

**The In Vivo Evaluation of Coronary Atheroma
and Endothelium-Dependent Vasomotor
Reactivity in Humans with Coronary Artery
Disease: Studies Utilizing Intravascular
Ultrasound**

A thesis submitted by

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THESIS SUMMARY

Although many consider plaque burden and vasoconstriction as critical components of ‘vulnerable’ coronary atheroma, their intrinsic relationship *in vivo* remains relatively unexplored. This thesis, presented as a series of experiments conducted in intact humans with coronary artery disease, explores the fundamental *in vivo* relationships between coronary atheroma volume, composition and topography in relation to underlying segmental epicardial coronary endothelium-dependent vasomotor reactivity. The contributions of segmental wall shear stress (WSS), and the first-in-man assessment of left main coronary arterial endothelium-dependent vasomotor reactivity and its determinants, are also explored. A novel feature was the utility of intravascular ultrasound (IVUS) for all coronary structural and functional assessments. In these experiments, IVUS was pivotal in enabling the first-in-man validation of intracoronary salbutamol as a novel epicardial endothelium-dependent stimulus.

Of the 3 introductory chapters, chapters 1 and 2 outline the utility of IVUS for exploring coronary atherosclerosis and ‘vulnerable’ plaques. Chapter 3 draws specific attention to the nature of endothelium-dependent stimulus required to safely explore, with greater precision, the coronary structure-function relationship in humans *in vivo*.

Chapters 4-9 comprise the results sections of this thesis. Chapter 4 outlines the utility of ‘provocation intravascular imaging’ [IVUS-upon-Doppler Flowire imaging during simultaneous intracoronary (IC) infusions] to validate IC salbutamol as a novel endothelium-dependent epicardial coronary and microvascular stimulus.

Chapter 5 describes the coronary structure-function relationship in patients with stable, minimally diseased coronary arteries (i.e. the population studied in chapter 4) compared with patient with non ST-segment elevation myocardial infarction (NSTEMI). Irrespective of the nature of clinical presentation, the magnitude of segmental lumen vasoreactivity, controlled for by the degree of atheroma volume, did not differ. Our results also suggested possible interactions between systemic inflammation and coronary atheroma in mediating coronary vasomotor reactivity.

Utilizing a custom-built IVUS console to deliver radio-frequency IVUS signals, Chapter 6 outlines the relationship between plaque composition and segmental vasomotor reactivity in the NSTEMI population evaluated in chapter 5. Both the volumes of lipidic and necrotic core composition predicted vasoconstriction, whereas greater fibrotic plaque predicted vasodilatation.

Chapter 7 describes a unique investigation into *in vivo* relationships between segmental WSS, arterial remodeling and vasomotor function in patients with stable, minimally diseased coronaries (population studied in chapter 4). Independent of plaque burden, WSS directly related to vasomotor reactivity, and inversely to arterial remodeling. Regions of high plaque burden associated with lower WSS, expansive remodeling and greater plaque eccentricity, thus providing a novel link between these known individual features of plaque vulnerability.

Chapter 8 outlines the first-in-man description of left main coronary arterial (LMCA) vasomotor reactivity, in comparison to downstream epicardial segments. The study population comprised of all patients across study protocols who underwent left-

sided coronary imaging with evaluable matched LMCA images. LMCA and proximal epicardial segments were least reactive, compared to more distal conduit segments, which may relate to higher WSS in smaller caliber distal segments. These results may also explain the propensity for culprit plaques to cluster proximally in humans.

Chapter 9 describes a unique comparison of *in vivo* lumen dimensions measured with IVUS, Fourier-domain optical coherence tomography (FD-OCT) and 3D quantitative coronary angiography (3D-QCA). Lumen dimensions were greater with IVUS compared to FD-OCT and 3D-QCA, and were magnified within smaller coronary segments. We concluded that specific cut-off values validated with IVUS should not be arbitrarily translated into the OCT hemisphere for clinical decision making.

DECLARATION

Name: Rishi Puri

Program: Doctor of Philosophy

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 thesis 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. The author acknowledges 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 catalogue, and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Date: 3rd Dec 2013

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Seduced by the field of Interventional Cardiology during my first year of Cardiology training, the concept of undertaking PhD research was the farthest thing from my mind. Following a few months involving countless discussions with numerous colleagues, mentors and family, I eventually embraced the concept of a PhD program. Little did I realize the enormous future impact this would make on my life, both professionally, and personally.

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PUBLICATIONS ARISING FROM THIS THESIS

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3. National Heart Foundation of Australia Overseas Travelling Fellowship (American College of Cardiology, New Orleans, Louisiana, USA), April 2011
4. Cardiac Society of Australia & New Zealand Travelling Fellowship (American Heart Association Meeting, Chicago, Illinois, USA), November 2010
5. 1st Prize (Best Poster Prize), Pfizer Cardiovascular Lipid Annual Symposium, July 2010