DEFINING THE IMAGING BIOMARKERS AND TEMPORAL EFFECTS OF ISCHAEMIC AND NON-ISCHAEMIC INJURY ON THE MYOCARDIUM

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Abstract

Following a myocardial insult, there are cellular and pathophysiological changes that occur, resulting in adverse remodelling and eventually clinical sequelae. By this latter stage, most of the treatment options have limited value and often palliate the situation. Injury to the myocardium can follow an ischaemic or non-ischaemic insult, resulting in different adaptive responses. Furthermore, before irreversible damage occurs, defined by necrosis (acutely) and fibrosis (chronically), the initial changes are characterized by myocardial oedema and are considered to be reversible. Targeting the myocardium at this vulnerable but salvageable state may form a basis of future therapeutic options.

Despite emerging evidence regarding reversible injury following an acute ischaemic insult, there is lack of evidence as to the role of myocardial oedema following non-ischaemic injury, such as may be caused by chemotherapy. Even in ischaemic injury, the adaptive responses of the myocardium differ depending on whether the injury is acute or chronic. Myocardial stunning (usually following acute injury) and myocardial hibernation (often described as myocardial state in a chronically occluded vessel) have varying clinical time course. The aim of any therapy is to prevent irreversible damage, but often revascularisation itself can trigger further injury. Particularly in chronic ischaemic injury, there is limited understanding regarding the interplay between cellular oxygenation, perfusion and contractile response of the myocardium.

The aim of this thesis are to 1) characterize the role of reversible and irreversible myocardial injury in acute and chronic ischaemic insult and 2) characterize the role of reversible and irreversible myocardial injury in non-ischaemic insult using non-invasive approaches.

The first study presented in this thesis in Chapter 3 explores the relationship between myocardial oedema defining area at risk and myocardial necrosis following an acute ischaemic insult such as anterior ST elevation myocardial infarction. We found that myocardial salvage index (calculated from area at risk) and degree of necrosis were predictive of adverse remodelling and left ventricular (LV) function at 90 days. In a multivariate model only infarct size assessed by late gadolinium enhancement remained the most robust marker for predicting late LV function.

Chapter 4 presents research investigating the relationship between LV dysfunction, myocardial oxygenation/perfusion and presence of scar in a chronically occluded vessel. The interplay between these factors is potentially important for predicting clinical outcome following revascularisation. The key finding in this chapter is that the blood oxygen level dependent (BOLD) response (measuring myocardial oxygenation) is impaired in hibernating myocardium and that oxygenation improves post revascularisation.

Chapters 5, 6 and 7 detail response of the myocardium to non-ischaemic injury. We use the model of chemotherapy toxicity and study two agents (anthracyclines and trastuzumab), evaluating the different mechanisms by which they affect myocardial function. We then study the effect of these drugs on aortic compliance and distensibility which either directly or

indirectly has a bearing on the remodelling observed in the myocardium. In chapter 5, we primarily discuss the effects of these drugs on the myocardium with acute reversible LV injury observed early following administration. We observed that the early functional LV decline, appeared to stabilize at 12 months. Chapter 6 evaluates persistent functional and more severe changes seen in the thinner walled right ventricle (RV) early after administration of these drugs and late (at 12-14 months). Chapter 7 examines changes in the aortic stiffness (using pulse wave velocity and distensibility) and show an acute rise in pulse wave velocity and decline in distensibility following administration of chemotherapy. These changes improve with cessation of potentially cardiotoxic drugs, although do not return to pre therapy levels. Furthermore, more severe changes were seen in the patients receiving anthracylines.

This thesis has led to an improved understanding of the mechanisms and adaptive responses of the myocardium following both acute and chronic ischaemic insult and non-ischaemic insult. Work of this nature may allow potential diagnostic and therapeutic targets as well as allow prediction of response to therapy in patients with these cardiomyopathies.

Declaration

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.

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Peer Reviewed Journal Publications

Chapter 1

Grover S, Leong DP, Selvanayagam JB. Evaluation of left ventricular function using cardiac magnetic resonance imaging. J Nucl Card. 2011; 18: 351-365.

Grover S, Srinivasan G, Selvanayagam JB. Evaluation of myocardial viability with cardiac magnetic resonance. Progress in Cardiovascular diseases. 2011; 54(3): 204-14

Grover S, Srinivasan G, Selvanayagam JB. Myocardial Viability Imaging: Does It Still Have a Role in Patient Selection Prior to Coronary Revascularisation? Heart, Lung and Circulation. 2012; 21(8):468-79.

Chapter 3

This manuscript has been submitted to a cardiovascular journal for consideration of publication.

Grover S, Bell G, Lincoff M, Joerg L, Madsen P, Huang S, Low S, Figtree G, Chakrabarty A, Leong DP, Woodman RJ, Selvanayagam JB. Utility of CMR markers of myocardial injury in predicting LV functional recovery: results from PROTECTION AMI CMR sub study.

Chapter 4

This manuscript is in its final draft form, being reviewed by the co-authors and will be sent to a cardiovascular imaging journal for consideration of publication.

Chapter 5 and 6

A shortened version (Letter to the Editor) of this manuscript has been published in International Journal of Cardiology, 2013.

Grover S, Leong DP, Chakrabarty A, Joerg L, Kotasek D, Cheong K, Joshi R, Joseph MX, DePasquale C, Koczwara B, Selvanayagam JB. Left and right ventricular effects of anthracycline and trastuzumab chemotherapy: a prospective study using novel cardiac imaging and biochemical markers. Int J Cardiol. 2013 Oct 15;168(6):5465-7.

Chapter 7

Grover S, Lou PW, Bradbrook C, Cheong K, Kotasek D, Leong DP, Koczwara B, Selvanayagam JB. Early and late changes in markers of aortic stiffness with breast cancer therapy. Internal Medical Journal 2014 (*in* press).

Chapters 8 and 9

This chapter summarizes the main findings of the Thesis and discusses what relevance these findings have for clinical purpose. I will also aim to discuss future applications of this work and how it can be incorporated into our therapeutic strategies.

Abstracts

Grover S, DePasquale C, Cheong K, Penhall A, Joseph M, Koczwara B, Kotasek D, Leong DP, Selvanayagam JB. *The utility of novel cardiac imaging markers in predicting chemotherapy cardiotoxicity*. CSANZ Annual Scientific Meeting 2011.

Grover S, Bell G , Edwards C, Huang S, Leong DP, Joerg L, Lav Madsen P, Low S, Chakrabarty A, Selvanayagam JB. *Correlation of CMR and biochemical markers of myocardial injury in a multi-centre study: PROTECTION AMI CMR sub study.* Society of Cardiovascular Magnetic Resonance Imaging Annual Meeting 2012.

Grover S, DePasquale C, Leong DP, Chakrabarty A, Cheong K, Kotasek D, Joshi R, Penhall A, Joerg L , Joseph M , Koczwara B, Selvanayagam JB. *Early cardiac changes following anthracycline chemotherapy in breast cancer: a prospective study using advanced cardiac imaging and biochemical markers*. Society of Cardiovascular Magnetic Resonance Imaging Annual Meeting 2012.

Grover S, DePasquale C, Leong DP, Chakrabarty A, Cheong K, Kotasek D, Joshi R, Penhall A, Joerg L , Joseph M , Koczwara B, Selvanayagam JB. *Biventricular dysfunction following administration of anthracycline based chemotherapy in breast cancer: a prospective multi-centre study using advanced cardiac imaging and biochemical markers*. ESC Annual Scientific Meeting 2012 (poster).

Grover S, Bell G , Edwards C, Huang S, Leong DP, Joerg L, Lav Madsen P, Low S, Chakrabarty A, Figtree G, Selvanayagam JB. *Correlation of CMR and biochemical markers of myocardial injury in a multi-centre study: PROTECTION AMI CMR sub study*. CSANZ Annual Scientific Meeting 2012 (oral).

Grover S, DePasquale C, Leong DP, Chakrabarty A, Cheong K, Kotasek D, Joshi R, Penhall A, Joerg L , Joseph M , Koczwara B, Selvanayagam JB. *Biventricular dysfunction following administration of anthracycline (AC) chemotherapy in breast cancer: a prospective multi-centre study using advanced cardiac imaging and biochemical markers*. CSANZ Annual Scientific Meeting 2012 (oral).

Grover S, Leong DP, Joerg L, lav Madsen P, Chakrabarty A, Bell G, Selvanayagam JB. *Comparison of left ventricular ejection fraction with Multiple- gated acquisition scan and cardiac magnetic resonance in anterior myocardial infarcts*. CSANZ Annual Scientific Meeting 2012 (poster).

Grover S, Srinivasan G, Bell G, Edwards C, Huang S, Leong DP, Bridgman C, Chakrabarty A, Figtree G, Selvanayagam JB. *Inter-observer variability for assessment of infarct size in a multi-centre study: PROTECTION AMI CMR sub study*. CSANZ Annual Scientific Meeting 2012 (poster).

Grover S, Srinivasan G, DePasquale C, Leong D, Chakrabarty A, Cheong K, Joshi R, Penhall A, Joseph M, Koczwara B, Selvanayagam JB. *Contemporary Breast Cancer*

chemotherapy leads to persistent late right ventricular myocardial dysfunction: a prospective multi-centre study. SCMR 2013 (poster).

Grover S, Srinivasan G, DePasquale C, Leong D, Chakrabarty A, Cheong K, Joshi R, Penhall A, Joseph M, Koczwara B, Selvanayagam JB. *Early and late left ventricular effects of breast cancer chemotherapy: a prospective multi-centre study using advanced cardiac imaging.* SCMR 2013 (poster).

Grover S, Perry R, Leong DP, Joseph MX, Koczwara B, Selvanayagam JB. *Serial monitoring of LV function following chemotherapy: assessment using advanced echocardiography and cardiovascular magnetic resonance.* SCMR 2014 (poster).

Grover S, Leong DP, Bradbrook C, Walls A, Mazhar J, Selvanayagam JB. *Myocardial oxygenation in hibernating myocardium: insights from blood oxygen level dependent imaging pre and post revascularisation.* SCMR 2014 (poster).

Grover S, Leong DP, Bradbrook C, Walls A, Mazhar J, Selvanayagam JB. *Myocardial oxygenation in hibernating myocardium: insights from blood oxygen level dependent imaging pre and post revascularisation.* World Heart Federation's World Congress of Cardiology 2014 (oral).

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