# Novel Clinical Insights into Acute Myocardial Infarction

SIVABASKARI PASUPATHY

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

September 2016


THE UNIVERSITY
*of* ADELAIDE

# TABLE OF CONTENTS

# ABSTRACT

**Background and objectives:** Acute myocardial infarction (Acute MI) reflects myocardial cell death due to prolonged myocardial ischaemia. At the turn of the 20th century, acute MI was a fatal condition and bed rest served as the principal management strategy. In the 1980's, pivotal early angiography studies demonstrated that patients with acute MI presenting with ST elevation on ECG were associated with an acute coronary artery occlusion in over 90% of cases. This prompted the therapeutic strategy of the 'open artery hypothesis' where re-establishing coronary patency became paramount in acute MI management. Thrombolytic therapy, percutaneous coronary intervention (PCI), and adjunctive pharmacologic strategies were all developed to re-open the occluded coronary artery and facilitate reperfusion of the myocardium. Despite these advances, acute MI remains a global issue and is associated with significant mortality and morbidity. The aim of this thesis is to examine contemporary clinical insights of acute MI, and in particular, to emphasize two novel aspects.

The first component of this thesis focuses on the identification and understanding of a clinically intriguing acute MI group. Coronary angiographic innovations have primarily focused on alleviating atherothrombotic processes that obstruct coronary blood flow, evident in most acute MI patients. However, acute MI registries report that approximately 10% of patients do not reveal obstructive coronary artery disease (CAD). The pathophysiological processes responsible for these presentations are not immediately evident at the time of angiography. These presentations are classified as "myocardial infarction with non-obstructive coronary arteries (MINOCA)", and are increasingly recognized as a clinical conundrum. In the absence of management guidelines, consequently, these patients are often discharged from hospital without secondary prevention therapies.

The specific objectives of this component are:

1. To systematically review existing literature on MINOCA (Chapter 2)
2. To evaluate contemporary clinical characteristics of MINOCA in comparison to myocardial infarction with obstructive coronary artery disease (MI-CAD) (Chapter 3)
3. To examine the risk of thrombosis in MINOCA patients (Chapter 4).

The second component of the thesis focuses on a novel management strategy for acute MI. Although timely reperfusion of the myocardium via restoration of the occluded coronary artery has evolved as the gold standard for the management of acute MI patients, reperfusion may be a double-edged sword, since the free radicals generated may also further damage myocardial tissue; a phenomenon referred to as ischaemia-reperfusion injury. Generation of reactive oxygen species (ROS) through incomplete reduction of oxygen during reperfusion has been well described and can quickly overwhelm the cell's endogenous free radical scavenging system. This, in turn, triggers additional cellular injury by reactions with intracellular components. N-acetylcysteine (NAC) has been established as a ROS scavenger, which also potentiates the vasodilator and anti-aggregatory effects of glyceryl trinitrate (GTN).

The specific objective of this component is:

4. To examine the role of NAC together with GTN in acute MI patients undergoing primary PCI (Chapter 5).

**Methods:** This thesis employs a number of methods to evaluate the two specific components. A comprehensive systematic review and meta-analysis were undertaken to review the literature concerning MINOCA. Contemporary clinical characteristics of MINOCA were identified via a clinical registry. Risk of thrombosis in MINOCA was assessed using thrombin generation test and thrombophilia screening. The role of NAC in acute MI patients was analysed using a randomized, double-blind, placebo-controlled clinical trial.

**Summary of Major findings:**

1. Chapter 2- Systematic review of the existing MINOCA literature provided the first comprehensive understanding of MINOCA and demonstrated that 6% of acute MI presentations fulfil the criteria for MINOCA. It also established that MINOCA patients are younger, more likely to be female, and have less cardiovascular risk factors compared to MI-CAD. In addition, MINOCA is associated with a guarded 12-month prognosis, and multiple aetiologies are implicated that require further evaluation.
2. Chapter 3- This is the first prospective comprehensive analysis of clinical characteristics, including chest pain features, amongst patients with MINOCA in comparison to MI-CAD. The results from this study demonstrate that MINOCA is a more common presentation (11% of acute MI) than reported from the systemic review. However consistent with the review findings, MINOCA patients were more likely to be female and present with fewer cardiovascular risk factors but the chest pain presentation is indistinguishable from MI-CAD.
3. Chapter 4- Spontaneous formation and lysis of coronary thrombosis is often hypothesised as a potential mechanism leading to MINOCA presentation. Overall thrombin generation potential, congenital thrombophilia states and acquired thrombophilia states were not different between MINOCA and MI-CAD. This suggests that despite the difference in

coronary artery anatomy of the disease progression, acute MI patients generate thrombin in a similar manner in response to local stimuli.

4. Chapter 5- In acute MI patients with an occluded coronary artery, final infarct size is determined by duration of ischaemia, area at risk, and ischaemia-reperfusion injury among others. Existing research studies indicate limiting the infarct size improves long term clinical outcomes of MI patients. Utilising a double-blind, placebo-controlled trial design, it was demonstrated that for patients with ST-elevation myocardial infarction (STEMI), early administration of NAC together with glyceryl trinitrate (GTN) reduced the final infarct size compared to placebo and GTN, as assessed by cardiac magnetic resonance imaging. NAC's intrinsic ROS scavenging properties resulting in reduced oxidative stress and its potentiation of GTN resulting in increased reperfusion may have limited the infarct size.

**Conclusions:** This thesis provides beneficial insights into two novel clinical aspects of acute MI in contemporary clinical practice. In regards to MINOCA, the systematic review (Chapter 2) presents the first comprehensive body of literature summarising MINOCA, especially in comparison to MI-CAD, identifying similar clinical features between these acute MI groups. Importantly, the systematic review implicates MINOCA as a working diagnosis given the role of multiple aetiologies. Subsequent to the systematic review, Chapter 3 and 4 provides contemporary clinical characteristics and mechanistic insights, in particular the risk of thrombosis, in MINOCA. Overall, this data highlights the need for optimal assessments in elucidating the underlying cause for the presentation and the requirement to generate diagnostic guidelines to inform appropriate management. In regards to MI-CAD, timely and effective myocardial reperfusion by PCI is the treatment of choice for limiting myocardial infarct size and improving clinical outcomes. However, reperfusion of the infarct artery leads to further myocardial damage via ischaemia reperfusion injury, highlighting the need for

additional pharmacological strategies. Chapter 5 presents a significant observation in that limiting infarct size is possible via the utilisation of NAC/GTN in STEMI patients. Further exploration of each of these components may enhance the diagnosis and treatment of acute MI patients and substantially improve clinical outcomes.

# DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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.

In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. 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.

I acknowledge that copyright of published works contained within this thesis 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 Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time

Signature: …… Date: ……

# ACKNOWLEDGEMENTS

Immeasurable appreciation and deepest gratitude for the following persons who made this possible.

Firstly, I would like to express my sincere gratitude to my principal supervisor, Professor John Beltrame for the continuous support, and guidance throughout my candidature. Thank you for the opportunities and encouragement during this journey, without which, this thesis would not have been possible.

I also would like to thank Dr Rosanna Tavella for the untiring support, supervision, statistical assistance, guidance, and friendship.

My sincere thanks also goes to Prof John Horowitz, Prof Joesph Selvanayagam, Dr Simon McRae, and Ms Susan Rodgers for their intellectual input and support in various studies within this thesis.

I thank my colleagues/friends from Basil Hetzel Institute and the staff at the coronary angiogram database of South Australia(CADOSA), cardiac catheterisation laboratory, coronary care unit, SA Pathology blood collection centre, and cardiac MRI unit of the Queen Elizabeth Hospital for their assistance with studies.

Last, but not least, I thank my very supportive and loving family. This thesis stands as a testament to unconditional love and encouragement from everyone mentioned here.

I dedicate this thesis to my Amma, my inspiration.

# ABBREVIATIONS

| | |
|---|---|
| AAR: | Area at risk |
| ACC: | American College of Cardiology |
| ACE: | Angiotensin converting enzyme |
| ACS: | Acute coronary syndrome |
| Ag: | Antigen |
| AHA: | American Heart Association |
| ANCOVA: | Analysis of covariance |
| ANOVA: | Analysis of variance |
| ANZCTRN: | Australian New Zealand Clinical Trials Registry |
| APC: | Activated protein C |
| APCR: | Activated protein C resistance |
| APTT: | Activated partial thromboplastin time |
| ARB: | Angiotensin II receptor blocker |
| AT: | Antithrombin |
| ATP: | Adenosine triphosphate |
| AVOID: | Air versus oxygen in myocardial infarction |
| BP: | Blood pressure |
| CABG: | Coronary artery bypass surgery |
| CAD: | Coronary artery disease |
| CADOSA: | Coronary Angiogram Database of South Australia |
| CAT: | Calibrated automated thrombogram |
| cGMP: | Cyclic guanosine monophosphate |
| CI: | Confidence interval |

| | |
|---|---|
| CK-MB: | Creatine kinase - myoglobin binding |
| CK: | Creatine kinase |
| CMR: | Cardiac magnetic resonance imaging |
| CSANZ: | Cardiac Society of Australia and New Zealand |
| CTPA: | Computed tomography pulmonary angiogram |
| CV: | Coefficient of variation |
| CVD: | Cardiovascular disease |
| DCM: | Dilated cardiomyopathy |
| ECG: | Electrocardiography |
| EDTA: | Ethylenediaminetetraacetic acid |
| EDV: | End diastolic volume |
| EF: | Ejection fraction |
| ELISA: | Enzyme-linked immunosorbent assay |
| ESC: | European Society of Cardiology |
| ESV: | End systolic volume |
| ETP: | Endogenous thrombin potential |
| FIX: | Factor IX |
| FIXa: | Activated factor IX |
| FV: | Factor V |
| FVa: | Activated factor V |
| FVII: | Factor VII |
| FVIIa: | Activated factor VII |
| FVIII | Factor VIII |
| FVIIIa: | Activated factor VIII |
| FVL: | Factor V Leiden |

| | |
|---|---|
| FXI: | Factor XI |
| FXIa: | Activated factor XI |
| FXII: | Factor XII |
| FXIIa: | Activated factor XII |
| GIK: | Glucose insulin potassium |
| GORD: | Gastro oesophageal reflux disease |
| GRACE: | Global registry of acute coronary events |
| GTN: | Glyceryl trinitrate |
| $H_2O_2$: | Hydrogen peroxide |
| HCM: | Hypertrophic cardiomyopathy |
| HDL: | High-density lipoprotein |
| HOCl: | Hypochlorous acid |
| Hx: | History |
| IBS: | Irritable bowel syndrome |
| IQR: | Interquartile range |
| IV: | Intravenous |
| IVUS: | Intravascular ultrasound |
| LBBB: | Left bundle branch block |
| LDL: | Low-density lipoprotein |
| LGE: | Late gadolinium enhancement |
| LV: | Left ventricle |
| MC: | Myocarditis |
| MI-CAD: | Myocardial Infarction with Obstructive Coronary Artery Disease |
| MI: | Myocardial infarction |
| MINOCA: | Myocardial Infarction with Non-Obstructive Coronary Arteries |

| | |
|---|---|
| MPTP: | Mitochondrial permeability transition pore |
| MVO: | Microvascular obstruction |
| n: | Number |
| NAC: | N-acetylcysteine |
| NACB: | National Academy of Clinical Biochemistry |
| NACIAM: | N-acetylcysteine in ST-segment elevation myocardial infarct patients |
| NAD: | Diagnosis not available |
| NADPH: | Nicotinamide adenine dinucleotide phosphate- |
| NCDR: | National cardiovascular data registry |
| NE: | Not examined |
| NO: | Nitric oxide |
| NSTEMI: | Non ST-segment elevation myocardial infarction |
| OR: | Odds ratios |
| $O_2$: | Oxygen |
| $O_2^{\cdot-}$: | Superoxide |
| PAD: | Peripheral artery disease |
| PC: | Protein C |
| PCI: | Percutaneous coronary intervention |
| PGM: | Prothrombin gene mutation |
| PICO: | Population, intervention, comparison, outcome |
| pM: | Picomolar |
| PS: | Protein S |
| PT: | Prothrombin time |
| RCT: | Randomised controlled trials |
| RISK: | Reperfusion injury salvage kinase |

| | |
|---|---|
| RNS: | Reactive nitrogen species |
| ROS: | Reactive oxygen species |
| rpm: | Revolutions per minute |
| SD: | Standard deviation |
| SPECT: | Single photon emission computed tomography |
| SR: | Sarcoplasmic reticulum |
| STEMI: | ST-segment Elevation Myocardial Infarction |
| t-PA: | Tissue-plasminogen activators |
| T2W: | T2-weighted |
| TF: | Tissue factor |
| TFPI: | Tissue factor pathway inhibitor |
| TM: | Thrombomodulin |
| TTC: | Tako-tsubo cardiomyopathy |
| USA: | United States of America |
| vWF: | Von willebrand factor |
| WHF: | World Heart Federation |
| WHO: | World Health Organization |

# LIST OF PUBLICATIONS

## PUBLISHED MANUSCRIPTS FROM THIS THESIS

**i.** Systematic Review of Patients Presenting with Suspected Myocardial Infarction and Non-Obstructive Coronary Arteries (MINOCA).

Pasupathy S, Air T, Dreyer R, Tavella R, Beltrame JF.

Circulation 01/2015; 131(10).

**ii.** The What, When, Who, Why, How and Where of Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA).

Pasupathy S, Tavella R, Beltrame JF.

Circ J. 2016;80(1):11-6.

**iii.** Myocardial Infarction with Non-Obstructive Coronary Arteries – Diagnosis and Management.

Pasupathy S, Tavella R, McRae S, Beltrame JF.

European Cardiology Review, 2015; 10 (2):79–82

**SUBMITTED MANUSCRIPTS FROM THIS THESIS**

---

**i.** The early use of N-acetylcysteine (NAC) with Glyceryl Trinitrate (GTN) in ST-segment Elevation Myocardial Infarction patients undergoing primary percutaneous coronary intervention (NACIAM Trial).

Pasupathy S, Tavella R, Grover S, Raman B, Du Y, Mahadavan G, Procter N, Stafford I, Heresztyn T, Holmes A, Zeitz C, Arstall M, Selvanayagam J, Horowitz J, Beltrame JF.

The Lancet.

**ii.** Risk of thrombosis in Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA).

Pasupathy S, Rodgers S, Tavella R, McRae S, Beltrame JF.

Coronary Artery Disease

---

**PUBLISHED ABSTRACTS FROM THIS THESIS**

**i.** The early use of N-acetylcysteine (NAC) with Glyceryl Trinitrate (GTN) in ST-segment Elevation Myocardial Infarction patients undergoing primary percutaneous coronary intervention (NACIAM Trial).

Pasupathy S, Tavella R, Raman B, Grover S, Mahadavan G, Zeitz C, Arstall M, Selvanayagam J, Horowitz J, Beltrame JF.

Late breaking clinical trial presentation

Annual meeting of European Society of Cardiology congress, Rome, Italy.

**ii.** Risk of thrombosis in Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA). 2016

Pasupathy S, Rodgers S, Pope S, Tavella R, McRae S, Beltrame JF.

Poster Presentation

Annual meeting of the Cardiac Society of Australia & New Zealand, Adelaide, Australia

Heart, Lung and Circulation , Volume 25 , S64

**iii.** Electrocardiographic-assessed myocardial area at risk in patients with Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA).

Pasupathy S, Leow K, Wu S, Lee A, Du Y, Tavella R, Beltrame JF. 2016

Poster Presentation

Annual meeting of the Cardiac Society of Australia & New Zealand, Adelaide, Australia.

Heart, Lung and Circulation , Volume 25 , S44

**iv.** Diagnostic utility of cardiac magnetic resonance imaging (CMR) in Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) Patients. 2016

Pasupathy S, Tavella R, Potaminos R, Arstall M, Chew D, Worthley M, Zeitz C, Beltrame JF.

Mini oral Presentation

Annual meeting of the Cardiac Society of Australia & New Zealand, Adelaide, Australia.

Heart, Lung and Circulation , Volume 25 , S41

**v.** Chest pain characteristics of myocardial infarction with non-obstructive coronary arteries (MINOCA) in comparison to myocardial infarction with coronary artery disease (MI-CAD). 2016

Pasupathy S, Tavella R, Arstall M, Chew D, Worthley M , Zeitz C, Beltrame JF.

Poster presentation

Annual meeting of American Heart Association, Quality of Care and Outcomes Research, Florida, USA.

Circ Cardiovasc Qual Outcomes. 2016;9:A129.

**vi.** Myocardial Infarction with Non-Obstructive Coronary Artery Disease (MINOCA): Prevalence, Clinical Features and Outcomes. 2015

Pasupathy S, Tavella R, Arstall M, Chew D, Worthley M , Zeitz C, Beltrame JF.

Poster Presentation

Annual meeting of American Heart Association, Quality of Care and Outcomes Research, Florida, USA.

Circ Cardiovasc Qual Outcomes. 2015;8:A273

**vii.** Clinical profile of acute myocardial infarction patients in the absence of significant coronary artery disease. 2015

Pasupathy S, Tavella R, Arstall M, Chew D, Worthley M , Zeitz C, Beltrame JF.

Poster Presentation

Annual meeting of the Cardiac Society of Australia & New Zealand, Melbourne, Australia.

Heart, lung and circulation 01/2015; 24:S142.

**viii.** Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA): A Systematic Review and Meta-analysis. 2014

Pasupathy S, Dreyer R, Tavella R, Beltrame JF.

Poster Presentation

World Congress of Cardiology: Melbourne, Australia.

Global Heart, Volume 9, Issue 1, e274.

**ix.** Measurement of Area at Risk by Cardiac Magnetic Resonance Imaging: Comparison of T2-Weighted Imaging with the Endocardial Surface Area Method.

Pasupathy S, Neil C, Beltrame JF.

Poster Presentation

Annual meeting of the Cardiac Society of Australia & New Zealand (CSANZ): Brisbane, Australia.

Heart, Lung and Circulation 12/2012; 21:S256-S257

**PRESENTATIONS AT INTERNATIONAL/LOCAL MEETINGS**

**i.** The early use of N-acetylcysteine (NAC) with Glyceryl Trinitrate (GTN) in ST-segment Elevation Myocardial Infarction patients undergoing primary percutaneous coronary intervention (NACIAM Trial).

Pasupathy S, Tavella R, Raman B, Grover S, Mahadavan G, Zeitz C, Arstall M, Selvanayagam J, Horowitz J, Beltrame JF.

Late breaking clinical trial Presentation

Annual meeting of European Society of Cardiology congress, Rome, Italy. 2016

**ii.** Myocardial Infarction with Non-Obstructive Coronary Artery Disease (MINOCA): Prevalence, Clinical Features and Outcomes. 2015

Pasupathy S, Tavella R, Arstall M, Chew D, Worthley M, Zeitz C, Beltrame JF.

Invited speaker Presentation

Annual meeting of the Cardiac Society of Australia & New Zealand, Adelaide, Australia. 2016

**iii.** Diagnostic utility of cardiac magnetic resonance imaging (CMR) in Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) Patients. 2016

Pasupathy S, Tavella R, Potaminos R, Arstall M, Chew D, Worthley M, Zeitz C, Beltrame JF.

Mini oral Presentation

Annual meeting of the Cardiac Society of Australia & New Zealand, Adelaide, Australia. 2016

# AWARDS AND RECOGNITION

| | |
|---|---|
| 2015 | Research Day (Basil hetzel institute for translational health research)<br><br>Ivan De La Lande Award |
| 2015 | School of Medicine Travel Grant (The University of Adelaide)<br><br>The University of Adelaide |
| 2013 | Research Day (Basil hetzel institute for translational health research)<br><br>Best Clinical Presentation Award |
| 2012 | Higher Degree by Research Scholarship (The University of Adelaide)<br><br>Australian Postgraduate Award (APA) |