INTERVENTIONS AIMED TO IMPROVE AUTONOMIC AND ENDOTHELIAL FUNCTION IN CHRONIC HEART FAILURE AND CORONARY ARTERY DISEASE

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DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and that to the best of my knowledge and belief, it does not contain any material previously published or written by another person except where due reference in made in the test.

Biju Paul

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PUBLICATIONS AND AWARDS

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2007 Flinders University Faculty of Health Sciences Research Grant for Autonomic Reflexes in Chronic Heart Failure.

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Publications:

1. Acute effects of 5-Methyltetrahydrofolate on arterial wave reflection and endothelial function in patients with chronic heart failure.

   Paul B, DePasquale CG, Mangoni AA. *Nutr.Metab.Cardiovasc.Dis.,* 2010 June; 20(5):341-349

2. Analysis of short-term reproducibility of arterial vasoreactivity by pulse-wave analysis after pharmacological challenge.

   Paul B, Hewitson CL, Woodman RJ, Mangoni AA. *Clin.Exp.Pharmacol.Physiol.* 2009 Jan; 36(1):49-54

ABSTRACT

The current epidemic of cardiovascular disease has defined itself as the healthcare priority of this generation. It ranges from coronary artery disease (CAD) (presenting with acute symptoms) to chronic heart failure (CHF) (presenting with debilitating and gradual worsening symptoms). An improved understanding of the pathophysiology of the disease has lead to new medications and reduced disease specific mortality. However, increased prevalence and chronic symptoms have adversely affected quality of life. Persistent angina in CAD and dyspnoea and fatigue in CHF remain the cardinal symptoms restricting quality of life. These debilitating symptoms are a reflection of end stage disease and are resistant to current therapeutic options. This thesis explores new therapeutic options to manage these debilitating symptoms.

Recent studies have highlighted the potential benefit of non toxic agent's- folic acid, tetrahydrobiopterin and oxygen in patients with cardiovascular risk factors. Previous studies done by our group and others have shown oxygen to improve symptoms and exercise performance in patients with CHF while folic acid and tetrahydrobiopterin are shown to improve vascular endothelial function in these patients. The low cost and largely non toxic potential of these agents has driven their further assessment for this thesis.

Existing literature provides information on the influence of these agents in patients with cardiovascular risk factors. The scope of this thesis is to add to this knowledge and assess the effects of these agents on cardiopulmonary reflexes and endothelial function in patients with established CAD and CHF.

The first part of the thesis analysed the influence of low flow nasal oxygen on cardiopulmonary reflex during sub-maximal and maximal exercise testing in CHF and the second part analysed the influence of folic acid and tetrahydrobiopterin on endothelial function in CHF and CAD. The thesis also conducted a technical analysis of the reproducibility of pulse wave analysis, used to analyse vascular endothelial function.

Folic acid, tetrahydrobiopterin and oxygen were well tolerated and no significant side effects were reported. Patients with CHF were characterised by autonomic imbalance; predominantly inefficient ventilation during sub-maximal and maximal exercise. Low flow inhaled oxygen significantly improved this imbalance and reduced the ventilatory overdrive during sub-maximal, but not maximal exercise. However, it did not influence cardiovascular parameters. This ventilatory benefit might explain the improvement in exercise performance and quality of life seen with its use in CHF. Further studies are required to assess its impact on disease progression and mortality.

Folic acid significantly reduced serum ADMA level in patients with CHF. ADMA is a well defined surrogate marker of endothelial injury. However, it did not concurrently improve endothelial function. Furthermore, the combined administration of folic acid and tetrahydrobiopterin did not improve endothelial function in both the large (aorta) and small arteries (brachial) of patients with CAD. The lack of effect of folic acid and tetrahydrobiopterin might be explained by the advanced irreversible nature of endothelial function in patients with well established cardiovascular disease. The technical analysis of pulse wave analysis emphasised its

usefulness in assessing baseline endothelial function; however, it correlated poorly when used to assess the impact of various therapeutic agents on endothelial function.

ABBREVIATIONS

5-MTHF	5-methyl tetrahydrofolate
AA	ascending aorta
ACE	Angiotensin converting enzyme inhibitors
ADMA	serum asymmetrical dimethylarginine
AIx	augmentation index
ANS	autonomous nervous system
BH4	Tetrahydrobiopterin
BMI	body mass index
CAD	coronary artery disease
CHF	chronic heart failure
CaO2	arterial oxygen content
CvO2	venous oxygen content
cGMP	cyclic guanosine monophosphate
CMR	cardiac magnetic resonance imaging
CPET	Cardiopulmonary exercise testing
CV	coefficient of variation
DBP	blood pressure
DDA	distal descending aorta
DDAH	dimethylarginine dimethylaminohydrolase
EF	ejection fraction
eNOS	Endothelial NOS
FMD	Flow mediated dilatation
GTN	Glyceryl trinitrate
HR	heart rate
HIF-1	hypoxia inducible translation factor
ICC	intraclass correlation coefficient
IHD	ischaemic heart disease
L-NMMA	N monomethly-L-arginine
MI	myocardial infarction
MRI	Magnetic resonance imaging
NADPH	nicotinamide adenine dinucleotide phosphate
NOS	nitric oxide synthase
NO	nitric oxide
PDA	proximal descending aorta
PGC-1 γ	peroxisome-proliferator-activated receptor-γ co-activator 1
PP	pulse pressure
PWA	Pulse wave analysis
RER	Respiratory exchange ratio
ROS	reactive oxygen species
SDMA	symmetrical dimethylarginine
SV	stroke volume
sBP	systolic blood pressure
VO2	ventilatory oxygen
VCO2	ventilatory Carbon dioxide
Ve	ventilation
Vt	tidal volume