enough for the MRI, and the images acquired for a second patient were not of sufficient quality for reliable assessment. None of the remaining patients had intracavitary thrombi (Figure 4).

Infant Growth Curves and Survival

All 21 children of the PPCM-Br and PPCM-Std patients showed normal growth curves when plotted on the World Health Organization standard weight-for-age growth charts (Figure 5A and B). Although the survival of all 21 children through the 6-month follow-up period was verified, weight-for-age data at 6 months were available for only 13 children.

Table 4. Comparison of NYHA Functional Class in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

	PPCM-Br at Baseline (n=10), n (%)	PPCM-Br at 6 mo (n=9), n (%)	PPCM-Std at Baseline (n=10), n (%)	PPCM-Std at 6 mo (n=6), n (%)	P*
NYHA functional class					0.008
I	0	9 (100)	0	0	
II	5 (50)		5 (50)	3 (50)	
III/IV	5 (50)		5 (50)	3 (50)	

*Comparing the change from baseline to 6 months in PPCM-Br and PPCM-Std patients.

The mothers of 5 children died during the course of the study and family members could not provide the children's growth charts, and the growth charts of the 3 other children with missing data were incomplete because of challenges in the delivery of quality care in the primary healthcare system in South Africa. However, all children had weight data up to the age of 3 months, and there were no significant differences in growth curves between the children of the PPCM-Br patients and those of the PPCM-Std patients.

Discussion

This prospective, single-center, randomized, open-label pilot study with blinded efficacy assessments showed that the addition of bromocriptine to standard heart failure therapy in women with PPCM appeared to result in significantly greater improvements in NYHA functional class, LV systolic and diastolic function, and degree of functional mitral regurgitation than seen with standard therapy alone. Bromocriptine seemed to be well tolerated, and no thrombotic complications were observed. Moreover, although bromocriptine stopped lactation and breast-feeding in the PPCM patients, the growth and survival of those infants were normal. However, our study was very small, and these findings are in no way definitive. On the other hand, these findings are encouraging and suggest that a larger study should be considered.

This proof-of-concept pilot study was performed in a group of homogeneous patients in terms of ethnic background, age, time point of diagnosis, and baseline characteristics. Unfortunately, blinding of the study was not possible because the PPCM-Std group continued to nurse their infants while the PPCM-Br group could not breast-feed because of bromocriptine-induced cessation of lactation. However, investigators were blinded for data analysis. We believe that the homogeneous patient cohort, well-balanced baseline characteristics, and blinded assessment of outcomes to some extent compensate for the small size of our study and its open-label design.

The design of the present study was chosen on the basis of our hypothesis that a cleaved form of the hormone prolactin initiates and drives PPCM and that early pharmacological blockade of prolactin with bromocriptine may improve the condition of patients with acute onset of PPCM before irreversible damage caused by cell death, fibrosis, and remodeling. Increased serum levels of 16-kDa prolactin and augmented cathepsin D activity at baseline in PPCM patients included in the present study support this hypothesis. The rationale for the dose and length of bromocriptine therapy was based on previous observations in animal models and a previous pilot study,[11] as well as several case reports in patients with PPCM.[12,23,24] We believe that some of the apparently beneficial effects of bromocriptine result from eliminating the detrimental 16-kDa prolactin form, the harmful effects of which on the heart and the vasculature have been described experimentally.[11,24] In addition, both forms of prolactin promote inflammation,[24] a reaction that seems to be associated with PPCM in this African cohort, because most patients displayed increased serum levels of the inflammatory marker hsCRP.[5]

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Table 5. Comparison of Laboratory Parameters in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

	PPCM-Br at Baseline (n=10)	PPCM-Br at 6 mo (n=9)	PPCM-Std at Baseline (n=10)	PPCM-Std at 6 mo (n=6)	P†
Hemoglobin, g/dL†	13.0±2.2	12.7±1.5	11.8±1.9	13.0±1.4	0.58
Creatinine, μmol/L‡	71 (6–109)	78 (52–113)	66 (5–96)	62 (41–73)	0.86
hsCRP, mg/L‡	7.8 (1.1–58.0)	4.7 (1.0–10)	6.0 (4.0–115.3)	1.8 (1.1–15.1)	0.18
Prolactin, μg/L‡	49.9 (3.8–135.0)	8.0 (5.9–25.0)	30.0 (5.1–233.0)	12.5 (7.4–60.0)	0.72
Log NT-proBNP†	8.54±1.14	5.62±0.80	8.45±1.24	6.64±0.60	0.056

*Comparing the change from baseline to 6 months in PPCM-Br and PPCM-Std patients.
†Values are mean±1SD.
‡Values are median (range).

Apart from its prolactin blocking role, bromocriptine may exert additional "off-target effects" in PPCM patients. For example, effects of bromocriptine on hemodynamic parameters in patients with heart failure were described 30 years ago[25] before treatment with ACE inhibitors and β-blockers was routine. Positive effects of bromocriptine on blood pressure, vascular resistance, and plasma norepinephrine levels have been described.[25] Moreover, bromocriptine has been shown to increase stroke volume index and to decrease LV filling pressure.[25,26] Whether these potential beneficial effects of bromocriptine on hemodynamic parameters play a role in contemporary patients with heart failure who are treated with ACE inhibitors and β-blockers remains to be elucidated.

Bromocriptine may also affect metabolic parameters. We observed that PPCM patients display increased oxidized low-density lipoprotein serum levels compared with healthy postpartum women,[9] suggesting impaired antioxidative defense mechanisms and potential metabolic perturbations. In turn, Wexler and McMurtry [27] reported that, experimentally, bromocriptine treatment reduced triglyceride, free fatty acid, total cholesterol, and glucose levels in isoproterenol-induced heart failure. Whether such parameters play a role in the pathophysiology of PPCM is currently under investigation in experimental models.

In addition, bromocriptine has been shown to inhibit oxidative stress–induced cell death in neuronal cells by dopamine D2 receptor–dependent transactivation of c-Src/endothelial growth factor receptor and downstream PI3K-Akt signaling, which results in upregulation of antiapoptotic Bcl-2.[28] Preliminary data show that bromocriptine treatment increases Akt activation and upregulates Bcl-2 expression in the heart of postpartum mice (D.H.-K., unpublished data, 2010), suggesting that bromocriptine may indeed have direct cardioprotective effects. Taken together, these data show that off-target effects of bromocriptine on metabolism, oxidative stress, and cytoprotection may act in concert with its prolactin-lowering capacity and may help to explain the positive effects of prolonged treatment with bromocriptine beyond an effective prolactin blockade.

We found that the overall mortality rate in the PPCM-Std group was high. Other studies have demonstrated a lower PPCM mortality rate (averaging ≈15%), including our own series of 100 patients[1,5,8] and the prospective long-term study by Fett et al.[4] One explanation for the differences in mortality rate between the present study and our other series of 100 patients might be the inclusion criteria. In the present study, patients were enrolled very early (within 24 hours after diagnosis). This timely enrollment was not possible for the previous cohort of 100 patients. As a consequence, some patients in that study died between diagnosis and enrollment. In addition, our previous study included patients diagnosed

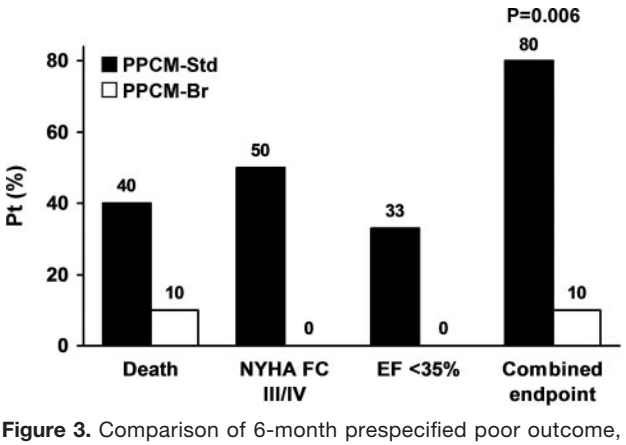


Figure 3. Comparison of 6-month prespecified poor outcome, including death, NYHA functional class (FC) III/IV, and LVEF <35% among survivors, and the combined end point including all 3 of these end points for PPCM-Br vs PPCM-Std patients (Pt).

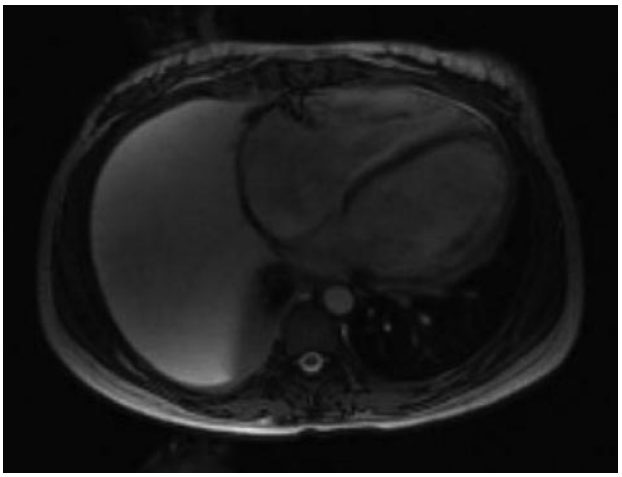


Figure 4. Cardiac MRI (transverse view, steady-state free-precession sequence) in a young African woman 2 months after delivery demonstrates marked dilation of both ventricles and the right atrium. LVEF is 8%.

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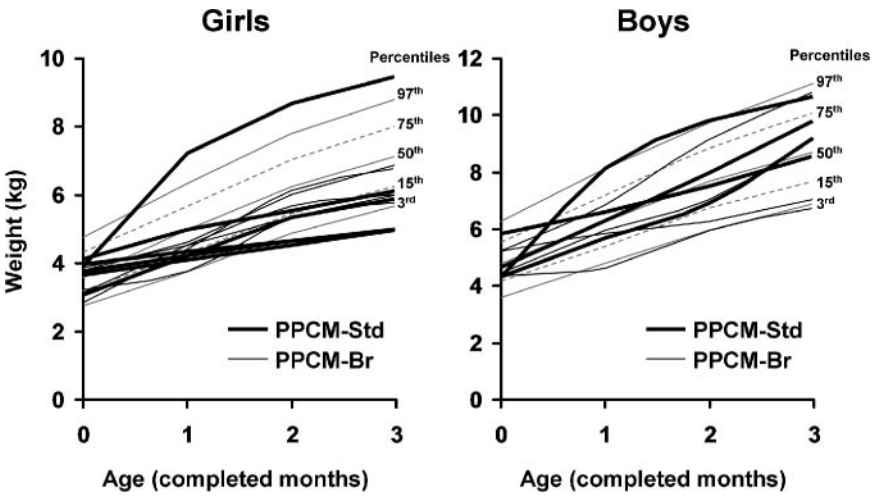


Figure 5. Growth and survival of children of PPCM study mothers from birth to 3 months plotted on World Health Organization growth charts.

between 4 weeks and 5 months postpartum. The development of symptoms >4 weeks postpartum may be a manifestation of milder forms of this disease.

In this study, the cause of death in the PPCM-Std group was either heart failure or sudden cardiac death, with all deaths occurring within 3 months of randomization. In contrast, the 1 patient who died in the PPCM-Br group was admitted with severe heart failure and died 7 days after diagnosis while still in the intensive care unit.

The safety of bromocriptine treatment during pregnancy has already been assessed by a survey of 1400 pregnant women who took bromocriptine primarily in the first few weeks of pregnancy and found no increased rates of abortion or congenital malformations.[29] In the postpartum phase, bromocriptine has been used worldwide since 1980 to suppress lactation. However, concerns have been raised about a potential risk for cerebral and cardiovascular complications, as emphasized in some case reports describing stroke,[13] seizure,[15] coronary artery thrombosis,[15] and coronary artery vasospasm.[14] Although these data were observational, bromocriptine was withdrawn from the market in the United States in 1994 for use as an agent to block lactation.

It is known that the postpartum period is associated with an increased risk of thrombosis and myocardial infarction, probably because of changes in coagulation that may have evolved as a protection from bleeding caused by miscarriage and childbirth.[30] We observed no adverse effects in any of the 9 surviving patients in the PPCM-Br group. However, the number of patients studied was small, and because of poor cardiac function, all patients in the present study received subcutaneous low-molecular-weight heparin during their index admission. Therefore, although the data suggesting that bromocriptine has a prothrombotic effect are not robust, we cannot rule out such an effect.

There has been some concern that PPCM patients in developing countries treated with bromocriptine will no longer be able to breast-feed, which may increase the risk for malnutrition and infection in their infants.[17] The survival rate of infants of the PPCM-Br patients was not affected, and no serious illnesses were reported, although the number of children we studied was very small. Normal weight gain from birth to 3 months was observed in all infants and continued to be normal during the 6-month follow-up period in those for whom data were available. Although this was a small study with only short-term follow-up, our results suggest no disadvantage to the infant of a PPCM patient who could not breast-feed because of bromocriptine treatment. However, we are aware that larger studies in Soweto and other developing areas in the world are needed to support this statement.

Conclusions

In this trial, the addition of bromocriptine to standard heart failure therapy appeared to improve LVEF and a composite clinical outcome in women, although the number of patients studied was small and the results cannot be considered definitive. Larger-scale multicenter and blinded studies are in progress to test this strategy more robustly.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease that occurs in previously healthy women. We identified prolactin, mainly its 16-kDa angiostatic and proapoptotic form, as a key factor in PPCM pathophysiology. Blockade of prolactin with the dopamine-2D agonist bromocriptine had previously been shown to prevent the onset of PPCM in mice and in women at high risk of this condition because of documented PPCM in a previous pregnancy. We recruited 20 women with onset of severe acute PPCM during the first month postpartum within 24 hours of diagnosis and randomized them into 2 groups: standard care (PPCM-Std; n=10) or standard care plus bromocriptine for 8 weeks (PPCM-Br, n=10). PPCM-Br patients displayed greater recovery of left ventricular ejection fraction compared with PPCM-Std patients at 6 months. Four PPCM-Std patients died; only 1 PPCM-Br patient did not survive. Significantly fewer PPCM-Br patients met the composite end point of poor outcome defined as death, New York Heart Association functional class III/IV, or left ventricular ejection fraction <35% at 6 months. Because the PPCM-Br mothers could not breast-feed, the outcome of their children was assessed. Infants of mothers in both groups showed normal growth and survival at 6 months. Our findings suggest that the addition of bromocriptine to standard heart failure therapy appears to improve left ventricular ejection fraction, functional class, and survival in women with severe acute PPCM with no obvious detriment to their children.

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Correction

In the article, "Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy: A Proof-of-Concept Pilot Study" by Sliwa et al, which appeared in the April 6, 2010 issue of the journal (Circulation. 2010;121:1465–1473), there was a misspelling of one author's name. Ingrid Struhman should be spelled Ingrid Struman.

The online version of the article has been corrected. The authors regret the error.

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3.5 Results of the Study on the Predictors of Outcome of PPCM:

"Predictors of outcome in 176 South African patients with Peripartum Cardiomyopathy"

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The aim of this study was to identify novel prognostic factors for patients with PPCM.

The study was one of a prospective cohort nature, conducted in a single tertiary care centre in South Africa, wherein 176 African women with newly diagnosed PPCM were studied.

The study findings suggest: that increased LVESD, lower BMI and lower serum cholesterol at baseline may be independent predictors of poor outcome in PPCM patients; while older age and smaller LVESD at baseline appear to be independently associated with a higher chance of LV recovery.

Article title:

Predictors of Outcome in 176 South African Patients with Peripartum Cardiomyopathy

Statement of Originality

NAME	**RESPONSIBILITY**
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Elena Libhaber University of the Witwatersrand	Analysed the data Performed statistical analysis
Kemi Tibazarwa **University of the Witwatersrand**	Acquired the data Analysed and interpreted the data Performed statistical analysis Drafted the manuscript
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Karen Sliwa University of the Witwatersrand	Conceived and designed the research Acquired the data Arranged funding Supervised the research Analysed and interpreted the data Drafted the manuscript
Candidate: I declare that this work is wholly my own, except where acknowledged as being the work of others (as listed above). I also acknowledge the contribution of others (as listed above) to this work in this Statement of Originality.	**Principle Advisor:** I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis, and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.
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ORIGINAL ARTICLE

Predictors of outcome in 176 South African patients with peripartum cardiomyopathy

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ABSTRACT

Objective Identify novel prognostic factors for patients with peripartum cardiomyopathy (PPCM).

Design and setting Prospective cohort study conducted in a single tertiary care centre in South Africa.

Patients 176 African women with newly diagnosed PPCM were studied.

Interventions Clinical assessment, echocardiography and laboratory results were obtained at baseline and at 6 months.

Main outcome measures Poor outcome was defined as the combined end point of death, left ventricular (LV) ejection fraction (LVEF) < 35%, or remaining in New York Heart Association (NYHA) functional class III/IV at 6 months. Complete LV recovery was defined as LVEF ≥55% at 6 months.

Results Forty-five (26%) patients had a poor outcome. Multiple logistic regression analysis revealed that, after adjustment for age, NYHA functional class, LVEF and systolic blood pressure, increased left ventricular end systolic dimension (LVESD), lower body mass index (BMI) and lower total cholesterol at baseline were independent predictors of poor outcome (adjusted OR 1.09, 95% CI 1.04 to 1.15, p=0.001; OR 0.89, 95% CI 0.83 to 0.96, p=0.004, and OR 0.50, 95% CI 0.34 to 0.73, p=0.0004, respectively). Thirty (21%) of the 141 surviving patients with echocardiographic follow-up recovered LV function at 6 months. Multiple logistic regression analysis revealed that, after adjustment for NYHA functional class, LVEF and left ventricular end diastolic dimension, older age and smaller LVESD at baseline were predictors of LV recovery (OR 1.08, 95% CI 1.01 to 1.17, p=0.02 and OR 0.92, 95% CI 0.86 to 0.98, p=0.007, respectively).

Conclusions This study suggests that increased LVESD, lower BMI and lower serum cholesterol at baseline may be independent predictors of poor outcome in patients with PPCM, while older age and smaller LVESD at baseline appear to be independently associated with a higher chance of LV recovery.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening disease that occurs in women of child-bearing age. This disease is characterised by new onset of heart failure between several months before and 6 months after delivery in previously healthy women. Although patients with PPCM have a higher rate of spontaneous recovery of left ventricular (LV) function than patients with other forms of non-ischaemic cardiomyopathy,[1] normalisation of LV function at 6 months has been reported to occur in only 23–54% of them.[1–5]

Factors predicting poor outcome in case series include degree of LV systolic dysfunction[2 3 6 7] and LV dilatation[2 8 9] on presentation, as well as LV thrombus.[8] Identifying additional prognostic factors, particularly factors that may be easily and relatively inexpensively assessed, would be beneficial in providing optimal care for patients with PPCM.

Body mass index (BMI) has been shown to be a predictor of outcome in patients with chronic heart failure,[10–13] as well as acute decompensated heart failure,[14] but this association has not previously been assessed in patients with PPCM. Renal and liver dysfunction have also both been shown to predict poor outcome in patients with heart failure, but, again, this association has not previously been investigated in patients with PPCM. Inflammation has been implicated in the pathogenesis and prognosis of PPCM,[5 15] and, while it has been shown that lipoproteins play a role in regulating cytokine production and the associated inflammatory response,[16] an association between cholesterol and outcome in patients with PPCM has not previously been reported. We sought to determine whether these variables, among others, may be predictors of outcome in patients with PPCM.

METHODS

Study design and patient recruitment

The study was conducted at Chris Hani Baragwanath (CHB) Hospital, Soweto, South Africa. Patients were referred from local clinics, secondary hospitals and the Department of Obstetrics at CHB Hospital. History of pre-existing cardiac signs or symptoms, pre-eclampsia or eclampsia and mode of delivery were obtained from the patient and confirmed by examining the obstetric card carried by each patient. Signs and symptoms were recorded during first presentation at the cardiac unit at CHB Hospital (baseline) and after a follow-up period of 6 months. Clinical assessment, echocardiography and blood analysis were performed at baseline and at 6 months.

Inclusion criteria were: (1) age ≥16 and ≤40 years; (2) symptoms of congestive heart failure that developed in the last month of pregnancy or during the first 5 months post partum; (3) no other identifiable cause of heart failure; (4) LV ejection fraction (LVEF) ≤45% by transthoracic echocardiography; and (5) sinus rhythm. Exclusion criteria were: (1) significant organic valvular heart disease; (2) systolic blood pressure >160 mm Hg or diastolic blood pressure

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>100 mm Hg; (3) clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers; (4) severe anaemia (haemoglobin <9 g/dl); and (5) any clinical condition that, according to the investigators, precluded inclusion in the study, such as ischaemic heart disease or malignancy.

Among the 176 patients included in the study, 164 (93%) received treatment with furosemide and 141 (80%) were treated with an ACE inhibitor. Digoxin was being taken by 113 (64%) of the 176 patients. Patients with an LVEF < 25% or LV thrombus were treated with warfarin. Carvedilol was initiated in 100 (57%) of the 176 patients after resolution of overt heart failure. ACE inhibitor and carvedilol doses were titrated upward as tolerated throughout the 6-month study period. Furosemide dose was titrated upward or downward as indicated according to clinical assessment. This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa and complies with the Declaration of Helsinki. All study participants gave written informed consent before study entry. A total of 176 consenting consecutive patients diagnosed with PPCM and fulfilling the inclusion criteria were enrolled in the study. All women were of African descent.

Echocardiography, assessment of New York Heart Association (NYHA) functional class, and non-invasive blood pressure measurements

Two-dimensional and targeted M-mode echocardiography with Doppler colour flow mapping were performed using either a Hewlett Packard Sonos 5500 (Royal Philips Electronics, Amsterdam, Netherlands) or a VIVID i (General Electric Company, Fairfield, Connecticut, USA) echocardiography machine. Systolic and diastolic LV dimensions were measured according to the American Society of Echocardiography (ASE) guidelines. LV dimensions and function were determined using the mean of three or more cycles. Echocardiography was taped on video or CD and stored within the Soweto Cardiovascular Research Unit Division for further reference and audit purposes.

NYHA functional class of each patient at baseline and follow-up visits was evaluated by a physician, who was provided with clinical data but blinded to the protocol and unaware of the results of the laboratory tests. Blood pressure and heart rate were measured non-invasively with a Critikon Dinamap vital signs monitor 1846 and calculated as mean values from five readings. Measurements were made after a 30 min resting period in the sitting position with 2 min intervals between successive measurements.

Research-specific blood tests

Between 10 am and 12 noon, 8 ml blood was withdrawn from an antecubital vein and collected in prechilled tubes containing ethylenediaminetetra-acetic acid or clot activator and mixed rapidly. Plasma or serum was separated by centrifugation at 2500 rpm for 7 min within 10 min of collection. Aliquots were stored at −80°C. Full blood count, liver function, renal function and total cholesterol were assessed.

Outcomes

Poor outcome was defined as the combined end point of death, LVEF <35%, or remaining in NYHA functional class III/IV at 6 months. Complete LV recovery was defined as LVEF ≥55% at 6 months.

Statistical analysis

Database management and statistical analyses were performed with SAS V.9.2 software. Continuous data are expressed as mean±SD or median (range). Comparison of means and proportions between groups at baseline was performed by independent t test and χ^2 statistics or Fisher exact test, respectively. A Wilcoxon rank-sum test was used where data were not normally distributed. Differences in class variables and continuous data between baseline and 6 months were assessed by a McNemar test and a paired t test or sign test (data not normally distributed), respectively.

Univariate and stepwise multiple logistic regression analyses were performed to establish independent predictors of poor outcome and LV recovery with cholesterol, blood pressure and echocardiographic variables in separate models after adjustment for age and BMI. Univariate logistic regression was used to examine associations with death. Significance was assumed at a two-sided p value of <0.05.

RESULTS

Baseline characteristics

Baseline clinical characteristics are listed in table 1. Notably, the mean age was 30.7±6.9 years, mean parity was 2 (range 1–7), mean BMI was 25.6±5.2 kg/m^2, and most of the women (82%) presented with NYHA functional class III or IV symptoms.

Table 1 Baseline characteristics of study population (n=176)

Clinical characteristic	Value
Age (years)	30.7±6.9
Parity, n (range)	2 (1–7)
BMI (kg/cm^2)	25.6±5.2
Systolic blood pressure (mm Hg)	111±17
Diastolic blood pressure (mm Hg)	72±13
Heart rate (beats/min)	97.3±19.1
NYHA functional class, n (%)	
I/II	33 (18)
III/IV	143 (82)
Echocardiography	
LVEDD (mm)	59.5±7.3
LVESD (mm)	51.8±7.6
Ejection fraction (%)	27.1±8.1
E velocity (m/s)	0.89±0.25
A velocity (m/s)	0.49±0.20
E/A	2.02±0.89
Deceleration time (ms)	134.5±63.2
LV thrombus, n (%)	19 (11.1)
Laboratory	
Haemoglobin (g/dl)	12.1±1.8
Creatinine (mmol/l)	84.1±20.5
Urea (mmol/l)	5.4±2.9
Total protein (g/l)	77.9±11.4
Albumin (g/l)	40.1±18.5
Total bilirubin (μmol/l)	17.3±26.8
Direct bilirubin (μmol/l)	9.2±23.2
Indirect bilirubin (μmol/l)	8.2±7.3
Alkaline phosphatase (U/l)	117.9±51.0
AST (U/l)	45.0±46.8
ALT (U/l)	54.7±67.1
GGT (U/l)	72.4±49.4
Total cholesterol (mmol/l)	4.0±1.1

Values are mean±SD unless otherwise specified.
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; GGT, γ-glutamyl transpeptidase; LV, left ventricular; LVEDD, LV end diastolic diameter; LVESD, LV end systolic diameter; NYHA, New York Heart Association.

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Table 2 Clinical, echocardiography and laboratory variables at baseline and 6 months among survivors (n=141)

Variable	Baseline*	6 months*	p Value
Clinical			
Systolic blood pressure (mm Hg)	111±17	113±17	0.18
Diastolic blood pressure (mm Hg)	72±13	72±12	0.65
NYHA functional class, n (%)			
I/II	30 (21)	128 (91)	<0.001
III/IV	111 (79)	13 (9)	
Echocardiography			
LVEDD (mm)	58.9±7.3	54.0±8.6	<0.0001
LVESD (mm)	51.3±7.6	42.3±9.5	<0.0001
Ejection fraction (%)	27.3±8.1	43.3±12.5	<0.0001
E velocity (m/s)	0.91±0.26	0.80±0.22	<0.0001
A velocity (m/s)	0.49±0.20	0.57±0.18	0.0002
E/A	2.01±0.86	1.51±0.65	<0.0001
Deceleration time (ms)	140.0±66.1	185.1±67.9	<0.0001
LV thrombus, n (%)	17 (12)	0	<0.0001
Laboratory			
Haemoglobin (g/d)	12.2±1.77	12.8±1.52	0.0004
Creatinine (mmol/l)	84.8±19.8	76.4±23.5	<0.0001
Urea (mmol/l)	5.2±2.5	4.4±1.6	0.002
Total protein (g/l)	77.8±11.5	82.2±8.9	0.003
Albumin (g/l)	40.4±19.8	43.7±13.5	<0.0001
Total bilirubin (μmol/l)	15.1±18.6	11.0±8.6	0.006
Direct bilirubin (μmol/l)	7.3±13.7	4.5±4.9	0.02
Indirect bilirubin (μmol/l)	8.0±7.3	6.1±4.4	0.002
Alkaline phosphatase (U/l)	118.2±51.5	97.4±36.4	<0.0001
AST (U/l)	42.0±33.5	26.4±12.9	<0.0001
ALT (U/l)	52.9±56.6	24.5±14.0	<0.0001
GGT (U/l)	74.6±50.3	52.8±40.8	<0.0001
Total cholesterol (mmol/l)	4.0±1.1	NR	NR

*Values are mean±SD unless otherwise specified.
ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl transpeptidase; LV, left ventricular; LVEDD, LV end diastolic diameter; LVESD, LV end systolic diameter; NYHA, New York Heart Association; NR, not reported.

Baseline versus 6-month characteristics among survivors

Table 2 lists the characteristics of the survivors among the study population at baseline and 6 months. Mean LV end systolic dimension (LVESD) decreased significantly from 51.3±7.6 mm to 42.3±9.5 mm (p<0.0001), while mean LV ejection fraction (LVEF) increased significantly from 27.3±8.1% to 43.3±12.5% (p<0.0001). Mitral inflow E/A decreased significantly from 2.01±0.86 to 1.51±0.65, and mitral inflow deceleration time increased significantly from 140.0±66.1 ms to 185±67.9 ms (p<0.0001 for both). Haemoglobin, renal function and liver function test results had all improved at 6 months. Total cholesterol results were not obtained in most of the study population at 6 months; hence these results were not tabulated.

Combined measure of poor outcome

During the 6-month study period, nine patients were lost to follow-up, three patients moved to remote areas where follow-up could not occur, and two patients did not undergo LVEF assessment at 6 months. Of the remaining 162 patients, 45 (28%) met the prespecified combined end point of death (21 patients, 13%), remaining in NYHA functional class III or IV (13 patients, 9%) or LVEF <35% at 6 months (40 patients, 25%).

Predictors of poor outcome

Univariate analysis revealed that predictors of the prespecified poor outcome include decreased systolic blood pressure, increased LVESD, decreased LVEF, increased mitral inflow E/A, decreased mitral inflow deceleration time, increased aspartate transaminase and alanine transaminase, and decreased total cholesterol (table 3).

Table 3 Univariate logistic regression analysis of predictors of poor outcome (n=162)

Predictor	Unadjusted OR	95% CI	p Value
Clinical characteristic			
Age (years)	1.02	0.95 to 1.07	0.52
Parity (number)	0.89	0.65 to 1.13	0.38
BMI (kg/cm^2)	0.95	0.89 to 1.02	0.17
Systolic blood pressure (mm Hg)	0.97	0.95 to 0.99	0.02
Heart rate (beats/min)	1.01	0.99 to 1.03	0.16
NYHA functional class	1.43	0.85 to 2.43	0.18
Medication			
Carvedilol (yes, no)	0.67	0.31 to 1.45	0.31
ACE inhibitors (yes, no)	0.71	0.38 to 1.34	0.29
Furosemide (yes, no)	0.81	0.24 to 2.78	0.74
Digoxin (yes, no)	1.31	0.68 to 2.52	0.42
Echocardiography			
LVEDD (mm)	1.05	1.00 to 1.11	0.052
LVESD (mm)	1.07	1.02 to 1.12	0.009
Ejection fraction (%)	0.95	0.91 to 0.99	0.019
E/A	2.09	1.29 to 3.39	0.003
Deceleration time (ms)	0.99	0.99 to 1.01	0.09
LV thrombus	0.97	0.37 to 2.53	0.95
Laboratory			
Haemoglobin (g/dl)	0.86	0.12 to 1.05	0.15
Creatinine (mmol/l)	1.01	0.99 to 1.03	0.35
Urea (mmol/l)	1.09	0.95 to 1.25	0.22
Total protein (g/l)	0.99	0.96 to 1.02	0.37
Albumin (g/l)	0.99	0.96 to 1.02	0.35
Total bilirubin (μmol/l)	1.01	0.99 to 1.03	0.29
Direct bilirubin (μmol/l)	1.01	0.99 to 1.04	0.37
Indirect bilirubin (μmol/l)	1.03	0.99 to 1.08	0.30
Alkaline phosphatase (U/l)	0.99	0.99 to 1.00	0.28
AST (U/l)	1.01	1.00 to 1.02	0.033
ALT (U/l)	1.01	1.00 to 1.02	0.03
GGT (U/l)	1.00	0.99 to 1.01	0.73
Total cholesterol (mmol/l)	0.53	0.36 to 0.77	0.001

Stepwise multiple logistic regression analysis revealed that, after adjustment for variables including age, systolic blood pressure, medications, LVEF and NYHA functional class, increased LVESD, lower BMI and lower total cholesterol at baseline were independent predictors of the prespecified poor outcome (adjusted OR 1.09, 95% CI 1.04 to 1.15, p=0.001; OR 0.89, 95% CI 0.83 to 0.96, p=0.004; and OR 0.50, 95% CI 0.34 to 0.73, p=0.0004, respectively).
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; GGT, γ-glutamyl transpeptidase; LV, left ventricular; LVEDD, LV end diastolic diameter; LVESD, LV end systolic diameter; NYHA, New York Heart Association.

Predictors of LV recovery

Thirty (21%) of the 141 surviving patients had fully recovered LV function (LVEF ≥55%) at 6 months. Baseline characteristics of patients who fully recovered versus patients who did not are listed in table 4. Univariate analysis revealed that predictors of LV recovery included older age, decreased LV end diastolic dimension (LVEDD), decreased LVESD, higher haemoglobin and lower creatinine (table 5). Stepwise multiple logistic regression analysis showed that, after adjustment for NYHA functional class, medication, LVEF and LVEDD, older age and smaller LVESD were predictors of LV recovery (adjusted OR 1.08, 95% CI 1.01 to 1.17, p=0.02 and OR 0.92, 95% CI 0.86 to 0.98, p=0.007, respectively).

Predictors of death

Univariate analysis showed that predictors of death included younger age (OR 0.93, 95% CI 0.87 to 1.00, p=0.04), lower

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Table 4 Baseline characteristics for patients with complete recovery of LVEF versus patients with non-recovery of LVEF (n=141)

Characteristic	Recovered LVEF (n=30)*	Non-recovered LVEF (n=111)*	p Value
Clinical			
Age (years)	33.2±5.9	30.4±6.6	0.035
Parity, n (range)	3 (1–4)	2 (1–7)	0.053
BMI (kg/cm^2)	26.5±6.0	25.8±5.4	0.66
Systolic blood pressure (mm Hg)	117±17	110±17	0.08
Diastolic blood pressure (mm Hg)	75±13	72±12	0.17
NYHA functional class, n (%)			
I/II	29 (97)	98 (89)	0.054
III/IV	2 (3)	12 (11)	
Echocardiography			
LVEDD (mm)	56.2±6.5	59.6±7.4	0.07
LVESD (mm)	48.1±6.3	52.2±7.8	0.026
Ejection fraction (%)	28.7±8.4	26.9±8.0	0.22
E velocity (m/s)	0.88±0.28	0.91±0.25	0.77
A velocity (m/s)	0.52±0.17	0.49±0.21	0.13
E/A	1.73±0.69	2.10±0.89	0.03
Deceleration time (ms)	141.5±59.2	139.7±68.0	0.74
LV thrombus, n (%)	6 (20)	11 (10)	0.20
Laboratory			
Haemoglobin (g/dl)	12.8±1.8	12.0±1.8	0.035
Creatinine (mmol/l)	73.8±19.5	87.8±18.8	0.0005
Urea (mmol/l)	5.0±3.5	5.3±2.2	0.09
Total protein (g/l)	79.1±10.5	77.5±11.7	0.28
Albumin (g/l)	46.7±30.8	38.8±15.4	0.02
Total bilirubin (μmol/l)	12.6±7.8	15.8±20.6	0.88
Direct bilirubin (μmol/l)	5.3±4.6	7.9±15.3	0.97
Indirect Bilirubin (μmol/l)	7.4±4.5	8.1±7.9	0.83
Alkaline phosphatase (U/l)	132.2±63.2	114.4±47.4	0.33
AST (U/l)	36.6±18.7	43.5±46.4	0.93
ALT (U/l)	45.8±31.8	54.8±61.6	0.64
GGT (U/l)	79.1±47.9	73.4±51.1	0.40
Total cholesterol (mmol/l)	4.1±1.2	4.0±1.1	0.60

*Values are mean±SD unless otherwise specified.
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; GGT, γ-glutamyl transpeptidase; LV, left ventricular; LVEDD, LV end diastolic diameter; LVESD, LV end systolic diameter; NYHA, New York Heart Association.

Table 5 Univariate logistic regression analysis of predictors of LV recovery (n=141)

Predictor	Unadjusted OR	95% CI	p Value
Clinical characteristics			
Age (years)	1.07	1.00 to 1.15	0.04
Parity (number)	1.26	0.96 to 1.65	0.09
BMI (kg/cm^2)	1.02	0.95 to 1.10	0.54
Systolic blood pressure (mm Hg)	1.02	0.99 to 1.05	0.07
Heart rate (beats/min)	0.98	0.96 to 1.00	0.06
NYHA functional class	0.74	0.41 to 1.35	0.33
Medication			
Carvedilol (yes, no)	0.80	0.35 to 1.80	0.58
ACE inhibitor (yes, no)	0.93	0.34 to 2.57	0.89
Furosemide (yes, no)	2.25	0.27 to 18.75	0.45
Digoxin (yes, no)	0.95	0.42 to 2.16	0.90
Echocardiography			
LVEDD (mm)	0.93	0.88 to 0.99	0.025
LVESD (mm)	0.93	0.87 to 0.98	0.01
Ejection fraction (%)	1.03	0.98 to 1.08	0.27
E/A	0.56	0.31 to 1.02	0.057
Deceleration time (ms)	1.00	0.99 to 1.01	0.90
LV thrombus	1.93	0.60 to 6.25	0.27
Laboratory			
Haemoglobin (g/dl)	1.33	1.05 to 1.69	0.02
Creatinine (mmol/l)	0.96	0.93 to 0.98	0.0008
Urea (mmol/l)	0.94	0.79 to 1.13	0.51
Total protein (g/l)	1.01	0.98 to 1.05	0.51
Albumin (g/l)	1.02	0.99 to 1.04	0.10
Total bilirubin (μmol/l)	0.99	0.95 to 1.02	0.42
Direct bilirubin (μmol/l)	0.98	0.92 to 1.03	0.40
Indirect bilirubin (μmol/l)	0.99	0.93 to 1.05	0.64
Alkaline phosphatase (U/l)	1.01	0.99 to 1.01	0.11
AST (U/l)	0.99	0.98 to 1.01	0.33
ALT (U/l)	0.99	0.99 to 1.01	0.45
GGT (U/l)	1.00	0.99 to 1.01	0.73
Total cholesterol (mmol/l)	1.10	0.76 to 1.61	0.61

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; GGT, γ-glutamyl transpeptidase; LV, left ventricular; LVEDD, LV end diastolic diameter; LVESD, LV end systolic diameter; NYHA, New York Heart Association.

BMI (OR 0.83, 95% CI 0.72 to 0.95, p=0.007), increased LVEDD (OR 1.08, 95% CI 1.01 to 1.15, p=0.02), increased LVESD (OR 1.07, 95% CI 1.01 to 1.14, p=0.02), and higher NYHA functional class (OR 2.35, 95% CI 1.12 to 4.94, p=0.02). The mean age of the patients who died (n=21) was 27.8±8.6 years, while the mean age of the patients who survived but were not lost to follow-up (n=141) was 31.0±6.6 years. The mean BMI of the patients who died was 22.6±3.3 kg/m^2, while the mean BMI of the patients who survived but were not lost to follow-up was 25.9±5.5 kg/m^2.

DISCUSSION

This prospective single-centre study of 176 newly diagnosed patients with PPCM summarises data on clinical, echocardiographic and laboratory characteristics at the time of diagnosis and after 6 months of standard clinical care. We confirmed previous findings in our collective[5] that a relatively high percentage of patients (79%) had failed to normalise LV function at 6 months compared with collectives from the USA.[3 8] Increased LVESD, lower BMI and lower total cholesterol were identified as potential novel predictors of poor outcome on stepwise multivariate logistic regression analysis. Older age appears to be a novel predictor of LV recovery, while younger age, lower BMI, increased LVEDD, increased LVESD and higher NYHA functional class all seem to be predictors of mortality.

Numerous factors predicting morbidity and mortality in patients with PPCM have previously been proposed but not validated. These factors include degree of decreased LVEF and LV dilatation at diagnosis,[2 7 8 17 18] presence of LV thrombus,[8] and being of African descent.[8 19] Previous studies performed at our own institution have shown that NYHA functional class,[5] N-terminal prohormone of brain natriuretic peptide,[20] and increased plasma markers of inflammation and apoptosis[5 20] at diagnosis are predictors of poor outcome as well.

The present analysis, using a much larger sample size than in most previous analyses, reveals different findings with regard to some predictors of morbidity and mortality, but confirms other findings. As previously reported,[2] increased LVESD at diagnosis was a significant predictor even when adjusted for other variables in multivariate analysis. In contrast with previous reports, LVEF and LVEDD at diagnosis,[2 3 6 8 9] NYHA functional class[5] and presence of LV thrombus[8] were not predictors of poor outcome. A novel finding in the present study was that lower BMI and lower total cholesterol at baseline were both associated with poor outcome.

Previous studies have shown that increased BMI is associated with decreased all-cause mortality in patients with chronic

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heart failure.[10 12 13] The potentially beneficial effect of being overweight or obese has been termed the 'obesity paradox'. Several hypotheses have been proposed to account for this paradox, including the suggestions that overweight and obese patients may have higher metabolic reserve, reduced cytokine and neuroendocrine activation, higher blood pressure, which may allow more aggressive upward titration of medication, and higher serum lipid levels. An association between higher BMI and improved survival in patients with acute decompensated heart failure has also been shown. An analysis of more than 100 000 patients enrolled in the Acute Decompensated Heart Failure National Registry showed that higher BMI was associated with lower in-hospital mortality.[14] The mechanisms by which a higher BMI may be protective for patients with either acute or chronic heart failure remain unclear.

Several studies have reported an inverse relationship between cholesterol and mortality in patients with chronic heart failure.[21–23] Rauchhaus and colleagues were among the first to demonstrate this paradox in a derivative/validation study in 417 patients with chronic heart failure whereby lower serum total cholesterol was independently associated with worse prognosis.[24] A more recent study demonstrated that higher serum high-density lipoprotein (HDL) cholesterol and higher serum triglycerides were associated with lower mortality in a cohort of 833 outpatients with chronic heart failure due to various aetiologies.[25] In contrast with the results of these studies, Christ and colleagues found that, in patients with idiopathic dilated cardiomyopathy, low cholesterol levels are dependent on the severity of cardiac disease and do not independently predict adverse outcomes in these patients.[26]

Low cholesterol has also been shown to be a predictor of adverse outcomes in acute heart failure. Findings from the Acute Heart Failure Database main registry show that low total cholesterol was one of several predictors for in-hospital mortality in patients admitted for acute heart failure.[27] In a cohort of 207 older patients, low cholesterol was associated with increased length of hospital stay and was among the best predictors of in-hospital mortality.[28]

Although the pathophysiological basis for the association of low cholesterol and impaired prognosis has not been fully elucidated, an 'endotoxin–lipoprotein' hypothesis has been proposed.[16] Patients with chronic heart failure have increased cytokine activation, which depends, at least in part, on exposure to bacterial endotoxins due to mesenteric venous congestion.[24 29] Lipoproteins serve as natural buffers because they bind to endotoxins. This, in turn, leads to reduced lipopolysaccharide activity and diminished immune activation.[16]

We have previously shown that patients with PPCM display increased cytokine levels and that failure to decrease interferon γ was associated with poor outcome.[5 20] On the basis of the results of the present study, low total cholesterol at diagnosis may be a marker for increased immune activation in patients with PPCM and portend a poor prognosis.

Predictors of LV recovery

In this study, only 21% of surviving patients had attained complete LV recovery at 6 months. Predictors of LV recovery were older age and smaller LVESD at diagnosis, confirming a previous study that reported that smaller LVESD at diagnosis is associated with better LV recovery.[2] Other studies have reported that smaller LVEDD,[8 9] higher LVEF,[2 6 19] higher fractional shortening[9] and absence of LV thrombus[8] at diagnosis may predict LV recovery, but none of these factors predicted LV recovery in our patient population. Of note, the LV recovery rate at 6 months in this study was quite low compared with a previous study of patients with PPCM in the USA, of whom only 19% were black, which reported an overall LV recovery rate of 54%.[3] More recently, another study from the USA in which 14 of 39 patients with PPCM were black reported that normalisation of LV function at 6 months occurred in 56% of white patients but only 30% of black patients.[1] The LV recovery rate in our study of black African patients with PPCM is even lower than that reported for black patients living in the USA, but similar to that reported in patients living in Haiti[4] and Turkey.[2] These findings suggest that patients of African ancestry with PPCM may be less likely to normalise their LV function at 6 months than patients of other racial or ethnic backgrounds.

Differences in nutrition between patients from various ethnic and sociodemographic backgrounds have not been evaluated and may also play a role. Fett and colleagues[30] have shown that, among 32 Haitian patients with severe heart failure, only 6% had recovered at 6 months, but 100% had recovered by 48 months. The long-term recovery rate of the patients with PPCM in the present study has not been assessed, but it may be that predictors of late LV recovery may differ from predictors of early LV recovery. This issue merits further investigation.

Age has not previously been reported as a predictor of LV recovery. The reason(s) why older patients with PPCM in this study had better LV recovery than younger patients remains unclear. It is possible that younger patients mounted a more severe immune response than older patients, resulting in more extensive myocardial damage, thereby decreasing the probability of functional recovery.

Predictors of mortality

Of the 162 patients with follow-up, 21 (13%) died within 6 months of diagnosis. Similar to previous reports, degree of LV dilatation[2] and higher NYHA functional class[5] at diagnosis were predictors of mortality in univariate analysis. Lower BMI and younger age at diagnosis seemed to be independent predictors of mortality, which are novel findings. Because of the relatively low number of deaths in the current cohort, multiple logistic regression analysis of mortality was not performed. Studies including larger numbers of patients with PPCM are warranted to further elucidate and validate predictors of death among this patient population.

Limitations

Total cholesterol was measured at baseline for all patients, but was not assessed at 6 months in the majority of patients, thus not allowing comparison of change over time. In addition, only total cholesterol was measured, so data on the levels of various types of cholesterol including HDL, low-density lipoprotein, triglycerides and non-HDL are not available. Assessment of cholesterol types at baseline and at follow-up may provide additional information in future studies. Finally, follow-up concluded at 6 months. Longer follow-up would probably increase our knowledge about predictors of poor outcome as well as LV recovery in patients with PPCM.

CONCLUSION

In this study, larger LVESD and low total cholesterol were found to be associated with a composite poor outcome in a large cohort of African women with PPCM, while smaller LVESD and older age were found to be associated with a better chance of LV recovery. These results confirm and expand upon previous findings by our group and others and merit further

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investigations on potential pathophysiological mechanisms underlying these findings.

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Predictors of outcome in 176 South African patients with peripartum cardiomyopathy

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4. DISCUSSION

The research projects within this thesis were designed to address the knowledge gap regarding the aetiology, prognostic indicators and targeted treatment of PPCM. I have attempted to unfold more on the aetiology of PPCM: through the evaluation of any genetic contribution, at both clinical and molecular level; as well as through in-depth analysis of any electrocardiographic abnormalities that could shed more light on aetio-pathogenesis in this aspect, respectively.

Given that my work began in an era when there was no insight as to how to treat PPCM differently to its closest disease simulant, DCM, it was important to explore the prognostic indicators for patients within the South African setting in the context of them being exposed to the local standard of care. However, through this renewed confirmation of the dismal outcome that many PPCM patients still endure, I needed to address the urgent task of exploring treatment modalities more specific to PPCM. By discovering a novel treatment modality effective in improving the outcome of PPCM, this in turn completed the research cycle by further reinforcing efforts to improve understanding of this aspect of the aetio-pathogenesis of PPCM.

The Genetics of PPCM

This thesis provides a detailed description of two cases of PPCM with at least one family member with DCM; this meets the definition of familial cardiomyopathy (Mestroni et al, 1999). Both families showed presentations compatible with autosomal dominant inheritance. On a larger scale, the research shows that almost one-quarter of PPCM patients belong to the spectrum of patients with active familial DCM, i.e. with at least one first degree relative with concurrent DCM. However, by including relatives who have early echocardiographic signs of DCM, who will inevitably develop DCM

over time (as is evident in this study, as well as in literature (Baig et al, 1998; Mahon et al, 2005)), this raises the proportion of PPCM patients who portray familial DCM to almost 40%.

To the best of my knowledge, this is the first study of its kind to have systematically performed thorough clinical evaluation of all accessible first degree relatives of PPCM; and it is also the first to suggest such a high prevalence of familial DCM amongst PPCM patients. This is of immense clinical importance in understanding the aetiology and natural history of PPCM patients with and without familial disease in terms of forming preventative efforts. There have been several reports of familial disease in PPCM (Sliwa et al, 2010; Pearl, 1995; van Spaendonck, 2010). Two Western studies and one South African case series suggest that a sub-set of PPCM patients may be part of the spectrum of familial DCM presenting in the perinatal period (Ntusi et al, 2011; Van Spaendonck et al, 2010; Morales et al, 2010).

Familial DCM manifests in an age-dependent manner with incomplete disease penetration (Mahon, 2005). As heterogeneous as familial DCM is, over 40 defective genes have been associated with inherited DCM, although they account for a minority of familial DCM cases (Mayosi et al, 2007). Genome-Wide Association Studies (GWAS) may succeed in identifying pathogenic mutations for PPCM. The only known attempt at GWAS in PPCM patients was done in Utah; it revealed 10 single nucleotide polymorphisms (SNPs) that may play a role in the pathogenesis of PPCM(Horne et al, 2011). Of these, one SNP (located on chromosome 12) demonstrated genome-wide significance for PPCM, likely triggering disease through abnormal immune-modulation.

Recent advances favouring PPCM as an independent disease shows *in vitro* and *in vivo* evidence of an abnormal 16kDa prolactin pathway that is intertwined with oxidative stress (Yamac et al, 2010). However, given that oxidative stress, together with signal transducer and activation of transcription factor-3 (STAT-3) depletion, as implicated in this model, may be common to most forms of severe heart failure (including idiopathic DCM (Peng et al, 2012), the only component to this pathway that could remain unique to PPCM is that fuelling production of the 16kDa fragment of prolactin. Still,

linking this abnormal prolactin pathway exclusively to PPCM would require proof of its absence in women with familial DCM (including relatives who subsequently fall pregnant and deteriorate). Hence, in the scenario set by our family screening study, for us to write off the 22% – 39% of PPCM patients who demonstrated familial DCM as being female FDCM patients presenting in pregnancy, we would have had to prove clinical disease prior to pregnancy, as well as the absence of predominance of 16kDa prolactin in their serum post-partum.

In continuation of these efforts to decipher the overlap between women with familial DCM presenting perinatally from PPCM patients who may have their own specific genetic predisposition to developing a form of familial DCM, there is a need for continued research into the clinical and bio-molecular similarities - not just the differences. For example, despite the GWAS described above (Horne et al, 2011) having failed to find any single variation on the STAT-3 gene to account for PPCM, it introduced the possibility of an association between SNPs on the STAT-5 gene, a known culprit in idiopathic DCM (Peng et al, 2012) and PPCM. Furthermore, the GWAS authors also described 30 other SNPs that appeared to predict the absence of PPCM16, suggesting a route for exploration of protective mechanisms against PPCM.

Familial DCM is characterized by a marked phenotypic and genetic/allelic heterogeneity that is also typical for other cardiomyopathies (Burkett et al, 2005; Perrot et al, 2007). Probably the most common cause of FDCM is Lamin A/C deficiency (Malhotra, 2009; Perrot et al, 2009), as a result of harmful abnormalities in the Lamin A/C gene (LMNA). Lamin A/C is a complicated gene that can present with multiple phenotypes extended above and beyond the heart. More than ten clinically distinct disease phenotypes have been attributed to LMNA mutation (termed ‘‘laminopathies’’), including accelerated aging disorders, lipodystrophy syndromes, as well as striated muscle diseases, like muscular dystrophy and cardiomyopathy (Perrot et al, 2009). Although it remains unclear how mutations cause the syndrome of FDCM, an animal model suggests that known mutations tend to cause apoptosis, especially in the conduction system of the heart (Malhotra, 2009). In humans,

LMNA mutations in the heart have been associated with DCM phenotypes with more aggressive heart failure, arrhythmias and high mortality. Still, penetrance is variable and no clear marker has been identified to predict which patients will develop symptoms and which are at risk for sudden death (Malhotra, 2009).

Two recent Western studies that attempted to screen PPCM patients for LMNA mutations reported no mutations (Van Spaendonck et al, 2010; Morales et al, 2010) - although their retrospective study design may have contributed to considerable under-estimation of the prevalence of LMNA mutations in PPCM patients. To date, the study reported in this thesis comprises the largest number of prospectively recruited PPCM patients to undergo genetic screening for LMNA mutation - yet we also failed to identify LMNA mutation in the cohort. Despite LMNA mutations being strongly correlated with various arrhythmias, as described above, no significant arrhythmia was recorded in the study cohort reported on in this thesis. However, whilst we do accept the limitation that some of our PPCM patients who died may have suffered an arrhythmia that was not recorded, it must be true that in PPCM, morbid outcomes are caused by factors other than LMNA gene abnormalities. In FDCM families bearing pathogenic LMNA mutations, the discovery of individuals who are genotype-negative yet phenotype positive has led to the suspicion that compound heterozyogosity may be more common in IDCM/FDCM than previously thought (Parks et al, 2008). Although the only anomalies that were found on the LMNA genes of this group of South African PPCM patients were SNPs that are likely harmless, one must keep an open mind when searching for causative mutation in the context of possible compound heterozygosity.

One major limitation of this study was the limited access to adequate samples of patient blood for sufficient DNA analysis; especially that of patients who died, or re-located to farther provinces, and so forth. This suggests an inevitable potential for under-estimation of the prevalence of any LMNA mutation in our PPCM cohort.

The ECG in PPCM

This is the first study to systematically describe the 12-lead ECG in *de novo* cases of PPCM. Our main aim was to examine the potential utility of the 12-lead ECG (a relatively inexpensive and easy-to-apply diagnostic tool) in detecting underlying LV dysfunction in confirmed cases of *de novo* PPCM in African women. This would require a high underlying level of ECG abnormalities in such a cohort in order to discriminate against (presumably) more normal 12-lead ECGs in African women experiencing healthier pregnancies.

Of the 78 cases studied: 49% demonstrated major ECG abnormalities, usually associated with significant underlying cardiac pathology; while 62% demonstrated one or more forms of minor variation/abnormality, potentially indicative of the same. We also attempted to examine whether the 12-lead ECG is a useful tool for discriminating between those cases that respond to treatment (seen as resolution of initially observed ECG abnormalities) and those who had persistent LV dysfunction. In this respect, we found that the presence of two major abnormalities (T-wave inversion and ST-segment depression) and a third Minnesota code criterion (not listed as one of the major or minor criteria (ST-segment elevation)) found on the baseline 12-lead ECG correlated with persistently poor LV systolic function at six months. T-wave inversion also correlated with LV systolic function at baseline. Typically, LV systolic function recovery in PPCM is a slow and drawn-out process that appears to take place during the second year of treatment (Tibazarwa et al, 2010). On this basis, while LVEF in those patients subjected to six-month follow up improved overall, just under half still had defined LV dysfunction. This represents a major therapeutic target for treatment. Therefore, long-term follow-up using the ECG in PPCM might well show ECG reversal to normality as late as 18 months after first diagnosis, as our long-term echocardiographic data suggest (Sliwa et al, 2011). Moreover, we have identified potentially useful markers (i.e. major T-wave inversion and/or ST-segment depression on the 12-lead ECG) as simple, but important, prognostic markers that might trigger more aggressive treatment and follow up in PPCM cases.

Our findings and the overall utility of the 12-lead ECG in this clinical setting require careful interpretation when fundamental investigations, such as echocardiography, remain inaccessible to most hospitals and patients in sub-Saharan Africa. Serum levels of NT-proBNP are known to strongly predict the degree of heart failure (Cardarrelli et al, 2003); yet this test is still not available in most referral hospitals in Africa where PPCM is prevalent. Surprisingly, because of vast differences in sensitivity and specificity in detecting HF, it has been suggested that the overall cost-effectiveness of measuring serum NT-proBNP becomes comparable to that of screening for HF using the 12-lead ECG alone (Lee et al, 2008; Galasko et al, 2006), due mainly to the relatively low specificity of the 12-lead ECG (Galasko et al, 2006). The scarcity of the serum NT-proBNP test in our setting almost mandates using something as inexpensive and easy to obtain as the 12-lead ECG to screen for PPCM, even if its sensitivity and specificity prove to be imperfect. These data will be particularly useful if (after comparing ECG patterns in healthy African women as derived from the Heart of Soweto cohort [Sliwa et al, 2008]) the 12-leadECG has the potential to be applied as a 'rule-out' test (i.e. high specificity to identify all truly negative for PPCM cases).

Unfortunately, the ability to combine 12-lead ECG with typical symptoms of HF (to increase its accuracy in detecting PPCM) is confounded by their parallel presence in the late stages of pregnancy (but not typically post-partum). We remain wary of the fact that inherent gender-based differences in ECG findings may exist; with reports often showing women to have a higher prevalence of ST-segment depression or T-wave changes than men, such that one might question the true significance of any association between ST-segment depression and T-wave abnormalities with mortality due to coronary heart disease (CHD) in women (Wu et al, 2008). However, we are greatly reassured by the number of large, population-based studies that show major ST-depression to be the most predictive ECG characteristic of cardiovascular disease (CVD) and CHD mortality, lending an average two-fold risk of CVD and CHD mortality, and, as with our study, predicting these outcomes from their mere presence at baseline (De Bacquer et al, 1998).

Studies reporting on the ECG in prognostication of PPCM remain scarce, with two from Nigeria suggesting it to be a weak predictor of recovery and long-term prognosis in PPCM (Boomsma et al, 1989; Fillmore et al, 1977). However these studies did not use echocardiography to confirm the diagnosis of PPCM, and each study had a greater proportion of patients with hypertension than those without. Given recent insight gained that patients with the PPCM phenotype who present with hypertension appear to follow a different natural history to those without (Sliwa et al, 2010), usually with better prognosis in those with hypertension, any comparison between data from PPCM patients with hypertension to those without hypertension should be interpreted with great caution.

The Treatment of PPCM Using Bromocriptine

This prospective, single-centre, randomized, open-label pilot study with blinded efficacy assessments showed that the addition of Bromocriptine to standard heart failure therapy in women with PPCM appeared to result in significantly greater improvement than seen with standard therapy alone in all of the following: NYHA functional class; LV systolic and diastolic function; and degree of functional mitral regurgitation. Bromocriptine seemed to be well tolerated, and no thrombotic complications were observed. Moreover, although Bromocriptine stopped lactation and breast-feeding in the PPCM patients, the growth and survival of those infants were normal. However, our study was very small and these findings are in no way definitive. On the other hand, the findings are encouraging and suggest that a larger study should be considered.

This proof-of-concept pilot study was performed in a group of homogeneous patients in terms of ethnic background, age, time of diagnosis and baseline characteristics. Unfortunately, blinding of the study was not possible because the PPCM-Std (Standard) group continued to nurse their infants while the PPCM-Br (Bromocriptine) group could not breast-feed because of Bromocriptine-induced cessation of lactation. However, investigators were blinded for data analysis. We believe that the

homogeneous patient cohort, well-balanced baseline characteristics and blinded assessment of outcomes to some extent compensate for the small size of our study and its open-label design. Apart from its prolactin blocking role, Bromocriptine may exert additional "off-target effects" in PPCM patients. For example, effects of Bromocriptine on hemodynamic parameters in patients with heart failure were described 30 years ago (Francis et al, 1983), before treatment with ACE inhibitors and blockers was routine. Bromocriptine may also affect metabolic parameters. We observed that PPCM patients display increased oxidized low-density lipoprotein serum levels compared with healthy postpartum women (Hilfiker et al, 2007). This suggests impaired anti-oxidative defence mechanisms and potential metabolic perturbations.

We observed no adverse effects in any of the nine surviving patients in the PPCM-Br group. However, the number of patients studied was small; and because of poor cardiac function, all patients in the study received sub-cutaneous low-molecular-weight heparin during their index admission. Therefore, although the data suggesting that Bromocriptine has a pro-thrombotic effect are not robust, we cannot rule out such an effect.

Prognostic Indicators in PPCM

Our prospective single-centre study of 176 newly diagnosed patients with PPCM summarises data on clinical, echocardiographic and laboratory characteristics at the time of diagnosis and after 6 months of standard clinical care. We confirmed previous findings in our collective that a relatively high percentage of patients (79%) had failed to normalise LV function at 6 months compared with collectives from the USA (Elkayam et al, 2005; Amos et al, 2006). Increased LVESD, lower BMI and lower total cholesterol were identified as potential novel predictors of poor outcome on stepwise multi-variate logistic regression analysis. Older age appears to be a novel predictor of LV recovery;

while younger age, lower BMI, increased LVEDD, increased LVESD and higher NYHA functional class all seem to be predictors of mortality.

Numerous factors predicting morbidity and mortality in patients with PPCM have previously been proposed, but not validated. These factors include degree of decreased LVEF and LV dilatation at diagnosis, presence of LV thrombus and being of African descent. Previous studies performed at our own institution have shown that NYHA functional class, N-terminal pro-hormone of brain natriuretic peptide and increased plasma markers of inflammation and apoptosis at diagnosis are predictors of poor outcome as well (Blauwet et al, 2012). The present analysis, using a much larger sample size than in most previous analyses, reveals different findings with regard to some predictors of morbidity and mortality, but confirms other findings. As previously reported, increased LVESD at diagnosis was a significant predictor, even when adjusted for other variables in multi-variate analysis. In contrast with previous reports, LVEF and LVEDD at diagnosis, NYHA functional class and presence of LV thrombus were not predictors of poor outcome. A novel finding in the present study was that lower BMI and lower total cholesterol at baseline were both associated with poor outcome (Blauwet et al, 2012). Several studies have reported an inverse relationship between cholesterol and mortality in patients with chronic heart failure. Low cholesterol has also been shown to be a predictor of adverse outcomes in acute heart failure. Although the pathophysiological basis for the association of low cholesterol and impaired prognosis has not been fully elucidated, an 'endotoxin–lipoprotein' hypothesis has been proposed.

Sixteen patients with chronic heart failure have increased cytokine activation, which depends, at least in part, on exposure to bacterial endotoxins due to mesenteric venous congestion (Blauwet et al, 2012). Lipoproteins serve as natural buffers because they bind to endotoxins. This, in turn, leads to reduced lipopolysaccharide activity and diminished immune activation (Rauchhaus et al, 2000). We have previously seen that patients with PPCM display increased cytokine levels and that failure to decrease interferon-γ was associated with poor outcome (Sliwa et al, 2006; Forster et al, 2008).

On the basis of the results of the present study, low total cholesterol at diagnosis may be a marker for increased immune activation in patients with PPCM and it may portend a poor prognosis.

In this study, only 21% of surviving patients had attained complete LV recovery at 6 months. Predictors of LV recovery were: older age and smaller LVESD at diagnosis. This confirmed a previous study that reported that smaller LVESD at diagnosis is associated with better LV recovery (Blauwet et al, 2012). Other studies have reported that smaller LVEDD, higher LVEF, higher fractional shortening and absence of LV thrombus at diagnosis may predict LV recovery; but none of these factors predicted LV recovery in this patient population. It should be noted that the proportion of LV recovery reported in this study of black African patients with PPCM was even lower than that reported for black patients living in the USA, but similar to that reported in patients living in Haiti and Turkey (Blauwet et al, 2012). These findings suggest that patients of African ancestry with PPCM may be less likely to normalise their LV function at 6 months than patients of other racial or ethnic backgrounds.

Differences in nutrition between patients from various ethnic and socio-demographic backgrounds have not been evaluated and may also play a role. Fett and colleagues (Fett et al, 2005) showed that among 32 Haitian patients with severe heart failure: only 6% had recovered at 6 months; but 100% had recovered by 48 months. The long-term recovery rate of patients with PPCM in the present study reported in this thesis has not been assessed, but it may be that predictors of late LV recovery differ from predictors of early LV recovery. This issue merits further investigation.

Age has not previously been reported as a predictor of LV recovery. The reason(s) why older patients with PPCM in this study had better LV recovery than younger patients remains unclear. It is possible that younger patients mounted a more severe immune response than older patients, resulting in more extensive myocardial damage, thereby decreasing the probability of functional recovery.

Of great importance is the acknowledgement of the community of international experts of the need to review all existing data on PPCM, merging old evidence with the new, to form comprehensive guidelines on the management of PPCM. It is through such efforts that in 2010, the European Society of Cardiology published a position statement on the aetiology, diagnosis, and management of PPCM; this having being compiled by a variety of experts consisting of cardiologists, obstetricians, intensivists, and imaging specialists, and incorporating modifications in the definition and diagnostic criteria of PPCM as per the emerging evidence (Sliwa et al, 2010).

5. CONCLUSIONS AND THE WAY FORWARD

This PhD has contributed considerably in narrowing the knowledge gap on the aetiology, risk factors, prognostic indicators and treatment of PPCM through a collection of observational and experimental studies.

There are several lessons to be learnt from our detailed family study of two cases with PPCM. First, we emphasise the need for family screening of PPCM and idiopathic DCM patients with long-term follow up of screened persons, particularly of females of child-bearing age. There is a need for well-structured incidence studies of PPCM and idiopathic DCM, with baseline echocardiograms of primary relatives (irrespective of symptoms), pre-pregnancy echocardiography of all women being followed-up (irrespective of underlying co-morbidities) and follow-up with echocardiography every 2-5 years. This exercise could mould routine practice, given: the high prevalence of familial DCM; its association with poor outcome; and the suggested benefits of treating asymptomatic relatives with LV dysfunction.

From a bench perspective, aside from the GWAS reported several years ago, the search for genetic abnormalities in PPCM has remained focused on screening for mutation (or SNP) associated with familial DCM. It is recommended that researchers expand on the reported GWAS by testing the clinical impact of the SNPs already suspected to be associated with PPCM. Until much larger studies can officiate the lack of harmful LMNA mutations in PPCM patients, information about the genotype in an individual from a PPCM family could still be useful for the clinician, especially when dealing with ‘‘pre-symptomatic’’ relatives unsure of their risk of developing DCM (Perrot et al, 2009). However, during such a search, one must be vigilant not to assume that identification of a single gene mutation is sufficient to explain FDCM; instead, it could greatly confound FDCM gene discovery using one-locus linkage analysis or candidate gene approach (Parks et al, 2009).

Given the high prevalence of FDCM amongst the PPCM patients in the study, the encouragement for more definitive identification of the underlying causative gene through whole-genome exome sequence couldn't be greater.

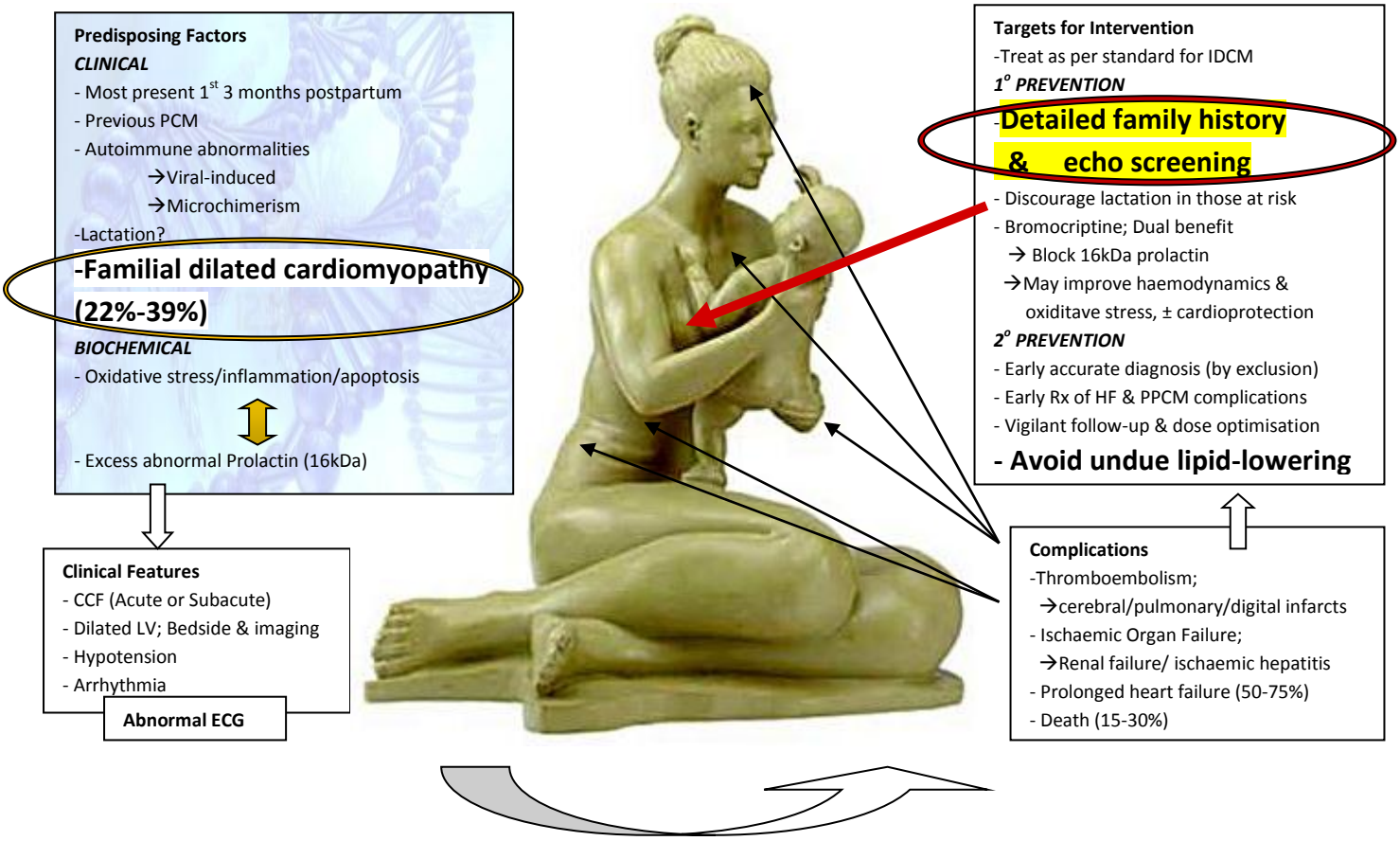
In exploring risk-factors at the bedside, the study on the use of ECG in the assessment of PPCM represents a unique study that will prove to be invaluable: in determining the future role of the 12-lead ECG as an inexpensive and simple 'rule-out' screening tool for PPCM; and perhaps as an important tool for increasing the intensity of subsequent treatment and management.

Overall, we found the majority (96%) of PPCM patients presented with 'abnormal' 12-lead ECGs, which improved significantly to 75% after the first six months of treatment. Over 80% of patients displayed either major abnormalities or minor variations using the Minnesota code. Of these, sinus tachycardia and QRS-axis deviation were most likely to be attenuated after six months. Even though these ECG abnormalities were mostly non-specific and similar to those of other dilated cardiomyopathies, this study further suggests the ECG may be useful in simple monitoring of clinical progress during treatment and prognostication. Specifically, the baseline presence of major T-wave and ST-segment abnormalities in the context of PPCM patients may place these patients at a similar risk of adverse outcomes to those with myocardial ischaemia. More definitive studies are required to determine if this simple and relatively inexpensive tool will be of particular clinical use in PPCM. Any progress in this regard would be welcome, given the persistently poor health outcomes associated with PPCM in resource-poor settings.

In addressing the treatment of PPCM, our ground-breaking proof-of-concept trial showed that the addition of Bromocriptine to standard heart failure therapy appeared to improve LVEF and a composite clinical outcome in women; although the number of patients studied was small and hence the results cannot be considered definitive. Larger-scale multi-centre and blinded studies are in

progress to test this strategy more robustly. Finally, regarding the prognostic indicators of PPCM, we have shown that larger LVESD and low total cholesterol were found to be associated with a composite poor outcome in a large cohort of African women with PPCM, while smaller LVESD and older age were found to be associated with a better chance of LV recovery. These results confirm and expand upon previous findings by this group and others and merit further investigation on potential pathophysiological mechanisms underlying these findings. **Figure 11** below summarises these findings together with those known for PPCM, and their contribution towards clinical features and the management of PPCM.

Figure 11. An illustration of the important aetio-pathogenic factors implicated in PPCM and their impact on clinical features and management



Although the studies towards this thesis have gone far in contributing to narrowing the knowledge gaps for PPCM, much still remains unsolved. Except for the trial of Bromocriptine, there are very few comparative observational studies on PPCM. Most literature, as with the group's other studies, comprises descriptive assessment of particular risk factors. It is be important to increase the number of comparative studies for these risk factors, including: direct comparison and clinical effect on the ECG and serum cholesterol levels in African women in the postpartum period; or the prevalence of a predominance of 16kDa Prolactin amongst healthy post-partum mothers as well as those at risk or known to have IDCM and FDCM. In addition to this, the paucity of data on the long-term outcome of PPCM, including patients with subsequent pregnancies, continues to limit many of the conclusions that one could draw from any such comparative study. It is thus highly recommended that long-term outcome data is pursued (for up to a decade of observation, if possible) in order to optimise our understanding of the risk factors, clinical characteristics and management of PPCM.

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7.0 Appendix

Appendix 1 – PPCM Consent Forms: Consent for PPCM Study (general) – Form 1a →Johannesburg

Form 1b →Cape Town

Consent for PPCM (Bromocriptine sub-study) → Form 1c

Appendix 2 – Genetics Consent Forms: Consent for PPCM Genetic Study – Form 2a →English

Form 2b →isiZulu

Appendix 3 – Data Collection Tools: Form 3a →Proposed Cardiomyopathy Registry of Africa

Form 3b →Echo-cardiography Form

Form 3c →The Minnesota Code

Appendix 4 - Ethical Approval: Ethical approval obtained - 4a →University of the Witwatersrand

4b → University of Cape Town

4c → Change of Title (Witwatersrand)

Appendix 5 - Documents advertising for PPCM patient recruitment: -5a → Poster (Johannesburg)

5b →Brochure (Johannesburg)

5c → Poster (Cape Town)

Appendix 6 – Cardiomyopathy Registry (electronic database): - 6a → One-page summary/guide

6b →Index of Data/Terminology

Appendix 7 - For Section 3.2.2 – Pedigrees of All Families Included in Final Analysis (N= 27):

<u>Appendix 1</u>. PPCM Consent Forms

Consent for PPCM Study (general) – Form 1a →Johannesburg

Familial Aggregation Study in Peripartum and Idiopathic Dilated Cardiomyopathy

Cardiac Clinic
E25 Groote Schuur Hospital
Observatory 7925
Tel: (021) 404-6361
Fax (021) 448-7062

Department of Cardiology
Chris Hani Baragwanath Hospital
Soweto, Johannesburg.
Tel: (011) 933-8197
Fax: (011) 938-8945

Informed Consent Form

I agree to participate in the study of genetic and environmental factors that may cause heart muscle disease (cardiomyopathy) either in the last month of pregnancy/ the first five month post-partum for postpartum cardiomyopathy (PCM) or otherwise for idiopathic dilated cardiomyopathy (DCM). I understand that I will be interviewed about my medical history, family history, social history and medications, and that my heart will be examined by an ultrasound scan and, if indicated, a nuclear medicine scan called the MUGA scan. In addition, I will have a blood sample drawn consisting of 12 tubes of blood. Most of this blood will be used to conduct routine tests for this heart condition, while 2 of the tubes will be used to test genetic factors that may increase the risk of heart muscle disease. Participation in this study will take about 90 minutes.

No extra visits will normally be required. However, if abnormalities are detected during the course of this study, I will be informed of the findings and referred to the appropriate health care team for further treatment.

I understand that my participation in this study is entirely voluntary. All information gathered in this study is strictly confidential, and will only be used for research relating to the heart diseases 'Peripartum Cardiomyopathy' and 'Idiopathic Dilated Cardiomyopathy' and their determinants. This information (including genetic material) will not be used to generate any profit. As well, genetic material will not be used for the purpose of gene alteration, and, prior to blood sampling, I will sign a separate DNA consent form that governs the use of genetic material under the rules of the University of Cape Town Research Ethics Committee.

I will not be identifiable in any published report. I understand that I am free to refuse to participate or withdraw from the study at any time, without jeopardising the future care of my relatives or myself. If I have any questions, I may contact Dr. Tibazarwa or Sister Mtshifulo at either of the address printed on the top of this page. Other investigators involved in this study that you may contact are Prof. K. Sliwa and Prof. B. Mayosi, reachable at the above two addresses, respectively.

I agree to participate in the study and I have been given a copy of this form.

_____	_____	_____
Subject name	Subject signature	Date
_____	_____	_____
(If necessary) Witness name	Witness signature	Date
_____	_____	_____
Investigator name	Investigator signature	Date

Consent for PPCM Study (general) – Form 1b →Cape Town

Familial Aggregation Study in Peripartum and Unexplained Dilated Cardiomyopathy
(Cape Town Cohort)

Cardiac Clinic
E25 Groote Schuur Hospital
Observatory 7925
Tel: (021) 404-6361
Fax⊗021) 448-7062

Department of Cardiology
Chris Hani Baragwanath Hospital
Soweto, Johannesburg.
Tel: (011) 933-8197
Fax: (011) 938-8945

Informed Consent Form

I agree to participate in the study of genetic and environmental factors that may cause heart muscle disease (cardiomyopathy) either in the last month of pregnancy/ the first five month post-partum for postpartum cardiomyopathy (PCM) or otherwise for idiopathic dilated cardiomyopathy (DCM). I understand that I will be interviewed about my medical history, family history, social history and medications, and that my heart will be examined by an ultrasound scan. In addition, I will have a blood sample drawn consisting of 5 tubes of blood. Most of this blood will be used to conduct routine tests for this heart condition, while 2 of the tubes will be used to test genetic factors that may increase the risk of heart muscle disease. Participation in this study will take about 90 minutes.

No extra visits will normally be required. However, if abnormalities are detected during the course of this study, I will be informed of the findings and referred to the appropriate health care team for further treatment.

I understand that my participation in this study is entirely voluntary. All information gathered in this study is strictly confidential, and will only be used for research relating to the heart diseases 'Peripartum Cardiomyopathy' and 'Idiopathic Dilated Cardiomyopathy' and their determinants. This information (including genetic material) will not be used to generate any profit. As well, genetic material will not be used for the purpose of gene alteration, and, prior to blood sampling, I will sign a separate DNA consent form that governs the use of genetic material under the rules of the University of Cape Town Research Ethics Committee.

I will not be identifiable in any published report. I understand that I am free to refuse to participate or withdraw from the study at any time, without jeopardising the future care of my relatives or myself. If I have any questions, I may contact Dr. Tibazarwa or Sister Ttshifularo at either of the address printed on the top of this page. Other investigators involved in this study that you may contact are Prof. K. Sliwa and Prof. B. Mayosi, reachable at the above two addresses, respectively.

I agree to participate in the study and I have been given a copy of this form.

_____	_____	_____
Subject name	Subject signature	Date
_____	_____	_____
(If necessary) Witness name	Witness signature	Date
_____	_____	_____
Investigator name	Investigator signature	Date

Consent for PPCM (Bromocriptine sub-study) → Form 1c

UNIVERSITY OF THE WITWATERSRAND
HUMAN RESEARCH ETHICS COMMITTEE

PATIENT INFORMATION LEAFLET AND INFORMED CONSENT

Each patient must receive, read and understand this document before any study-related procedure!

STUDY NUMBER:

STUDY TITLE: Prevention of irreversible left ventricular remodelling in patients with postpartum cardiomyopathy by addition of bromocriptine to standard heart failure therapy

SPONSOR: Soweto Cardiovascular Research Unit
Division of Cardiology
Chris Hani Baragwanath Hospital
Soweto 2013

INVESTIGATOR: Prof. Karen Sliwa-Hähnle,
Subinvestigators: Dr. Olaf Forster, Dr. Kemi Tibazarwa
Dr. L. Motsekuoa

INSTITUTION: Soweto Cardiovascular Research Unit
Division of Cardiology
Chris Hani Baragwanath Hospital
Soweto 2013

TIME AND DATE OF FIRST INFORMED CONSENT DISCUSSION:

Date (dd/mm/yyyy):

Time:

INTRODUCTION:

Good day, my name is Prof. Karen Sliwa-Hähnle / Dr. Olaf Forster/Dr. Tibazarwa. I am a Medical Doctor at the Division of Cardiology, Chris Hani Baragwanath Hospital. I would like to invite you participating in a research study, entitled "Prevention of irreversible left ventricular remodelling in patients with postpartum cardiomyopathy by addition of bromocriptine to standard heart failure therapy"

- Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any time. This information leaflet is to help you to decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study.
- If you have any questions, do not hesitate to ask me.
- You should not agree to take part unless you are satisfied about all the procedures involved.
- You may not participate in another medical research study, nor take any other investigational medicine during your participation in this study. You should not have participated in an investigational medicine research study within the past 30 days.
- Please be completely truthful with me regarding your health history, since you may otherwise harm yourself by participating in this study.
- If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.
- If you have a personal doctor, please discuss with or inform him/her of your possible participation in this study. If you wish, I can also notify your personal doctor in this regard.

PURPOSE OF THE STUDY:

- You have been diagnosed as suffering from peripartum cardiomyopathy and I would like you to consider taking part in the research of a new medicine called "bromocriptine".
- The purpose of this study is to determine the improvement of your cardiac function.
- This study will compare standard treatment for peripartum cardiomyopathy" plus placebo with standard treatment for peripartum cardiomyopathy" plus bromocriptine.

A placebo is an inactive substance and it does not contain any medicine. You will be randomly allocated to one or other treatment (i.e. like spinning a coin). Neither you nor I will know which treatment you are receiving during your participation in the study. This procedure helps to ensure that the information gathered during the study is accurate. In case of an emergency, it will however be possible to determine which treatment you have been receiving.

LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS:

- The study will be performed at the Division of Cardiology, Chris Hani Baragwanath Hospital
- 20 patients will participate in this study
- The patients will be between the ages of 18 and 50 years
- You will be required to come for follow up to Cardiac Clinic at Chris Hani Baragwanath Hospital once a month for a duration of 6 months after enrolment.

PROCEDURES:
If you agree to take part in this study, you will first be asked questions and examined to see if you qualify for this study. Before receiving your first dose of study medicine, I will examine you and draw several blood samples from you.

Screening Visit:
- History
- Physical examination
- Blood pressure measurement
- Echocardiography
- 6 minutes walking test

Baseline (enrolment) visit:
- Informed consent
- Physical examination
- ECG
- Blood pressure measurement by Dinamap
- Echocardiography
- MRI
- Routine blood tests10 ml (=2 teaspoons): Full blood count, urea & creatinine, liver function test, thyroid function test
- Special blood tests 15 ml (=3 teaspoons): Pro-inflammatory markers (hs-CRP), markers of re-modeling (MMP-2, MMP-3, MMP-9, TIMP-1, cathepsin D, PlGF and sFLT), cardiac function biomarkers (NT-proBNP, Fas/APO-1, oxLDL, ACE, angiotensin II) and hormones (Prolactin, estrogen).
- Randomisation / Study medication: After enrolment you will be randomly assigned to one of two forms of treatment. Both forms of treatment will include the standard medication for your condition "peripartum cardiomyopathy". For a period of 8 weeks, you will, in addition to standard medication, either receive the study drug bromocriptine or an inactive substance (placebo).

Follow-up visits 1, 2, 3, 4 and 5:
After enrolment, monthly visits will be scheduled for clinical assessments, echocardiography (if clinically indicated) and evaluation of medication compliance.

Final visit after 6 months of treatment:

- Physical examination
- ECG
- Blood pressure measurement by Dinamap
- Echocardiography
- MRI
- Routine blood tests10 ml (=2 teaspoons): Full blood count, urea & creatinine, liver function test, thyroid function test
- Special blood tests 15 ml (=3 teaspoons): Pro-inflammatory markers (hs-CRP), markers of re-modeling (MMP-2, MMP-3, MMP-9, TIMP-1, cathepsin D, PlGF and sFLT), cardiac function biomarkers (NT-proBNP, Fas/APO-1, oxLDL, ACE, angiotensin II) and hormones (Prolactin, estrogen).

Echocardiography will be taped on video and stored at the Soweto Cardiovascular Research Unit, Division of Cardiology at Chris Hani Baragwanath Hospital for further reference and audit purposes.

The blood samples will be analysed to determine the effect of the treatment you received on your peripartum cardiomyopathy and will help to find out the cause of peripartum cardiomyopathy. Echocardiography will be done to determine the effect of the treatment you received on the performance of your heart muscle.

WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

- Venipunctures (i.e. drawing of blood) are normally done as part of routine medica1 care and present a slight risk of discomfort. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. There is also a slight possibility of infection. Your protection is that experienced personnel perform the procedures under sterile conditions. A total of 50 ml of blood (i.e. 15 teaspoons) will be collected over the total period of 6 months.
- Echocardiography and cardiac MRI are diagnostic procedures in cardiology that allows the examiner to assess the function of your heart muscle. It does not pose any harm to the patient
  ECG (Electrocardiogram): This examination allows the doctor to determine the rhythm of your heart. It is a commonly used diagnostic procedure and does not pose any harm to the patient.

RISKS OF THE STUDY MEDICINE:

Bromocriptine is a drug that is registered and used in South Africa to suppress lactation after stillbirth or when breastfeeding is contra-indicated. Adverse effects of bromocriptine are nausea, postural hypotension and dizziness. Serious events, including hypertension, myocardial infarction, seizures and stroke may occur. Dyskinesia, hallucinations, confusion and behavioural disturbances are more common in patients receiving high doses for prolonged periods. Less frequent - urticaria and skin rashes, peptic ulceration, nasal stuffiness, visual disturbance, impotence and urinary retention may occur. Rare adverse effects include retroperitoneal fibrosis, pleural thickening and effusions and digital vasospasm.

UNFORSEEN RISKS:

The study medicine is investigational in the treatment of peripartum cardiomyopathy and there may be other risks or side effects which are unforeseen or unknown. You should immediately contact me if any side effects occur throughout your participation in this study.

BENEFITS:
The potential benefit from your participation in this study may be control of your peripartum cardiomyopathy. However, you may not benefit from this study. Your participation in this study will contribute to medical knowledge that may help other patients that, that like you, have "Peripartum Cardiomyopathy"

ALTERNATIVE TREATMENT:
- Alternative treatment in the form of standard treatment is used to treat peripartum cardiomyopathy.
- If you decide not to take part in this study you will still receive the best current care, from your usual doctor; this may or may not include the study medicine.

BENEFITS AND RISKS OF STANDARD ALTERNATIVE TREATMENT:
Participating in the study you will always receive standard treatment. Some patients will additionally receive the new treatment "bromocriptine", some will receive a placebo.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS STUDY?
You should not participate in the study if you have any of the following:
- Allergy to ergot alkaloids
- Uncontrolled hypertension or severe cardiovascular disease
- Psychotic disorders
- Parkinsonism with dementia
- Compromised cerebral circulation
- Ischaemic heart disease
- Liver disease
- History of peptic ulcers.

Due to your diagnosis "Peripartum Cardiomyopathy" you should not fall pregnant again. Therefore effective contraception is strongly recommended.

INTERACTIONS:
It is important that you let me know of any medicines (both prescriptions and over-the-counter medicines), alcohol or other substances that you are currently taking.

RIGHTS AS A PARTICIPANT IN THIS STUDY:
- Voluntary: Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your access to medical care at our Clinic. In fact you will receive standard medical therapy as clinically indicated.
- Discontinuation of study treatment: You must inform me if you wish to stop taking your study medicine. I will supervise any discontinuation with your health as the first priority.
- New findings: I will provide you with any additional information that becomes available during the study, which may affect your willingness to continue on the study

WITHDRAWAL FROM THIS STUDY:
- Your withdrawal will not affect your access to medical care at our Clinic. In fact you will receive standard medical therapy as clinically indicated.
- I retain the right to withdraw you from the study if it is considered to be in your best interest. If your participation is ended early, you may be asked to return for study-ending tests and procedures for your safety.

- If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you may be withdrawn from the study at any time.
- Pregnancy: Peripartum cardiomyopathy is defined as a cardiomyopathy without any other attributable cause in the period of one month antepartum to 5 months postpartum. Pregnancy is therefore no defined reason for withdrawal from the study.

EMERGENCY CARE AND HOSPITALISATION:
If you seek emergency care or if hospitalisation is required at any time during the study, please inform the treating doctor that you are/were enrolled in this research study and that you are diagnosed with "Peripartum Cardiomyopathy". Please ask the treating doctor to inform me about your condition.

FINANCIAL ARRANGEMENTS:
- The Soweto Cardiovascular Research Unit, Division of Cardiology, Chris Hani Baragwanath Hospital will provide payment for all study procedures and reasonable medical expenses that you may incur as a direct result of this study as determined by the Soweto Cardiovascular Research Unit, Division of Cardiology, Chris Hani Baragwanath Hospital.
- Neither you nor your medical scheme will be expected to pay for any study medication, study related visit or study procedures.

REIMBURSEMENT FOR STUDY PARTICIPATION:
You will not be paid to participate in this study but your transport costs will be reimbursed adequately.

ABPI STATEMENT ON COMPENSATION:
All patients enrolled in this study are public hospital patients at Chris Hani Baragwanath Hospital. No specific sponsor exists for this study. It is an investigator driven study.

ETHICAL APPROVAL:
- This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee.
- The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2000), which deals with the recommendations guiding doctors in biomedical research involving human subjects. A copy may be obtained from me should you wish to review it.

SOURCE OF ADDITIONAL INFORMATION:
- For the duration of the study, you will be under the care of Dr. Olaf Forster. If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact me.
  Doctors from the Soweto Cardiovascular Research Unit, Division of Cardiology who are working on this study are:

Professor Karen Sliwa-Hähnle	083-457-4823
Dr. Olaf Förster	082-555-9859
Dr. Kemi Tibazarwa	011 9338197
Dr. Lerato Motsekuoa	011 9338197

  They can be contacted at the above 24 hour telephone numbers.
- If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Cleaton-Jones,

Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at the following number: 011-717-2229

- For research information you can contact Prof Huddle, Head of Department of Medicine, Chris Hani Baragwanath Hospital on 011-933-8940
- South African Medicines Control Council: If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

  The Registrar
  SA Medicines Control Council
  Department of Health
  Private Bag X828
  Pretoria 0001
  Fax: 012-323-4474
  e-mail: labusa@health.gov.za

CONFIDENTIALITY:

- All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.
- This information will be reviewed by authorised representatives of the Soweto Cardiovascular Research Unit, Division of Cardiology, Chris Hani Baragwanath Hospital.

The information might also be inspected by the University of the Witwatersrand. Human Research Ethics Committee (HREC), the South African Medicines Control Council (MCC), as well as your personal doctor. Therefore, you hereby authorise me to release your medical records to the Department of Cardiology, Chris Hani Baragwanath Hospital, its employees or agents, domestic and foreign regulatory health authorities, the South African Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC). These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.
Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorised state agency.

PERSONAL DOCTOR / SPECIALIST NOTIFICATION OPTION:
Please indicate below, whether you want me to notify your personal doctor or your specialist of your participation in this study:

( ) Yes, I want you to inform my personal doctor / specialist of my participation in this study.
( ) No, I do not want you to inform my personal doctor / specialist of my participation in this study
( ) I do not have a personal doctor / specialist

INFORMED CONSENT:

I hereby confirm that I have been informed by the study doctor, Dr. Olaf Forster / Prof Karen Sliwa-Hähnle/Dr. Kemi Tibazarwa/Dr. Lerato Motsekuoa, about the nature, conduct, benefits and risks of the clinical study "Prevention of irreversible left ventricular remodelling in patients with postpartum cardiomyopathy by addition of bromocriptine to standard heart failure therapy", protocol number 123456.

- I have also received, read and understood the above written information (Patient Information leaflet and Informed Consent) regarding this clinical study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the Soweto Cardiovascular Research Unit, Division of Cardiology, Chris Hani Baragwanath Hospital or on its behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and of my own free will declare myself prepared to participate in the study.

Patient: _____

Printed Name Signature/Mark/Thumbprint Date and Time

I, Prof. Karen Sliwa-Hähnle / Dr. Olaf Forster/Dr. Kemi Tibazarwa/Dr. Lerato Motsekuoa, herewith confirm that the above patient has been fully informed about the nature, conduct and risks of the above study.

Study Doctor: _____

Printed Name Signature Date and Time

Study nurse/translator/other person explaining Informed Consent (Designation):

_____

Printed Name Signature Date and Time

Witness (if applicable):

_____

Printed Name Signature Date and Time

<u>Appendix 2</u>. Genetics Consent Forms

Consent for PPCM Genetic Study – Form 2a →English

REQUEST FOR MOLECULAR STUDIES (DNA)

Molecular Laboratory
Division of Human Genetics
1st Floor, Anatomy Building
UCT Medical School, Observatory 7925

Tel: (021) 406 6425 Fax: (021) 448-0906

Blood should be drawn in 2 plastic EDTA Tubes (Purple top) +/- 10ml each using a yellow barrel.
Each tube should be inverted to mix and should be clearly labelled with the patient's name and DOB
Keep blood in fridge at 4°C until able to send to laboratory

Please DO NOT send specimens on ice or frozen.

Please fill in all the information requested:

Surname:_____First Name(s):_____

New Family: Yes ☐ No ☐ (If no, please fill in family name) Family name: _____

Medical Aid: _____Medical Aid No: _____

Sex: M ☐ F ☐ Date of Birth: Year:_____ Month:_____ Day: _____

Number of children: _____

Ethnic Origin : (please indicate ancestry of both your mother and father)_____

Contact Address: _____ Town: _____ Fax: Tel: _____

Referring Doctor/Sister: _____ Town: _____ Fax: Tel: _____

Hospital or Address: _____ Town: _____ Fax: Tel: _____

Reason for Referral (Clinical diagnosis):

Affected ☐ At Risk ☐ Carrier ☐ Spouse ☐ Query ☐ Unaffected ☐

ARVC	☐	Hypertrophic Cardiomyopathy	☐	Other Cardiomyopathy	☐
Dilated Cardiomyopathy	☐	HIV Cardiomyopathy	☐	Duchenne Muscular Dystrophy	☐
Peripartum Cardiomyopathy	☐	Restrictive Cardiomyopathy	☐	Hypertension	☐

Additional disorders (apparent or previously treated): _____

Additional family history _____

Clinical Details:

Physical disability ☐ Mental retardation ☐ Deafness ☐ Impaired vision ☐ Night blindness ☐

Other: _____

Have samples from this patient been sent to a DNA lab before? (DELETE WHERE NOT APPLICABLE) YES / NO / Don't Know

If Yes, where: _____

For Laboratory use only:

DNA number: _____ *Vol.Blood:* _____*(ml)* *Other:* _____

Date Received: Year: _____ *Month:* _____ *Day:* _____ *Computer Index No:*_____

CONSENT FOR DNA ANALYSIS AND STORAGE

1. I, _____ , request that an attempt be made using genetic material to assess the probability that: I / my child / my unborn child (DELETE WHERE NOT APPLICABLE) might have inherited a disease-causing mutation in the gene for:_____

2. I understand that the genetic material for analysis is to be obtained from: blood cells/skin sample/other (specify) (DELETE WHERE NOT APPLICABLE) :

3. I request that **no** portion of the sample be stored for later use. ☐ **(**MARK IF APPLICABLE)
   Or
   I request that a portion of the sample be stored indefinitely for (DELETE WHERE NOT APPLICABLE):
   (a) possible re-analysis
   (b) analysis for the benefit of members of my immediate family
   (c) research purposes, subject to the approval of the University of Cape Town Research Ethics Committee, provided that any information from such research will remain confidential.

4. The results of the analysis carried out on this sample of stored biological material will be made known to me, via my doctor, in accordance with the relevant protocol, if and when available.
   In addition, I authorise that they may be made known to: (DELETE WHERE NOT APPLICABLE) :
   other doctors involved in my care
   the following family members: _____
   other: _____

5. I authorise / do not authorise my doctor(s) (DELETE WHERE NOT APPLICABLE) to provide relevant clinical details to the Division of Human Genetics, UCT.

6. I have been informed that:
   (a) there are risks and benefits associated with genetic analysis and storage of biological material and these have been explained to me.
   (b) the analysis procedure is specific to the genetic condition mentioned above and cannot determine the complete genetic makeup of an individual.
   (c) the genetics laboratory is under an obligation to respect medical confidentiality .
   (d) genetic analysis may not be informative for some families or family members.
   (e) even under the best conditions, current technology of this type is not perfect and could lead to incorrect results.
   (f) where biological material is used for research purposes, there may be no direct benefit to me.

7. I understand that I may withdraw my consent for any aspect of the above at any time without this affecting my future medical care.

8. **ALL OF THE ABOVE HAS BEEN EXPLAINED TO ME IN A LANGUAGE THAT I UNDERSTAND AND MY QUESTIONS ANSWERED BY:**

_____ DATE: _____

Patient signature _____ **Witnessed consent** _____

NOTE - PLEASE INSERT A FAMILY PEDIGREE DRAWING ON THE REVERSE OF THIS FORM

Consent for PPCM Genetic Study – Form 2b →isiZulu

REQUEST FOR MOLECULAR STUDIES (DNA)

Molecular Laboratory
Division of Human Genetics
1st Floor, Anatomy Building
UCT Medical School, Observatory 7925

Tel: (021) 406 6425 Fax: (021) 448-0906

Blood should be drawn in 2 plastic EDTA Tubes
(Purple top) +/- 10ml each using a yellow barrel.
Each tube should be inverted to mix and should be clearly labelled with the patient's name and DOB
Keep blood in fridge at 4°C until able to send to laboratory

Please DO NOT send specimens on ice or frozen.

Please fill in all the information requested:

Surname:_____First Name(s):_____

New Family: Yes ☐ No ☐ (If no, please fill in family name) Family name: _____

Medical Aid: _____Medical Aid No: _____

Sex: M ☐ F ☐ Date of Birth: Year:_____ Month:_____ Day: _____

Number of children: _____

Ethnic Origin : (please indicate ancestry of both your mother and father)_____

Contact Address: _____ Town: _____ Fax: Tel: _____

Referring Doctor/Sister: _____ Town: _____ Fax: Tel: _____

Hospital or Address: _____ Town: _____ Fax: Tel: _____

Reason for Referral (Clinical diagnosis):

Affected ☐ At Risk ☐ Carrier ☐ Spouse ☐ Query ☐ Unaffected ☐

ARVC	☐	Hypertrophic Cardiomyopathy	☐	Other Cardiomyopathy	☐
Dilated Cardiomyopathy	☐	HIV Cardiomyopathy	☐	Duchenne Muscular Dystrophy	☐
Peripartum Cardiomyopathy	☐	Restrictive Cardiomyopathy	☐	Hypertension	☐

Additional disorders (apparent or previously treated): _____

Additional family history _____

Clinical Details:

Physical disability ☐ Mental retardation ☐ Deafness ☐ Impaired vision ☐ Night blindness ☐

Other: _____

Have samples from this patient been sent to a DNA lab before? (DELETE WHERE NOT APPLICABLE) YES / NO / Don't Know

If Yes, where: _____

For Laboratory use only:

DNA number: _____ *Vol.Blood:* _____*(ml)* *Other:* _____

Date Received: Year: _____ *Month:* _____ *Day:* _____ *Computer Index No:*_____

CONSENT FOR DNA ANALYSIS AND STORAGE

IMVUMO YE DNA ANALYSIS NOKUGCINWA KWAYO

1. Mina ……,ngicela kuzanywe ukuthi kusetshenziswe lokhu okuphathelene neDNA, kubhekisiswe ukuthi kungenzeka ukuthi mina / ingane yami / ingane yami engakabelethwa (susa okungaqondene) kungahle kwenzeke ukuthi kutholwe isifo esitholakala ngofuzo, esibanga uguquko kholokhu okuqala ofuzo kwisifo se :…….

2. Ngiyaqonda ukuthi lokhu okuzohlolwa kuzotholakala: kwigazi / isampuli yesi khumba / nokunye (ohaza) (susa okungaqondene) :

3. Ngicela kungabikho ucezu lwe sampule elizogcinwa ukuze lusetshenziswe esikhathini esizayo. (cikica ngokufanele)

   Noma

4. Ngicela ucezu lwesampule luqcinnwe isikhashana noma singaphi ukuze lusetshenziswe (SUSA OKUNGAQONDENE)
   (a) uma kungenzeka lihlaziwe
   (b) kuhlaziyo oluzoba uncedo kumndeni wami
   (c) kucwaningo (Research) ngemvume ye University of Cape Town Research Ethics Committee (ikomiti emele ucwaningo ngokomthetho, uma nje umbiko uzokubayimifihlo.

5. Umbiko wohlaziyo olwenziwe ngamasampule ngizokwaziswa ngawo ngudokotela wami, ngendlela efanelekile yomgimo, uma noma usukhona. Futhi, nginikenza imvume ukuthikutshelwe:

(SUSA OKUNGAQONDENE):
udokotela ongilaphayo
umndeni wami : _____
abanye :_____

6. Nginikeza imvume\ anginikezi imvume udokotela noma odokotela (SUSA OKUNGAQONDENE) ukuthi kunikezwe ngemininingwane ephathelene nempilo yami kwi Division of Human Gentics, UCT.

Ngitsheliwe ukuthi :
   (a) kungaba nengozi futhi kungaba noncedo oluhambisana naloluhlahlubo nokugcinwa kwalokhu okuphathelene nako ngachazelwa futhi.
   (b) Indlela okuqhutshwa ngayo kuloluhlahlubo oluqondene nofuzo osluchaziwe ngenhla, ngeke lukhombe ufuzo lonke lwendalo yomuntu.
   (c) I Genetics Laboratory ingaphansi kwesibopho sokuhlonipha imfihlo yokwelapha.
   (d) loluhlahlubo kungenzeka lungachazi lutho kweminye imindeni nezihlobo.
   (e) noma ngabe ubuchwephesha kwesanyensi yaluphi uhlobo , kungenzeka imiphumela ingabi yiqiniso.
   (f) Angizukuba namvuzo kukho konke okuphathelene nesayensi yaloluhlahlubo

a)

Ngiyaqonda ukuthi ngingayihlehlisa imvume emayelana naluphi uhlobo olungenhla noma inini, ngaphandle kokuthinteka kokulashwa kwami esikhathini esizayo

Konke okungenhla ngichazelwe ngakho ngolwimi engilizwayo futhi ngiphenduliwe imibuzo, ngu:
_____ DATE_____

Igama lomguli (sayina _____ Igama lofakazi _____
NOTE PLEASE INSERT A FAMILY PEDIGREE DRAWING ON THE REVERSE OF THIS FORM.

Patient signature _____ **Witnessed consent** _____

NOTE - PLEASE INSERT A FAMILY PEDIGREE DRAWING ON THE REVERSE OF THIS FORM

<u>Appendix 3</u>. Data Collection Tools

Form 3a →Proposed Cardiomyopathy Registry of Africa

Cardiomyopathy Questionnaire

(DCM Study)

- Patient Information

1. Last Name_____
2. First Name_____
3. Date of Birth (dd/mm/yr)_____
4. Sex 1) Male 2) Female
5. Education (1) No Schooling (2) Primary (3) Secondary (4)Post Secondary
6. Occupation

   (1) Formal Employment: **a**.Skilled (Professional) **b**.Skilled (otherwise) **c**.Unskilled

   (2) Informal Employment : **a**.Skilled **b**.Unskilled [specify_____]

   (3) Unemployed
7. Marital status (1) Married (2) Single (3)Divorced/Separated (4)Co-habiting
8. National ID Number_____
9. Nationality_____
10. Home language____ 1=English 2=Afrikaans 3=Xhosa 4=Zulu 5=Sutu 6=Tshangani 7=Other
11. Hospital number_____
12. Date of enrollment_ (dd/mm/yyyy)_____
13. Address – a) home _____ - b) postal_____
14. Address- work_____
15. Telephone number – a) home _____ – b) work_____
16. Cell phone number_____
17. Email address_____
18. Height (metres)_____
19. Weight (kg)_____
20. BMI (kg/m^2)_____

– Referring Physician Information

Last Name_____

First Name_____

Name of Hospital/ Health facility_____

Address_____

City_____

Province/State_____

Phone – work_____

Cellular phone number_____

- HISTORY

Date of first diagnosis of cardiomyopathy (dd/mm/yy)
Date of earliest symptoms (dd/mm/yy)
Presenting complaints

- Present NYHA Functional Class: (1) I (2) II (3) III (4) IV
- Palpitations (0) No (1) Yes
- Dizziness
- Syncope
- Chest pain
- Leg swelling
- Cardiac arrest
- Other complaints _____

Date of first hospitalization for treatment or diagnosis of cardiomyopathy (dd/mm/yyyy)

Past medical history

	Specify	(0) No (1) Yes
• Blood transfusion	_____	
• Cardiovascular	_____	
• Pulmonary	_____	
• Gastrointestinal	_____	
• Renal	_____	
• Endocrine	_____	
• Dermatological	_____	
• Haematological	_____	
• Neuromuscular/skeletal	_____	
• Gynaecological	_____	
• Liver	_____	
• Ophthalmic	_____	
• ENT	_____	
• Repeated infections	_____	
• Flu-like illness	_____	

Obstetrics & Gynaecological history

- Last menstrual period (dd/mm/yyyy)_____
- Date of last delivery (dd/mm/yyyy)_____
- Any suggestion of amniotic fluid embolism in any pregnancy? (0) No (1) Yes

Family history

- Family history of heart disease (0) No (1) Yes
- Type of heart disease _____
- Family history of sudden death (0) No (1) Yes
- Number of sudden deaths in family members <35yrs old _____

Name	Relationship	Arrhythmic Events	Cardiomyopathy Diagnosed
1._____	_____	_____	_____
2._____	_____	_____	_____
3. ._____	_____	_____	_____

Social history

- Smoking (0) No (1) Yes
  - pack years _____
- Alcohol intake (0) No (1) Yes
  - Quantity_____
  - Quantity/week_____

Medications	Dose (mg)	Date started (dd/mm/yr)
_____	_____	_____
_____	_____	_____
_____	____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Sports participation
Prior level of participation in sports **before** diagnosis of Cardiomyopathy
(1) Inactive (2) Recreational (3) Competitive/Professional (4) Unknown

Prior level of participation in sports **after** diagnosis of Cardiomyopathy
(1) Inactive (2) Recreational (3) Competitive/Professional (4) Unknown

Sports practiced most often (0) No (1) Yes

- Rugby
- Soccer
- Baseball
- Basketball
- Hockey
- Cricket
- Tennis
- Running
- Biking
- Swimming
- Surfing
- Other _____

Family Tree

Physical examination and signs

(0) Absent (1) Present

- Pitting oedema of the legs
- Blood pressure (mmHg) _____
- Raised JVP
- Pulse
  - Rate _____
  - Character_____
- Heart sounds
  - S3
  - S4
  - Gallop rhythm
- Murmur
  - Systolic
  - Diastolic
  - Location _____
  - Grade _____
  - Timing _____
  - Character _____
- Basal crepitations
- Tender hepatomegaly
- Ascites
- Proximal muscle weakness
- Deep tendon reflexes (1=normal or 2=abnormal)
- Gait disturbance

Chest X Ray

Cardiothoracic ratio_____

Lung fields (0) Normal (2) Congested

Left atrial enlargement (0) No (1) Yes

Right ventricular enlargement (0) No (1) Yes

- ECG

Standard measurements (25mm/sec)

(0) Done (1) Not done

Date (dd/mm/yyyy)

- Ventricular rate (beats/min) _____
- Baseline rhythm
  - (1) Sinus rhythm
  - (2) Junctional
  - (3) Sinus arrhythmia
  - (4) Sinus pause > 1.2sec (abrupt pause)
  - (5) Pacemaker (mode) _____
  - (6) Other _____
- PR interval (ms) _____
- QRS axis _____
- ST depression(leads) _____
- ST elevation (leads) _____
- T wave inversion (depth in mm) _____
- Abnormal Q waves (0) No (1) Yes
- QT Interval(ms) _____
- QTc (ms) _____
- QT dispersion _____
- Left atrial enlargement (0) No (1) Yes
- Right atrial enlargement(0) No (1) Yes
- QRS morphology (0) Normal (1) Delta wave (2) RBBB (3) LBBB) (4) LAH (5) LPH (6) RBBB + LAH or LPH
- Arrhythmias
  - (1) None
  - (2) Atrial flutter
  - (3) Atrial fibrillation
  - (4) Supraventricular tachycardia
  - (5) Ventricular ectopy
  - (6) Non-sustained ventricular tachycardia (3-10 consecutive beats)
  - (7) Sustained ventricular tachycardia (> 10 consecutive beats)
  - (8) Torsade de Pointes
  - (6) Ventricular fibrillation

2. PVC morphology
   (0) No PVC (1) RBBB
   (2) LBBB (4)Both RBBB and LBBB (5) Indeterminate

- Others _____
- Heart block
  - (0)None
  - (1)1st degree
  - (2)2nd degree_____
  - (3)3rd degree block
- Presence of epsilon wave 0) No (1) Yes

- LVH
    - Sokolow-Lyon 0) No (1) Yes
    - Cornell voltage 0) No (1) Yes

- ECHOCARDIOGRAPHY

(0) Done (1) Not done

Date (dd/mm/yy) _____
Heart rate (b/min) _____
Left atrial diameter (cm) _____
Aortic root diameter (cm)
Left ventricle
IVSTd (cm)
PTWd (cm)
IVSTd/ PTWd ratio
LVEDD (cm)
LVESD (cm)
FS (%)
EF (%)
EPSS (cm)
SAM at rest: (0) No (1) Yes

Short axis view
Prominent LV trabeculation and deep intratrabecular recesses-Apical level (0) No (1) Yes
Colour flow in recesses (0) No (1) Yes
Ratio of noncompacted/compacted >2 (0) No (1) Yes
LV wall motion (Global) (1) Normal (2) Mildly reduced (3) Severely reduced

Regional LV Wall Motion
(0) Normal (1) diastolic bulge (2) Mild hypokinesia (3) Severe hypokinesia (4)Akinesia
(5) Dyskinesia (aneurysms) (6) LV thinning

Septal ____
Anterior_____
Posterolateral_____
Inferior_____
Apical_____

Mitral Valve Prolapse (1) None (2) Mild (3) Moderate (4) Severe

Right ventricle
Right ventricular outflow tract (RVOT) (cm) _____
Ratio of RVOT/Aortic valve _____

Dilated RA (0) No (1) Yes
Valve lesions (0) No (1) Yes
Specify valve_____options 1=tricuspid 2=pulmonary

Doppler studies
Left ventricular outflow tract (LVOT) Velocity (m/s)
LVOT pressure gradient at rest (continous wave)
Aortic velocity
Right ventricular pressure in systole (RVPs) (mmHg):

Colour flow
Presence of regurgitation (0) No (1) Yes
(Grade1-4, use 0 if not present)Mitral regurgitation grade _____
Aortic regurgitation grade _____
Tricuspid regurgitation grade _____
Pulmonary regurgitation grade _____

Diastolic function

1. *Using pulsed wave Doppler*
Mitral E wave (m/s) _____
Mitral A wave (m/s) _____
Mitral E/A Ratio _____
Deceleration time (ms) _____

Tricuspid E wave (m/s) _____
Tricuspid A wave (m/s) _____
Tricuspid E/A Ratio _____
Deceleration time (ms) _____

2. *Using tissue Doppler imaging*
LV (lateral annulus)
Systolic myocardial velocity (Sm) (m/s) ___
E wave (m/s) _____
A wave (m/s) _____
E/A ratio _____
LV (medial annulus)
Systolic myocardial velocity (Sm) (m/s) ___
E wave (m/s) _____
A wave (m/s) _____
E/A ratio _____

Presence of pericardial effusion (0) no (1) Yes
Presence of mural thrombus (0) none (1) Yes
RA _____
RV_____
LA _____
LV _____

- Cardiac catheterization

(0) Done (1) Not done

Date (dd/mm/yy)

Left Ventricle

Dilated LV (0) No (1) Yes

LV global function (1) Normal (2) Mildly reduced (3) Severely reduced

LV regional wall motion abnormalities

(1) Normal (2) Diastolic bulge (3) Mild hypokinesia (4) Severe hypokinesia
(5) Akinesia (6) Dyskinesia (aneurysms) (7) Unknown

Septal
Anterior
Posterior Submitral
Inferior
Apical

Mitral regurgitation grade (1-4, use 0 if not present) (5) Prolapse

LV Measurements

LVEDV (ml)
LVESV (ml)
LVEF (%)
LV systolic pressure (mmHg)
LV diastolic pressure (mmHg)
LVEDP (mmHg)
Aortic pressure (mmHg)
LV systolic gradient

Right Ventricle

Dilated RV (0) No (1) Yes

RV global function (1) Normal (2) Mildly reduced (3) Severely reduced

RV Abnormalities- Morphology

(0) Normal (1) Scalloped contours (series of sacs or pouches) (2) Trabecular traverse deep fissure (3) Trabecular hypertrophy (>4mm) (4) Aneurysm (5) Unknown

RVOT
Anteroseptal free wall
Subtricuspid posterobasal
Apical

RV regional wall motion abnormalities

(1) Normal (2) Diastolic bulge (3) Mild hypokinesia (4) Severe hypokinesia
(5) Akinesia (6) Dyskinesia (aneurysms) (7) Unknown

RVOT
Anteroseptal free wall
Subtricuspid posterobasal
Apical

RV Measurements
RVEDV (ml)
RVESV (ml)
RVEF (%)
Pulmonary artery pressure mean (mmHg)
RA pressure (mmHg)
RVEDP (mmHg)
Pulmonary capillary wedge pressure (mmHg)
Tricuspid regurgitation grade (1-4, use 0 if not present)
Tricuspid valve prolapse

Coronary angiography
Dominance (1) Right (2) Left (3) Balanced
Presence of coronary artery obstruction (0) No (1) Yes
Percentage of obstruction _____
Location of Stenosis (1) LMCA (2) LAD (3) LCx (4) RCA

BLOOD TEST RESULTS

	(0) Done (1) Not done	(0) Done (1) Not done
Haemoglobin (g/dl)		
White cell count		
MCV (fl)		
Platelet count		
Random blood sugar (mmol)		
Serum sodium (mmol/l)		
Potassium (mmol/l)		
Chloride (mmol/l)		
Urea (mmol/l)_____		
Creatinine (µmol/l)		
Bilirubin (µmol/l)		
Alanine transferase (ALT) (U/l)		
Aspartate transferase(AST) (U/l)		
Albumin (g/dl)		
Total protein (g/dL)_____		
GGT		
ESR in 1 Hr		
C-reactive protein (mg/dl)		
Pro-BNP		
Total Cholesterol (mmol/l)		
HDL (mmol/l)		
TG (mmol/l)		
LDL (mmol/l)		
TSH (mIU/l)		
fT3 (pmol/l)		
fT4 (pmol/l)		

HIV screening _____ HIV confirmatory test _____

GENETIC TESTING

(0) Done (1) Not done

Chromosomal location
Genes identified
Other _____

– Diagnosis

Suspected diagnosis
Final diagnosis
Other_____

- FOLLOW – UP

Follow –up number _____
Date of follow –up _____(dd/mm/yyyy)
Type of follow –up (1) Regularly scheduled follow up (2) unscheduled (3) lost to follow up

Presenting complaints _____
_____
Events since last follow up (1) No (2) Yes
Details of Event _____

Current Medications

Drug name	Total daily Dose (mg)
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Surgery (1) No (2) Yes
Type of surgery_____
Pacemaker insertion (1) No (2) Yes
Date of Insertion (dd/mm/yr)
Type of pacemaker _____
ICD implantation (1) No (2) Yes
Date of Insertion (dd/mm/yr)
Catheter ablation (1) No (2) Yes
Date performed dd/mm/yr
Indication _____

TERMINAL EVENTS

Cardiac death (1) No (2) Yes (3) Unknown
Sudden death (1) No (2) Yes (3) Unknown
Heart failure (1) No (2) Yes (3) Unknown
Non cardiac death (1) No (2) Yes (3) Unknown
Details _____
_____

AUTOPSY (1) No (2) Yes (3) Unknown
Results _____
_____

_____
_____

Form 3b →Echocardiography Form

Echocardiography Report Form (Courtesy of Groote Schuur Hospital)

PD390 **ECHOCARDIOGRAPHY REPORT**

DATE: DD / MM / YYYY

WARD/DEPT: _____

NAME: _____ **DIAGNOSIS:** _____

I.D.: _____ _____

DOB: _____ **Sex :** _____ **RECORDING NO:** _____

HEIGHT_____(cm) **WEIGHT**_____(Kg) **BSA**_____(m^2)

LEFT VENTRICULAR STUDY					**AORTIC VALVE STUDY**		
	DIASTOLIC		SYSTOLIC				
RVW		cm (-)		cm	AORTA (2-3.8)		cm
RVID		cm (2.8)		cm	L.A. (2-4)		cm
IVS		cm (0.5-1.3)		cm	PEAK GRADIENT		mmHg
LVID		cm (3-5.3)		cm	MEAN GRADIENT		mmHg
LVPW		cm (0.8-1.2)		cm	PEAK VELOCITY		m/Sec
					PRESSURE HALFTIME		m/Sec
SHORTENING FRACTION			% (24 - 41)				
EJECTION FRACTION			%				

MITRAL VALVE STUDY			**TRICUSPID VALVE STUDY**		
D.E.		cm	REGURG. VELOCITY		m/Sec
E-F		cm/Sec	RV SYSTEM PRESS.		mmHg + JVP
MITRAL VALVE AREA		cm^2			
PEAK E. VELOCITY		m/Sec			
PEAK A. VELOCITY		m/Sec	**PULMONARY VALVE STUDY**		
E:A RATIO			PEAK VELOCITY		m/Sec
MEAN GRADIENT		mmHg	PEAK GRADIENT		mmHg
PRESSURE HALFTIME		m/Sec			
MV DECT		m/Sec			
TDI					
LATERAL Ea VELOCITY		cm/Sec			
LATERAL Sa VELOCITY		cm/Sec			
PW/TDI E/Ea RATIO					

REPORT	
OPERATOR:	**CONSULTANT:**

Form 3c →The Minnesota Code

The Minnesota Code Classification System† for Electrocardiographic Findings

Q and QS Patterns

(Do not code in the presence of WPW code 6-4-1.) To qualify as a Q- or QS-wave, the deflection should be at least 0.1 mV (1 mm in amplitude).

Anterolateral site (leads I, aVL, V_6)

1-1-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.03 sec in lead I or V_6.

1-1-2 Q duration ≥ 0.04 sec in lead I or V_6.

1-1-3 Q duration ≥ 0.04 sec, plus R amplitude ≥ 3 mm in lead aVL.

1-2-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead I or V_6.

1-2-2 Q duration ≥ 0.03 sec and < 0.04 sec in lead I or V_6.

1-2-3 QS pattern in lead I. Do not code in the presence of 7-1-1.

1-2-8 Initial R amplitude decreasing to 2 mm or less in every beat (and absence of codes 3-2, 7-1-1, 7-2-1, or 7-3 between V_5 and V_6. (All beats in lead V_5 must have an initial R > 2 mm.)

1-3-1 Q/R amplitude ratio ≥ 1/5 and < 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead I or V_6.

1-3-3 Q duration ≥ 0.03 sec and < 0.04 sec, plus R amplitude ≥ 3 mm in lead aVL.

Posterior (inferior) site (leads II, III, aVF)

1-1-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.03 sec in lead II.

1-1-2 Q duration ≥ 0.04 sec in lead II.

1-1-4 Q duration ≥ 0.05 sec in lead III, plus a Q-wave amplitude ≥ 1.0 mm in the majority of beats in lead aVF.

1-1-5 Q duration ≥ 0.05 sec in lead aVF.

1-2-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead II.

1-2-2 Q duration ≥ 0.03 sec and < 0.04 sec in lead II.

1-2-3 QS pattern in lead II. Do not code in the presence of 7-1-1.

1-2-4 Q duration ≥ 0.04 sec and < 0.05 sec in lead III, plus a Q-wave ≥ 1.0 mm amplitude in the majority of beats in aVF.

1-2-5 Q duration ≥ 0.04 sec and < 0.05 sec in lead aVF.

1-2-6 Q amplitude ≥ 5.0 mm in leads III or aVF.

1-3-1 Q/R amplitude ratio ≥ 1/5 and < 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead II.

1-3-4 Q duration ≥ 0.03 sec and < 0.04 sec in lead III, plus a Q-wave ≥ 1.0 mm amplitude in the majority of beats in lead aVF.

1-3-5 Q duration ≥ 0.03 sec and < 0.04 sec in lead aVF.

1-3-6 QS pattern in each of leads III and aVF. (Do not code in the presence of 7-1-1.)

Anterior site (leads V_1, V_2, V_3, V_4, V_5)

1-1-1 Q/R amplitude ratio ≥ 1/3 plus Q duration ≥ 0.03 sec in any of leads V_2, V_3, V_4, V_5.

1-1-2 Q duration ≥ 0.04 sec in any of leads V_1, V_2, V_3, V_4, V_5.

1-1-6 QS pattern when initial R-wave is present in adjacent lead to the right on the chest, in any of leads V_2, V_3, V_4,V_5, V_6.

1-1-7 QS pattern in all of leads V_1-V_4 or V_1-V_5.

1-2-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec, in any of leads V_2, V_3, V_4, V_5.

1-2-2 Q duration ≥ 0.03 sec and < 0.04 sec in any of leads V_2, V_3, V_4, V_5.

1-2-7 QS pattern in all of leads V_1, V_2, and V_3. (Do not code in the presence of 7-1-1).

1-2-8 Initial R amplitude decreasing to 2.0 mm or less in every beat (and absence of codes 3-2, 7-1-1, 7-2-1, or 7-3) between any of leads V_2 and V_3, V_3 and V_4, or V_4 and V_5. (All beats in the lead immediately to the right on the chest must have an initial R > 2 mm.)

1-3-1 Q/R amplitude ratio ≥ 1/5 and < 1/3 plus Q duration ≥ 0.02 and < 0.03 sec in any of leads V_2, V_3, V_4, V_5.

1-3-2 QS pattern in lead V_1 and V_2. (Do not code in the presence of 3-1 or 7-1-1.)

QRS Axis Deviation

(Do not code in presence of low-voltage QRS, code 9-1, WPW 6-4-1, ventricular conduction defects, or 7-1-1, 7-2-1, and 7-4.)

2-1 Left. QRS axis from -30^0 through -90^0 in leads I, II, III. (The algebraic sum of major positive and major negative QRS waves must be zero or positive in I, negative in III, and zero or negative in II.)

2-2 Right. QRS axis from $+120^0$ through -150^0 in leads I, II, III. (The algebraic sum of major positive and major negative QRS waves must be negative in I, and zero or positive in III, and in I must be one-half or more of that in III.)

2-3 Right (optional code when 2-2 is not present). QRS axis from $+90^0$ through $+119^0$ in leads I, II, III. (The algebraic sum of major positive and major negative QRS waves must be zero or negative in I and positive in II and III.)

2-4 Extreme axis deviation (usually S1, S2, S3 pattern). QRS axis from -90^0 through -149^0 in leads I, II, and III (The algebraic sum of major positive and major negative QRS waves must be negative in each of leads I, II, and III.)

2-5 Indeterminate axis QRS axis approximately 90^0 from the frontal plane. (The algebraic sum of major positive and major negative QRS waves is zero in each of leads I, II and III, or the information from these three leads is incongruous.)

High Amplitude R Waves

3-1 Left: R amplitude > 26 mm in either V_5 or V_6, or R amplitude > 20.0 mm in any of leads I, II, III, aVF, or R amplitude > 12.0 mm in lead aVL. (All criteria measured only on second to last complete normal beat.)

3-2 Right: R amplitude ≥ 5.0 mm and R amplitude ≥ S amplitude in the majority of beats in lead V_1, when S amplitude is > R amplitude somewhere to the left on the chest of V_1 (codes 7-3 and 3-2, if criteria for both are present).

3-3 Left (optional code when 3-1 is not present): R amplitude > 15.0 mm but ≤ 20.0 mm in lead I, or R amplitude in V_5 or V_6, plus S amplitude in V_1 > 35.0 mm. (Measured only on second to last complete normal beat.)

3-4 Criteria for 3-1 and 3-2 both present.

ST Junction (J) and Segment Depression

(Do not code in the presence of codes 6-4-1, 7-1-1, 7-2-1 or 7-4. When 4-1, 4-2, or 4-3 is coded, then a 5-code must also be assigned except in lead V_1.)

Anterolateral site (leads I, aVL, V_6)

4-1-1 STJ depression ≥ 2.0 mm and ST segment horizontal or downward sloping in any of leads I, aVL, or V_6.

4-1-2 STJ depression ≥ 1.0 mm but < 2.0 mm, and ST segment horizontal or downward sloping in any of leads I, aVL, or V_6.

4-2 STJ depression ≥ 0.5 mm and < 1.0 mm and ST segment horizontal or downward sloping in any of leads I, aVL, or V_6.

4-3 No STJ depression as much as 0.5 mm but ST segment downward sloping and segment or T-wave nadir ≥ 0.5 mm below P-R baseline, in any of leads I, aVL, or V_6.

4-4 STJ depression ≥ 1.0 mm and ST segment upward sloping or U-shaped, in any of leads I, aVL, or V_6.

Posterior (inferior) site (leads II, III, aVF)

4-1-1 STJ depression ≥ 2.0 mm and ST segment horizontal or downward sloping in lead II or aVF.

4-1-2 STJ depression ≥ 1.0 mm but < 2.0 mm and ST segment horizontal or downward sloping in lead II or aVF.

4-2 STJ depression ≥ 0.5 mm and < 1.0 mm and ST segment horizontal or downward sloping in lead II or aVF.

4-3 No STJ depression as much as 0.5 mm, but ST segment downward sloping and segment or T-wave nadir ≥ 0.5 mm below P-R baseline in lead II.

4-4 STJ depression ≥ 1.0 mm and ST segment upward sloping, or U-shaped, in lead II.

ST Junction (J) and Segment Depression (continued)

Anterior site (leads V_1, V_2, V_3, V_4, V_5)

4-1-1 STJ depression ≥ 2.0 and ST segment horizontal or downward sloping in any of leads V_1, V_2, V_3, V_4, V_5.

4-1-2 STJ depression ≥ 1.0 mm but < 2.0 mm and ST segment horizontal or downward sloping in any of leads V_1, V_2, V_3, V_4, V_5

4-2 STJ depression ≥ 0.5 mm and < 1.0 mm and ST segment horizontal or downward sloping in any of leads V_1, V_2, V_3, V_4, V_5.

4-2 No STJ depression as much as 0.5 mm, but ST segment downward sloping and segment or T-wave nadir ≥ 0.5 mm below P-R baseline in any of leads V_2, V_3, V_4, V_5.

4-4 STJ depression ≥ 1.0 mm and ST segment upward sloping or U-shaped in any of leads V_1, V_2, V_3, V_4, V_5.

T-Wave Items

(Do not code in the presence of code 6-4-1, 7-1-1, 7-2-1 or 7-4.)

Anterolateral site (leads I, aVL, V_6)

5-1 T amplitude negative 5.0 mm or more in either of leads I, V_6, or in lead aVL when R amplitude is ≥ 5.0 mm.

5-2 T amplitude negative or diphasic (positive-negative or negative-positive type) with negative phase at least 1.0 mm but not as deep as 5.0 mm in lead I or V_6, or in lead aVL when R amplitude is ≥ 5.0 mm.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1.0 mm negative phase in lead I or V_6, or in lead aVL when R amplitude is ≥ 5.0 mm.

5-4 T amplitude positive and T/R amplitude ratio < 1/20 in any of leads I, aVL, V_6; R wave amplitude must be ≥ 10.0 mm.

Posterior (inferior) site (leads II, III, aVF)

5-1 T amplitude negative 5.0 mm or more in lead II, or in lead aVF when QRS is mainly upright.

5-2 T amplitude negative or diphasic with negative phase (negative-positive or positive-negative type) at least 1.0 mm but not as deep as 5.0 mm in lead II, or in lead aVF when QRS is mainly upright.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1.0 mm negative phase in lead II; not coded in lead aVF.

5-4 T amplitude positive and T/R amplitude ratio < 1/20 in lead II; R wave amplitude must be ≥ 10.0 mm.

Anterior site (leads V_2, V_3, V_4, V_5)

5-1 T amplitude negative 5.0 mm or more in any of leads V_2, V_3, V_4, V_5.

5-2 T amplitude negative (flat), or diphasic (negative-positive or positive-negative type) with negative phase at least 1.0 mm but not as deep as 5.0 mm, in any of leads V_2, V_3, V_4, V_5.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1.0 mm negative phase, in any of leads V_3, V_4, V_5.

5-4 T amplitude positive and T/R amplitude ratio < 1/20 in any of leads V_3, V_4, V_5; R wave amplitude must be ≥ 10.0 mm.

A-V Conduction Defect

6-1 Complete (third degree) A-V block (permanent or intermittent) in any lead. Atrial and ventricular complexes independent, and atrial rate faster than ventricular rate, with ventricular rate < 60.

6-2-1 Mobitz Type II (occurrence of P-wave on time with dropped QRS and T).

6-2-2 Partial (second degree) A-V block in any lead (2:1 or 3:1 block).

6-2-3 Wenckebach's Phenomenon (P-R interval increasing from beat to beat until QRS and T dropped).

6-3 P-R (P-Q) interval ≥ 0.22 sec in the majority of beats in any of leads I, II, III, aVL, aVF.

6-4-1 Wolff-Parkinson-White Pattern (WPW), persistent. Sinus P-wave. P-R interval < 0.12 sec, plus QRS duration ≥ 0.12 sec, plus R peak duration ≥ 0.06 sec, coexisting in the same beat and present in the majority of beats in any of leads I, II, aVL, V_4, V_5, V_6. (6-4-1 suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 3, 4, 5, 9-2, 9-4, 9-5 codes.)

6-4-2 WPW Pattern, intermittent. WPW pattern in ≤ 50% of beats in appropriate leads.

6-5 Short P-R interval. P-R interval < 0.12 sec in all beats of any two of leads I, II, III, aVL, aVF.

6-6 Intermittent aberrant atrioventricular conduction. P-R > 0.12 sec (except in presence of 6-5 or heart rate greater than 100); wide QRS complex > 0.12 sec; normal P-wave when most beats are sinus rhythm. (Do not code in the presence of 6-4-2.)

6-8 Artificial pacemaker.

Ventricular Conduction Defect

7-1-1 Complete left bundle branch block (LBBB). (Do not code in presence of 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2.) QRS duration ≥ 0.12 sec in a majority of beats in any of leads I, II, III, aVL, aVF, *plus* R peak duration ≥ 0.06 sec in a majority of beats (of the same QRS pattern) in any of leads I, II, aVL, V_5, V_6. (7-1-1 suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 2, 3, 4, 5, 9-2, 9-4, 9-5 codes. If any other codable Q-wave coexists with the LBBB pattern, code the Q and diminish the 7-1-1 code to a 7-4 code.)

7-1-2 Intermittent left bundle branch block. Same as 7-1-1 but with presence of normally conducted QRS complexes of different shape than the LBBB pattern.

7-2-1 Complete right bundle branch block (RBBB). (Do not code in the presence of 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2.) QRS duration ≥ 0.12 sec in a majority of beats in any of leads I, II, III, aVL, aVF, *plus*: R' > R in V_1 or V_2; or QRS mainly upright, with R peak duration ≥ 0.06 sec in V_1 or V_2; or S duration >R duration in all beats in lead I or II. (7-1 suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 2, 3, 4, 5, 9-2, 9-4, 9-5 codes.

7-2-2 Intermittent right bundle branch block. Same as 7-2-1 but with presence of normally conducted QRS complexes of different shape than the RBBB pattern.

7-3 Incomplete right bundle branch block. QRS duration < 0.12 sec in each of leads I, II, III, aVL, aVF, and R' > R in either of leads V_1, V_2 .(Code as 3-2 in addition if those criteria are met. 7-3 suppresses code 1-2-8.)

7-4 Intraventricular block. QRS duration ≥ 0.12 sec in a majority of beats in any of leads I, II, III, aVL, aVF. (7-4 suppresses all 2, 3, 4, 5, 9-2, 9-4, 9-5 codes.)

7-5 R-R' pattern in either of leads V_1, V_2 with R' amplitude ≥ R.

7-6 Incomplete left bundle branch block. (Do not code in the presence of any codable Q- or QS-wave.) QRS duration ≥ 0.10 sec and < 0.12 in the majority of beats of each of leads I, aVL, and V_5 or V_6.

7-7 Left anterior hemiblock (LAH). QRS duration < 0.12 sec in the majority of beats in leads I, II, III, aVL, aVF, plus Q-wave amplitude ≥ 0.25 mm and < 0.03 sec duration in lead I, plus left axis deviation of -45^0 or more negative. (In presence of 7-2, code 7-8 if axis is < -45^0 and the Q-wave in lead I meets the above criteria.)

7-8 Combination of 7-7 and 7-2.

Arrhythmias

8-1-1 Presence of frequent atrial or junctional premature beats (10% or more of recorded complexes).
8-1-2 Presence of frequent ventricular premature beats (10% or more of record complexes).
8-1-3 Presence of both atrial and/or junctional premature beats and ventricular premature beats (so that individual frequencies are < 10% but *combined* premature beats are ≥ 10% of complexes).
8-1-4 Wandering atrial pacemaker.
8-1-5 Presence of 8-1-2 and 8-1-4.
8-2-1 Ventricular fibrillation or ventricular asystole.
8-2-2 Persistent ventricular (idioventricular) rhythm.
8-2-3 Intermittent ventricular tachycardia. Three or more consecutive ventricular premature beats occurring at a rate ≥100. This includes more persistent ventricular tachycardia.
8-2-4 Ventricular parasystole (should not be coded in presence of 8-3-1).
8-3-1 Atrial fibrillation (persistent).
8-3-2 Atrial flutter (persistent).
8-3-3 Intermittent atrial fibrillation (code if 3 or more clear-cut, consecutive sinus beats are present in any lead).
8-3-4 Intermittent atrial flutter (code of 3 or more clear-cut, consecutive sinus beats are present in any lead).
8-4-1 Supraventricular rhythm persistent. QRS duration < 0.12 sec; and absent P-waves or presence of abnormal P-waves (inverted or flat in aVF); and regular rhythm.
8-4-2 Supraventricular tachycardia intermittent. Three consecutive atrial or junctional premature beats occurring at a rate ≥ 100.
8-5-1 Sinoatrial arrest. Unexpected absence of P, QRS and T, plus a R-R interval at a fixed multiple of he normal interval, ± 10%.
8-5-2 Sinoatrial block. Unexpected absence of P, QRS and T, preceded by progressive shortening of P-P intervals. (R-R interval at a fixed multiple of the normal interval, ± 10%.
8-6-1 A-V dissociation with ventricular pacemaker (without capture). Requires: P-P and R-R occur at variable rates with ventricular rate as fast as or faster than the atrial rate, plus variable P-R intervals, plus no capture beats.
8-6-2 A-V dissociation with ventricular pacemaker (with capture).
8-6-3 A-V dissociation with atrial pacemaker (without capture).
8-6-4 A-V dissociation with atrial pacemaker (with capture).
8-7 Sinus tachycardia (over 100/min).
8-8 Sinus bradycardia (under 50/min).
8-9 Other arrhythmias. Heart rate may be recorded as a continuous variable.

ST Segment Elevation

Anterolateral site (leads I, aVL, V_6)

9-2 ST segment elevation ≥ 1.0 mm in any of leads I, aVL, V_6.

Posterior (inferior) site (leads II, III, aVF)

9-2 ST segment elevation ≥ 1.0 mm in any of leads II, III, aVF.

Anterior site (leads V_1, V_2, V_3, V_4, V_5)

9-2 ST segment elevation ≥ 1.0 mm in lead V5 or ST segment elevation ≥ 2.0 mm in any of leads V_1, V_2, V_3, V_4.

Miscellaneous Items

9-1 Low QRS amplitude. QRS peak-to-peak amplitude < 5 mm in all beats in each of leads I, II, III, or < 10 mm in all beats in each of leads V_1, V_2, V_3, V_4, V_5, V_6. (Check calibration before coding.)

9-3 P-wave amplitude ≥ 2.5 mm in any of leads II, III, aVF, in a majority of beats.

9-4-1 QRS transition zone at V_3 or to the right of V_3 on the chest. (Do not code in the presence of 6-4-1, 7-1-1, 7-2-1 or 7-4.)

9-4-2 QRS transition zone at V_4 or to the left of V_4 on the chest. (Do not code in the presence of 6-4-1, 7-1-1, 7-2-1 or 7-4.)

9-5 T-wave amplitude > 12 mm in any of leads I, II, III, aVL, aVF, V_1, V_2, V_3, V_4, V_5, V_6. (Do not code in the presence of 6-4-1, 7-1-1, 7-2-1 or 7-4.)

9-8-1 Technical problems which interfere with coding.

9-8-2 Technical problems which do not interfere with coding.

Incompatible Codes

The codes in the left column suppress codes in the right column.

Code	Suppress this code(s)
All Q-, QS-codes	7-6
Q > 0.03 in lead I	7-7
3-1	1-3-2
3-2	1-2-8, 7-3
6-1	All other codes except 8-2
6-4-1	All other codes
6-8	All other codes
7-1-1	1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 2-, 3-, 4-, and 5- codes, 7-7, 9-2, 9-4, 9-5
7-2-1	1-2-8, all 2-, 3-, 4-, and 5-codes, 9-2, 9-4, 9-5
7-3	1-2-8
7-4	All 2-, 3-, 4-, and 5-codes, 9-2, 9-4, 9-5
8-1-2	8-2-4
8-1-4	8-1-1, 9-3
8-2-1	All other codes
8-2-2	All other codes
8-2-3	8-1-2
8-3-1	8-1-1, 8-1-2
8-3-2	6-2-2, 8-1-1, 8-1-2
8-3-3	8-1-1, 8-1-2
8-3-4	6-2-2
8-4-1	6-5
8-4-1 + heart rate ≥ 140	All other codes except 7-4 or 6-2
Heart rate > 100	6-5
8-4-2	8-1-1
9-1	All 2-codes

Categories of Minnesota ECG Abnormalities

Diagnostic ECG:
(any ECG may be used for this classification)

D1. An ECG record with any Diagnostic Q-code (Minn. code 1-1-1 through 1-2-5 plus 1-2-7).

D2. An ECG record with ST-segment elevation code 9-2 PLUS (T-wave inversion code 5-1 or 5-2 in the absence of 7-2-1 or 7-4).

Equivocal ECG:
(any ECG may be used for this classification)

E1. An ECG record with an Equivocal Q-code [(Minn. code 1-2-8 in the absence of a 7-1-1 or 7-3 or (any 1-3-code)].

E2. An ECG record with ST-segment depression (code 4-1-x or 4-2 or 4-3 in the absence of 7-2-1 or 7-4), or 1-3-x.

E3. An ECG record with T-wave inversion (code 5-1 or 5-2 or 5-3 in the absence of 7-2-1 or 7-4).

E4. An ECG record with ST-segment elevation code 9-2.

Other ECG:

01. Reference ECG coded 7-1-1.

02. Any ECG coded 7-1-1.

03. Normal ECG(s), defined as 1 in "clear" field of all ECGs.

04. Other findings including 1-2-6.

Uncodable ECG:

U1. Technical errors coded 9-8-1 by Minnesota Code.

Absent ECG:

A1. No ECG available for coding.

† Prineas R, Crow R, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. John Wright-PSG, Inc. Littleton, MA, June 1982.

Appendix 4. Ethical Approval

Ethical approval obtained - 4a →University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Tibazarwa

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070127**
PROJECT	Peripartal and Idiopathic Dilated Cardio-myopathy; Incidence, Prevalence and Familial Cobntribution
INVESTIGATORS	Dr K Tibazarwa
DEPARTMENT	Department of Medicine
DATE CONSIDERED	07.01.26
DECISION OF THE COMMITTEE*	Approved Unconditionally

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

DATE 07.02.20 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof K Sliwa

DECLARATION OF INVESTIGATOR(S)

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 as 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

Ethical approval obtained - 4b → University of Cape Town

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: prenward@curie.uct.ac.za

11 September 2006

REC REF: 309/2006

Prof BM Mayosi
Medicine

Dear Prof Mayosi

PROJECT TITLE: FAMILIAL AGGREGATION OF DILATED CARDIOMYOPATHY IN PATIENTS WITH PERIPARTUM CARDIOMYOPATHY

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

Asley Henley

DR. M. BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

pp

lemjedi

4c → Change of Title (University of the Witwatersrand)

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2745

Reference: Ms Tania Van Leeve
E-mail: tania.vanleeve@wits.ac.za
03 May 2010
Person No: 0416842P
TAA

Dr K Tibazarwa
E25 Cardiac Clinic
New Groote Schuur Hospital
Observatory
7925
Cape Town, South Africa

Dear Dr Tibazarwa

Doctor of Philosophy: Change of title of research

I am pleased to inform you that the following change in the title of your Thesis for the degree of has been approved:

From:	**Familial aggregation of dilated cardiomyopathy in patients with unexplained dilated and peripartum cardiomyopathy**
To	**Peripartum cardiomyopathy: Risk factors profile, familial aggregation, and prognostic indicators**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 5. Documents advertising for PPCM patient recruitment

5a → Poster (Johannesburg)

THE SOWETO CARDIAC RESEARCH UNIT (CRU)



is launching a new study on familial

PERIPARTUM CARDIOMYOPATHY

and would like to invite you and your family to participate in the study!

WHAT IS PERIPARTUM CARDIOMYOPATHY?

Peripartum cardiomyopathy (PPCM) is one of several types of heart diseases where the main heart chamber is enlarged and so the heart does not pump properly (Dilated Cardiomyopathy).

We are seeking women in late pregnancy or within their first 6 months after delivery who experience the following :

- Unusual shortness of breath
- Feeling of heart racing
- Chest pain
- Fainting
- Recent new diagnosis of heart failure associated with pregnancy

OR

- Swelling of the legs combined with any one of the above



WHO AND WHAT ARE WE STUDYING?

We would like to examine the women with PPCM, and her adult close family members, as we suspect family members may be at risk of developing similar problems with their heart. We will perform all necessary tests and provide follow up care for these women and their adult family members.

If you or any woman that you know fit this profile, please contact us by either :

Calling the Heart Failure clinic on (011) 933 8879 and speaking to:

OR

Coming straight to the "Heart of Soweto" Cardiac Research Unit at the Cardiology department, Chris Hani Baragwannath Hospital, on any working day of the week.

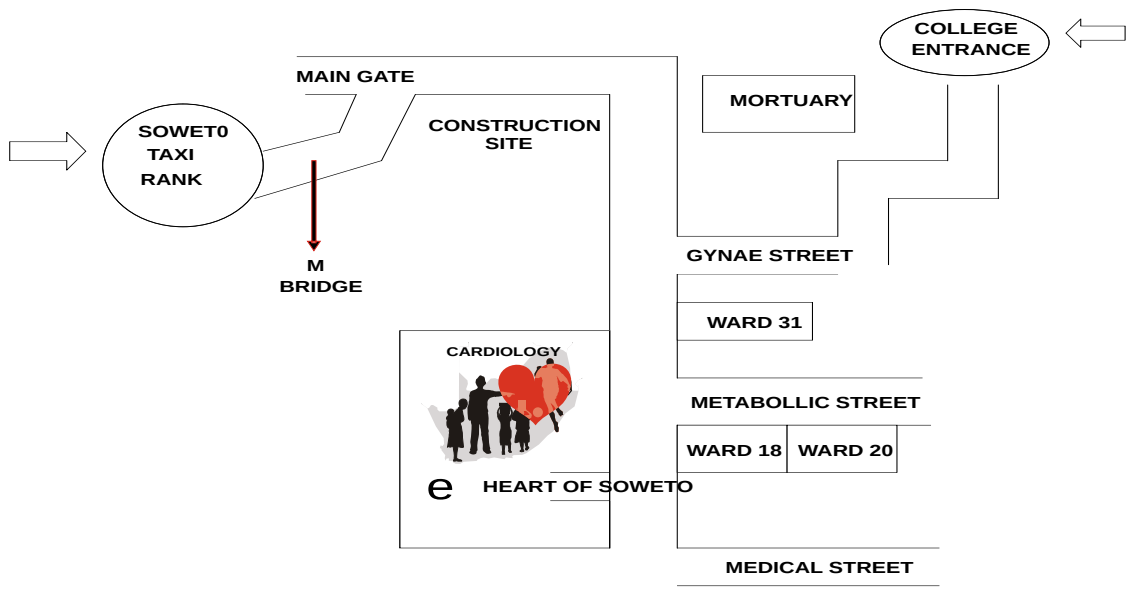
Sr. Bridget Phooke (Research Nurse)

Louis Kunika (Also : 933 8000 #6501)

Dr. Tibazarwa

Prof. Sliwa (933 8000 #6513)

Division of Cardiology
Chris Hani Baragwanath Hospital
P O Bertsham
Johannesburg 2013



THANK YOU FOR HELPING

5b →Brochure (Johannesburg)

PERIPARTUM CARDIOMYOPATHY

A NEW STUDY

Peripartum cardiomyopathy (PCM) is an acute form of heart failure whereby the left ventricle is enlarged and systolic function is reduced.

We are seeking women in late pregnancy or within their first 5 months after delivery who present with symptoms or signs of:

Recent or new diagnosis of acute heart failure *unexplained* by any known prior/concurrent condition

And who fit with the following inclusion and exclusion criteria:

INCLUSION CRITERIA

- ***Unexplained*** acute left sided failure with LV dilatation; REGARDLESS of HIV status
- On full treatment and ambulant

EXCLUSION CRITERIA

1. Hypertension or hypertensive heart disease (alone or in pregnancy; current or in prior pregnancies)
2. Valvular heart disease
3. Structural heart disease of any kind

We would greatly appreciate you would ask these patients to visit our Tuesday morning clinic at the Cardiac Clinic, New Groote Schuur Hospital, to be seen at our clinic as soon as possible when they have stabilised from initial hospital discharge. We will see the patient for 2 visits, after which we will refer them back to their original clinics for follow-up.

OR

Please contact either of the following:

- Dr. Tibazarwa (Bleep XXXX)
- Dr. Ntusi (Bleep 2345)
- Sister Tshifularo (UCT – 021 406 6361)

THANK YOU FOR HELPING

5c → Poster (Cape Town)

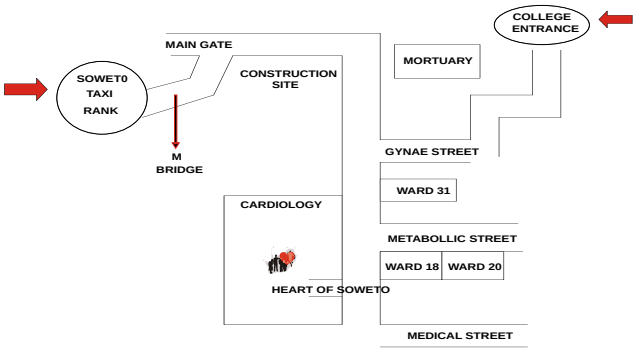
If you know of any woman who fits this profile, and who would like to join in our study, please ask them to contact us by either:

Calling the Heart Failure Clinic on (011) 933 8879 and speaking to:

Sr. Bridget Phooke
Louis Kunika (933 8000 #6501)
Dr. Tibazarwa
Prof. Sliwa (933 8000 #6513)

OR

Coming straight to the "Heart of Soweto" Cardiac Research Unit at the Cardiology Department, Chris Hani Baragwanath Hospital, on any working day of the week.



SOWETO



DIVISION OF CARDIOLOGY

Chris Hani
Baragwanath Hospital
P.O Bertsham,
Johannesburg 2013



WE NEED YOUR HELP TO HELP THESE WOMEN AND THEIR FAMILIES

What Is Peripartum Cardiomyopathy?

Peripartum Cardiomyopathy, or PPCM, is one of several types of heart diseases where the main heart chamber is enlarged and the heart does not pump properly (Dilated Cardiomyopathy).

Who Can Get PPCM?

PPCM is a rare illness that occurs in women any time between their last month of pregnancy and within the first 5 months of delivery.

A woman in her last month of pregnancy or in the first 5months after delivery may have PPCM if she feels any of the following:

- Unusual shortness of breath
- Feeling of heart racing
- Chest pain
- Fainting
- Recent diagnosis of heart failure associated with pregnancy

OR

- Swelling of the legs combined with any of the above

BUT!!!!

Not everybody who feels this has PPCM!

If you or any woman you know has experienced the symptoms listed on the previous page between her last month of pregnancy and the first 5 months after pregnancy, we would like to see her, and later also her close family members.

WHY???

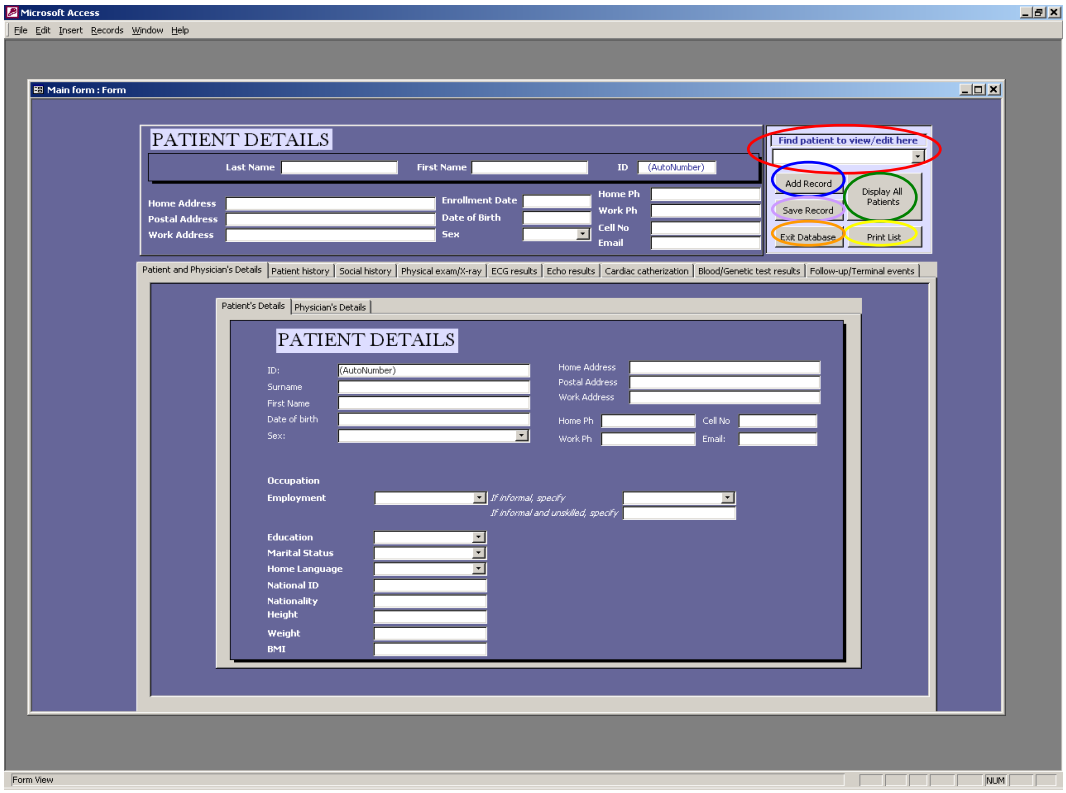
- To be able to help more women with PPCM, we want to better understand this rare disease.
- We strongly suspect family members may be at risk of developing similar problems with their heart.

<u>Appendix 6</u>. Cardiomyopathy Registry (electronic database)

6a → One-page summary/guide

Cardiomyopathy Database

How to open the Cardiomyopathy database
Open it with Access database and enter **research** when asked for a password.



How to enter new record
When the database is first opened, the screen is ready to accept new record. If it currently displays a certain record, just click on the 'Add Record' button (circled in blue) found on the upper right corner of the screen. To go from one field to another, simply click the **tab** key. When the end of the field on a page is reached, it will automatically go to the next window/page.

How to save record
Each time a data is entered in a field, the data is automatically saved. But for your ease of mind, simply click the 'Save Record' button (circled in purple) to save a record or updated data.

How to display an existing record
Click on the drop down button (shown below in red circle) and a list of existing record will be displayed. Select the record you want to display and it will show up on your form.

How to display a list of all the patients recorded on the database
A list of all the patients with their date of birth and gender will be displayed when the 'Display All Patients' (circled in green) button is clicked.

How to print a list of all the patients recorded on the database
Click the 'Print List' button (circled in yellow) and a list of patients recorded in the database will be printed in the default printer. Note: Make sure that the computer is connected to a printer.

How to exit from the database
Click the 'Exit database' button (circled in orange).

6b →Index of Data/Terminology

CC&Blood/Genetic test results	Data Type	Description
ID	Long	Automated Primary ID
Cardiac_cath	Integer	Cardiac catherization (0:Done; 1:Not done)
Date_Cardiac_Cath	Date	Date of cardiac catherization
Dilated_LV	Integer	Left ventricle- Dilated LVt (0:No; 1:Yes)
LVfunc	Integer	LV Global Function (1:Normal; 2:Mildly reduced; 3:Severely reduced)
LVab_septal_wall	Integer	LV septal wall motion abnormalitites (1:Normal; 2:Diastolic bulge; 3:Mild Hypokinesia; 4:Severe Hypokinesia; 5:Akinesia; 6:Dyskinesia-aneurysms; 7:Unknown)
LVab_ant_wall	Integer	LV anterior wall motion abnormalitites (1:Normal; 2:Diastolic bulge; 3:Mild Hypokinesia; 4:Severe Hypokinesia; 5:Akinesia; 6:Dyskinesia-aneurysms; 7:Unknown)
LVab_post_wall	Integer	LV posterior submitral wall motion abnormalitites (1:Normal; 2:Diastolic bulge; 3:Mild Hypokinesia; 4:Severe Hypokinesia; 5:Akinesia; 6:Dyskinesia-aneurysms; 7:Unknown)
LVab_inf_wall	Integer	LV inferior wall motion abnormalitites (1:Normal; 2:Diastolic bulge; 3:Mild Hypokinesia; 4:Severe Hypokinesia; 5:Akinesia; 6:Dyskinesia-aneurysms; 7:Unknown)
LVab_apical_wall	Integer	LV apical wall motion abnormalitites (1:Normal; 2:Diastolic bulge; 3:Mild Hypokinesia; 4:Severe Hypokinesia; 5:Akinesia; 6:Dyskinesia-aneurysms; 7:Unknown)
Regurg_mitral_mode	Integer	Mitrarl regurgitation mode (1-4,0 if not present, 5 if Prolapse)
LVEDV	Integer	LVEDV (ml)
LVESV	Integer	LVESV (ml)
LVEF	Integer	LVEF (%)
LV_sys	Integer	LV systolic pressure (mmHg)
LV_dia	Integer	LV diastolic pressure (mmHg)
LVEDP	Integer	LVEDP (mmHg)
AortPress	Integer	Aortic Pressure (mmHg)
LV_sys_grad	Integer	LV systolic gradient
RV_dilated	Integer	Dilated right ventricle (0:No; 1:Yes)
RVfunc	Integer	Right ventricle global function (1:Normal; 2:Mildly reduced; 3:Severely reduced)
RVOT_Morph	Integer	RV Abnormalities - Morphology: RVOT (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unknown) - abnormalities
Anteroseptal_Morph	Integer	RV Abnormalities - Morphology: Anteroseptal free wall (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unknown) - ab
Subtri_Morph	Integer	RV Abnormalities - Morphology: Subtricuspid posterobasal (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unknown)
Apical_Morph	Integer	RV Abnormalities - Morphology: Apical (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unknown) - abnormalities
RVOT_reg_wall	Integer	RV regional wall motion abnormalities: RVOT (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unknown)
Anteroseptal_reg_wall	Integer	RV regional wall motion abnormalities: Anteroseptal free wall (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unknow
Subtri_reg_wall	Integer	RV regional wall motion abnormalities: Subtricuspid posterobasal (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unk
Apical_reg_wall	Integer	RV regional wall motion abnormalities: Apical (0:Normal; 1:Scalloped Contours; 2:Trabecular traverse deep fissure; 3:Trabecular hypertrophy>4mm; 4:Aneurysm; 5:Unknown)
RVEDV	Integer	RVEDV (ml)
RVESV	Integer	RVESV (ml)
RVEF	Integer	RVEF (%)

PAP	Integer	Pulmonary artery pressure mean (mmHg)
RA_press	Integer	RA pressure (mmHg)
RVEDP	Integer	RVEDP (mmHg)
Pulm_capwedge_press	Integer	Pulmonary capillary wedge pressure (mmHg)
Regurg_tri_grade	Integer	Tricuspid regurgitation grade (1-4, 0 if not present)
Tri_prolapse	Integer	Tricupsid valve prolapse
Dominance	Integer	Dominance (1:Right; 2:Left; 3:Balanced)
CA_obstruct	Integer	Presence of Coronary artery obstruction (0:No; 1:Yes)
CA_obstruct_percent	Integer	Percentage of obstruction
Stenosis	Integer	Location of stenosis (1:LMCA; 2:LAD; 3:LCx; 4:RCA)
Blood_test	Integer	Blood test (0:Done; 1:Not done)
Hb	Integer	Haemoglobin (g/dl)
WCC	Integer	White cell count
MCV	Integer	MCV (fl)
Plt	Integer	Platelet count
BSL	Integer	Random blood sugar (mmol)
Na	Integer	Serum sodium (mmol/l)
K	Integer	Potassium (mmol/l)
Cl	Integer	Chloride (mmol/l)
Urea	Integer	Urea (mmol/l)
Cr	Integer	Creatinine (umol/l)
Bilirubin	Integer	Bilirubin (umol/l)
ALT	Integer	Alanine transferase (U/l)
AST	Integer	Aspartate transferase (U/l)
Alb	Integer	Albumin (g/dL)
Protein	Integer	Total protein (g/dL)
GGT	Integer	gamma GT
ESR	Integer	ESR in one hour
CRP	Integer	C-reactive protein (mg/dl)
Pro_BNP	Integer	Pro-BNP
TC	Double	Total cholesterol (mmol/l)
HDL	Double	High Density Lipoprotein (mmol/l)
TG	Double	TG (mmol/l)
LDL	Double	Low Density Lipoprotein (mmol/l)
TSH	Integer	Thyroid Stimulating Hormone (mIU/l)

fT3	Integer	fT3 (pmol/l)
fT4	Integer	fT4 (pmol/l)
HIV_screen	Integer	HIV screening
HIV_confirm	Integer	HIV confirmatory test
GeneTest	Integer	Genetic testing (0:Done; 1:Not done)
Chrom_loc	Text	Chromosomal location test
GeneID	Text	Genes identified
Genes_other	Text	Other
Diag_Suspect	Text	Suspected Diagnosis
Diag_Final	Text	Final Diagnosis
Diag_Other	Text	Other
FUpNo	Long	Follow-up Number
Date_FUp	Date	Date of follow-up
Type_FUp	Integer	Type of follow-up (1:Regularly scheduled follow up; 2:Unscheduled follow up; 3:Lost to follow up)
Complaints	Text	Presenting complaints
Events_FUp	Integer	Events since last follow up (0:No; 1:Yes)
Events_details	Text	Details of events
Med1	Text	Current medications (drug name)
Dose1	Integer	Total daily dose (mg)
Med2	Text	Current medications (drug name)
Dose2	Integer	Total daily dose (mg)
Med3	Text	Current medications (drug name)
Dose3	Integer	Total daily dose (mg)
Med4	Text	Current medications (drug name)
Dose4	Integer	Total daily dose (mg)
Med5	Text	Current medications (drug name)
Dose5	Integer	Total daily dose (mg)
Med6	Text	Current medications (drug name)
Dose6	Integer	Total daily dose (mg)
Med7	Text	Current medications (drug name)
Dose7	Integer	Total daily dose (mg)
Surgery	Integer	Surgery (0:No; 1:Yes)
SurgType	Text	Type of surgery
Pacemaker	Integer	Pacemaker insertion (0:No; 1:Yes)
Date_pacemaker	Date	Date of insertion of pacemaker

Type_pacemaker	Text	Type of pacemaker
ICD	Integer	ICD implantation (0:No; 1:Yes)
Date_ICD	Date	Date of insertion
Cath_abl	Integer	Catheter ablation (0:No; 1:Yes)
Date_Cath_abl	Date	Date performed
Indication	Text	Indication
Cardiac_terminal	Integer	Terminal Events: Cardiac death (0:No; 1:Yes; 2:Unknown)
Sudden_terminal	Integer	Terminal Events: Sudden death (0:No; 1:Yes; 2:Unknown)
HF_terminal	Integer	Terminal Events: Heart failure (0:No; 1:Yes; 2:Unknown)
NonCardiac_terminal	Integer	Terminal Events: Non-Cardiac death (0:No; 1:Yes; 2:Unknown)
Detail_terminal	Text	Details of terminal event
Autopsy	Integer	Autopsy (0:No; 1:Yes; 2:Unknown)
Autopsy_Results	Text	Autopsy results

Patient/Physician Information	***Data Type***	***Description***
ID	Long	
LastName	Text	Last Name
FirstName	Text	First Name
DOB	Date	Date of Birth (dd/mm/yyyy)
Sex	Integer	Sex (1:Male; 2:Female)
Education	Integer	Education (1:No schooling; 2:Primary; 3:Secondary; 4:Post Secondary)
Employment	Integer	Employment (1:Formal; 2:Informal; 3:Unemployed)
FormalEmp_type	Integer	Formal employment (1:Skilled professional; 2:Skilled otherwise; 3:Unskilled)
InformalEmp_type	Integer	Informal specified (1:Skilled; 2:Unskilled)
UnskilledEmp_type	Text	Informal Unskilled Employment specified
Housewife	Integer	Housewife (0:No; 1:Yes)
Unemployed	Integer	Unemployed (0:No; 1:Yes)
Student	Integer	Student (0:No; 1:Yes)
Marital_Status	Integer	Marital status (1:Married; 2:Single; 3:Divorced/Separated; 4:Co-habiting;4:Widowed)
National_ID	Long	National ID Number
Nationality	Text	Nationality
Home_Lang	Integer	Home Language (1:English; 2:Afrikaans; 3:Xhosa; 4:Zulu; 5:Sutu; 6:Tshangani; 7:Other)
HospNo	Long	Hospital Number
DOE	Date	Date of enrollment

Add_Home	Text	Home Address
Add_Post	Text	Postal Address
Add_Work	Text	Work Address
PhHome	Text	Home Telephone Number
PhWk	Text	Work Telephone Number
CellNo	Text	Cell Phone Number
Email	Text	Email Address
Height	Double	Height(metres)
Weight	Double	Weight (kg)
BMI	Double	BMI(kg/m2)
PhysLastName	Text	Physicians Last Name
PhysFirstName	Text	Physicians First Name
Hosp_FacName	Text	Name of Hospital/Health Facility
PhysAdd	Text	Physicians Address
PhysCity	Text	Physicians City of Location
Phys_Prov_State	Text	Physcians Province/State
Phys_PhWk	Text	Physicians Work Telephone Number
Phys_CellNo	Text	Physicians Cell Phone Number

Physical examination and signs	***Data Type***	***Description***
ID	Long	
Date_diag_CM	Date	Date of first diagnosis of cardiomyopathy
Date_symp_CM	Date	Date of earliest symptoms
NYHA	Integer	Present NYHA (0:No; 1:Yes)
NYHA_Class	Integer	Present NYHA Functional Class (1:I; 2:II, 3:III; 4:IV)
Palpitations	Integer	Palpitations (0:No; 1:Yes)
Dizziness	Integer	Dizziness (0:No; 1:Yes)
Syncope	Integer	Syncope (0:No; 1:Yes)
Chest_Pain	Integer	Chest Pain (0:No; 1:Yes)
Leg_Swelling	Integer	Leg Swelling (0:No; 1:Yes)
Cardiac_arrest	Integer	Cardiac Arrest (0:No; 1:Yes)
Other_ complaints	Text	Other complaints
Date_FirstHosp_CM	Date	Date of first hospitalization for treatment/diagnosis of cardiomyopathy
Blood_Trans	Integer	Blood Transfusion (0:No; 1:Yes)

Blood_Trans_Sp	Text	Blood Transfusion - Specified
Cardiovascular	Integer	Cardiovascular (0:No; 1:Yes)
Cardiovascular_Sp	Text	Cardiovascular - Specified
Pulmonary	Integer	Pulmonary (0:No; 1:Yes)
Pulmonary_Sp	Text	Pulmonary - Specified
GI	Integer	Gastrointestinal (0:No; 1:Yes)
GI_Sp	Text	Gastrointestinal - Specified
Renal	Integer	Renal (0:No; 1:Yes)
Renal_Sp	Text	Renal - Specified
Endocrine	Integer	Endocrine (0:No; 1:Yes)
Endocrine_Sp	Text	Endocrine - Specified
Dermatological	Integer	Dermatological (0:No; 1:Yes)
Dermatological_Sp	Text	Dermatological - Specified
Haematological	Integer	Haematological (0:No; 1:Yes)
Haematological_Sp	Text	Haematological - Specified
Neuromuscular	Integer	Neuromuscular/Skeletal (0:No; 1:Yes)
Neuromuscular_Sp	Text	Neuromuscular/Skeletal - Specified
Gynaecological	Integer	Gynaecological (0:No; 1:Yes)
Gynaecological_Sp	Text	Gynaecological - Specified
Liver	Integer	Liver (0:No; 1:Yes)
Liver_Sp	Text	Liver - Specified
Ophthalmic	Integer	Opthalmic (0:No; 1:Yes)
Opthalmic_Sp	Text	Opthalmic - Specified
ENT	Integer	ENT (0:No; 1:Yes)
ENT_Sp	Text	ENT - Specified
Repeat_Infec	Integer	Repeated Infections (0:No; 1:Yes)
Repeat_Infec_Sp	Text	Repeated Infections - Specified
Flu_illness	Integer	Flu-like illness (0:No; 1:Yes)
Flu_ illness_Sp	Text	Flu-like illness - Specified
Date_Menstrual	Date	Last Menstrual Period
Date_Delivery	Date	Date of last delivery
Amniotic_Fluid	Integer	Any suggestion of amniotic fluid in any pregnancy (0:No; 1:Yes)
FamHxHD	Integer	Family History of Heart Disease (0:No; 1:Yes)
HD_type	Text	Type of Heart Disease
FamHxSuddenDeath	Integer	Family History of sudden death (0:No; 1:Yes)

SuddenDeath_no	Integer	Number of sudden deaths in family members <35 years old
SuddenDeath_name1	Text	Name of family member suffering sudden death
SuddenDeath_relation1	Text	Relationship to family member suffering death
SuddenDeath_arrhy_events1	Text	Arrythmic events suffered during sudden death
SuddenDeath_CM1	Text	Cardiomyopathy diagnosis of family member suffering sudden death
SuddenDeath_name2	Text	Name of family member suffering sudden death
SuddenDeath_relation2	Text	Relationship to family member suffering death
SuddenDeath_arrhy_events2	Text	Arrythmic events suffered during sudden death
SuddenDeath_CM2	Text	Cardiomyopathy diagnosis of family member suffering sudden death
SuddenDeath_name3	Text	Name of family member suffering sudden death
SuddenDeath_relation3	Text	Relationship to family member suffering death
SuddenDeath_arrhy_events3	Text	Arrythmic events suffered during sudden death
SuddenDeath_CM3	Text	Cardiomyopathy diagnosis of family member suffering sudden death
HxSmoking	Integer	Smoking History (0:No; 1:Yes)
Pack_yrs	Integer	Pack years
Alcohol	Integer	Alcohol Intake (0:No; 1:Yes)
Alcohol_qty	Integer	Alcohol Quantity
Alcohol_qty_week	Integer	Alcohol Quantity per Week
Medications	Integer	Medication (0:No; 1:Yes)
Meds1	Text	Medicine
Dose1	Integer	Dose (mg)
Date_start1	Date	Date Started Medication
Meds2	Text	Medicine
Dose2	Integer	Dose (mg)
Date_start2	Date	Date Started Medication
Meds3	Text	Medicine
Dose3	Integer	Dose (mg)
Date_start3	Date	Date Started Medication
Meds4	Text	Medicine
Dose4	Integer	Dose (mg)
Date_start4	Date	Date Started Medication
Meds5	Text	Medicine
Dose5	Integer	Dose (mg)
Date_start5	Date	Date Started Medication
Meds6	Text	Medicine

Dose6	Integer	Dose (mg)
Date_start6	Date	Date Started Medication
Meds7	Text	Medicine
Dose7	Integer	Dose (mg)
Date_start7	Date	Date Started Medication
Meds8	Text	Medicine
Dose8	Integer	Dose (mg)
Date_Start8	Date	Date Started Medication
Sport_prior	Integer	Sport Participation prior to myopathy diagnosis (1:Inactive; 2:Recreational; 3:Competitive/Professional; 4:Unknown)
Esthr_prior	Integer	Estimated hours of activity per week prior to diagnosis
Sport_after	Integer	Sport Participation following myopathy diagnosis (1:Inactive; 2:Recreational; 3:Competitive/Professional; 4:Unknown)
Esthr_after	Integer	Estimated hours of activity per week after diagnosis
Rugby	Integer	Rugby (0:No; 1:Yes)
Soccer	Integer	Soccer (0:No; 1:Yes)
Baseball	Integer	Baseball (0:No; 1:Yes)
Basketball	Integer	Basketball (0:No; 1:Yes)
Hockey	Integer	Hockey (0:No; 1:Yes)
Cricket	Integer	Cricket (0:No; 1:Yes)
Tennis	Integer	Tennis (0:No; 1:Yes)
Running	Integer	Running (0:No; 1:Yes)
Biking	Integer	Biking (0:No; 1:Yes)
Swimming	Integer	Swimming (0:No; 1:Yes)
Surfing	Integer	Surfing (0:No; 1:Yes)
Sport_Other	Text	Other sport practiced most often
Oedema	Integer	Pitting oedema of the legs (0:Absent; 1:Present)
BP	Text	Blood Pressure (mmHg)
JVP	Integer	Raised JVP (0:Absent; 1:Present)
PulseRate	Integer	Pulse Rate
Pulse_Character	Integer	Pulse Character
HeartSounds	Integer	Heart Sounds (0:No; 1:Yes)
Heart Sounds_sp	Integer	Heart Sounds Specified (1:S3; 2:S4; 3:Gallop Rhythm)
Systolic	Integer	Systolic (0:No; 1:Yes)
Diastolic	Integer	Diastolic (0:No; 1:Yes)
Location	Integer	Location (0:No; 1:Yes)
Location_sp	Text	Location specified

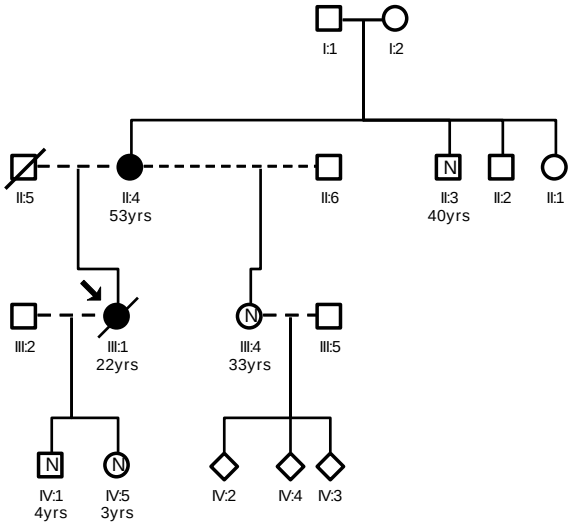
Grade	Integer	Grade (0:No; 1:Yes)
Grade_sp	Text	Grade specified
Timing	Integer	Timing (0:No; 1:Yes)
Timing_sp	Text	Tminig specified
Character	Integer	Character (0:No; 1:Yes)
Character_sp	Text	Characer specified
Crepitations	Integer	Basal crepitations (0:Absent; 1:Present)
hepatomegaly	Integer	Tender hepatomegaly (0:Absent; 1:Present)
Ascites	Integer	Ascites (0:Absent; 1:Present)
muscle_weak	Integer	Proximal muscle weakness (0:Absent; 1:Present)
Tendon_Reflexes	Integer	Deep tendon reflexes (0:Absent; 1:Present)
TendonReflexes_sp	Integer	Deep tendon reflexes specified (1:Normal; 2:Abnormal)
Gait_disturb	Integer	Gait disturbance (0:Absent; 1:Present)
Cardiothor_ratio	Double	Cardiothoracic ratio
Lung_fields	Integer	Lung fields (0:Normal; 2:Congested)
LAenlarge	Integer	Left atrial enlargement (0:No; 1:Yes)
RVenlarge	Integer	Right ventricular enlargement (0:No; 1:Yes)
ECG	Integer	ECG (0:Done; 1:Not done)
ECG_Date	Date	Date of ECG
Ventricular_rate	Integer	Ventricular rate
Baseline_rhythm	Integer	Baseline rhythm (1:Sinus rhythm; 2:Junctional; 3:Sinus arrythmia; 4:Sinus pause>1.2sec-abrubt pause; 5:Pacemaker; 6:Other)
Pacemaker_mode	Text	Pacemaker mode
Pacemaker_other	Text	Other
PRint	Integer	PR interval (ms)
QRSaxis	Integer	QRS axis
STd	Integer	ST depression (leads)
STd_sp	Text	ST depression (leads) specified
STe	Integer	ST elevation (leads)
STe_sp	Text	ST elevation (leads) specified
Twave	Integer	T wave inversions (depth in mm)
AbnormalQ	Integer	Abnormal Q waves (0:No; 1:Yes)
QTint	Integer	QT interval (ms)
QTc	Integer	QTc (ms)
QTdisp	Integer	QT dispersion
LA_enlargement	Integer	Left atrial enlargement (0:No; 1:Yes)

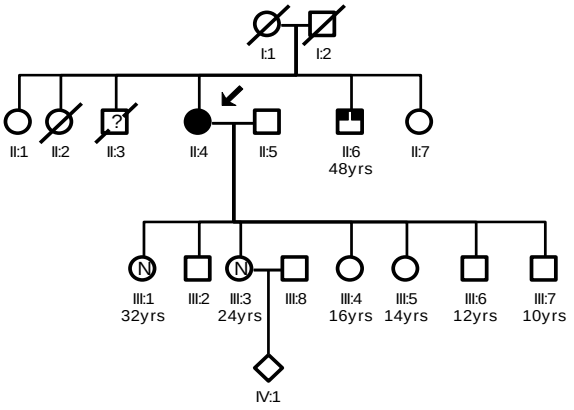
RA_enlargement	Integer	Right atrial enlargement (0:No; 1:Yes)
QRS_morph	Integer	QRS morphology (0:Normal; 1:Delta wave; 2:RBBB; 3:LBBB; 4:LAH; 5:LPH; 6:RBBB+LAH or LPH)
Arrhythmia	Integer	Arrhythmias (1:None; 2:Atrial flutter; 3:Atrial fibrillation; 4:Supraventric tachy; 5:Ventricular ectopy; 6:Non-sustained ventric tachy=3-10 consecut beats; 7:Sustained ventricr tachy=>10 cons
PVC	Integer	PVC morphology (0:No PVC; 1:RBBB; 2:LBBB; 3:Both RBBB and LBBB; 4:Indeterminate)
Others	Text	Others
Hrt_Blk	Integer	Heart Block (0:None; 1:1st degree; 2:2nd degree; 3:3rd degree block)
Epsilon	Integer	Presence of Epsilon wave (0:No; 1:Yes)
Sokolow_Lyon	Integer	Sokolow-Lyon (0:No; 1:Yes)
Cornell_voltage	Integer	Cornell voltage (0:No; 1:Yes)
Echo	Integer	Echocardiography (0:Done; 1:Not done)
Date_echo	Date	Date of Echocardiography
HR	Integer	Heart rate (b/min)
LA_diameter	Integer	Left atrial diameter (cm)
Aortic_root_diameter	Integer	Aortic root diameter (cm)
IVSTd	Single	IVSTd (cm)
PTWd	Single	PTWd (cm)
IVSTd/PTWd ratio	Single	IVSTd/PTWd ratio
LVEDD	Integer	LVEDD (cm)
LVESD	Integer	LVESD (cm)
FS	Integer	FS (%)
EF	Integer	EF (%)
EPSS	Integer	EPSS (cm)
SAM	Integer	SAM at rest (0:No; 1:Yes)
LV_level	Integer	Prominent LV trabeculation and deep intrabecular recesses-Apical level (0:No; 1:Yes)
Colour_flow	Integer	Colour flow in recesses (0:No; 1:Yes)
Ratio_compact	Integer	Ratio of noncompacted/compacted >2 (0:No; 1:Yes)
LV_WallMotion	Integer	Global LV wall motion (1:Normal; 2:Mildly reduced; 3:Severely reduced)
Septal_WallMotion	Integer	Regional LV wall motion - septal (0:Normal; 1:Diastolic bulge; 2:Mild hypokinesia; 3:Severe hypokinesia; 4:Akinesia; 5:Dyskinesia(aneurysms); 6:LV thinning)
Anterior_WallMotion	Integer	Regional LV wall motion - anterior (0:Normal; 1:Diastolic bulge; 2:Mild hypokinesia; 3:Severe hypokinesia; 4:Akinesia; 5:Dyskinesia(aneurysms); 6:LV thinning)
Posterolateral_WallMotion	Integer	Regional LV wall motion - posterolateral (0:Normal; 1:Diastolic bulge; 2:Mild hypokinesia; 3:Severe hypokinesia; 4:Akinesia; 5:Dyskinesia(aneurysms); 6:LV thinning)
Inferior_InferiorWotion	Integer	Regional LV wall motion - Inferior (0:Normal; 1:Diastolic bulge; 2:Mild hypokinesia; 3:Severe hypokinesia; 4:Akinesia; 5:Dyskinesia(aneurysms); 6:LV thinning)
Apica_WallMotion	Integer	Regional LV wall motion - apical (0:Normal; 1:Diastolic bulge; 2:Mild hypokinesia; 3:Severe hypokinesia; 4:Akinesia; 5:Dyskinesia(aneurysms); 6:LV thinning)
Mitral_ prolapse	Integer	Mitral Valve Prolapse (1:None; 2:Mild; 3:Moderate; 4: Severe)
RVOT	Integer	Right ventricular outflow tract (cm)
Ratio_RVOT_Aortic	Single	Ratio of right ventricular outflow tract/aortic valve

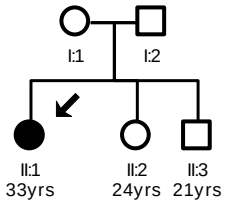
Dilated_RA	Integer	Dilated RA (0:No; 1:Yes)
Valve_lesions	Integer	Valve lesions (0:No; 1:Yes)
Valve_sp	Integer	Valve specifed (1:tricuspid; 2:pulmonary)
LVOT_Velocity	Integer	Left ventricular outflow tract velocity (m/s)
LVOT_PressGrad	Integer	Left ventricular outflow tract pressure gradient at rest (continous wave)
Aortic_Velocity	Integer	Aortic velocity
RVP_sys	Integer	Right ventricular pressure in systole (mmHg)
Regurg	Integer	Presence of regurgitation (0:No; 1:Yes)
Regurg_Mitral	Integer	Mitral regurgitation grade
Regurg_Aortic	Integer	Aortic regurgitation grade
Regurg_Tri	Integer	Tricuspid regurgitation grade
Regurg_Pulm	Integer	Pulmonary regurgitation grade
E_Mitral_wave	Integer	Mitral E wave (m/s)
A_Mitral_wave	Integer	Mitral A wave (m/s)
EA_Mitral_ratio	Single	Mitral E/A ratio
Decel_time1	Integer	Deceleration time (ms)
E_tri_wave	Integer	Tricuspd E wave (m/s)
A_tri_wave	Integer	Tricuspid A wave (m/s)
EA_tri_ratio	Single	Tricuspid E/A ratio
Decel_time2	Double	Deceleration time (ms)
SMV_lat_ann	Integer	Systolic myocardial velocity (m/s)_lateral annulus
Ewave_lat_ann	Integer	E wave (m/s)_lateral annulus
Awave_lat_ann	Integer	A wave (m/s)_lateral annulus
EAratio_lat_ann	Integer	E/A ratio_lateral annulus
SMV_med_ann	Integer	Systolic myocardial velocity (m/s)_medial annulus
Ewave_med_ann	Integer	E wave (m/s)_medial annulus
Awave_med_ann	Integer	A wave (m/s)_medial annulus
EAratio_med_ann	Integer	E/A ratio_medial annulus
Pericardial_effusion	Integer	Presence of pericardial effusion (0:No; 1:Yes)
Mural_thrombus	Integer	Presence of mural thrombus(0:No; 1:Yes)
RA	Integer	RA
RV	Integer	RV
LA	Integer	LA
LV	Integer	LV

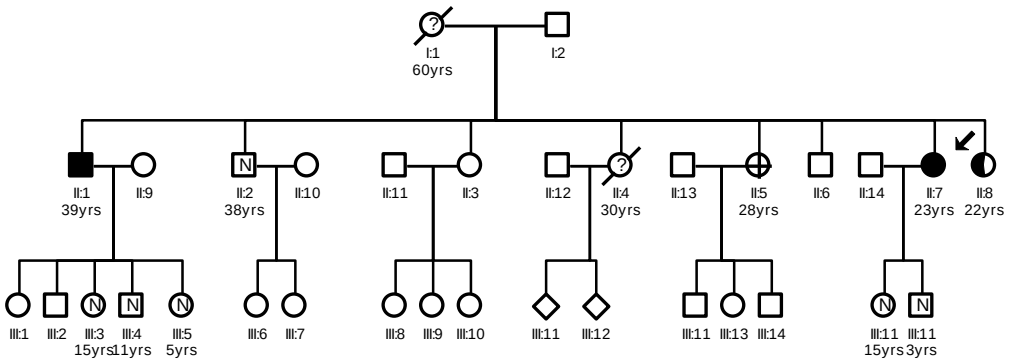
<u>Appendix 7.</u> For Section 3.2.2 – Pedigrees of All Families Included in Final Analysis (N= 27)

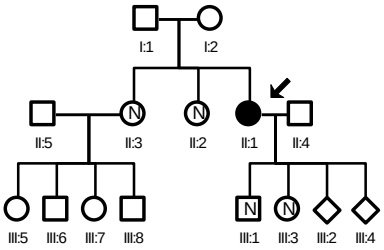
I. Probands with no history of hypertension

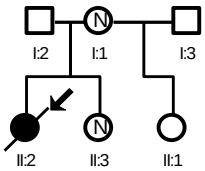


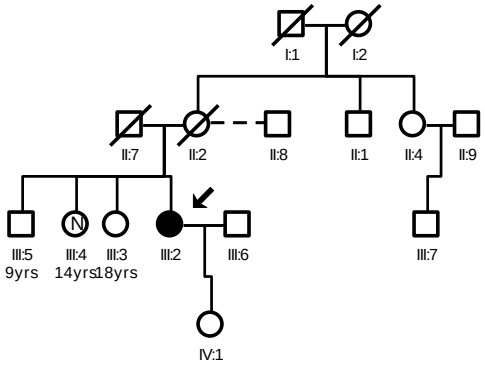


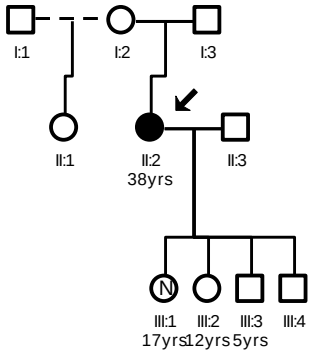


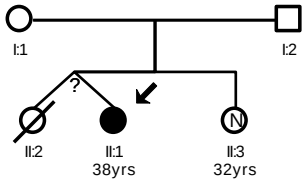

I:1
60yrs
I:2
II:1
39yrs
II:9
II:2
38yrs
II:10
II:11
II:3
II:12
II:4
30yrs
II:13
II:5
28yrs
II:6
II:14
II:7
23yrs
II:8
22yrs
III:1
III:2
III:3
15yrs
III:4
11yrs
III:5
5yrs
III:6
III:7
III:8
III:9
III:10
III:11
III:12
III:11
III:13
III:14
III:11
15yrs
III:11
3yrs

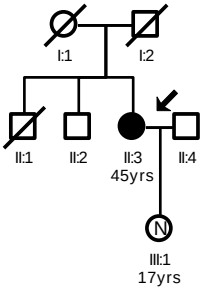

I:1
I:2
II:5
II:3
II:2
II:1
II:4
III:5
III:6
III:7
III:8
III:1
III:3
III:2
III:4

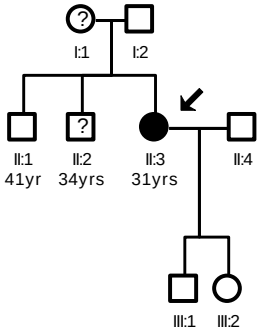

I:2
I:1
I:3
II:2
II:3
II:1

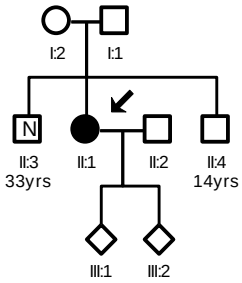

I:1
I:2
II:7
II:2
II:8
II:1
II:4
II:9
III:5
9yrs
III:4
14yrs
III:3
18yrs
III:2
III:6
III:7
IV:1

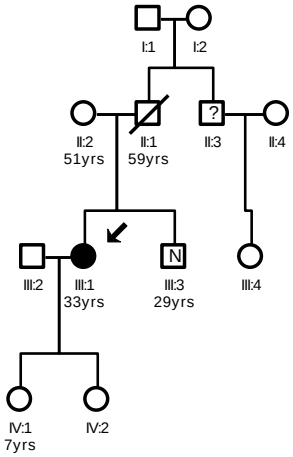

I:1
I:2
I:3
II:1
II:2
38yrs
II:3
III:1
17yrs
III:2
12yrs
III:3
5yrs
III:4

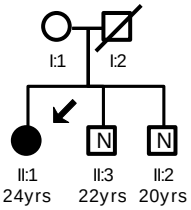

I:1
I:2
?
N
II:2
II:1
38yrs
II:3
32yrs

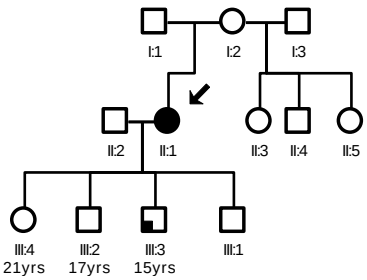

I:1
I:2
II:1
II:2
II:3
45yrs
II:4
N
III:1
17yrs

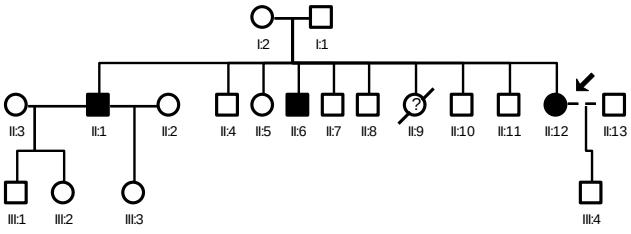

?
I:1
I:2
II:1
41yr
?
II:2
34yrs
II:3
31yrs
II:4
III:1
III:2

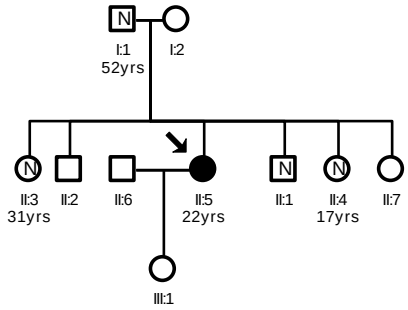

I:2
I:1
N
II:3
33yrs
II:1
II:2
II:4
14yrs
III:1
III:2

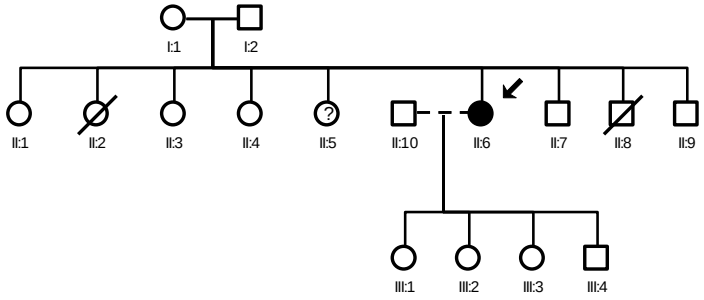

I:1
I:2
II:2
51yrs
II:1
59yrs
?
II:3
II:4
III:2
III:1
33yrs
N
III:3
29yrs
III:4
IV:1
7yrs
IV:2


I:1
I:2
II:1
24yrs
N
II:3
22yrs
N
II:2
20yrs

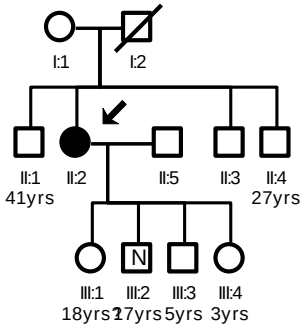

I:1
I:2
I:3
II:2
II:1
II:3
II:4
II:5
III:4
21yrs
III:2
17yrs
III:3
15yrs
III:1

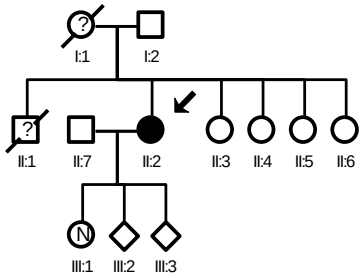

I:2
I:1
II:3
II:1
II:2
II:4
II:5
II:6
II:7
II:8
?
II:9
II:10
II:11
II:12
II:13
III:1
III:2
III:3
III:4

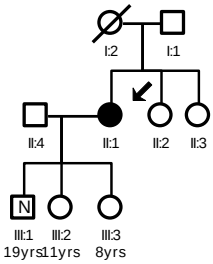


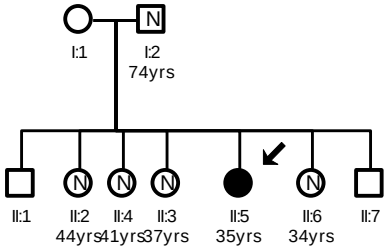


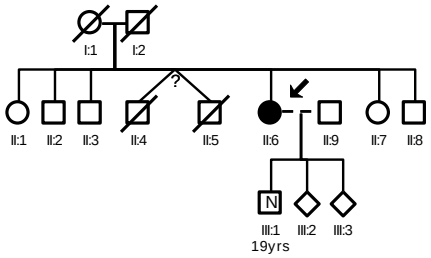
II. Probands with a history of hypertension

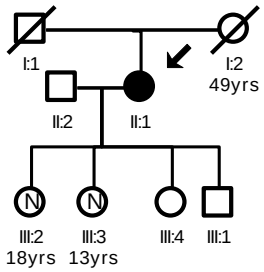


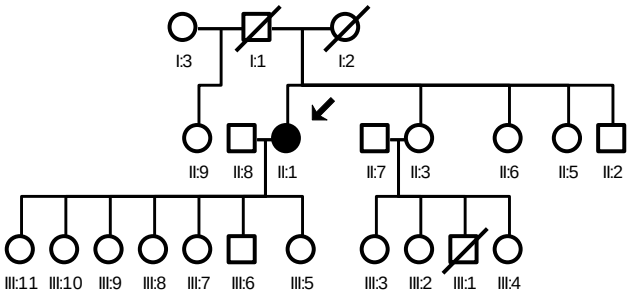


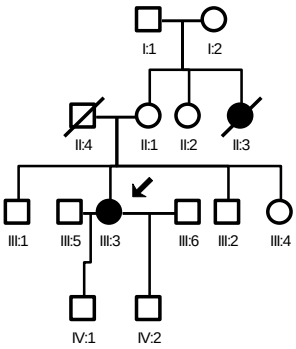


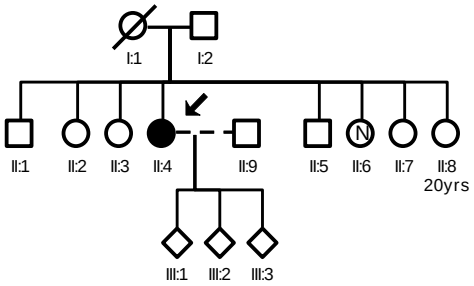





I:1
I:2
49yrs
II:2
II:1
III:2
18yrs
III:3
13yrs
III:4
III:1


I:3
I:1
I:2
II:9
II:8
II:1
II:7
II:3
II:6
II:5
II:2
III:11
III:10
III:9
III:8
III:7
III:6
III:5
III:3
III:2
III:1
III:4


I:1
I:2
II:4
II:1
II:2
II:3
III:1
III:5
III:3
III:6
III:2
III:4
IV:1
IV:2


I:1
I:2
II:1
II:2
II:3
II:4
II:9
II:5
II:6
II:7
II:8
20yrs
III:1
III:2
III:3