

TABLE OF CONTENTS

	PAGE NO
Declaration	i
Acknowledgements	ii
Conference attendance and presentations	iii
Abstract	iv
Abbreviations	vi
Tables	ix
Figures	x
1. Introduction	
1.1. Epidemiology of cardiac hypertrophy and failure	1
1.2. Normal cardiac metabolism	2
1.2.1. Regulation of cardiac metabolism by AMP-activated protein kinase	4
1.2.2. Transcriptional regulation of fatty acid metabolism	5
1.3. Cardiac metabolism in LVH and heart failure	12
1.4. Neurohormonal activation in heart failure	14

1.5. Hypothesis	17
1.6. Study objectives	17
2. Materials and Methods	
2.1. Materials	20
2.2. Methods	21
2.2.1. Ethical approval	21
2.2.2. Preparations	21
a) Isoproterenol preparation	21
b) Gelatine cubes preparation	21
c) Anaesthetic preparation	22
2.2.3. Animal model and experimental protocol	22
2.2.4. Metabolic substrate measurements	23
2.2.5. Echocardiography	26
2.2.6. Tissue measurements	27
2.2.7. mRNA extraction, cDNA synthesis and quantitative RT-PCR	29
a) mRNA extraction	29
b) cDNA synthesis and quantitative RT-PCR	30
2.2.8. Electron transmission microscopy	31
2.2.9. Statistical analysis	33

3. Results

3.1. Body mass, visceral fat mass and tibial length	34
3.2. Fenofibrate prevents isoproterenol-induced lowering of blood triglycerides	34
3.3. Fenofibrate delays the onset of isoproterenol-induced left ventricular hypertrophy	36
3.4. Fenofibrate prevents isoproterenol-induced LV systolic chamber dysfunction	38
3.5. Cardiac mRNA expression of metabolic regulation genes	41
3.5.1. Increased AMPK α_2 gene expression following co-administration of isoproterenol and fenofibrate	41
3.5.2. Downregulation of PPAR α and PGC-1 α gene expressions following co-administration of isoproterenol and fenofibrate	42
3.5.3. Fenofibrate administration preserves the mRNA expression of TFAM	48
3.6. Mitochondrial analysis	50
3.6.1. No evidence of mitochondrial biogenesis following administration of isoproterenol and fenofibrate	50
3.6.2. Fenofibrate prevents isoproterenol-induced mitochondrial pathology	50
3.7. Correlations between gene expression and cardiac function	51

4. Discussion

4.1. Main outcomes of the study	56
4.2. Fenofibrate prevents isoproterenol-induced LVH and LV systolic dysfunction	57
4.3. Fenofibrate preserves mitochondrial integrity against isoproterenol-induced damage	60
4.4. Fenofibrate may protect against isoproterenol cardiac damage via metabolic remodeling	63
4.5. The role of AMPK α_2 in fenofibrate-induced cardioprotection	67

5. Conclusion

5.1. Summary and conclusions	70
5.2. Limitations and future studies	70

6. References

7. Appendices

DECLARATION

I, Tlangelani Maswanganyi, hereby declare that this dissertation is my own work (except where acknowledgements indicate otherwise). It is being submitted for the degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....

Mr Tlangelani Maswanganyi

Signed at.....this.....day of..... 2010

Dr Siyanda Makaula (Supervisor)

Signed at.....this..... day of 2010

Dr Richard Brooksbank (Co-Supervisor)

Signed at.....this..... day of 2010

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CONFERENCE ATTENDANCE AND PRESENTATIONS

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ABSTRACT

The role of metabolic remodelling in heart failure is not fully understood, significant evidence has accumulated to suggest that it may be central to the development of left ventricular (LV) remodelling and LV dysfunction. Heart failure is also characterized by sustained neurohumoral activation. We have previously demonstrated that chronic low dose administration of isoproterenol contributes to cardiac structural and functional changes, however, little is known about metabolic and mitochondrial changes that may accompany the development of isoproterenol-mediated heart failure. In the current study, we hypothesised that metabolic dysregulation and loss of mitochondrial integrity mediates left ventricular hypertrophy (LVH) and left ventricular (LV) systolic dysfunction in the isoproterenol model of heart failure. Furthermore, modulation of expression of key metabolic genes and mitochondrial transcription factors by fenofibrate, a peroxisome proliferator-activated receptor alpha (PPAR α) agonist, will preserve left ventricular function.

To achieve this, male Sprague-Dawley rats weighing between 250-300g were injected with low dose isoproterenol (0.04 mg.kg⁻¹.day⁻¹) and/or administered with fenofibrate (100 mg.kg⁻¹.day⁻¹) for five weeks. Thereafter, metabolic substrates such as glucose, FFAs and TG concentrations were obtained. Left ventricular hypertrophy (LVH) and cardiac function were assessed using echocardiography. Expressions of metabolic and mitochondrial genes such as PPAR α , AMP-activated protein kinase alpha 2 (AMPK α_2), PPAR γ coactivator-1 (PGC-1 α), mitochondrial transcription factor (TFAM) and nuclear respiratory factor-1 (NRF-1) were determined using real-time polymerase chain reaction. Mitochondrial integrity was assessed using transmission electron microscopy.

Administration of isoproterenol significantly increased left ventricular mass (LVM) and decreased endocardial fractional shortening (FS_{end}); isoproterenol also induced myofibrillar

derangement, mitochondrial derangement and cristae disruption. Fenofibrate prevented isoproterenol-induced increase in LVM and improved FS_{end}. Fenofibrate co-administration prevented loss of mitochondrial integrity possibly via TFAM. Furthermore, fenofibrate may have induced metabolic remodelling via upregulation of AMPK α_2 and downregulation of cardiac PPAR α and PGC-1 α .

Therefore our data suggests that fenofibrate-mediated cardioprotection against isoproterenol-induced LVH and LV systolic dysfunction was accompanied by metabolic switching and preservation of mitochondrial integrity. While isoproterenol did not induce any changes in metabolic genes, fenofibrate-mediated cardioprotection could have been through changes in metabolic genes.

ABBREVIATIONS

ACC	Acetyl CoA carboxylase
ACS	Acyl-CoA synthetase
ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
AMPK α_2	AMP-activated protein kinase alpha 2
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BM	Total body mass
CPT	Carnitine palmitoyl transferase
FA	Fatty acid
FABP	Fatty acid binding protein
FAO	Fatty acid oxidation
FARE	Fatty acid response element
FAT	Fatty acid translocase
FATP	Fatty acid transport protein
FFA	Free fatty acid
FS _{end}	Endocardial fractional shortening

FS _{mid}	Midwall fractional shortening
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GLUT-4	Glucose transporter-4
HM/TL	Total heart mass-to-tibial length ratio
LCAD	Long-chain acyl-CoA dehydrogenase
LVED PWT	Left ventricular end-diastolic posterior wall thickness
LVEDD	Left ventricular end-diastolic diameter
LVES PWT	Left ventricular end-systolic posterior wall thickness
LVEDS	Left ventricular end systolic diameter
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVM/TL	Left ventricular mass-to-tibial length ratio
MCAD	Medium chain acyl-coA dehydrogenase
NRF-1	Nuclear respiratory factor-1
NS	Not significant
PGC-1 α	Peroxisome proliferator-activated receptor gamma coactivator-1 alpha

PPAR α	Peroxisome proliferator-activated receptor alpha
ROS	Reactive oxygen species
RT-PCR	Real-time polymerase chain reaction
RVM	Right ventricular mass
RVM/TL	Right ventricular mass-to-tibial length ratio
RXR α	Retinoid X receptor-alpha
SD	Sprague-Dawley
SEM	Standard error of the mean
SNS	Sympathetic nervous system
TFAM	Mitochondrial transcription factor
TG	Triglyceride
TL	Tibial length
UCP	Uncoupling protein
VFM	Visceral fat mass
VLCAD	Very long-chain acyl-CoA dehydrogenase

TABLES

TABLE	PAGE NO
1. Primers sequences that were used in RT-PCR experiments	32
2. Body mass, visceral fat mass and tibial length among all groups	35
3. Fenofibrate prevents isoproterenol-induced lowering of blood triglycerides	37
4. Fenofibrate prevents the onset of isoproterenol-induced left ventricular hypertrophy	39
5. Correlation coefficients between cardiac function and metabolic gene regulators	55

FIGURES

FIGURE	PAGE NO
1. Fatty acid uptake, transport and mitochondrial β -oxidation	6
2. Regulation of FA and glucose metabolism by AMPK	7
3. Transcriptional control of FAO and mitochondrial biogenesis by PGC-1 α	9
4. Transcriptional control of mitochondrial structure, function and respiration	11
5. Hypothesis	19
6. Experimental design	24
7. Determination of cardiac function using echocardiography	28
8. Cardiac diastolic dimensions as determined by echocardiography in rats	43
9. Cardiac systolic dimensions as determined by echocardiography in rats	44
10. Fenofibrate prevents isoproterenol-induced LV systolic chamber dysfunction	45
11. Increased AMPK α_2 gene expression following co-administration of isoproterenol and fenofibrate	46
12. Downregulation of PPAR α gene expression following co-administration of isoproterenol and fenofibrate	47
13. Fenofibrate co-administration preserves mRNA expression of TFAM	49
14. No evidence of mitochondrial biogenesis following administration of isoproterenol and fenofibrate	52
15. Fenofibrate prevents isoproterenol-induced mitochondrial derangement	53
16. Fenofibrate prevents isoproterenol-induced disruption and swelling of mitochondrial cristae	54

CHAPTER ONE: INTRODUCTION

CHAPTER TWO: MATERIALS AND METHODS

CHAPTER THREE: RESULTS

CHAPTER FOUR: DISCUSSION

CHAPTER FIVE: CONCLUSION

CHAPTER SIX: REFERENCES

CHAPTER 7: APPENDICES