Myocardial Material Properties and Cardiac Dilatation Following Chronic Sympathetic Activation in Hypertension

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ABSTRACT

Increases in internal dimensions of the chambers of the heart (cardiac dilatation), mediated by right shifts in cardiac chamber diastolic pressure-volume (P-V) relations, predict mortality in patients with established heart failure. However, the mechanisms responsible for the transition from concentric cardiac hypertrophy to cardiac dilatation are unclear. Recent evidence suggests that decreases in the cross-linked properties of myocardial collagen may increase the propensity of collagen to cleavage and hence reduce cardiac myocyte tethering, thus promoting cardiac dilatation. However, decreases in myocardial collagen cross-linking may also reduce myocardial stiffness, thus explaining right shifts in cardiac diastolic P-V relations. In the present dissertation I evaluated whether right shifts in diastolic P-V relations produced by chronic β-adrenoreceptor activation (isoproterenol, a β-adrenoreceptor agonist, 0.02 $mg.kg^{-1}$.day) in spontaneously hypertensive rats (SHR) with compensated cardiac hypertrophy (12 months of age), can be explained by adverse chamber remodelling or alterations in the myocardial material properties of the heart.

After 7 months of daily isoproterenol administration, SHR had marked right shifts in left ventricular (LV) diastolic P-V relations as determined in isolated, perfused hearts, with increases in the volume intercept of these relations, a change that translated into increases in LV cavity diameters (echocardiography). LV dilatation was associated with reductions in LV pump function (decreases in LV endocardial fractional shortening and the slope of the LV systolic P-V relation [LV E]). The reductions in pump function were attributed to the LV dilatation rather than to alterations in intrinsic myocardial contractile properties as LV midwall fractional shortening and myocardial systolic elastance (LV

En) were unchanged. Although SHR not receiving isoproterenol had increases in the LV diastolic wall thickness-to-radius ratio, a change commensurate with compensatory concentric LV hypertrophy, LV wall thickness-to-radius ratio in SHR exposed to chronic β-adrenoreceptor activation was reduced to values similar to those noted in normotensive Wistar Kyoto (WKY) control rats, despite further increases in LV weight. SHR not receiving isoproterenol had a marked increase in myocardial stiffness (slope of the linearized LV diastolic stress-strain relationship) as compared to WKY rats, a change that was associated with an increased myocardial collagen of the cross-linked phenotype. Although SHR receiving daily isoproterenol had further increases in myocardial collagen, this did not translate into changes in LV diastolic myocardial stiffness, as the further increase in myocardial collagen was of the non cross-linked phenotype. However, through a susceptibility to digestion, this collagen phenotype could have contributed to LV dilatation. In conclusion, these data suggest that LV dilatation in SHR following chronic β-adrenoreceptor activation is attributed to adverse chamber remodelling rather than to alterations in myocardial material properties as indexed by diastolic stress-strain relations.

DECLARATION

I declare that this dissertation is my own, unaided work except to the extent indicated in the acknowledgements. It is being submitted for the degree of Master of Science in the Faculty of Medicine, University of the Witwatersrand, Johannesburg. The work contained in this dissertation has not been submitted for any degree or examination in this university, or any other university.

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Mark Gibbs

……day of ……., 2008

I certify that the studies contained in this thesis have the approval of the Animal Ethic Screening Committee of the University of the Witwatersrand, Johannesburg. The ethics number is:

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Mark Gibbs

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Gavin R. Norton (Supervisor) Angela J Woodiwiss (Supervisor)

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LIST OF ABBREVIATIONS

ANOVA: analysis of variance

β: beta

BP: blood pressure

CNBr: cyanogens bromide

CO_2: carbon dioxide

-dP/dt: differential of the rate of change of pressure during isovolumic relaxation

E: end systolic chamber elastance

En: end systolic myocardial elastance

FSend: endocardial fractional shortening

FSmid: midwall fractional shortening.

$g.cm^{-2}$: grams per centimetre^2

h: wall thickness

HPRO: hydroxyproline

h/r: wall thickness-to-radius ratio

h/r_0: wall thickness-to-radius ratio intercept and an LVEDP of 0 mm Hg

ISO: isoproterenol

K^+: potassium

k: constant

LV: left ventricle

LV_{dev}Pressure: left ventricular developed pressure.

LVED: left ventricular end diastolic

LVES: left ventricular end systolic

LVEDD: left ventricular end diastolic diameter

LVEDP: left ventricular end diastolic pressure

LVEDV: left ventricular end diastolic volume

LVESD: left ventricular end systolic diameter

LVH: left ventricular hypertrophy

M: molar

$Mg.kg^{-1}$: milligrams per kilogram

MHz: megahertz

min: minutes

ml: millilitres

$ml.min^{-1}.g^{-1}$: millilitres per minute per gram

mM: millimoles

mm Hg: millimeters of mercury

MMP: matrix metalloproteinase

O_2: oxygen

P: pressure

PWT: posterior wall thickness

r: radius

r^2: coefficient of determination

SEM, standard error of the mean

SHR: Spontaneously Hypertensive Rat

TIMP: tissue inhibitor of matrix metalloproteinases

V: volume

V_0: volume intercept at a pressure of 0 mmHg of a pressure-volume relationship

WKY: Wistar Kyoto

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PREFACE

Although there is substantial evidence to suggest that enlargement in cardiac chamber dimensions is associated with an increased mortality and morbidity in chronic heart failure, the fundamental mechanisms responsible for cardiac dilatation have not been provided. The past decade has nevertheless heralded an impressive increase in the scientific literature suggesting some evidence in favour of the mechanisms involved. Although the original suggestion was that cardiac chamber dilatation occurred as a consequence of increases in cardiomyocyte lengthening, our group has provided evidence to indicate that this mechanism may not be critical for the development of cardiac dilatation. In contrast, most of the evidence in favour of the mechanisms responsible for cardiac dilatation has pointed toward side-to-side slippage of cardiomyocytes, a change that occurs because of disruption of the collagen tethers between cells.

With respect to the mechanisms that may contribute toward disruption of collagen tethers between cardiomyocytes, two mechanisms may play a role in chronic cardiac disease. The first is activation of enzymes in the myocardium responsible for degrading myocardial collagen, and the second is an increased susceptibility of myocardial collagen to cleavage by these enzymes. The hypothesis that an increased susceptibility of myocardial collagen to cleavage by enzymes may play a role in cardiac dilatation arose as the myocardial collagen that accumulates in chronic cardiac disease associated with cardiac dilatation, is non-cross-linked (soluble to digestion) (Woodiwiss et al 2001). What has not been given due consideration however, is that this type of collagen may also contribute toward cardiac dilatation by modifying the material properties of the myocardium (decreasing myocardial stiffness), thus allowing the heart to accommodate

greater volumes of blood at lower filling pressures. In the present dissertation, using an animal model of cardiac dilatation, I tested the hypothesis that cardiac dilatation could occur as a consequence of alterations in the material properties of the heart. In support of this dissertation, the work described within has been published in a high impact peer-reviewed journal (Gibbs M., Veliotes D.G.A., Anamourlis C., Badenhorst D., Osadchii O., Norton G.R, Woodiwiss A.J. Chronic β-adrenoreceptor activation increases cardiac cavity size through chamber remodeling and not via modifications in myocardial material properties. *Am J Physiol* 2004;287:H2762-H2767).