Clinical and Biological Determinants of the
Coronary Slow Flow Phenomenon

Victoria A. Kopetz
BSc(Honours), Grad. Cert. ST&C

Faculty of Health Sciences
Discipline of Medicine
The University of Adelaide
South Australia
Australia

A thesis submitted in fulfilment of the requirement of the degree of
Doctor of Philosophy
July 2012
Table of Contents

Declaration ........................................................................................................................................VII
Acknowledgements ......................................................................................................................... IX
Abbreviations .................................................................................................................................. XII
Abstract ........................................................................................................................................... XVII
Statement of Authorship .................................................................................................................. XX
Published Abstracts and Presentations Arising from this Thesis ........................................... XXV
Peer Reviewed Publications Arising from this Thesis ....................................................... XXVI
Other Abstracts and Presentations .............................................................................................. XXVII
Preface .............................................................................................................................................. XXIX

CHAPTER I ........................................................................................................................................... 1
1.1. Basic Principles of the Coronary Circulation ................................................................. 2
   1.1.1 Functional Anatomy ...................................................................................................... 2
      1.1.1.1 Arteries ................................................................................................................. 2
      1.1.1.2 Pre-arterioles ..................................................................................................... 3
      1.1.1.3 Arterioles .......................................................................................................... 3
   1.1.2 Functional Histology ..................................................................................................... 4
      1.1.2.1 Tunica intima ..................................................................................................... 4
      1.1.2.2 Tunica media ..................................................................................................... 6
      1.1.2.3 Tunica adventitia .............................................................................................. 7
   1.1.3 Summary .......................................................................................................................... 7
1.2. Regulation of the Coronary Circulation ......................................................................... 9
   1.2.1 Neural ............................................................................................................................ 10
      1.2.1.1 Sympathetic innervation .................................................................................... 10
      1.2.1.2 Parasympathetic innervation .......................................................................... 12
   1.2.2 Humoral ........................................................................................................................ 12
   1.2.3 Metabolic ...................................................................................................................... 14
   1.2.4 Endothelial ................................................................................................................... 15
1.2.4.1 Vasodilators ................................................................. 16
1.2.4.2 Vasoconstrictors .......................................................... 20
1.2.5 Mechanical ........................................................................ 23
1.2.6 Summary ........................................................................... 23

1.3. Coronary Circulatory Dysfunction ........................................ 24
1.3.1 Endothelial Dysfunction ...................................................... 24
   1.3.1.1 Asymmetric Dimethylarginine (ADMA) ....................... 27
1.3.2 Neural Mechanisms .............................................................. 28
1.3.3 Inflammation ...................................................................... 28
   1.3.3.1 C-reactive protein ....................................................... 29
   1.3.3.2 Myeloperoxidase ......................................................... 30
1.3.4 Atherosclerosis .................................................................. 31
1.3.5 Oxidative Stress .................................................................. 36
   1.3.5.1 Malondialdehyde ......................................................... 37
   1.3.5.2 Homocysteine .............................................................. 38
1.3.6 Spasm ............................................................................... 39
1.3.7 Thrombosis ...................................................................... 40
1.3.8 Summary ........................................................................... 42

1.4. Consequences of Coronary Dysfunction ................................. 44
1.4.1 Myocardial Ischaemia .......................................................... 44
1.4.2 Ischaemic Cascade ............................................................... 44
1.4.3 Angina Pectoris ................................................................. 45
1.4.4 Summary ........................................................................... 46

1.5. Evaluation of the Coronary Circulation .................................. 48
1.5.1 Structural imaging of the coronary arteries ......................... 49
   1.5.1.1 Coronary angiography and intra-vascular ultrasound .... 49
   1.5.1.2 CT and MR angiography ............................................. 49
1.5.2 Ischaemia detection techniques .......................................... 50
   1.5.2.1 ECG and metabolic indicators .................................. 50
   1.5.2.2 Myocardial Perfusion Imaging .................................. 51
   1.5.2.3 Echocardiography ...................................................... 51
1.5.3 Coronary blood flow assessment in the microvasculature ...... 52
1.5.4 Summary ........................................................................... 53

1.6. Role of Microvascular Dysfunction in Disease ....................... 54
1.6.1 Coronary Microvascular Dysfunction ................................ 54
1.6.2 Defining angina and normal coronary arteries ........................................56
  1.6.2.1 Cardiac Syndrome X .................................................................57
  1.6.2.2 Microvascular Angina .................................................................58
  1.6.2.3 Coronary Slow Flow Phenomenon ............................................58
  1.6.2.4 Primary Coronary Microvascular Dysfunction ..........................60
1.6.3 Summary ..................................................................................................61

1.7. Cardiac Syndrome X .................................................................................62
  1.7.1 Pathophysiological mechanisms ......................................................62
  1.7.2 Clinical features ..................................................................................65
  1.7.3 Treatments ..........................................................................................66
  1.7.4 Summary .............................................................................................69

1.8. Coronary Slow Flow Phenomenon .........................................................70
  1.8.1 Pathophysiological Mechanisms ......................................................70
  1.8.2 Clinical Features ................................................................................72
  1.8.3 Treatments ..........................................................................................74
  1.8.4 Summary .............................................................................................76

1.9. Thesis Objectives .....................................................................................77

CHAPTER II ....................................................................................................80

2.1. Introduction ..............................................................................................82

2.2. Methods ....................................................................................................84
  2.2.1 Patient Recruitment and Blood Collection .....................................84
  2.2.2 Proteomic Analysis ..........................................................................85
    2.2.2.1 Depletion of abundant plasma proteins .....................................86
    2.2.2.2 Fluorescence labelling ..............................................................86
    2.2.2.3 Two-dimensional electrophoresis .............................................87
    2.2.2.4 Gel imaging ...............................................................................87
    2.2.2.5 Power analysis ..........................................................................88
    2.2.2.6 Liquid chromatography mass spectrometry .............................88
  2.2.3 Western Blotting Validation ...............................................................89
  2.3.1 Patient Characteristics .....................................................................91
  2.3.2 Proteomic Analysis ..........................................................................91
  2.3.3 Western blot analysis .......................................................................92

2.4. Discussion ................................................................................................108
  2.4.1 Potential role of inflammation in the ACS associated with the CSFP..109
2.4.2 Potential role of oxidative stress in the ACS associated with the CSFP ................................................................. 111
2.4.3 Fibronectin and the CSFP ........................................................................................................................................... 112
2.4.4 Study Limitations ........................................................................................................................................................ 112
2.4.5 Clinical use of Proteomic Profiling Strategy ............................................................................................................ 114

2.5 Conclusion ....................................................................................................................................................................... 115

CHAPTER III ........................................................................................................................................................................ 116

3.1. Introduction ...................................................................................................................................................................... 118

3.2. Methods ............................................................................................................................................................................. 120
  3.2.1 Study Subjects ............................................................................................................................................................. 120
  3.2.2 Study Protocol ............................................................................................................................................................. 121
  3.2.3 Endothelial Function Assessment ................................................................................................................................ 121
  3.2.4 Plasma Biochemical Assays ......................................................................................................................................... 122
    3.2.4.1 Homocysteine and high-sensitivity CRP assays ........................................................................................................ 123
    3.2.4.2 Myeloperoxidase assay ............................................................................................................................................... 123
    3.2.4.3 Asymmetric dimethylarginine assay ......................................................................................................................... 123
    3.2.4.4 Malondialdehyde assay ............................................................................................................................................ 124
  3.2.5 Data and Statistical Analysis ....................................................................................................................................... 124

3.3. Results .............................................................................................................................................................................. 126
  3.3.1 Endothelial Function Studies ........................................................................................................................................ 126
  3.3.2 Plasma Biochemical Markers ....................................................................................................................................... 127

3.4. Discussion ......................................................................................................................................................................... 133
  3.4.2 Alternative Potential Mechanisms for the CSFP ........................................................................................................... 136
  3.4.3 Study Limitations ........................................................................................................................................................ 137

3.5. Conclusion ......................................................................................................................................................................... 138

CHAPTER IV .......................................................................................................................................................................... 139

4.1. Introduction ....................................................................................................................................................................... 141

4.2. Methods .............................................................................................................................................................................. 143
  4.2.1 Study Patients ............................................................................................................................................................... 143
  4.2.2 Study Protocol ............................................................................................................................................................... 143
  4.2.3 Study Endpoints ......................................................................................................................................................... 144
  4.2.4 Clinical Assessments ................................................................................................................................................... 145
4.2.5 Endothelial Function Assessment ...............................................145
4.2.6 Plasma Biochemical Assays ......................................................146
  4.2.6.1 Homocysteine and high-sensitivity CRP assays .........................147
  4.2.6.2 Myeloperoxidase assay ..................................................147
  4.2.6.3 Asymmetric dimethylarginine assay ....................................148
  4.2.6.4 Malondialdehyde assay ..................................................148
4.2.7 Data Analysis .........................................................................149

4.3 Results .......................................................................................150
  4.3.1 Patient Characteristics .........................................................150
  4.3.2 Clinical Endpoints ................................................................150
  4.3.3 Endothelial Function Studies .................................................151
  4.3.4 Endothelial, Inflammatory and Oxidative Stress Biomarkers .........151

4.4 Discussion ................................................................................158

4.5. Conclusion .................................................................................161

CHAPTER V ....................................................................................162

5. Thesis Conclusion .......................................................................163

APPENDICES ................................................................................170
  Appendix A – Publication 1 ..........................................................171
  Appendix B – Publication 2 ..........................................................171

References .......................................................................................187
Declaration

I, Victoria Kopetz, certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis (as listed below*) resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

………………………

Victoria A. Kopetz                     Date

Potential mechanisms of the Acute Coronary Syndrome Presentation – Insight from a plasma proteomic approach.

*International Journal of Cardiology* 2012;156:84-91


*Cardiology* 2012;121:197-203
Acknowledgements

After six long years faced with many challenges, it is an absolute pleasure and relief to present the finished document contained herein. An enormous amount of blood, sweat and tears went into undertaking this PhD project and it would definitely not have been achievable without the tremendous support of my colleagues, friends and family. Although I could never thank all of you enough personally, I will attempt to mention most of you and of all your contributions in these acknowledgements.

First and foremost, I would like to give my utmost gratitude and thanks to my principal PhD supervisor, Professor John Beltrame for guiding me in my PhD journey and providing me with the wisdom, strength, motivation, perseverance and confidence in pursuing this project from start to finish. After meeting me for the first time as a young, shy student, Professor Beltrame contributed significantly to my personal and professional development and has made me the confident and driven woman I am today. There were many technical and personal challenges faced throughout the duration of the PhD project and thanks to his continued support, I am so proud and happy to say “we finally made it”.

From a clinical perspective, I would like to thank all TQEH staff that assisted me in recruiting patients and collecting blood samples. In particular, special mention goes to the Coronary Care staff for paging me when patients presented to the ward, the clinical trial nurses (Cate Green, Marilyn Black and
Sue Leslie) for obtaining blood samples for my studies and providing invaluable clinical advice relating to patient recruitment and professional conduct.

To the staff at the Adelaide Proteomics Centre, thanks go to teaching me all the essential skills and knowledge required to undertake such a vastly difficult proteomics project. Undertaking such a comprehensive project would not have been possible or enjoyable if not for the help from my fellow PhD colleague Mark Condina and partner-in-crime Megan Penno.

Given the extensive laboratory work required throughout this PhD project, special mention must also go to the dedicated technicians, senior research scientists and fellow colleagues that taught me my lab skills and persevered with me following all the technical problems encountered. My utmost gratitude goes to Dr. David Wilson for teaching me invaluable scientific skills and challenging my knowledge base, my co-supervisor Dr. Jenny Kennedy for her wisdom, laboratory teachings and guidance on how to write manuscripts, Ms Irene Stafford for her continuous support in the laboratory, especially when I had lost all hope of my experiments ever working, Mrs. Geraldine Murphy for teaching me meticulous scientific practices and Dr. Scott Willoughby for providing me with advice regarding my clinical pulse wave analysis methods.
For all my friends, colleagues and fellow PhD students who kept me sane, motivated and focused; an enormous thank you goes out to you guys. To Linda Gallina, who kept me from losing my marbles over regular coffee therapy sessions, to Rosanna Tavella who frequently helped me out with statistical and thesis matters, to Natalie Cutri who gave me emotional and moral support during the dark periods, you were all part of the team that contribute to the successful completion of this thesis. It was an absolute pleasure to be a part of such a close knit and wonderful group of people that I now have the honour of calling my dearest friends.

Last but not least, I cannot express enough gratitude and thanks to my close friends and family who supported me in various forms throughout the six years of my candidature. During the hard times, it was you guys that stood by me and kept me going and so a large part of this thesis belongs to you. In particular, I have to thank my wonderful mother Janina Kopetz for her continued emotional and financial support, my father Paul Kopetz for his faith in me, Mr. Peter Grabb for the regular motivational speeches, Mr. Robert Dragoljevic for the weekly counselling sessions, my closest friend Ms Philippa Dean for her love and unconditional support, Mrs. Elizabeth Johnson who looked out for my health and well-being and Dr. Timothy Lovell for his emotional and technical support towards the latter stages of the thesis writing process.
Abbreviations

2D-DIGE = Two-dimensional Difference Gel Electrophoresis
AAT = Alpha-1 Anti-trypsin
ACE = Angiotensin Converting Enzyme
ACE-1 = Angiotensin Converting Enzyme Inhibitor
ACh = Acetylcholine
ACN = Acetonitrile
ACS = Acute Coronary Syndrome
ACT = Alpha-1 Anti-chymotrypsin
ADMA = Asymmetric Dimethylarginine
ADP = Adenosine Diphosphate
AF = Angina Frequency
AIx = Augmentation Index
ATP = Adenosine Triphosphate
BH₄ = Tetrahydrobiopterin
CAD = Coronary Artery Disease
CBG = Corticosteroid Binding Globulin
CCU = Coronary Care Unit
CFR = Coronary Flow Reserve
CHAPS = [3- (3 Cholamidopropyl)dimethylammonio] -1- propanesulfonate]
CHD = Coronary Heart Disease
Cl⁻ = Chloride ion
CK = Creatine Kinase
CMD = Coronary Microvascular Dysfunction
CRP = C-reactive protein
CSFP = Coronary Slow Flow Phenomenon
CSX = Coronary Syndrome X
CT = Computed Tomography
DDAH = Dimethylarginase
DNA = Deoxyribose Nucleic Acid
DTT = Dithiothreitol
E-selectin = Endothelial selectin
ECG = Electrocardiogram
EDHF = Endothelial Derived Hyperpolarising Factor
EDTA = Ethylenediaminetetraacetic Acid
ELISA = Enzyme-linked immunosorbent assay
ET-1 = Endothelin-1
eNOS = Endothelial NOS
FA = Formic Acid
FMD = Flow-mediated Dilatation
FN = Fibronectin
GTN = Glyceryl Trinitrate
H$_2$O$_2$ = Hydrogen Peroxide
HMG-CoA = 3-hydroxy-3-methyl-glutaryl-CoA
HOCl = Hypochlorous Acid
HPLC = High Performance Liquid Chromatography
hsCRP = High-sensitivity C-Reactive Protein
ICAM-1 = Intercellular Adhesion Molecule
IEF = Isoelectric Focusing
IFN-γ = Interferon Gamma
IL-1 = Interleukin 1
IL-6 = Interleukin 6
IL-8 = Interleukin 8
IPG = Immobilised pH gradient
iNOS = Inducible NOS
IP-10 = Inducible Protein 10
IVUS = Intravascular Ultrasound
LAD = Left Anterior Descending
LRα2GP = Leucine-rich alpha-2-glycoprotein
LV = Left Ventricular
MARS = Multiple Immunooaffinity Removal System
MCP-1 = Monocyte Chemotactic Protein-1
MDA = Malondialdehyde
MMP = Matrix Metalloproteinases
MPO = Myeloperoxidase
MRI = Magnetic Resonance Imaging
MS = Mass Spectrometry
MVA = Microvascular Angina
mRNA = Messenger RNA
NADPH = Nicotinamide adenine dinucleotide phosphate
NO = Nitric Oxide
NO₂⁻ = Nitrite
NOS = Nitric Oxide Synthase
NMMA = N-monomethylarginine
NMR = Nuclear Magnetic Resonance
nNOS = Neuronal NOS
O$_2^-$ = Superoxide
OD = Optical Density
ONOO$^-$ = Peroxynitrite
oxLDL = Oxidised Low-density Lipoprotein
PA = Persistant Angina
PAF = Platelet Activating Factor
PBS = Phosphate Buffered Solution
PBS-BSA = Phosphate Buffered Solution + 0.1% Bovine Serum Albumin
PBST = Phosphate Buffered Solution + 0.001% Tween
PCI = Percutaneous Coronary Intervention
PDGF = Platelet Derived Growth Factor
PET = Positron Emission Tomography
PGH$_2$ = Prostaglandin
PGL$_2$ = Prostacyclin
PON-1 = Paraoxonase -1
PTM = Post-translational Modification
PVD = Primary Microvascular Dysfunction
ROS = Reactive Oxygen Species
RCA = Right Coronary Artery
SAQ – Seattle Angina Questionnaire
SDMA = Symmetric Dimethylarginine
SDS- PAGE = Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SF-36 = Short-Form 36
SNC = Sublingual Nitrate Consumption
SOD = Superoxide Dismutase
SPECT = Single-photon Emission Computed Tomography
TBA = Thiobarbituric Acid
TBST = Tris-buffered saline + Tween
TIMI = Thrombolysis in Myocardial Infarction
TNF-α = Tumor Necrosis Factor Alpha
TXA₂ = Thromboxane A₂
TnT = Troponin T
U.S = United States
VSMC = Vascular Smooth Muscle Cell
VCAM-1 = Vascular Cell Adhesion Molecule
vWF = von Willebrand Factor
Abstract

Background

This thesis investigates the clinical and biological factors that contribute to the cardiovascular condition known as the Coronary Slow Flow Phenomenon (CSFP). From its initial description, little remains understood regarding the mechanisms contributing to this curious condition. The research efforts in this thesis have focused upon further characterising the CSFP and identifying an effective therapy, by investigating the mechanisms involved during different periods of presentation.

The specific objectives include:

1) Identifying the possible mechanisms of the acute coronary syndrome (ACS) presentation in CSFP patients by comparing plasma protein profiles from samples obtained from initial presentation and during a quiescent phase of the disorder;

2) Investigating the role of the endothelium during the chronic phase of the disorder. Specifically, this includes looking at mechanisms of endothelial dysfunction, inflammation and oxidative stress and comparisons with a healthy control group;

3) Evaluating the efficacy of a dual endothelin-1 (ET-1) receptor blocker (Bosentan) in ameliorating angina symptoms in CSFP patients. This project also involves monitoring improvements in health-related quality of life, clinical profiles, endothelial function, inflammation and oxidative stress following Bosentan treatment.


Methods

This thesis employed a number of methods to comprehensively assess the pathophysiological mechanisms contributing to CSFP aetiology. In order to identify possible protein biomarker candidates, a state-of-the-art proteomic approach was used to obtain plasma protein profiles. A paired-longitudinal study design was employed by which blood samples were obtained from CSFP patients during the ACS and compared to a quiescent phase. During the chronic phase of the condition, a cross-sectional study was conducted to assess endothelial function, inflammation and oxidative stress parameters compared with a healthy control group that had no history of chest pain or coronary disease. The clinical trial employed a randomised, double-blind, placebo-controlled, cross-over design that involved evaluating changes in chest pain, clinical characteristics, endothelial function, inflammation and oxidative stress parameters following treatment with bosentan therapy.

Summary of major findings

The above studies yielded the following findings:

1) Proteomic investigations identified specific inflammatory and oxidative stress protein markers that were elevated during the ACS presentation compared to the chronic phase (Chapter 2).

2) There was no evidence of impairments in endothelial vasomotor function or increases in inflammatory and oxidative stress parameters during the chronic phase of the condition compared to control subjects (Chapter 3).

3) Bosentan therapy did not significantly improve angina symptoms, clinical profiles, endothelial function, inflammation and oxidative stress
parameters compared to placebo. Despite not reaching statistical significance, reductions in angina frequency and severity in addition to improvements in quality of life parameters were identified (Chapter 4).

Conclusion

This thesis provides a new platform for future investigations into the CSFP. Pathophysiologival differences identified between the acute and chronic presentations have initiated the need to further conduct research on the specific mechanisms that contribute to both the ACS presentation and persistent symptoms. Additionally, investigating the role of ET-1 receptor blockade in CSFP patients has identified a number of inherent problems associated with clinical trial design in CSFP patients.
Statement of Authorship

Potential mechanisms of the Acute Coronary Syndrome Presentation – Insight from a plasma proteomic approach.

*International Journal of Cardiology* 2012;156:84-91

Kopetz, V.A. (Candidate)

Study conception and design, proteomic and western blot experimentation, project management, data analysis and interpretation, critical review and manuscript preparation.

I hereby certify that the statement of the contribution is accurate.

………………………………………

Signed

Date

Penno, M.A.S.

Study conception and design, proteomic experimentation, data analysis, critical review and manuscript preparation.

I hereby certify that the statement of the contribution is accurate.

………………………………………

Signed

Date

XX
Hoffmann, P.

Study conception and design, supervision of proteomic investigation and mass spectrometry analysis.

I hereby certify that the statement of the contribution is accurate.

………………………………………...……………………………

Signed

Date

Wilson, D.P.

Study management, supervision of western blotting experimentation, data analysis and interpretation, critical review and manuscript preparation.

I hereby certify that the statement of the contribution is accurate.

………………………………………...……………………………

Signed

Date

Beltrame, J.F.

Study conception and design, project supervision, data interpretation, critical review and manuscript preparation.

I hereby certify that the statement of the contribution is accurate.

………………………………………...……………………………

Signed

Date
Statement of Authorship

Endothelial function, oxidative stress and inflammatory studies in chronic Coronary Slow Flow Phenomenon Patients.

Cardiology 2012;121:197-203

Kopetz, V. (Candidate)
Study conception and design, clinical and laboratory experimentation, project management, data analysis and interpretation, critical review and manuscript preparation.
I hereby certify that the statement of the contribution is accurate.

………………………………………...………………………………………...
Signed .................................................. Date

Kennedy, J.
Study conception and design, project supervision, laboratory assistance, data analysis and interpretation, critical review and manuscript preparation.
I hereby certify that the statement of the contribution is accurate.

………………………………………...………………………………………...
Signed .................................................. Date
Heresztyn, T.
Assistance with laboratory work, data analysis and interpretation.
I hereby certify that the statement of the contribution is accurate.

…………………………  ………………………
Signed  Date

Stafford, I.
Assistance with laboratory work, data analysis and interpretation, critical review and manuscript preparation.
I hereby certify that the statement of the contribution is accurate.

…………………………  ………………………
Signed  Date

Willoughby, S.R.
Assistance with clinical experimentation, data analysis and interpretation, critical review and manuscript preparation.
I hereby certify that the statement of the contribution is accurate.

…………………………  ………………………
Signed  Date
Beltrame, J.F.

Study conception and design, project supervision, data interpretation, critical review and manuscript preparation.

I hereby certify that the statement of the contribution is accurate

………………………………………
Signed

………………………………………
Date
Published Abstracts and Presentations Arising from this Thesis

2009


*Heart, Lung and Circulation, Volume 17, Supplement 3 2009, Page S307*

Abstract and poster presentation at the Cardiac Society of Australia and New Zealand (CSANZ) Conference, August 13th-16th 2009, Sydney, Australia

2008


*Heart, Lung and Circulation, Volume 17, Supplement 3 2008, Page S235*

Abstract and oral presentation at the Cardiac Society of Australia and New Zealand (CSANZ) Conference, August 7th-10th 2008, Adelaide, Australia.
Peer Reviewed Publications Arising from this Thesis

Potential mechanisms of the Acute Coronary Syndrome Presentation – Insight from a plasma proteomic approach.
*International Journal of Cardiology* 2012;156:84-91

Endothelial function, oxidative stress and inflammatory studies in chronic
Coronary Slow Flow Phenomenon patients.
*Cardiology* 2012;121:197-203
Other Abstracts and Presentations

2009 - National

Poster Presentations


Plasma proteomic investigations into the mechanisms of ACS presentation in
Coronary Slow Flow Patients.

Presented at the 57th Annual Scientific Meeting of the Cardiac Society of
Australia and New Zealand (CSANZ), August 13th-16th, Sydney, Australia.

2008 - International

Oral Presentations

Kopetz V.A.

Plasma Proteomic Studies into the Coronary Vasculature. Exploring
mechanisms of the Acute Coronary Syndrome Presentation.

Invited presentation – Institut fur Pharmakologie und Klinische
Pharmakologie, Heinrich Heine University Duesseldorf, August 2008

Poster Presentations

Kopetz V.A, Penno M.A.S, Hoffmann P, Beltrame J.F.

Human plasma proteome investigations into acute coronary microvascular
disorders.

Presented at the 7th Human Proteome Organisation (HUPO) Annual World
Congress, August 16th-20th, Amsterdam, The Netherlands.
2008 – National

Oral Presentations

Kopetz, V.A.

Plasma Proteomic Investigations into the Coronary Slow Flow Phenomenon.
Presented at the 56th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand (CSANZ), August 7th-10th, Adelaide, Australia

Poster Presentations

Kopetz V.A. Penno M.A.S, Hoffmann P, Beltrame J.F.

Plasma Proteomic Investigations into the Human Coronary Vasculature:
Exploring mechanisms of the acute coronary syndrome presentation.
Presented at the 4th Asian-Oceanic Human Proteome Organisation Conference, June 22nd-26th, Cairns, Australia.
Coronary heart disease (CHD) is a disorder characterised by dysfunction in the large and/or small coronary vessels. Impairments in coronary vascular function result in reduced flow of oxygen and nutrient-rich blood to the myocardium thereby producing myocardial ischaemia. This in turn may manifest as chest pain (referred to as angina) or in severe cases may result in myocardial infarction or even death. Indeed, CHD is the leading cause of death globally, responsible for an estimated 17.3 million deaths worldwide in 2008 (1) and more than 2200 deaths every day in the United States of America (U.S.A) alone (2). Accordingly, it is imperative that we increase our knowledge and understanding of the condition that is responsible for considerable global morbidity and mortality.

This thesis will provide a comprehensive summary of cardiovascular pathology, with a particular focus on coronary microvascular disorders, namely the coronary slow flow phenomenon (CSFP). The introductory chapter will provide the necessary background relating to CHD and will begin by describing contemporary facets of CHD with a discussion on the contribution of both large (coronary artery disease) and small vessel dysfunction (coronary microvascular disease) in determining clinical outcomes. This will then be followed by an extended discussion of the clinical conditions associated with coronary microvascular dysfunction (CMD), with particular reference to coronary syndrome X (CSX) and the CSFP. Thereafter, the thesis objectives and proposed investigations will be outlined.