SYSTOLIC CHAMBER FUNCTION IN RATS WITH EXERCISE-INDUCED COMPARED TO PATHOLOGICAL CARDIAC DILATATION

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ABSTRACT

In pathological left ventricular hypertrophy (LVH) with a normal intrinsic myocardial function, eccentric chamber remodelling (cardiac dilatation) can produce a right shift in systolic pressure-volume (P-V) relations (systolic chamber dysfunction). Whether comparable degrees of cardiac dilatation in physiological (exercise-induced eccentric left ventricular remodelling) and pathological LVH produce similar effects on chamber function has not been determined. Hence, the aim of my thesis was to determine the impact of cardiac dilatation on systolic chamber function in chronically exercised rats with comparable increases in cardiac diastolic volumes as those produced by two rat models of pathological dilatation.

Methods: Two models of cardiac dilatation were used, namely: (1) a model of pathological cardiac hypertrophy and dilatation (induced by chronic β-adrenoreceptor agonist administration to either Sprague-Dawley or spontaneously hypertensive rats), and (2) a model of physiological cardiac hypertrophy and dilatation (induced in Sprague-Dawley rats by 4-5 months of voluntary running activity on exercise wheels). 33 Sprague-Dawley rats were placed on spontaneous running wheels for 4-5 months (Exer group) and 24 Sprague-Dawley sedentary control rats (Con group) were placed individually in normal rat cages. To induced pathological dilatation, the β-agonist, isoproterenol (ISO) was administered daily to Sprague-Dawley rats for 7 months (SD-ISO, n=10) and to spontaneously hypertensive rats (SHR) for 4-5 months (SHR+ISO, n=22). Saline was administered daily to controls (SD, n=10; SHR, n=21) and to normotensive Wistar Kyoto rats (WKY, n=17). In isolated, perfused heart preparations, left ventricular (LV) dilatation was determined from the diastolic pressure-volume (P-V)

relation and the volume intercept of the diastolic P-V relation (LV V_0). Systolic chamber function was assessed by comparing LV developed pressures at specific filling volumes. Intrinsic systolic myocardial function was determined from the slope of the LV systolic developed stress-strain relation (myocardial systolic elastance).

Results: ISO adminstered to SD and to SHR rats produced cardiac dilatation [LV V_0 (ml): SD 0.20±0.01, SD-ISO 0.27±0.02, $p<0.005$; SHR 0.21±0.01, SHR-ISO 0.30±0.01, $p<0.001$], systolic chamber dysfunction (decrease in left ventricular developed pressures at incremental filling volumes) but normal intrinsic systolic myocardial function. Habitual exercise resulted in a right shifted LV diastolic P-V relation and an increased LV V_0 (Exer 0.22±0.01, Con 0.18±0.01, $p<0.005$). In exercised rats (Exer-dilated, n=10) with equivalent dilatation as SD-ISO and SHR-ISO (LV V_0 within 95% CI of SD-ISO and SHR-ISO), despite comparable LV diastolic P-V relations and LV V_0 values (0.28±0.01); both systolic chamber function and intrinsic systolic myocardial function were normal.

Conclusions: These data provide evidence to indicate that as compared to pathological dilatation, a similar extent of exercise-induced dilatation does not produce the same adverse effects on systolic chamber function.

DECLARATION

I declare that this dissertation is my own, unaided work. 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 thesis has not been submitted for any degree or examination in this university, or any other university.

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CHRISTOPHER ANAMOURLIS

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I certify that the studies contained in this thesis have the approval of the Animal Ethics Committee of the University of the Witwatersrand, Johannesburg. The ethics approval numbers are: 99:01:2b, 2002:37:5 and 2002:39:5.

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ANGELA WOODIWISS (Supervisor) GAVIN R. NORTON (Supervisor)

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DEDICATION

This thesis is dedicated to my family, especially my mother and father, who have always given us what we needed, so that we can have what we want.

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Firstly I would like to thank my supervisors Prof. A Woodiwiss and Prof. G Norton for their patience, support and invaluable teaching.

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LIST OF ABBREVIATIONS

ANOVA:	analysis of variance
ATP:	adenosine triphosphate
β:	beta
BP:	blood pressure
Ca^{2+}:	calcium
CI:	confidence interval
CIBIS-II:	Cardiac Insufficiency BIsoprolol Study II
Con:	sedentary control group
Exer:	exercise group
h:	myocardial wall thickness
ISO:	isoproterenol
LVEDD:	left ventricular end diastolic diameter
LV V_0:	volume intercept of LV diastolic pressure-volume relation
LV:	left ventricle
LVH:	left ventricular hypertrophy
MERIT-HF:	Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure
MMP:	matrix metalloproteinases
P:	pressure
r:	radius
SD:	group of Sprague-Dawley rats receiving vehicle
SD-ISO:	group of Sprague-Dawley rats receiving isoproterenol
SEM:	standard error of the mean
SHR:	spontaneously hypertensive rats and group of SHR receiving vehicle
SHR+ISO:	group of spontaneously hypertensive rats receving isoproterenol
WKY:	Wistar Kyoto

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PREFACE

It is generally perceived that regular exercise is beneficial to the cardiovascular system. However, as exercise is recognized as a factor that promotes the development of cardiac hypertrophy, a change that in pathological states such as hypertension has adverse prognostic implications, whether exercise has deleterious effects on the heart has in the past and is now again being questioned. It is presently acknowledged that exercise-induced cardiac hypertrophy does not appear to predict adverse cardiovascular outcomes and may not be associated with the progression to cardiac dysfunction. In contrast to cardiac hypertrophy which occurs in pathological states (pathological hypertrophy), exercise-induced cardiac hypertrophy is thought to be a compensatory response to the normal demands of activity and as such is called "physiological cardiac hypertrophy".

However, with respect to physiological cardiac hypertrophy, regular, sustained, medium-to-high intensity exercise programs may induce cardiac hypertrophy with a geometric change that may not maintain wall stress during exercise-induced increases in blood pressure and chamber filling. Indeed, in this form of exercise the cardiac chamber increases in size to accommodate continuously high pre- and after-loads and this cardiac geometric change is reminiscent of cardiac dilatation in chronic heart failure, where a greater cavity size predicts a worse clinical outcome. As cardiac chamber dilatation contributes to pump dysfunction in heart failure and subsequent end stage heart failure, the question that arises is whether increases in cardiac cavity size in exercise-induced cardiac hypertrophy also promote pump dysfunction?

In this regard, presently there is little understanding of the pathophysiological significance of increases in cardiac cavity size in exercise-induced cardiac hypertrophy. Although a reduced pump function has been noted to occur with increased cavity

dimensions in endurance athletes, whether the dilated chamber promotes pump dysfunction or is the consequence of alternative changes such as a reduced contractile function and heart rate or an increased preload, is unclear.

This dissertation is aimed at attempting to understand the pathophysiological relevance of increases in cardiac cavity size in exercise-induced cardiac hypertrophy. As a major pathophysiological change thought to be responsible for cardiac dilatation in heart failure is excessive sympathetic nervous system activation, in the present dissertation I compared the impact of exercise-induced cardiac dilatation on pump function to that of cardiac dilatation induced by sympathetic over-activation (pathological dilatation). Importantly, I assessed whether pump dysfunction occurs in rats with exercise-induced cardiac dilatation the extent of which is comparable with that produced by pathological dilatation.