The Relationship Between Markers Of Disease Severity In Obstructive Sleep Apnea Patients To Hemodynamic And Respiratory Function During Graded Exercise

by

Jennifer Susanne Blevins

Committee Chairman: William G. Herbert Clinical Exercise Physiology

(ABSTRACT)

Obstructive sleep apnea (OSA) is estimated to affect 2 to 4 percent of the adult population (Young T 1993, Skomro and Kryger 1999). However, an estimated 80 to 90 percent of adults with moderate to severe OSA may be clinically undiagnosed. Identification of those at risk and their subsequent diagnosis is, obviously, of great concern to clinicians. This investigation included three distinct research aims, which were the following: (1): In order to establish reliability of hemodynamic measures to be used during exercise testing, a study was conducted on the acetylene single-breath cardiac output (Q_c) technique in 15 healthy subjects. This was completed in order to establish reliability of exercise Q_c and total peripheral resistance (TPR), these responses could then be investigated acutely in the context of evaluating the relation of these measures to markers of disease in OSA patients. (2): The primary research aim was to describe the extent to which graded exercise testing may reveal abnormalities in hemodynamic function in obstructive sleep apnea (OSA) patients, particularly with respect to cardiac output (Qc), mean arterial pressure (MAP), and TPR that may be related to polysomnography (PSG) markers of OSA severity. Cardiorespiratory and hemodynamic responses that were evaluated included the following: peak oxygen consumption (VO₂pk), end-tidal carbon dioxide production (P_{ET}CO₂), end-tidal oxygen pressure $(P_{ET}O_2)$, heart rate (HR), blood pressure (systolic = SBP and diastolic = DBP), rate pressure product (RPP), TPR and its derivatives including MAP and Q_c , in OSA patients. A global biochemical marker of vascular function, 24-hour urinary nitrite/ nitrate elimination was also determined for each patient. (3): The last aim was included in order to provide qualitative information concerning treatment, subjective sleep and daytime function, and physical activity levels of the OSA patients in this investigation as well as to give insights into the special challenges and potential for doing trials involving nCPAP and physical exercise training with OSA patients. Results from this study can be used to improve clinical evaluation procedures as well as to better understand underlying mechanisms relative to the link between cardiovascular disease and OSA.

DEDICATION

This dissertation is dedicated to my mother and father, Nancy J. Blevins and Roy K. Blevins. Words cannot describe the undying gratitude I have for them. Not many of us have people who we know that no matter what the circumstances, their love, caring, support, laughter, and trust are always there. They have taught me so much in 30 years. Thank you. I love you both very much.

ACKNOWLEDGEMENTS

A lot of work and support from many people goes into making sure a dissertation is completed. Much of the credit for the success of this project should be given to the committee chair, Dr. William G. Herbert. His devotion to clinical research in human pathophysiology

Special thanks to the rest of the dissertation committee. Dr. Don Zedalis should be highly commended for his collaborative efforts with Virginia Tech and his unyielding support for clinical exercise physiology research at the Allergy and Sleep Disorders Network in Christiansburg, VA. Special thanks also should be given to Dr. John Gregg for initiating much of the research with regard to obstructive sleep apnea in the New River Valley.

I thank Dr. Lawrence Cross for his instruction and advisement in statistics and research design and for his willingness to offer expert advise in many research projects over the past four years, and for his support. I thank Dr. Ron Bos for his I thank Dr. Richard Lock for his enthusiastic approach to clinical advisement and instruction.

A special thank you to Howard Ballentine for his assistance with data collection and for always listening. I thank Ali Arner, Tony Kaleth, and Tom Chittenden for their assistance in completing the ResMed project.

To Curtis Carter, thank you for enduring this with me and for having faith in me no matter what. I couldn't have done it without you.

To Stephanie Herbert, my friend, my "sister", I am so glad you came into my life.

Thank you for always listening.

TABLE OF TABLES

Table		Page
Chapter I		
I1.	Cardiovascular and Hemodynamic Consequences of Apneic and Hypopneic Events during Sleep	24
Chapter IIIa		
IIIa-1	Cardiac output values measured under resting conditions in eight different trials over two days	63
IIIa-2	Exercise responses and coefficients of determination cardiac output at two different fixed-load intensities during cycle ergometry exercise on Day 1 and Day 2	64
Chapter IIIb		
IIIb-1.	Selected descriptive and physical characteristics of OSA patients	101
IIIb-2	Polysomnography measures of sleep function in OSA patients	102
IIIb-3a.	Comorbid conditions among OSA patients	103
IIIb-3b.	Medications use separated by disease category among all OSA patients	104
IIIb-4.	Sitting resting cardiorespiratory responses taken while seated on a bicycle ergometer before exercise testing	105
IIIb-5	Hemodynamic and ventilatory responses during graded exercise testing	106
IIIb-6.	Relationships between resting hemodynamic measures and polysomnography markers of disease severity	107
IIIb-7.	Relationships between submaximal hemodynamic measures and polysomnography markers of disease severity	108
IIIa-8.	Predictor variables significantly correlated with lowest SaO ₂ as a criterion variable	109

TABLE OF FIGURES

Chapter I		Page
I1.	Biosynthesis of nitric oxide	30
I2.	Mechanism of action of NO on vascular smooth muscle in the intact endothelium (a) and in the damaged endothelium (b)	32
Chapter IIIa		
IIIa-1	Inter-trial reproducibility for acetylene single-breath cardiac output measurements for ramping cycle ergometer exercise in apparently healthy adults	66
IIIa-2	Comparative values between the ramp and fixed-load exercise test for acetylene single-breath cardiac output measurements at the same power output and oxygen consumption	67
IIIa-3	Acetylene single-breath cardiac output responses during low- intensity and high-intensity fixed-load exercises. Vertical bars show stability of cardiac output responses, when repeated determinations are made, using either 1- or 5-min intervals	68
IIIa-4	Individual differences from mean acetylene single-breath cardiac output Qc for fixed-load exercise. Each data point represents an individual Qc measure relative to that persons mean Qc values for four FL trials over the two day period. The mean Qc value is represented as the "0" point on the vertical axis	69
IIIa-5	Individual differences from mean acetylene single-breath cardiac output Qc for ramp exercise. Each data point represents an individual Qc measure relative to that persons mean Qc values for the two RL trials. The mean Qc value is represented as the "0" point on the vertical axis	70
Chapter IIIb		
IIIb-1	Changes in P _{ET} O ₂ from rest to peak exercise plotted for each OSA patient response	110
IIIb-2	Changes in P _{ET} CO ₂ from rest to peak exercise plotted	111
	according to each OSA patient response	111

TABLE OF CONTENTS

		Page
Dedicatio	n	i
Acknowle	edgements	ii
Table of T	-	iii
Table of I		iv
CHAPTER		PAGE
I.	Introduction	1
II.	Review of the Literature	16
	Morbidity Mortality	16
	Pathogenesis of Obstructive Sleep Apnea	19
	Cardiovascular Consequences of Obstructive Sleep Apnea	22
	Hemodynamic changes during sleep in Obstructive Sleep Apnea	22
	Daytime cardiovascular abnormalities associated with OSA	25
	Left ventricular dysfunction and ischemic heart disease.	25
	Hypertension	26
	Total peripheral resistance and vascular function in OSA	29
	patients	2)
	Biosynthesis of NO	30
	Mechanisms of action of NO relative to the endothelium	30
		35
	Role of NO-dependent vasodilation in OSA	35 36
	Physiological Responses to Exercise in OSA Patients	
	Ventilatory and hemodynamic responses to exercise testing	36
	Effects of treatment on cardiovascular responses during exercise	43
	Summary	44
IIIa.	Results: Journal Manuscript I.	46
	(Reliability of Acetylene Single-Breath Cardiac Output in Exercise)	
	Abstract	47
	Introduction	48
	Methods	50
	Results	53
	Discussion	
		54
	References	60
IIIb.	Results: Journal Manuscript II.	71
	(Reliability of Acetylene Single-Breath Cardiac Output in Exercise)	
	Abstract	72
	nonact	12

	Introduction	74
	Methods	76
	Results	81
	Discussion	84
	References	93
IIIc.	Qualitative Investigation Regarding treatment and physical activity after short term CPAP treatment	112
IV.	Summary and Conclusions	118
	Practical and Clinical Applications	121
	Recommendations for Future Research	122
	References Cited	125
APPENDICES		
A	List of Abbreviations	136
В	Informed Consent	139
C	Recruitment Flyer	148
D	Screening Questionnaires	150
E	Data Collection Worksheets	156
F	Detailed Methodology	160
G	Raw Data	168
Н	Summary ANOVA Tables	172
VITA		173