The Role of Myocardial Fibrosis and Ventricular Mechanical Dyssynchrony in the Pathogenesis and Treatment of Contractile Myocardial Dysfunction

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Abstract

Structural and functional abnormalities of the left ventricle and atrium are important prognostic factors in patients with cardiovascular disease. Dysfunction of the left ventricle in heart failure exposes the left atrium to elevated pressures during diastole, which result in adverse left atrial remodelling and impairment.

Although the development of systolic left ventricular impairment has been linked with a number of causative factors, the pathophysiological cascade between these initiators of myocardial dysfunction and its overt manifestation has been incompletely characterised. Amongst the proposed intermediaries of systolic heart failure, recent attention has focussed on myocardial fibrosis and ventricular dyssynchrony. Myocardial fibrosis describes the extracellular deposition of collagen in response to an injurious process. This collagen deposition plays an important role in left ventricular remodelling, and may perpetuate myocardial dysfunction. Ventricular dyssynchrony refers to the incoordinate contraction of the ventricles: inter-ventricular dyssynchrony is the temporal uncoupling of left from right ventricular contraction, and intra-left ventricular dyssynchrony pertains to heterogeneity in the time to regional mechanical activation within the left ventricle. Ventricular dyssynchrony has also been implicated in the pathogenesis of systolic heart failure, and its treatment by cardiac resynchronisation has been proven efficacious in selected patients with systolic left ventricular dysfunction.

Despite emerging evidence implicating myocardial fibrosis and ventricular dyssynchrony in heart failure, their causal relationship with each other, and their relative importance in the pathogenesis of myocardial dysfunction have been poorly characterised. The aims of this thesis are to 1) characterise the role of myocardial

fibrosis and ventricular dyssynchrony in the development of left ventricular and atrial mechanical dysfunction, and 2) examine the importance of myocardial fibrosis and ventricular dyssynchrony in the response to therapy of patients with systolic heart failure using non-invasive imaging approaches.

The first study presented in this thesis in Chapter 3 explores the relationship between left atrial mechanical and left ventricular function by evaluating the effects on left atrial mechanical function of eliminating left ventricular function through the temporary induction of ventricular fibrillation in patients undergoing routine defibrillation threshold testing following implantable cardioverter-defibrillator insertion. In this mechanistic study, the dependence of left atrial function on left ventricular function is demonstrated. This finding establishes the context for the subsequent research in this thesis on the effects of left ventricular function on the left atrium in idiopathic dilated cardiomyopathy and cardiac pacing.

Chapter 4 presents research investigating the prevalence of myocardial fibrosis and ventricular dyssynchrony in patients with a first presentation of idiopathic dilated cardiomyopathy. The influence of these factors, amongst other recognised prognostic factors in heart failure, on recovery of left ventricular systolic function is examined. The key finding of this chapter is that myocardial fibrosis and ventricular dyssynchrony are independent predictors of improvement in left ventricular systolic dysfunction amongst these patients. These results relate directly to the chief aims of this thesis.

In Chapter 5, abnormalities in left atrial structure and function in patients with a first presentation of idiopathic dilated cardiomyopathy are explored. This research demonstrates that structural and functional abnormalities are prevalent early in the time course of this condition, but that these derangements are reversible following appropriate medical therapy. This chapter extends on the findings of the previous two

chapters to illustrate how disease processes primarily affecting the left ventricle can impact upon the left atrium.

Chapter 6 aims to further develop the evidence that left ventricular dyssynchrony promotes ongoing left ventricular dysfunction through the study of patients who had been enrolled in a randomised trial of right ventricular apical versus right ventricular outflow tract septal pacing for bradycardia. The major findings of this research are that right ventricular apical pacing is associated with greater ventricular dyssynchrony, poorer left ventricular function and worse adverse left ventricular remodelling than outflow tract septal pacing. Moreover, the adverse left atrial structural and functional effects of right ventricular apical pacing and ventricular dyssynchrony are demonstrated. These results lend support to the theme that ventricular dyssynchrony, in this instance induced by pacing site, adversely influences left ventricular function, which in turn impacts in a deleterious manner on left atrial structure and function.

In chapter 7, the final study conducted in this thesis, the intuitive question arising from the findings of chapter 6 is addressed, namely: if induction of ventricular dyssynchrony is deleterious, is its reversal therapeutic? This study randomised patients undergoing cardiac resynchronisation therapy for advanced heart failure to routine simultaneous bi-ventricular pacing, or echocardiographic optimisation of V-V timing during bi-ventricular pacing, with the goal of further reduction in ventricular dyssynchrony. This study was unable to demonstrate a benefit of routine V-V optimisation in recipients of cardiac resynchronisation therapy despite achieving less left ventricular dyssynchrony. A trend towards improved functional status was observed, however.

This thesis has led to an improved understanding of the mechanisms underlying the development and perpetuation of left ventricular and atrial dysfunction, and the determinants of their response to heart failure therapy. Work of this nature

may allow the identification of novel diagnostic and therapeutic approaches to heart failure in the future.

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

- Darryl P. Leong, Carmine G. De Pasquale, Joseph B. Selvanayagam. Imaging in Heart Failure With Normal Ejection Fraction: The Complementary Roles of Echocardiography and Cardiac Magnetic Resonance Imaging. ***J Am Coll Cardiol Img*** 2010; 3(4): 409-20.
- Darryl P. Leong, Per L. Madsen, Joseph B. Selvanayagam. The Non-Invasive Evaluation of Myocardial Fibrosis: Implications for the Clinician. ***Heart*** 2010; 96: 2016-24.

Chapter 3

Manuscript awaiting supervisor approval for submission.

Chapter 4 and 5

European Heart Journal invited (3rd) revision currently under review.

Chapter 6

- Darryl P. Leong, Anne-Marie Mitchell, Anthony G. Brooks, Muayad Alasady, Han S. Lim, Gautam Sharma, Ingrid Salna, Malcolm Barlow, James Leitch, Prashanthan Sanders, Glenn D. Young. Long-term mechanical consequences of permanent right ventricular pacing: Effect of pacing site. ***Journal of Cardiovascular Electrophysiology*** 2010; 21(10): 1120-6.

Chapter 7

Manuscript awaiting supervisor approval for submission.

Table of Contents

Abbreviations

CHF = congestive heart failure

CMR = cardiovascular magnetic resonance

CRT = cardiac resynchronisation therapy

DCM = idiopathic dilated cardiomyopathy

HFNEF = heart failure with normal ejection fraction

HFREF = heart failure with reduced ejection fraction

IVMD = interventricular mechanical dyssynchrony

LA = left atrial

LAAEV = left atrial appendage emptying velocity

LAVI = left atrial volume index

LASEC = left atrial spontaneous echocardiographic contrast

LGE = late-gadolinium enhancement

LV = left ventricular

LVEDVI = left ventricular end-diastolic volume index

LVEF = left ventricular ejection fraction

LVESVI = left ventricular end-systolic volume index

NICM = non-ischaemic dilated cardiomyopathy

NT-pro-BNP = N-terminal pro-brain natiuretic peptide

NYHA = New York Heart Association

RV = right ventricular

RVA = right ventricular apical

RVEF = right ventricular ejection fraction

RVOT = right ventricular outflow tract

TAPSE = tricuspid annular plane systolic excursion