Clinical Studies of Patients with Acute Coronary Syndromes in the Absence of Obstructive Coronary Artery Disease

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Discipline of Medicine

The University of Adelaide

March 2011


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Table of Contents

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Acknowledgements

First and foremost I would like to sincerely thank my supervisor Professor John Beltrame for his unrelenting patience, understanding, and encouragement. I feel very blessed to have been given the opportunity to work alongside a truly a gifted cardiologist and researcher; whose dedication and brilliance in both his clinical and research work is to be admired. One could not have asked for a better teacher, mentor and friend. I am deeply grateful for his guidance and academic expertise throughout my PhD. John, now you can stop getting grey hairs!

I would like to thank the other members of the supervisory panel Professor Robert Adams and Dr Angela Kucia, for their academic contribution, professionalism and constant support. I could not have asked for better teachers to guide me through this journey. I would also like to acknowledge Professor Chris Zeitz, for his professional guidance and words of wisdom over the past 5 years. I am forever grateful for his kindness and generosity. Chris, now you can finally call me "Dr Cutri"!

To all the members of the Neurogenetics Unit from the Stroke Research Program at The Queen Elizabeth Hospital, I would like to sincerely thank you for your collaboration and academic input towards the theoretical framework of the genetic polymorphisms study.

I would like to extend my thanks to all the staff in Cath Lab, Coronary Care Unit and Cardiology Department, especially the nurses and secretaries, for assisting me with various components of this research project. A special thank you to Cate Green, who took me under her wing on my first day and is one of the best clinical research nurses I've worked with. Thank you to all my PhD colleagues, in particular Rosanna Tavella, for being such a strong

pillar of support and for always helping me with my million stats questions; and to my friend Roger Yazbeck, for all his professional and personal guidance over the years.

I would also like to acknowledge John Field for his assistance with statistical analyses and Rosemary Purcell for her editing services and high level of professionalism.

I am deeply grateful to the cardiac patients and healthy volunteer subjects who so kindly participated—without any expectations or monetary reward—in the clinical studies documented in this thesis.

To my sisters Francesca and Laura, thank you for your constant encouragement; and to my fiancé Bruno, I am indebted to you for being incredibly understanding and supportive. It takes a very patient man to put up with a PhD student writing her thesis.

Lastly I would like to thank my parents, Cosimo and Angela Cutri, who have been a constant source of emotional, moral and financial support during my postgraduate years. This thesis would certainly not have existed without them. It is thanks to my mother, who was not given the opportunity to pursue tertiary education that inspired me to want to go to university. She has always encouraged me to pursue my dream of becoming a scientist—and it is to her that this thesis is dedicated.

Abstract

Background: Although there is extensive data on patients with obstructive coronary artery disease in relation to clinical manifestations, health outcomes and genetic predisposition, little is known about these features in patients with Non-obstructive Coronary Artery Disease (NoCAD), despite these patients representing 20-30% of patients undergoing angiography.

Objectives: This thesis examined the clinical features, health outcomes and genetic polymorphisms in patients with NoCAD. The specific objectives include (1) comparing the health outcomes of NoCAD patients who present with an acute coronary syndrome (ACS) to those who have a stable chest pain pattern; (2) examining the prevalence of acute ischaemic electrocardiographic (ECG) changes in patients with the coronary slow flow phenomenon (CSFP) admitted with an ACS; and (3) to investigate the frequency of an endothelial nitric oxide synthase (eNOS) and endothelin-1 (ET-1) polymorphism in patients with: (a) chest pain and NoCAD and, (b) the CSFP.

Summary of Thesis Chapters: **Chapter 1** summarises the relevant background for the studies described in this thesis. **Chapter 2** examines health outcomes, including health related quality of life (HRQoL) measures, in ACS versus stable chest pain presentations in patients with NoCAD, over 12 months follow-up. HRQoL measures were assessed using both a generic (Short-Form-36) and disease-specific (Seattle Angina Questionnaire) instrument. This study found no significant differences in health outcomes between the two clinical cohorts. **Chapter 3** assesses evidence of myocardial ischemia, utilising continuous ST/T wave monitoring to examine the frequency of ST/T wave fluctuations during an ACS in patients with the CSFP compared to healthy control subjects. This study found 92% of patients with the CSFP showed ECG evidence of myocardial ischaemia on continuous ST monitoring

during an ACS presentation, with significant ST segment and T-wave fluctuations occurring in 24% and 86% of CSFP patients; respectively. In comparison, ST/T wave fluctuations were observed in 5% of healthy control subjects. **Chapter 4** is a case-control study that investigates the frequencies of the eNOS (T-786C) and ET-1 (+138A del/ins) polymorphisms in patients with: (a) chest pain and NoCAD and (b) the CSFP. There were no significant differences in the frequency of each polymorphism associated with patients diagnosed with chest pain and NoCAD. However, the frequency of the +138 del/ins polymorphism from the ET-1 gene was significantly more prevalent in the CSFP patients compared to the control groups.

Conclusion: This thesis has demonstrated that NoCAD patients who present with an ACS have similar health outcomes to those with stable chest pain. Patients with the CSFP frequently present with an ACS and this is associated with dynamic ST/T wave fluctuations and in particular T-wave inversion. The underlying pathogenesis of the CSFP requires further study; however, endothelin appears to have an important role. Consistent with this mechanism, this study found an increased prevalence of the +138 del/ins polymorphism from the ET-1 gene in patients with the CSFP. We therefore postulate that endothelin-1 (possibly derived from inflammatory cells) produces acute microvascular vasoconstriction in patients with the CSFP resulting in myocardial ischaemia and thus an ACS presentation. Further studies are required to assess this hypothesis.

Publications and Presentations Derived from this Thesis

- **Refereed Journal Articles**

1. **Cutri N.**, Zeitz C., Kucia AM., Beltrame JF. *ST/T wave changes during Acute Coronary Syndrome Presentation in Patients with the Coronary Slow Flow Phenomenon*. International Journal of Cardiology. 2011 Feb 3;146(3):457-8.

2. Beltrame JF, Tavella R, **Cutri N**. *Quality of Life with PCI versus Medical Therapy in Stable Coronary Disease*. New England Journal of Medicine. 2008, Nov 20;359(21)2289-90.

3. Tavella, R, **Cutri N**, Adams, R, and Beltrame JF. *Health Status of Stable Patients With Obstructive or Non-Obstructive Coronary Artery Disease Compared With Healthy Controls*. Circulation: Cardiovascular Quality and Outcomes, 2011, In Press

4. Tavella, R, **Cutri N**, and Beltrame JF. *Health Status Outcomes in Patients With Non-Obstructive Coronary Artery Disease*. Circulation: Cardiovascular Quality and Outcomes, 2011, In Press

- **Conference Presentations**

5. **Cutri N**, AM Kucia, Zeitz C, Beltrame JF: *ST/T wave Analysis in Patients with the Coronary Slow Flow Phenomenon* (Poster Presented at the National Heart Foundation Conference Annual Scientific Meeting in Brisbane, Australia June 2009)

6. **Cutri N**, Kucia AM, Zeitz C, Beltrame JF: *Continuous ST/T wave Monitoring During an Acute Coronary Syndrome Presentation in Patients with the Coronary Slow Flow Phenomenon* (Oral Presentation at The Queen Elizabeth Hospital Annual Research Day in Adelaide, Australia October 2008)

7. **Cutri N**, Kucia AM, Zeitz C, Beltrame JF: *ST/T wave Analysis in Patients with the Coronary Slow Flow Phenomenon* (Poster Presented at the 56th Cardiac Society of Australia and New Zealand, Annual Scientific Meeting in Adelaide, Australia August 2008)

8. **Cutri N**, Kucia AM, Zeitz C, Beltrame JF: *The Effects of Positional Changes on T-wave Amplitude in Healthy Controls* (Poster Presented at the 56th Cardiac Society of Australia and New Zealand Annual Scientific Meeting in Adelaide, Australia August 2008)

9. **Cutri N**, Tavella R, Beltrame JF: *Gene Polymorphisms in Non-Obstructive Coronary Heart Disease* (Oral Presentation Australian Society for Medical Research Annual Scientific Meeting in Adelaide, Australia June 2008)

10. **Cutri N**, Kucia AM, Beltrame JF, Adams R: *T wave Changes in patients with Normal Coronary Arteries* (Poster Presented at The Queen Elizabeth Hospital Annual Research Day in Adelaide, Australia October 2007)

11. **Cutri N**, Tavella R, Green CA, Beltrame JF: *Is the Severity of Coronary Artery Disease Related to Health-Related Quality of Life* (Poster Presented at the National Heart Foundation Conference Annual Scientific Meeting in Sydney, Australia March 2006)

Abbreviations

A2RB	Angiotensin 2 Receptor Blocker
ACE	Angiotensin Converting Enzyme
Ach	Acetylcholine
ACS	Acute Coronary Syndrome
ADMA	Asymmetric Dimethylarginine
AP-1	Activator Protein 1
ATP	Adenosine Tri-Phosphate
bp	base pair
Ca^{2+}	Calcium Ions
CAD	Coronary Artery Disease
CaM	Calcium Calmodulin
cAMP	cyclic Adenosine Monophosphate
CCB	Calcium Channel Blocker
CCSC	Canadian Cardiovascular Society Classification
CCU	Coronary Care Unit
cDNA	complementary Deoxyribonucleic Acid
CFR	Coronary Flow Reserve
cGMP	Cyclic Guanosine Monophosphate
CHD	Coronary Heart Disease
CK	Creatine Kinase
Cls	Confidence Intervals
cNOS	constitutive Nitric Oxide Synthase
COPD	Chronic Obstructive Airways Disease

CRP	C-Reactive Protein
CSFP	Coronary Slow Flow Phenomenon
CTFC	Corrrected TIMI Frame Count
DNA	Deoxyribonucleic Acid
ECE	Endothelin Converting Enzyme
ECG	Electrocardiogram
EDHF	Endothelial Derived Hyperpolarising Factor
EDTA	Ethylenediaminetetraacetic Acid
eNOS	endothelial Nitric Oxide Synthase
EQ-5D	Euroqol-5D
ET-1	Endothelin-1
ETA	Endothelin Receptor A
ETB	Endothelin Receptor B
ETT	Exercise Treadmill Testing
GATA	Globin Transcription Factor
GEMS	General Electric Medical Systems
GTP	Guanosine Triphosphate
H^+	Hydrogen Ions
HCl	Hydrochloric Acid
HLA	Human Leukocyte Antigen
HR	Heart Rate
HT	Hypertension
IMR	Index of Myocardial Resistance
iNOS	inducible Nitric Oxide Synthase
IP_3	Inositol triphosphate

K^+	Potassium Ions
KB	Kilobase
KCl	Potassium Chloride
LAD	Left Anterior Descending
L'Arg	L'arginine
LSM	Lymphocyte Separation Medium
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
MOS	Medical Outcomes Study
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MSS	Mental Summary Score
MUSE	Marquette Universal System for Electrocardiology
Na^+	Sodium Ions
Na_2PO^4	Disodium Hydrogen Orthophasphate
NaCl	Sodium Chloride
NCBI	National Centre for Biotechnology Information
NF-1	Nuclear Factor-1
NMR	Nuclear Magnetic Resonance
nNOS	neuronal Nitric Oxide Synthase
NO	Nitric Oxide
NSTEMI	Non-ST-Elevation Myocardial Infarction
NYHA	New York Heart Association

OCAD	Obstructive Coronary Artery Disease
Ors	Odds Ratios
PBS	Phosphate Buffered Saline
PCR-SSP	Polymerase Chain Reaction-Sequence Specific Primer
PET	Positron Emission Tomography
PG_2	Prostacyclin
PIP_2	Phosphatidylinositol
PKG	Protein Kinase G
PreproET-1	Preproendothelin-1
PSS	Physical Summary Score
RNA	Ribonucleic Acid
SAQ	Seattle Angina Questionnaire
SF-36	Short-Form 36
SMC	Smooth Muscle Cell
SNP	Single Nucleotide Polymorphism
SPECT	Single Photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences
SR	Sarcoplasmic Reticulum
STEMI	ST-Elevation Myocardial Infarction
STM	Middle of ST Segment
SV	Stroke Volume
TGF	Transforming Growth Factor
TIMI	Timi Frame Count
TNF	Tumour Necrosis Factor
WT	Wild-Type