Cardiopulmonary assessment through stress testing

Ang, Kok Chiang

2005

Ang, K. C. (2005). Cardiopulmonary assessment through stress testing. Master's thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/5729>

<https://doi.org/10.32657/10356/5729>

Nanyang Technological University

Downloaded on 26 Apr 2023 09:45:22 SGT

Cardiopulmonary Assessment Through Stress Testing

Ang Kok Chiang

School of Mechanical & Aerospace Engineering

A thesis submitted to the Nanyang Technological University
in fulfilment of the requirement for the degree of
Master of Engineering (Research)

2005

ABSTRACT

This dissertation presents the results from a collaborative project between Nanyang Technological University and Singapore General Hospital (Department of Respiratory and Critical Care Medicine). Three studies were conducted with interpretative strategies and clinical indications of performing indices for the purpose of monitoring disease progression and response to rehabilitation treatment.

The first study observed the importance of spirometry parameters for the diagnosis of patients with pulmonary diseases (obstructive/restrictive), referred for pulmonary rehabilitation. These parameters were used to construct a new graphical technique to visually differentiate patients with pulmonary diseases from the normal population. This graphical technique produced good diagnostic results for both positive and negative tests.

The second study examined the importance of oxygen parameters for the diagnosis of patients with cardiomyopathy, referred for heart transplant evaluation. These parameters were used to construct a new graphical technique and a non-dimensional index to visually distinguish cardiomyopathy patients from the normal population. This graphical technique produced better diagnostic results for negative tests, while the non-dimensional index produced better diagnostic results for positive tests.

The third study evaluated the importance of carbon dioxide by comparing the correlation of heart rate with carbon dioxide against the correlation of heart rate with oxygen. The heart rate in both normal and heart disease groups had a higher significant correlation for carbon dioxide than for oxygen. Also, carbon dioxide in both normal and heart disease groups had a smaller standard deviation than oxygen. Heart rate with oxygen and heart rate with carbon dioxide were then mathematically modeled in cases of normal and heart diseases to describe and predict the dynamic physiological system accurately regardless of a linear or nonlinear relationship. The mathematical model identified an important demarcation strategy of heart patients from the normal population for clinical indications.

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation and gratitude to the following personnel who have contributed to the completion of this dissertation.

1. Associate Professor Ong Jor Huat and Associate Professor Lim Geok Hian, the supervisors from Nanyang Technological University, for their invaluable advice and guidance throughout this meaningful and challenging research project. They had also rendered their continuous support and precious time, without which the success of this research project would be impossible.
2. Professor Dhanjoo N. Ghista, the visiting professor from Nanyang Technological University, for his experienced suggestions and guidance, especially during those unsuccessful attempts in the analysis of this research project.
3. Doctor Loo Chian Min, the director from the Department of Respiratory and Critical Care Medicine (Singapore General Hospital), for his professional support and effective coordination in imparting experienced medical knowledge and expertise. He had also kindly released the patients' data for this research project, at the same time, protecting the confidentiality of the patients' particulars.
4. Miss Philine Chan, the laboratory technician from the Department of Respiratory and Critical Care Medicine (Singapore General Hospital), for her precious time and kind support in coordinating and arranging patients' data.

5. My family and Miss Tristin Ong, who have shown much understanding, support and encouragement during those very difficult times when I could not be by their side.

TABLE OF CONTENTS

	Page
ABSTRACT	i
ACKNOWLEDGEMENT	ii
TABLE OF CONTENTS	iv
LIST OF ABBREVIATIONS	vii
LIST OF FIGURES	x
LIST OF TABLES	xi
CHAPTER 1: INTRODUCTION.....	1
1.1 Cardiopulmonary Exercise Testing (CPET)	1
1.2 Pulmonary Function Testing (PFT)	3
1.3 Test Indications.....	5
1.3.1 Indications for CPET (Idelle <i>et al.</i> , 2003)	5
1.3.2 Indications for PFT (ATS. 1994).....	6
1.4 Objectives	7
1.4.1 Study 1 & 2	7
1.4.2 Study 3	8
1.5 Scopes	8
1.5.1 Study 1 & 2	8
1.5.2 Study 3	9
1.6 Variations	9
1.6.1 Technical Variation.....	10
1.6.2 Biological Variation.....	11
1.6.3 Disease Variation	12
1.7 Thesis Outline	12
CHAPTER 2: LITERATURE REVIEW	14
2.1 Interpretations.....	14
2.1.1 Lung Diseases	14
2.1.2 Cardiomyopathy.....	15

2.2	Pulmonary Function Testing (PFT)	16
2.2.1	Forced Vital Capacity (FVC)	16
2.2.2	Forced Expiratory Volume in 1 Second (FEV ₁)	17
2.2.3	Ratio of FEV ₁ versus FVC (FEV ₁ /FVC).....	17
2.2.4	Reference Values	17
2.3	Cardiopulmonary Exercise Testing (CPET)	19
2.3.1	Maximal Oxygen Consumption (VO _{2max}).....	21
2.3.2	VO ₂ Kinetics	24
2.3.3	Oxygen Consumption versus Work Rate (VO ₂ /P)	27
2.3.4	Maximal Oxygen Pulse (O ₂ pulse _{max}).....	28
2.3.5	Parameters Compilation.....	29
2.4	Medication	30
CHAPTER 3: METHODS		32
3.1	Setting	32
3.2	Subjects.....	33
3.2.1	Study 1 (Spirometry Data Interpretation & Representation).....	33
3.2.2	Study 2 (Data Interpretation & Representation of CPET)	33
3.2.3	Study 3 (Mathematical Models of HR vs . VO ₂ & HR vs. VCO ₂)	34
3.3	Procedures (Protocols)	35
3.3.1	Pulmonary Function Testing.....	35
3.3.2	Exercise Testing.....	37
3.4	Research Design	40
3.4.1	Study 1 (Spirometry Data Interpretation & Representation).....	41
3.4.2	Study 2 (Data Interpretation & Representation of CPET)	47
3.4.3	Study 3 (Mathematical Models of HR vs. VO ₂ & HR vs. VCO ₂)	54
3.5	Statistical Analysis	57
CHAPTER 4: RESULTS		58
4.1	Study 1 .Spirometry Data Interpretation & Representation	58
4.1.1	Subject Characteristics.....	58
4.1.2	Graphical Presentation	59
4.2	Study 2 .Data Interpretation & Representation of CPET	62
4.2.1	Subject Characteristics.....	62
4.2.2	Graphical Presentation	62
4.3	Study 3 - Mathematical Models of HR vs. VO ₂ & HR vs. VCO ₂	67
4.3.1	Subject Characteristics.....	67
4.3.2	Correlation	67
4.3.3	Mathematical Model (With reference to section 3.4.3)	68

CHAPTER 5: DISCUSSION	69
5.1 Study 1 (Spirometry Data Interpretation & Representation)	69
5.2 Study 2 (Data Interpretation & Representation of CPET)	70
5.3 Study 3 (Mathematical Models of HR vs. VO ₂ & HR vs. VCO ₂)	71
5.3.1 Correlation	71
5.3.2 Mathematical Model	72
CHAPTER 6: CONCLUSION & FUTURE WORK	74
6.1 Summary	74
6.2 Conclusion	75
6.2.1 Study 1 (Spirometry Data Interpretation & Representation)	75
6.2.2 Study 2 (Data Interpretation & Representation of CPET)	75
6.2.3 Study 3 (Mathematical Models of HR vs. VO ₂ & HR vs. VCO ₂)	75
6.3 Recommendations	76
6.3.1 Predicted Reference Values	76
6.3.2 Study 1 (Spirometry Data Interpretation & Representation)	77
6.3.3 Study 2 (Data Interpretation & Representation of CPET)	77
6.3.4 Study 3 (Mathematical Models of HR vs. VO ₂ & HR vs. VCO ₂)	79
REFERENCES	81
APPENDICES.....	110
Appendix A Contraindications	110
Appendix B 1 Pre-exercise Checklist	111
Appendix B2 Evaluation Form	112
Appendix C Study 1 (Spirometry Data Interpretation & Representation) Results	114
Appendix D Study 2 (Data Interpretation & Representation of CPET) Results	130
Appendix E Conference	139

LIST OF ABBREVIATIONS

The following abbreviations were used in this study:

A = age

a_1 = age (measured)

ABS = absolute

ACE = angiotensin-converting enzyme

ARVC = arrhythmogenic right ventricular cardiomyopathy

BMI = body mass index

BP = blood pressure

b.p.m. = beats per minute

BTPS = body temperature and pressure, saturated

CI = confidence interval

cm = centimeter

COPD = chronic obstructive pulmonary disease

CPET = cardiopulmonary exercise test

CPI = cardiopulmonary index

DCM = dilated cardiomyopathy

ECG = electrocardiogram

F = cost function

FEV_1 = forced expiratory volume in 1 second

FEV_1/FVC = ratio of forced expiratory volume in 1 second over forced vital capacity

FEV_6 = forced expiratory volume in 6 seconds

FN = false-negative

FP = false-positive

FVC = forced vital capacity

H = height

h_1 = height (measured)

HCM = hypertrophic cardiomyopathy

Hg = mercury

HR = heart rate

hr_2 = heart rate (predicted)

HR_{max} = maximal heart rate

IE = incomplete expiration

kg = kilogram

kg/m^2 = kilogram per square meter

ℓ = liters

ℓ/s = liters per second

LVEF = left ventricular ejection fraction

m^2 = square meter

MET = metabolic equivalent

min = minute

$ml/min.kg$ = milliliter per minute per kilogram

mm = millimeter

mmHg = millimeters mercury

MVV = maximal voluntary ventilation

N = number of observations

NPV = negative predictive value

O = obstructive pulmonary disease

O_2 pulse = oxygen pulse

O_2 pulse_{max} = maximal oxygen pulse

P = power

PFT = pulmonary function test

PPV = positive predictive value

pred = predicted

PRP = pulmonary rehabilitation program

r = correlation coefficient

R = restrictive pulmonary disease

RCM = restrictive cardiomyopathy

s = second

S.D. = standard deviation

t = time

TN = true-negative

TP = true-positive

UF = ultrafiltration

VC = vital capacity

VCO_2 = carbon dioxide produced (ml/min)

VE = minute ventilation

VO_2 = oxygen consumption (ml/min)

VO_2/P = oxygen consumption per work rate (ml/W.min)

$\text{VO}_{2\text{max}}$ = maximal oxygen consumption

W = watts

w_1 = weight (measured)

w_2 = weight (predicted)

LIST OF FIGURES

	Page
Figure 3.1 Clinical spirometer (Masterlab; Jaeger. Wurzburg. Germany).....	36
Figure 3.2 Normal spirogram used to measure FVC and FEV ₁	37
Figure 3.3 Clinical Cycle Ergometer (ER 900; Jaeger. Wiirzburg. Germany)	39
Figure 3.4 Electrocardiography (ECG)	39
Figure 3.5 Spirometry flow chart to assess pulmonary diseases	42
Figure 3.6 Graphical presentation to assess pulmonary diseases	46
Figure 3.7 CPET flow chart to assess cardiomyopathy	47
Figure 3.8 Graphical presentation to assess cardiomyopathy	51
Figure 3.9 Cardiopulmonary index (CPI) to assess cardiomyopathy.....	51
Figure 3.10 Physiological response during incremental exercise	55

LIST OF TABLES

	Page
Table 2.1 Spirometry Classification of Ventilatory Abnormalities	15
Table 2.2 Summary of Clinical Parameters	29
Table 3.1 Predicted Equations for FVC	43
Table 3.2 Predicted Equations for FEV ₁	43
Table 3.3 Predicted Equations for FEV ₁ /FVC	43
Table 3.4 Standard Spirometry Reference Values (ATS. 1986).....	44
Table 3.5 Normalized Spirometry Reference Values	46
Table 3.6 Predictive Accuracy Terms of Diagnostic Test	46
Table 3.7 Predicted Equations for VO _{2max}	48
Table 3.8 Predicted Equations for O ₂ pulse _{max}	48
Table 3.9 Predicted Equations for Weight (w ₂)	48
Table 3.10 Predicted Equations for Heart Rate (hr ₂)	48
Table 3.11 Standard CPET Reference Values	49
Table 3.12 Normalized CPET Reference Values	52
Table 3.13 Predictive Accuracy Terms of Diagnostic Test	52
Table 3.14 Terms Used to Demonstrate the Diagnostic Value of a Test.....	54
Table 4.1 Subject Characteristics for Study 1.....	59
Table 4.2 Graphical Presentation for Study 1	60
Table 4.3 Sensitivity and Specificity of Graphical Presentation	61
Table 4.4 Predictive Accuracy of Graphical Presentation	61
Table 4.5 Subject Characteristics for Study 2	62
Table 4.6 Graphical Presentation for Study 2	63
Table 4.7 Sensitivity and Specificity of Graphical Presentation	64
Table 4.8 Predictive Accuracy of Graphical Presentation	64
Table 4.9 Cardiopulmonary Index (CPI) for Study 2	65
Table 4.10 Sensitivity and Specificity of CPI.....	66
Table 4.11 Predictive Accuracy of CPI	66
Table 4.12 Subject Characteristics for Study 3	67
Table 4.13 Correlation of Heart Rate in Normal and Heart Patients	68
Table 4.14 Mathematical Model Constants (A _j and B _j)	68

CHAPTER 1: INTRODUCTION

This chapter is divided into the following subsections: 1) Cardiopulmonary Exercise Testing (CPET) 2) Pulmonary Function Testing (PFT) 3) Test Indications 4) Objectives 5) Scope 6) Variations and 7) Thesis Outline

1.1 Cardiopulmonary Exercise Testing (CPET)

The Cardiopulmonary Exercise Test (CPET) globally assesses integrative physiological responses of pulmonary and cardiovascular systems by evaluating undiagnosed exercise intolerance, exercise-related symptoms, functional capacity and impairment. CPET is a safe procedure. The risk of death for every 100,000 exercise tests performed on patients is between 2 and 5 (Richard *et al.*, 2003). CPET, being a non-invasive test, is increasingly being used for its ability to provide physician with relevant information on implicated diseases where resting pulmonary and cardiac function testing is incapable (Wasserman *et al.*, 1999; Weber & Janicki, 1986; Weisman & Zeballos, 1995, 2001). At the same time, exertional symptoms correlate poorly with resting cardiopulmonary measurements (Franciosa *et al.*, 1981; Killian *et al.*, 1992; Szlachcic *et al.*, 1985). The practical relevance of CPET is further highlighted by Curtis's findings, which showed that subjective measures of a patient's quality of life reveal a stronger correlation with exercise tolerance rather than with spirometry or oxygenation (Curtis *et al.*, 1994).

The importance of CPET in assessing exercise capacity and therapy response of patients with heart failure (also candidates for heart transplantation) is demonstrated in Committee on Exercise Testing (1997). Myers *et al.* (1998) recommended that all patients evaluated for heart failure should undergo CPET. Stelken *et al.* (1996) further confirmed prognostic value of CPET for patients with ischemic and dilated cardiomyopathy. Most of the studies that provide data for CPET use in the clinical setting have been conducted on populations in Western countries (Fairbairn *et al.*, 1994; Hansen *et al.*, 1984; Jones *et al.*, 1985; Neder *et al.*, 1999; Wasserman *et al.*, 1994).

CPET has been established as a useful method in monitoring physiological improvement in patients with heart failure undergoing exercise training for cardiac rehabilitation (Braith *et al.*, 1998; Coats *et al.*, 1992; Hambrecht *et al.*, 2000; Keteyian *et al.*, 1996). However, the routine use of CPET still requires additional studies of pulmonary function testing with spirometry before commencement of test, study of monitoring of the electrocardiogram (ECG) and blood pressure (BP) during exercise. Likewise, although CPET has been used to demonstrate the value of early exercise training after heart transplantation on quality of life and increased capacity for physical work, its routine use in this setting also remains uncertain and requires additional investigation (Kobashigawa *et al.*, 1999).

1.2 Pulmonary Function Testing (PFT)

Spirometry (Hutchinson, 1846) is the study of ventilatory physiological function, and a detection and quantification of pulmonary diseases. It is an additive diagnostic method for CPET. It reflects the muscular effort to start the process, elastic recoil of lungs and thorax, small airways function, large airways function, and the interdependence between airways and alveoli. As one of the most frequently performed pulmonary function test (Baltopoulos *et al.*, 2000; Gibson *et al.*, 2002), it is essential for lung disease patients before the commencement of CPET. Spirometry is a useful screen of general health and correlates well with morbidity and life expectancy. Spirometry is also used to affect decisions about individual patients, including the nature of lung defect, its severity, and the response to therapy. Therefore, it has an effect on a person's lifestyle, standard of living, and future treatment (Renzetti *et al.*, 1986). Similarly, accurate and precise spirometers are required for epidemiological studies. The rates of improvement or deterioration of pulmonary function measured in relation to environmental exposures and/or personal characteristics may be erroneous if inaccurate spirometers are used or less sensitive/ imprecise spirometers are used (Hankinson, 1986). Maximizing the clinical usefulness of spirometry depends on a number of steps, ranging from equipment selection to interpretation, and ultimately involves clinical assessment.

Spirometry is an effort-dependent maneuver that requires understanding, coordination, and cooperation by the patient-subject, who must be carefully instructed. Thus, procedural recommendations and interactions between technicians and subjects are important components of testing.

Spirometry has many applications and is an excellent predictor of prognosis in all stages of chronic obstructive pulmonary disease (COPD), which defines as a condition with decreased ability to exhale or inhale. Mannino *et al.* (2000) discovered in the US population, a high prevalence of COPD in both current and former smokers that was not diagnosed, even in the face of clinical respiratory symptoms of classic cough and dyspnea. Therefore, it is necessary to evaluate responses for early therapy using spirometer. Abnormal spirometry also predicts death from heart attack (Friedman *et al.*, 1976; Marcus *et al.*, 1989), a fourfold to sixfold higher risk of lung cancer than if airflow is normal (Skillrud *et al.*, 1986; Tockman *et al.*, 1987), and all cause mortality (Bang *et al.*, 1993; Beaty *et al.*, 1982, 1985; Hole *et al.*, 1996; Krzyzanowski & Wysocki, 1986; Lange *et al.*, 1990; Neas & Schwartz, 1998; Schunemann *et al.*, 2000).

Today, many primary care physicians see the vast majority of smokers in their offices at least once a year, and others with diseases characterized by premature morbidity and mortality. Spirometry measurements emerge as an important indicator of incipient disease. It alerts physicians and the patients that they serve the importance of early treatment for COPD and related disorders.

1.3 Test Indications

1.3.1 Indications for CPET (Idelle *et al.*, 2003)

There are several useful indications for CPET. These include the following:

1. Evaluation of exercise tolerance
2. Evaluation of undiagnosed exercise intolerance
3. Evaluation of patients with cardiovascular diseases
4. Evaluation of patients with respiratory diseases/symptoms
5. Preoperative evaluation
6. Exercise evaluation and prescription of pulmonary rehabilitation
7. Evaluation of impairment/disability
8. Evaluation for lung, heart, and heart-lung transplantation

1.3.2 Indications for PFT (ATS, 1994)

There are also a number of specific indications for PFT. These include the following:

1. Evaluation of symptoms, signs or abnormal laboratory tests
2. Measurement of disease effect on pulmonary function
3. Screening risk of having pulmonary diseases
4. Assessment of preoperative risk
5. Assessment of prognosis
6. Assessment of health status before enrollment in strenuous physical activity program
7. Assessment of therapeutic interventions
8. Description of disease course affecting lung function
9. Monitoring persons in occupations with exposure to injurious agents
10. Monitoring for adverse reactions to drugs with known pulmonary toxicity
11. Assessment of patients as part of a rehabilitation program
12. Assessment risks as part of an insurance evaluation
13. Assessment individuals for legal reasons
14. Epidemiologic surveys
15. Derivation of reference equations

1.4 Objectives

The aim of this project is to: a) improve and facilitate the clinical assessment of cardiomyopathy and pulmonary disease, b) discuss the importance of carbon dioxide, and c) mathematically model heart rate with oxygen and heart rate with carbon dioxide. From the above indications for CPET and PFT, the objectives are subdivided into three studies as follows:

Study 1: To analyze obstructive/restrictive lung diseases from PFT evaluation

Study 2: To analyze cardiomyopathy from CPET evaluation

Study 3: To correlate and develop models of heart rate versus oxygen consumption and heart rate versus carbon dioxide production for normal and heart disease subjects

1.4.1 Study 1 & 2

From PFT and CPET, the objective assessment of performance indices for monitoring disease progression and response to treatment (rehabilitation) (O'Donnell, 1994; Sue & Wasserman, 1991; Weisman & Zeballos, 1994) are presented in the form of flow charts. Then, graphical presentations are contributed to facilitate interpretations strategies and clinical applications.

1.4.2 Study 3

From CPET, the importance of carbon dioxide is presented by comparing the correlation of heart rate with carbon dioxide against the correlation of heart rate with oxygen consumption. Then, heart rate with oxygen and carbon dioxide are mathematically modeled in normal and heart diseases to demarcate regions for clinical indications. Also, from this mathematical modeling, the indirect relationship of heart rate equation is used to estimate both oxygen consumption and carbon dioxide production.

1.5 Scopes

The scope focuses on the interpretative strategies for Study 1 and 2, and clinical indications for Study 3.

1.5.1 Study 1 & 2

The major drawback is that the decision-making process of diagnosis can be cumbersome and subjective. This can affect the progress in rehabilitation and treatment procedure. Therefore, this analysis aims to produce a simple graphical presentation encompassing the decision-making process. From there, this study can perhaps proceed to developing a graphical platform for computer programs.

1.5.2 Study3

Many studies have been using oxygen consumption (VO_2) as a norm in prognostic significance and mortality. Furthermore, VO_2 is also an index for aerobic capacity and functional capability. Together with other parameters, they can serve as cardiac and pulmonary health assessments. To date, there are few studies on carbon dioxide production (VCO_2), which can also serve as an important parameter (Milani *et al.*, 1996; Reybrouck *et al.*, 1998; Ross *et al.*, 2003). This study shall compare the correlation of VCO_2 with heart rate against the correlation of VO_2 with heart rate. At the same time, it will also look into a new mathematical model of heart rate using VO_2 and VCO_2 in the category of normal and heart disease groups. This analysis hopes to develop a demarcation between normal and heart disease patients, and at the same time, sub-divided these heart patients according to medication classification.

1.6 Variations

Variations can be caused by uneven surface contact using ECG leads, motion artifacts, discomfort, and even psychological factors. All clinical measurements are subjected to (1) technical variation related to instrument, procedure, subjects, and their interactions; (2) biologic variation related to intraindividual and interindividual factors; and (3) variations caused by dysfunction or disease. These variations make physiological CPET difficult to analyze.

1.6.1 Technical Variation

Technical variation related to cycle ergometer plays an important factor on heart rate (HR) and oxygen consumption (VO_2). Groot *et al.* (1994) showed that the geometry of the cycle ergometer was the primary factor dictating the lower-limb kinematic patterns of movement, which had a significant relationship with submaximal HR and VO_2 . Also, preferred geometry adapted by patients was equally important as it resulted in architectural adaptations in the active musculature that were joint-specific (Herzog *et al.*^{1,2}, 1991). Thus, this adaptation would probably influence the efficiency power produced by the musculature, which indirectly affected VO_2 (Cavanagh & Kram, 1985).

Technical variation related to procedure with rather small increments in work rate per stage is preferred instead of large increments so that the range from extreme fit to impairment by heart and/or lung diseases will not limit the reliability of VO_2 estimates (Myers *et al.*, 1991). Together with computerized systems for data collection and analysis available for clinical laboratory, it is still important that the procedure used be validated, that appropriate calibration performed, and that quality assurance be undertaken and maintained. CPET, especially when it features breath-by-breath gas exchange analysis, requires meticulous attention to calibration procedures in order to assure accurate and reproducible measurements. Therefore, the system is calibrated daily as a good practice.

Technical variation related to subjects assumed that all participants are familiar with the cycle ergometry. It was discovered in Nohria *et al.* (2002)'s study, the predictive value of VO_2 and other measurements may be increased when assessed after optimization of therapy and conditioning. In his work, Nohria also found that repeat subject testing was not performed as the variation in repeated testing has been reported to be small. Jones *et al.* (1975) reported that the majority of healthy subjects who are tested on a cycle ergometer will have similar results on 2 successive days and only rarely does a subject show an improvement in performance on the 2nd occasion.

1.6.2 Biological Variation

Intraindividual variations are related to body positions, head position, effort dependence, and circadian rhythms (Baltopoulos *et al.*, 2000). The interindividual variability includes the most important host factors such as sex, body size, age, race, past and present health, habitual activity, and the environmental factors such as geographic factors, exposure to environmental and occupational pollution, and socioeconomic status.

The habitual activity and obesity of subjects are not accounted in the analysis. The habitual activity level of Singapore population is found to be lower than North America population (Epidemiology, 1998; Jones *et al.*, 1985). Therefore, the lower habitual activity level may account for the differences in the predicted values when our subjects are compared with these studies. Overweight subject are expected to have different results (e.g. $\text{VO}_{2\text{max}}$) than subjects of normal weight.

1.6.3 Disease Variation

Variation caused by dysfunction or disease explains that the body system is incapable to respond physiologically to exercise due to impairment. However, there are other reasons that may not be caused by diseases. Therefore, it is important to define maximal exercise. Maximal exercise was defined as the fulfillment of at least 2 of the following three conditions: (i) failure of VO_2 to rise with increasing work load of exercise; (ii) respiratory gas exchange ratio greater than 1.5; or (iii) heart rate within 15 b.p.m of the predicted maximal heart rate (HR_{max}) (Spiro, 1977).

In summary, it is important to minimize the variations caused by the technical factors and to take biologic variations into consideration so that variations by disease can be properly interpreted (ATS, 1991; Bercklake, 1986).

1.7 Thesis Outline

This thesis covers 2 main aspects (CPET and PFT) and subdivided them into 3 studies.

Chapter 1 introduces CPET and PFT with clinical indications and derives objectives for this dissertation.

Chapter 2 reviews more on CPET and PFT with parameters involved in the evaluation that affect the analysis.

Chapter 3 covers on the methodology of this thesis.

Chapter 4 discuss on the subjects' characteristics and results derived from the methodology designed in this study.

Chapter 5 evaluates the results and compares them with the objectives.

Chapter 6 draws the final conclusion and findings from this study and recommends future potential research.

CHAPTER 2: LITERATURE REVIEW

This chapter is divided into the following subsections: 1) Interpretations 2) PFT Parameters 3) CPET Parameters and 4) Medications.

2.1 Interpretations

Physiological concepts are presented in an easy and simplified way in this study to enable a better understanding of CPET and PFT.

2.1.1 Lung Diseases

Airway lung disorder is a common pulmonary disease, which can be detected early through spirometry measurement. The two main airway lung disorders identified are obstructive and restrictive ventilatory problems. The lungs find difficulty to exhale air in obstructive disorder and to inhale air in restrictive disorder. A person with obstructive symptoms will have normal/reduced forced vital capacity (FVC), along with a reduction in forced expiratory volume in 1 second (FEV_1) and reduction in FEV_1/FVC . A person with restrictive symptoms will have reduced FVC, along with a normal/reduction in FEV_1 and increased/normal in FEV_1/FVC . These are summarized in Table 2.1.

Table 2.1 Spirometry Classification of Ventilatory Abnormalities

	Obstructive	Restrictive	Mixed
FEV ₁	↓	↓ or Normal	↓
FVC	↓ or Normal	↓	↓
FEV ₁ /FVC	↓	Normal or ↓	↓

2.1.2 Cardiomyopathy

Cardiomyopathy, according to its Latin derivation, refers to heart muscle disease. There are four separate and distinct conditions of cardiomyopathy. They are dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC).

The vast majority of exercise testing is performed in most adults with known or suspected symptoms of ischemic heart or pulmonary diseases. The certainties in diagnosis, history, resting physical measurements and symptoms have been noted before the exercise tests were conducted. These certainties were based on the referral reports (pre- or post- operative and rehabilitation), basis of age, gender, height, weight, and individual’s physical pre-test condition. Lastly, risk and prognostic assessments were applied before the commencement of the exercise test.

2.2 Pulmonary Function Testing (PFT)

The routine measurements of respiratory function (volumes, flows, and indices of gas exchange) in respiratory, occupational and sports medicine, and in public health screening (Crapo, 1994; Zibrak *et al.*, 1990), though nonspecific in relation to diagnosis, give useful indirect information about respiratory muscle performance (Baltopoulos *et al.*, 2000; Gibson *et al.*, 2002). Therefore, much can be concluded on the mechanical properties of the lungs through spirometric measurements of forced maximal expiration and inspiration based on airflow (in liters) from fully inflated lungs over time (Hutchinson, 1846).

2.2.1 Forced Vital Capacity (FVC)

Forced vital capacity (FVC) is the maximal volume of air exhaled with maximally forced effort from a position of maximal inspiration, expressed in liters (BTPS) (ACCP, 1983; ATS, 1994; Milic-Emili *et al.*, 1997). This FVC maneuver is the basic spirometric maneuver for the evaluation of the mechanics of breathing. In 1980, the Framingham study of 5,209 men over the age of 30 years reported that the vital capacity was a powerful prognostic indicator of respiratory abnormalities (Baur *et al.*, 1999; Kannel *et al.*, 1980). Also, Hutchinson (1846) recognized that vital capacity is a powerful indicator of longevity and premature mortality (Petty, 2002).

Hutchinson recognized that fibrotic complications from tuberculosis resulted in reduced vital capacity and early death (Petty, 2002). Similar observations were made in heart failure of coal miners (Bishop, 1977).

2.2.2 Forced Expiratory Volume in 1 Second (FEV₁)

After Hutchinson (1846) coined vital capacity, Tifineau added a second measurement, forced expiratory volume in 1 second (FEV₁) in 1947 (Milic-Emili *et al.*, 1997). FEV₁ is the amount of air exhaled in the specific time of 1 second during the performance of FVC maneuver, expressed in liters (BTPS) (ACCP, 1983; ATS, 1994; Milic-Emili *et al.*, 1997). Together, these two parameters (FVC and FEV₁) are useful in identifying patients at risk of many diseases, including chronic obstructive pulmonary disease (COPD), lung cancer, heart attack, stroke and all-cause mortality (Petty, 2002). Macklem & Permutt (1979) even commented that with the determination of FEV₁, its potential use in detecting abnormalities early prevents a disastrous outcome.

2.2.3 Ratio of FEV₁ versus FVC (FEV₁/FVC)

When comparing FEV₁ with FVC, FEV₁ serves as an indicator for grading the seriousness of obstruction and as an index of the average flow over the initial two thirds or more of FVC.

2.2.4 Reference Values

Anthonisen *et al.* (1994) reported that even smokers with only mild airflow obstruction revealed a high prevalence of lung cancer (the most common cause of death in a 5-year follow-up), heart attack, and stroke.

Selection of appropriate reference values is often an important first step in the discrimination of patterns of normal or abnormal responses. This is essential for the interpretation of exercise tests. Everyday decision-making (e.g. with regard to preventive measures, treatment, and/or compensation for occupational lung diseases) involves lung function interpretation in relation to reference values. These normal lung function values and ranges are conventionally calculated according to variables such as age, sex, and height, which contribute independently to predictions of lung function (ATS, 1991; Crapo *et al.*, 1981; Enright *et al.*, 1993; Knudson *et al.*, 1976, 1983; Morris *et al.*, 1971; Quanjer *et al.*, 1993; Roberts *et al.*, 1991; Sherman *et al.*, 1993; Zibrak *et al.*, 1990). The weight variable, on the other hand, has little effect on the lung function (Crapo *et al.*, 1981; Hutchinson, 1846; Knudson *et al.*, 1976, 1983; Roberts *et al.*, 1991). Moreover, this weight variable is not considered as an independent variable in other studies (Enright *et al.*, 1993; Quanjer *et al.*, 1993). However, Bande *et al.* (1980) suggested that one might improve the precision of FEV₁ by including the weight into the regression equation. Lately, Baltopoulos *et al.* (2000) also discovered that weight played an important role in the correlation of the predicted equation. This added significantly to the standard indexes, especially in the women.

These reference equations are derived from a normal and representative population tested by standardized technical methods and subjected to appropriate statistical analysis. Reference equations used by most North American and European pulmonary function laboratories are derived from one of the major studies: Brandli *et al.* (1996); Cherniak & Raber, 1972; Cotes *et al.* (1993); Crapo *et al.*, 1981;

Glindmeyer *et al.* (1995); Hankinson *et al.*, 1999; Matthys *et al.* (1995); Morris *et al.*, 1971; Knudson *et al.*, 1976, 1983; Quanjer *et al.*, 1993; Roca *et al.* (1986). These studies were specifically conducted on healthy nonsmokers without lung disease. Cara & Hentz (1971), Riihle & Matthys (1976), and Ulmer *et al.* (1991), on the other hand, gave no details on the smoking behavior of their subjects, while Roca *et al.* (1998), and Berger *et al.* (1996) gave the smoking details of the subjects.

In this present study, the predicted values for FEV_1 and FVC were determined using the predictive equations from Chia *et al.* (1993). This is an improved version of Knudson *et al.* (1983) corrected with an Asian factor of 0.88. Here, the predictive equations based on subjects from the Western population tend to overestimate the actual clinical values of our Asian subjects.

2.3 Cardiopulmonary Exercise Testing (CPET)

If appropriate exercise mode and intensity are chosen, much of the energy production is obtained from aerobic metabolism. Increased aerobic metabolism is achieved by increasing tissue oxygen delivery and extraction. This in turn, is accomplished through changes in the body's cardiocirculatory, pulmonary and metabolic systems. By studying the responses of these systems to exercise, a significant amount of information can be obtained regarding the diagnosis and evaluation of various diseases. The physical response during CPET is critical as it indicates whether the subject is capable to continue the assessment. Therefore, good clinical judgment is necessary in deciding the protocol for patients suited to undergo

the procedure, limited by the absolute and relative contraindications illustrated in Appendix A.

The development of cardiac transplantation (Frazier & Macris, 1994; Nisco & Reitz, 1994; Regina, 2000; Rodeheffer & McGregor, 1992) has led to an increase in the survival rate and quality of life expectancies for severe cardiac patients. However, the growth of potential recipients is faster than the supply of suitable donors (Evans *et al.*, 1986). Therefore, the selection and management of potential candidates to develop objective criteria is critical in order to optimize the benefit in terms of prognosis (Constanzo *et al.*, 1995; Mancini *et al.*, 1991; Stevenson, 1994).

The most common criteria used to evaluate transplant candidacy for chronic heart failure is left ventricular ejection fraction (LVEF). LVEF shows a significant relationship with mortality in large populations of patients with cardiac disorders due to diverse causes (Cohn *et al.*, 1988, 1993; Sugrue *et al.*, 1992). However, among severe heart failure patients, LVEF has failed to predict differences in terms of prognosis and mortality (Dec & Fuster, 1994; Franciosa *et al.*, 1983; Griffin *et al.*, 1991).

The oxygen consumption (VO_2), as one of the primary ventilatory analysis during exercise, is a useful adjunctive tool in assessment of patients with cardiovascular disease (Gibbons *et al.*, 2002). Furthermore, VO_2 can provide important information to evaluate functional capacity and distinguish cardiovascular from pulmonary limitation based on work rate during exercise.

From oxygen consumption (VO_2), maximal oxygen consumption ($\text{VO}_{2\text{max}}$), volume of oxygen per watt (VO_2/P), and maximal oxygen pulse ($\text{O}_2\text{pulse}_{\text{max}}$) are formulated to detect cardiomyopathy early so that patients can receive the necessary therapy and treatment. These cardiac patients often show poor aerobic responses to CPET. From Gibbons *et al.* (2002), low $\text{VO}_{2\text{max}}$ indicated poor aerobic capacity, which indirectly indicates possible presence of cardiomyopathy.

From here, a comparison of the discrete value $\text{VO}_{2\text{max}}$ and kinetics VO_2 with other studies are discussed.

2.3.1 Maximal Oxygen Consumption ($\text{VO}_{2\text{max}}$)

$\text{VO}_{2\text{max}}$ defines the greatest amount of oxygen a person can take in from inspired air while performing dynamic exercise involving a large part of total muscle mass (Cohn, 1987). In other words, $\text{VO}_{2\text{max}}$ is defined as a point at which no further increase in VO_2 occurs despite an increase in work rate (a plateau) during graded exercise testing (Gibbons *et al.*, 2002). Data derived from CPET with $\text{VO}_{2\text{max}}$ have proved to be reliable and important measures in evaluation of patients with heart failure (Linkoff *et al.*, 1987; Mancini *et al.*, 1991; Osada *et al.*, 1998; Pardaens *et al.*, 2000; Stelken *et al.*, 1996; Williams *et al.*, 1995). Myers *et al.* (1998) even recorded that $\text{VO}_{2\text{max}}$ outperformed all other clinical, exercise, and hemodynamic data in determining risk among patients with severe heart failure. The use of $\text{VO}_{2\text{max}}$ for the selection of heart transplant candidates is based on the assumption that peak VO_2 is primarily determined by cardiovascular factors. Accurate prediction of this $\text{VO}_{2\text{max}}$ is

important because comparison with predicted values is often an important first step in CPET interpretation.

Advantages

$\text{VO}_{2\text{max}}$ is considered as the best index of aerobic capacity and cardiorespiratory function (Gibbons *et al.*, 2002). Therefore, when $\text{VO}_{2\text{max}}$ is reached, the subject is believed to have true maximum cardiopulmonary effort. The assessment of functional capacity by measurement of $\text{VO}_{2\text{max}}$ has been proposed as a good predictor of mortality (Peters *et al.*, 1983; Weiner *et al.*, 1995), which allows for the stratification of patients with low left ventricular ejection fraction (LVEF) in terms of prognosis (Cohn *et al.*, 1993; Linkoff *et al.*, 1987; Mancini *et al.*, 1991; Szlachcic *et al.*, 1985). Szlachcic *et al.* (1985) also reported that congestive heart failure patients with severely impaired exercise capacity had a significantly higher mortality rate with medical therapy during the first year of follow-up. Stelken *et al.* (1996) also proposed that the usefulness of $\text{VO}_{2\text{max}} < 50\%$ predicted in patients with ischemic and dilated cardiomyopathy is the most significant predictor of cardiac death in multivariant analysis. Mancini *et al.* (1991), Pardaens *et al.* (2000) and Stevenson *et al.* (1995) found that the measurement of $\text{VO}_{2\text{max}}$ could be used to stratify ambulatory patients and select those with the poorest medical prognosis for transplantation. Their results suggested that cardiac transplantation can relatively be deferred safely in ambulatory patients with left ventricular dysfunction whose peak exercise $\text{VO}_2 > 14 \text{ ml/min/kg}$. In 1993, a Consensus Conference addressed the issues of candidate selection criteria, arguing that it should be based primarily on the assessment of functional limitation by means of exercise testing and measurement of

VO₂ (Miller *et al.*, 1995). VO₂ at peak exercise seems useful for identification of patients not benefiting from the ultrafiltration (UF) procedure (Gian *et al.*, 1995).

Disadvantages

Studies providing predictive equations for VO_{2max} in both sexes and over a wide age span in incremental cycle exercise testing are limited to only several sets. Most studies of maximum exercise performance in a healthy population have quantified age, sex and body size. However, when comparing equations that include these covariates, marked differences in predicted values may occur (Jones, 1997) and different sets of reference values on maximal CPET are provided from different study centres (Weisman & Zeballos, 1995). Therefore, discrepancies may result from analytics bias and different weighting in the population. These discrepancies may even create large accuracy differences in different CPET systems (Winter *et al.*, 1994) or even in different populations. Hsi *et al.* (1998) reported that the normative data pertaining to exercise capacity were higher in Caucasian than Chinese subjects, suggesting the discrepancies in different populations. Neder *et al.* (1999) also found that equations derived from studies that include volunteers typically overestimated VO_{2max} of their randomly selected subjects. Authors from some studies attributed this discrepancy to selection bias, as volunteers tend to be fitter subjects.

It has been suggested that the limitations in VO_{2max} may not be as closely associated with cardiac dysfunction as originally thought (Coats *et al.*, 1992; Sullivan *et al.*, 1989; Wilson *et al.*, 1995, 1995). Studies using VO_{2max} as a criterion for candidate selection do not take the level of deconditioning of patients with severe

heart failure into consideration (Piña, 1995). Furthermore, a major determinant of peak VO_2 is the level motivation of the subject, and hence peak VO_2 is not necessarily an accurate estimation of $\text{VO}_{2\text{max}}$. Ramos-Barbon (1999) also reported that a defined objective exercise limitation is necessary to avoid biasing the selection of heart transplant candidates with low peak VO_2 .

2.3.2 VO_2 Kinetics

However, consideration of a single value for these variables of interest may not be suitable as a frame of reference for the continuous, dynamic cardiopulmonary responses that develop from these tests. Therefore, it is necessary to change from a discrete point to a continuous kinetic analysis. The regressed baseline value (intercept or constant) and the rate of change (slope or gradient) are likely to be of substantial importance (Neder *et al.*, 2001).

Advantages

This form of analysis maximizes the use of massive amount of data generated during routine CPET. In addition, the European Respiratory Society (1997) provided CPET monograph that stressed on the importance of interpreting the trends of this physiological response profile with recognition of the paucity in the extant information on the topic.

The trending of certain variables has already been considered as a crucial component of the interpretative strategy. For example, the shift from a linearly increasing profile of oxygen uptake with respect to work rate (VO_2/P) to a gentler

slope was an indicator of circulatory dysfunction (Hanson *et al.*, 1987; Jones *et al.*, 1998; Koike & Wasserman, 1992; Solal *et al.*, 1990). Similarly, a steep increase of heart rate as a function of metabolic demand could be regarded as an indirect evidence of cardiac abnormalities or peripheral muscle impairment for oxygen utilization ($\Delta HR/\Delta VO_2$) (Fairbairn *et al.*, 1994; Jones, 1997; Jones *et al.*, 1998; Wasserman *et al.*, 1994).

Jones & Moran (1982) commented that besides VO_2 abnormality, heart response to exercise is also important in the analysis. When VO_{2max} is not reached, heart rate becomes the surrogate factor to determine maximum cardiopulmonary effort (Gibbons *et al.*, 2002). Heart rate response is one of the important parameters that are easily obtainable. Also, it gives excellent information regarding cardiovascular response to exercise (Spence & Mason, 1992). However, careful steps need to be taken, as there are many external factors that will affect the results of the measurement. These include medication and psychological factors. Previous studies reported that nonlinear regression analysis of predicted heart rate characterized by exponential function of measured oxygen uptake, failed to significantly fit the measured heart rate. Thus, a second approach was used in this study to better describe this nonlinear dynamic response of measured heart rate. Unlike these previous studies, nonlinear techniques have been used to develop predictive equations in order to improve the precision of predictions in estimating the original nature of non-linearity phenomena. Although there has been a reluctance to use nonlinear modeling techniques in the past, there are several good theoretical reasons for developing these forms of modeling in the prediction process (Jones, 1997). For

example, it becomes apparent that nonlinear equations are to describe expected normal exercise capacity in a population that include the whole range of statures and ages as an increase with age cannot be considered linear in an absolute sense.

Past researchers have described the heart rate-oxygen consumption (HR:VO₂) relationship as being linear (Becklake *et al.*, 1965; Ekelund & Holmgren, 1967; Francis *et al.*, 1989; Higginbotham *et al.*, 1986; Jensen *et al.*, 1998). This later formed the basis of developing prediction equations to calculate oxygen consumption using heart rate (Astrand & Rhyning, 1954).

Although Francis *et al.* (1989) documented a linear response in heart rate for 9 untrained males; close inspection revealed that the individual heart rate data for a small number of subjects did in fact have a slightly nonlinear response. Wyndham *et al.* (1959) found a nonlinear increase in heart rate, followed by a more linear portion as exercise intensity increased. These authors commented further on this response and concluded that this type of heart rate response would underestimate the prediction of VO₂, thus, caution must be taken when predicting VO₂ from heart rate values. Brooke & Hamley (1972) also described a similar nonlinear increase in the heart rate response during incremental exercise. Chapman *et al.* (1960), Ekblom *et al.* (1968), Hermansen *et al.* (1970), Hofmann *et al.*¹ (1997), and Pokan *et al.* (1993) further supported the findings of Wyndham *et al.* by showing that the common, nonlinear response in heart rate was a “downward” deflection from linearity in trained and untrained individuals. Hofmann *et al.*¹ (1997) also illustrated a positive, curvilinear relationship between heart rate and oxygen consumption in the majority

of subjects in their study (93%). However, these heart rate responses have been found to be more variable from subject to subject in other investigations (Hofmann *et al.*², 1997; McDonough & Danielson, 1974).

The reason that an interest in the relationships between heart rate with oxygen consumption (HR:VO₂) and heart rate with carbon dioxide production (HR:VCO₂) is that little is known about the normal values for the trending phenomena of kinetics relationships, especially with carbon dioxide during cycle ergometry in randomly selected subjects. In some studies the values of normalcy were provided at a discrete level (Cotes *et al.*, 1972; Fairbairn *et al.*, 1994; Hansen *et al.*, 1988; Spiro *et al.*, 1974; Wasserman *et al.*, 1999). This is especially apparent in heart transplant evaluation where the cutoff value for deferring heart transplantation was also assessed at a discrete level (David *et al.*, 1999).

2.3.3 Oxygen Consumption versus Work Rate (VO₂/P)

When the patient is subjected to CPET, the oxygen uptake response versus work rate forms another important variable of interest. With the increase of energy dissipated by large groups of working muscles in the resistance workout (P), oxygen consumption (VO₂) and demand are increased in accordance with the power increment. This VO₂/P is a linear equation used to determine fitness level of individuals. Often, with the shift from a linearly increasing profile of oxygen uptake with respect to work rate (VO₂/P) to a gentler slope was an indicator of circulatory dysfunction (Hanson *et al.*, 1987; Jones *et al.*, 1998; Koike & Wasserman, 1992; Solal *et al.*, 1990). This estimation of aerobic capacity with

published formulas based on work rate with direct measurement is not limited by physiological and methodological inaccuracies in wide and confusing scatter of data entries. Neder *et al.* (2001) described the importance of this rate change in the variables of interest for the continuous, dynamic cardiopulmonary responses.

2.3.4 Maximal Oxygen Pulse ($O_2\text{pulse}_{\max}$)

Besides VO_2/P , $O_2\text{pulse}_{\max}$ further supports the efficiency of VO_2 in the CPET. The ratio of $VO_{2\max}$ to $HR_{\max}$ is normally lower for subjects with hypertrophic cardiomyopathy, thus accounting for low oxygen ratio due to thickened heart wall. $O_2\text{pulse}$ is commonly used to evaluate HR/VO_2 , which is a good index of stroke volume or cardiac pump function (Whipp *et al.*, 1996). It was reported that a steep increase of heart rate as a function of metabolic demand could be regarded as an indirect evidence of cardiac abnormalities or peripheral muscle impairment for oxygen utilization ($\Delta HR/\Delta VO_2$) (Fairbarn *et al.*, 1994; Jones, 1997; Jones *et al.*, 1998; Wasserman *et al.*, 1994). It was reported that the indexed peak oxygen pulse was an additive importance to $VO_{2\max}$ as it better detects patients who are at risk stratification of future death. However, a fallback is that this slope does not intercept at the origin and the scale is not in ratio (Jones & Moran, 1992).

As mentioned earlier that selection of appropriate reference values is often an important first step in the discrimination of patterns of normal or abnormal responses, which are essential for the interpretation of exercise tests. Studies reported that the best prognostic value in CPET could be obtained by normalizing the measured value with respect to the predicted value of these relevant parameters (Ino

et al., 1996; Pelliccia, 2000). Also, most investigators opine that the measurement of indexed $\text{VO}_{2\text{max}}$ yields reliable prognostic information in heart failure patients (Cohen-Solal *et al.*, 1997). At the same time, indexed $\text{O}_2\text{pulse}_{\text{max}}$ further improves the risk stratification of $\text{VO}_{2\text{max}}$ in high-risk patients, as it is more dependent on the cardiac pump function. Jones *et al.* (1998) also illustrated that severe distinct abnormalities in maximal indices of pulmonary gas exchange were found in a cohort of hypertrophic cardiomyopathy patients attending a referral cardiovascular clinic.

2.3.5 Parameters Compilation

A summary of clinical parameters is compiled into three studies as shown in Table 2.2.

Table 2.2 Summary of Clinical Parameters

Study 1	FEV ₁ (Forced Expired Volume, 1 second)
	FVC (Forced Vital Capacity)
Study 2	P (Power)
	VO ₂ (Oxygen Consumption)
	O ₂ pulse (Oxygen Pulse)
Study 3	HR (Heart Rate)
	VO ₂ (Oxygen Consumption)
	VCO ₂ (Carbon Dioxide Production)

2.4 Medication

Those patients under medication have to be observed closely and excluded from analysis if effects from medication affect the results. The following medications were found in most heart disease patients:

ACE inhibitors

Angiotensin-Converting Enzyme (ACE) inhibitors treat blood pressure, and congestive heart diseases. However, the interaction between the right dosage of ACE inhibitors and aspirin attenuates the benefit for patients with chronic heart failure (Cleland *et al.*, 1995, 2001; Guazzi *et al.*^{1,2},1999; Hall, 2000; Latini *et al.*, 2000; Leor *et al.*, 1999; Massie & Teerlink, 2000; Nawarskas & Spinler, 2000; Peterson *et al.*, 2000; Song *et al.*, 1999; Spaulding *et al.*, 1997; Stys *et al.*, 2000; Teerlink & Massie, 1999).

Beta-blockers

Beta-blockers decrease heart rate, blood pressure, anxiety, and contractility of the heart, which reduce the demand for oxygen. These, in turn increase exercise capacity in patients with angina, decrease exercise capacity in patients without angina, and decrease exercise ischemia (Mulieri *et al.*, 1992; Pechat, 1998; Waagstein *et al.*, 1975).

Digitalis

Digitalis improves myocardial contraction, disturbance of rhythm and reduced beat frequency. It also causes arteriolar constriction, venous dilation, nausea and visual disturbances. Therefore, it decreases heart rate and improves exercise capacity only in patients with atrial fibrillation or chronic heart failure (Erdmann, 1998; Ferguson *et al.*, 1989) & Digoxin (Krum *et al.*, 1995).

Diuretics

Diuretics treat high blood pressure, congestive heart failure, and swelling due to excess body water. They decrease blood pressure, may affect chronic heart failure patients and may induce arrhythmias.

CHAPTER 3: METHODS

This chapter contains the methodology used in conducting this study and is divided into the following sections: 1) setting 2) subjects 3) procedures (protocols) 4) research design and 5) statistical analysis.

3.1 Setting

All pulmonary function and exercise testing were conducted in the Pulmonary Function Laboratory at the Singapore General Hospital. Pre-test checklist and evaluation form (Appendix B1, B2) were prepared before these tests were performed. For all tests, close attention was paid to patients' safety (Schlant *et al.*, 1990). Although CPET is usually safe, both myocardial infarction and death can still be expected to occur at a rate of up to 1 per 2500 tests (Stuart & Ellestad, 1980). Thus, electrocardiogram (ECG), heart rate and blood pressure are monitored carefully during stages of exercise and during ST-segment abnormalities and chest pain symptoms (Piña *et al.*, 1995).

The height (cm) and weight (kg) of each subject in exercise attire (excluding shoes) were measured using a standard physician's scale. Weight was measured to the nearest 0.1 kg and height was assessed to the nearest cm. Age was recorded as of last birthday.

Previous medical histories, occupation, exercise-related symptoms, smoking and medication were obtained and a thorough physical examination and a 12-lead electrocardiogram (ECG) were completed prior to exercise testing. The extent of physical activity in leisure time and occupation were graded according to a questionnaire (Saltin & Grimby, 1968).

3.2 Subjects

3.2.1 Study 1 (Spirometry Data Interpretation & Representation)

The subjects are classified into 7 groups under the description of normal, mild obstructive, moderate obstructive, severe obstructive, mild restrictive, moderate restrictive, and severe restrictive conditions. The normal group comprised of the general population who responded to the health screening recruitment exercise advertised by the Singapore General Hospital. The pulmonary disease group was patients referred to the Pulmonary Function Laboratory for lung rehabilitation. A total of 62 subjects were randomly selected from these 7 groups. Medications that affect the pulmonary performances were noted.

3.2.2 Study 2 (Data Interpretation & Representation of CPET)

The subjects are classified into 2 groups (normal and cardiomyopathy). The normal group belonged to the general population recruited by the Singapore General Hospital for health screening. The cardiomyopathy group comprised of patients referred to the Pulmonary Function Laboratory for heart transplant evaluation. A

total of 50 subjects were randomly selected from these 2 groups. Medications that affect the cardiac and pulmonary performance were noted.

3.2.3 Study 3 (Mathematical Models of HR vs. VO_2 & HR vs. VCO_2)

The subjects are classified into 2 groups (normal and heart disease). The normal group referred to the general population recruited by the Singapore General Hospital for health screening. The heart disease group contained patients from the National Heart Centre, referred to the Pulmonary Function Laboratory for heart transplant evaluation. A total of 90 subjects (70 normal and 20 heart patients) were analysed in the study. 5 in the normal group were excluded from the data analysis as they were found to have ambiguous data due to instrumental errors. Ambiguous data here defines that the subsequent values for HR, VO_2 and VCO_2 are not within the tolerance when compared to the established 95% confidence interval (CI). Heart patients with lung diseases as secondary conditions were excluded as inefficient gas exchange in the lungs are due to a deterioration of lung function.

3.3 Procedures (Protocols)

The clinical value of measurements critically depends on the correct operation and accuracy of the instrument, subject's performance and the use of relevant reference values.

Studies have illustrated that the physiological responses for different protocols may vary significantly for the same individual (Buchfuhrer *et al.*, 1983; Hambrecht *et al.*, 1992; Myers *et al.*, 1991; Wicks *et al.*, 1978). Furthermore, each protocol responses differently to work load variations (Myers *et al.*, 1991). Therefore, measurement procedures are included in this study so as to ensure that uniform methods are applied and comparable results are obtained.

3.3.1 Pulmonary Function Testing

Spirometry was taken just before the commencement of CPET for bicycle as ergometer. All lung function tests were performed with the subjects seated. Vital capacity (VC), forced expiratory volume in 1 second (FEV₁) and maximal voluntary ventilation (MVV) were measured with a clinical spirometer (Masterlab system; Jaeger, Wiirzburg, Germany) shown in Figure 3.1. For measurement of VC, the spirometer must be capable of accumulating a volume of at least 30 seconds, measuring volume of at least 8 liters (BTPS) and with flows between 0 and 14 L/s and volume accuracy of at least $\pm 3\%$ of reading or ± 0.050 L, whichever is greater (ATS, 1994). A trained laboratory technician demonstrated each respiratory maneuver to the subject prior the initiation of the test. Forced expiratory maneuvers were conducted 3 times, with at least 1-minute intervals between each test. In order

to ensure an acceptable result, FVC maneuver was performed with maximal effort immediately after a maximum inspiration. The best of 3 technically acceptable tests were used to determine FEV_1 and FVC (With reference to Figure 3.2). All volumes were corrected to body temperature, ambient pressure and saturated with water vapour (BTPS). Predicted values for FEV_1 and FVC were determined using the predictive equations from Chia *et al.* (1993). This is an improved version of Knudson *et al.* (1983) corrected with an Asian factor of 0.88.

Figure 3.1 Clinical spirometer (Masterlab system; Jaeger, Wiirzburg, Germany)

Figure 3.2 Normal spirogram used to measure FVC and FEV₁

3.3.2 Exercise Testing

The basic objective of CPET is to evaluate the body’s physiological “aerobic” metabolic response to exercise. The normal subjects received instructions similar to the routine instructions sent to both the heart and lung diseases patients referred for clinical exercise testing (ERS, 1997). Symptom-limited incremental CPET was performed to the tolerance limit (ERS, 1997) using an electrically braked cycle ergometer (model ER 900, Jaeger; shown in Figure 3.3) and under physician supervision with defined contraindications for termination (Appendix A). A constant work rate of 5-25 W was increased every minute after an initial unloaded pedaling of 3 minutes. This specific work rate was chosen to enable the subject to reach estimated VO_{2max} in targeted 10 minutes with achieved maximal effort. Standard 12-

lead electrocardiogram (ECG) and blood pressure were measured at rest, every 3 minutes during exercise, and at peak exercise. The subjects wore a tight-fitting facemask connected to a breath-by-breath turbine volume transducer. Mixed expired oxygen, mixed expired carbon dioxide and expired air volume were measured at rest and during exercise using a metabolic gas exchange analyzer (Oxycon Alpha, Jaeger), which was calibrated for both accuracy and linearity prior each test. Oxygen consumption, carbon dioxide production, gas exchange ratio, minute ventilation, respiratory rate, and tidal volume were measured every 5 seconds. Oxygen saturation and heart rate were measured via pulse oximetry and electrocardiography (ECG; shown in Figure 3.4) at rest and during exercise. At the end of the exercise, the reasons for termination and Borg dyspnoea score (Borg, 1982) were recorded. Symptoms that terminate the exercise often include leg discomfort, chest pain, or fatigue (Hamilton *et al.*, 1995; Killian *et al.*, 1992).

Figure 3.3 Clinical Cycle Ergometer (ER 900; Jaeger, Wiirzburg, Germany)

Figure 3.4 Electrocardiography (ECG)

3.4 Research Design

Using the parameters that have already been identified by the physiologists, the trends/patterns of these groups were studied and analyzed carefully. Graphical presentations were made to facilitate interpretations and clinical applications on the basis of the current best scientific knowledge and technical advances. The focus here is on interpretative strategies for Study 1 and 2, and clinical indications for Study 3. Interpretative strategies of results for Study 1 and 2 are based on the degree of deviation from predicted normal values calculated from regression equations. Then, indices are developed from these deviations, where a single value is able to indicate the patient's condition and stage of severity.

The present study specified strict criteria for maximal testing to ensure that only the results from subjects who had completed the test to maximal effort were included in this analysis.

3.4.1 Study 1 (Spirometry Data Interpretation & Representation)

The proposed graphical method employs the predicted and measured respiratory data to assess respiratory abnormalities and severities, adhering to the procedures as depicted in Figure 3.5. The Singapore General Hospital adopts these predicted respiratory data (listed in Tables 3.1-3.3), derived from Knudson *et al.* (1976) with Asian correction of 0.88. The spirometric procedure, as mentioned in Section 3.3.1, evaluates the measured respiratory data. The present analysis assesses patients by comparing the deviation degree of spirometry measurements with predicted or standardized reference values (Baltopoulos *et al.*, 2000) and from there, develop them into indices.

Figure 3.5 Spirometry flow chart to assess pulmonary diseases

Table 3.1 Predicted Equations for FVC

Sex	Age	Predicted Equation (Caucasian)	(Non- Caucasian)
M	5 - 11	$(4.4 * 10^{-6}) * H^{2.67}$	PEC * 0.88
	12 - 19	$(0.0590 * H) + (0.0739 * A) - 6.89$	
	> 20	$4.84 + [5.83 * (H - 1.75)] + [-0.025 * (A - 45)]$	
F	5 - 10	$(3.3 * 10^{-6}) * H^{2.72}$	
	11 - 19	$(0.0416 * H) + (0.0699 * A) - 4.45$	
	> 20	$3.54 + [4.53 * (H - 1.65)] + [-0.024 * (A - 45)]$	

Table 3.2 Predicted Equations for FEV₁

Sex	Age	Predicted Equation (Caucasian)	(Non- Caucasian)
M	5 - 11	$0.774 * (H / 100)^{3.00}$	PEC * 0.88
	12 - 19	$[(\text{pred FEV}_1 / \text{FVC}) / 100] * \text{pred FVC}$	
	> 20	$3.63 + [3.62 * (H - 1.75)] + [-0.032 * (A - 45)]$	
F	5 - 10	$0.868 * (H / 100)^{2.68}$	
	11 - 19	$[(\text{pred FEV}_1 / \text{FVC}) / 100] * \text{pred FVC}$	
	> 20	$2.72 + [3.5 * (H - 1.65)] + [-0.025 * (A - 45)]$	

Table 3.3 Predicted Equations for FEV₁/FVC

Sex	Age	Predicted Equation (Caucasian)	(Non- Caucasian)
M	5 - 11	$(\text{pred FEV}_1 / \text{pred FVC}) * 100$	PEC * 0.88
	12 - 19	$(-0.0813 * H) + 100.4$	
	> 20	$80.9 + [-13 * (H - 1.75)] + [-0.15 * (A - 45)]$	
F	5 - 10	$(\text{pred FEV}_1 / \text{pred FVC}) * 100$	
	11 - 19	$(-0.1909 * H) + (0.665 * A) + 110$	
	> 20	$80.2 + [-0.24 * (A - 45)]$	

A = age (years)
H = height (m)
PEC = predicted equation (Caucasian)

The flow chart in Figure 3.5 uses FEV₁/FVC ratio to detect the presence of obstructive disease. With FEV₁, a mild obstructive is adjusted for 60-80% predicted, moderate obstructive for 41-59% predicted, and severe obstructive for below 40% (ATS, 1986). Next, the third non-dimensional index, FVC, is analyzed for restrictive evaluation. A mild restrictive is adjusted for 60-80% predicted, moderate restrictive for 51-59%, and severe restrictive for below 50% (ATS, 1986). For diagnostic purposes, the analysis adopts these measured values of FEV₁ and FVC in the range of 72-120% of the predicted values as normal limits, varying by as much as about 20% (AARC, 1996). These are summarized in Table 3.4.

Table 3.4 Standard Spirometry Reference Values (ATS, 1986)

Condition	(%)	ABS	ABS
	FEV ₁ /FVC (Measured)	FVC (% Predicted)	FEV ₁ (%Predicted)
Normal	0.75	0.81	0.81
Mild	0.20	0.60	0.60
Moderate	0.20	0.51	0.41
Severe	0.20	0.20	0.20

ABS = absolute

The three normalized respiratory data, P_1 , P_2 , and P_3 are defined as

$$P_1 = \frac{FVC(Measured)}{FEV_1(Measured)} \quad (3.1)$$

$$P_2 = \frac{FVC(Measured - Predicted)}{FVC(Predicted)} \times 10 \quad (3.2)$$

$$P_3 = \frac{FEV_1(Measured - Predicted)}{FEV_1(Predicted)} \times 10 \quad (3.3)$$

where these variables are then depicted on a 3-axes triangular planar space as illustrated in Figure 3.6. Based on the classification of severity as defined in the flow chart (Figure 3.5), the graphical presentation locates the boundaries of normal, mild, moderate and severe conditions as a series of triangles (With reference to Table 3.5). Therefore, the area of the triangle from the data depicts the pulmonary condition. The larger the area, the more severe is the abnormality condition. At the same time, the skewness of the triangle towards a particular axis indicates the obstructive/restrictive nature of abnormality. This skewness is due to the fact that individuals with low FEV_1 are diagnosed to have obstructive lung disease, and individuals with low FVC are diagnosed to have restrictive lung disease (ACCP, 1983). To further enhance this visual presentation, different colors are incorporated, i.e. blue for normal condition, light blue for mild pulmonary problem, pink for moderate pulmonary problem, and red for severe pulmonary problem. These color codes help discern clearly, the severity degree of the pulmonary disease. Then, this analysis is compared against the standard plethymography test for predictive accuracy (Table 3.6).

Figure 3.6 Graphical presentation to assess pulmonary diseases

Table 3.5 Normalized Spirometry Reference Values

Condition	P_1	P_2	P_3
Normal	1.33	1.90	1.90
Mild	5.00	4.00	4.00
Moderate	5.00	4.90	5.90
Severe	5.00	8.00	8.00

Table 3.6 Predictive Accuracy Terms of Diagnostic Test

Test Diagnosis	Plethysmography Diagnosis	Outcome
Normal	Normal	True Negative
Abnormal	Abnormal	True Positive
Abnormal	Normal	False Positive
Normal	Abnormal	False Negative

3.4.2 Study 2 (Data Interpretation & Representation of CPET)

The proposed graphical technique employs the predicted and measured oxygen parameters to assess cardiomyopathy abnormalities, adhering to the procedures as depicted in Figure 3.7. The Singapore General Hospital adopts these predicted oxygen parameters data (listed in Tables 3.7-3.10), recommended by ACSM (2000) with Asian correction. The CPET procedure, as mentioned in Section 3.3.2, evaluates the measured values. The present analysis assesses patients by comparing the deviation degree of CPET measurements from predicted or standardized reference values (Table 3.11) and develop them into indices.

Figure 3.7 CPET flow chart to assess cardiomyopathy

Table 3.7 Predicted Equations for $\text{VO}_{2\text{max}}$

Sex	Weight	Predicted Equation (Asian)
M	Normal	$w_1 * [50.72 - (0.372 * a_1)]$
	Over	$\{w_2 * [50.72 - (0.372 * a_1)]\} + [6 * (w_1 - w_2)]$
	Under	$[(w_2 + w_1) / 2] * [50.72 - (0.372 * a_1)]$
F	Normal	$(w_1 + 43) * [22.78 - (0.17 * a_1)]$
	Over	$(w_2 + 43) + [22.78 - (0.17 * a_1)] + [6 * (w_1 - w_2)]$
	Under	$[(w_2 + w_1 + 86) / 2] * [22.78 - (0.17 * a_1)]$

Table 3.8 Predicted Equations for $\text{O}_2\text{pulse}_{\text{max}}$

Sex	Age	Predicted Equation (Asian)
M	Normal	$\{w_1 * [50.72 - (0.37 * a_1)]\} / \text{hr}_2$
	Over	$\{w_2 * [50.72 - (0.372 * a_1)] + [6 * (w_1 - w_2)]\} / \text{hr}_2$
	Under	$\{[(w_2 + w_1) / 2] * [50.72 - (0.372 * a_1)]\} / \text{hr}_2$
F	Normal	$\{(w_1 + 43) * [22.78 - (0.17 * a_1)]\} / \text{hr}_2$
	Over	$\{(w_2 + 43) * [22.78 - (0.17 * a_1)] + [6 * (w_1 - w_2)]\} / \text{hr}_2$
	Under	$\{(w_2 + w_1 + 86) / 2 * [22.78 - (0.17 * a_1)]\} / \text{hr}_2$

Table 3.9 Predicted Equations for Weight (w_2)

Sex	Predicted Equation (Asian)
M	$(0.79 * h_1) - 60.7$
F	$(0.65 * h_1) - 42.8$

Table 3.10 Predicted Equations for Heart Rate (hr_2)

Sex	Predicted Equation (Asian)
M/F	$210 - (0.65 * a_1)$

a_1 = age (measured)
 h_1 = height (measured)
 hr_2 = heart rate (predicted)

w_1 = weight (measured)
 w_2 = weight (predicted)

Table 3.1 1 Standard CPET Reference Values

Condition	(M/P) O_2pulse_{max}	(M) VO_2/P	(M/P) VO_{2max}
Normal	0.80	10.3	0.85
Cardiomyopathy	0.20	1.8	0.20

Peak VO_2 and O_2pulse were given as percentages of their maximum predicted values, expressed as peak $\frac{VO_{2Measured}}{VO_{2Predicted}}$ and peak $\frac{O_2pulse_{Measured}}{O_2pulse_{Predicted}}$ respectively. These VO_{2max} HR_{max} and HR_{max}/VO_{2max} were selected as the highest values obtained any 30 seconds measurement period from the test termination.

In Figure 3.7, the design of flow chart uses the following sequence: VO_{2max} (% predicted), VO_2/P and O_2pulse_{max} (% predicted) to detect the presence of cardiomyopathy condition. It is safe to indicate normal cardiac conditions only when normal values are displayed in either one of these three parameters. On the other hand, when all the oxygen parameters indicate abnormal values, the analysis shows possible presence of cardiomyopathy.

The three normalized oxygen parameters, P_1 , P_2 , P_3 , and cardiopulmonary index, CPI are defined as

$$P_1 = \frac{O_2 pulse_{\max}(Measured - Predicted)}{O_2 pulse_{\max}(Predicted)} \times 100 \quad (3.4)$$

$$P_2 = \frac{\frac{VO_2}{P}(Measured - Predicted)}{\frac{VO_2}{P}(Predicted)} \times 100 \quad (3.5)$$

$$P_3 = \frac{VO_{2\max}(Predicted)}{VO_{2\max}(Measured)} \times 100 \quad (3.6)$$

$$CPI = \frac{P_1 \times P_2 \times P_3}{1000} \quad (3.7)$$

where P_1 , P_2 , P_3 are depicted on a 3-axes triangular planar space as illustrated in Figure 3.8, and CPI is shown on a color-coded bar as illustrated in Figure 3.9. Based on the design specified in the flow chart (Figure 3.7), the graphical presentation locates the boundaries of normal and cardiomyopathy conditions as a series of triangles (With reference to Table 3.12). Therefore, the area of the triangle from the data depicts the cardiac condition. The larger the area, the more severe is the cardiac problem. To further enhance this visual presentation, different colors are incorporated, i.e. blue for normal condition, and red for cardiomyopathy problem. Thus, these color codes present clearly the presence of cardiomyopathy. In addition, this new graphical technique further develops into a single cardiopulmonary index, CPI (Figure 3.9), made up of a multiplication of these three non-dimensional parameters (P_1 , P_2 , P_3) to indicate possible cardiomyopathy. Color code is also

incorporated to indicate different cardiac conditions, i.e. blue for normal, and red for cardiomyopathy. Then, this analysis is compared against the standard echocardiography test for predictive accuracy (Table 3.13).

Figure 3.8 Graphical presentation to assess cardiomyopathy

Figure 3.9 Cardiopulmonary index (CPI) to assess cardiomyopathy

Table 3.12 Normalized CPET Reference Values

Table 3.13 Predictive Accuracy Terms of Diagnostic Test

An Overview on Predictive Accuracy for Study 1 & 2

The judicious and appropriate use of test in evaluating patients requires clinical judgment, contraindications, sensitivity, specificity, predictive value, and limitation of each test (ACSM, 2000). These tests are used to confirm diagnosis, thus to assess prognosis and the risk for future events.

The calculation of predictive accuracy (Table 3.6 or

3. In contrast, for a *false-positive* test, the patient is normal and the test findings are abnormal.
4. For a *false-negative* test, the patient is abnormal and the test findings are normal.

In order to be more conservative, a false-positive test is preferred as compared to a false-negative test. The sensitivity is the percentage of true-positive tests in patients with abnormality. The specificity is the percentage of true-negative tests in normal subjects. The predictive value of a positive test is the percentage of patients with abnormal test results, while the predictive value of a negative test is the percentage of subjects with normal test results. This predictive value measures the accuracy of the test for identifying patients with disease and subjects with normal results. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented as follow (With reference to Table 3.14):

$$\text{Sensitivity} = \frac{TP}{TP + FN} \times 100\% \quad (5.1)$$

$$\text{Specificity} = \frac{TN}{TN + FP} \times 100\% \quad (5.2)$$

$$\text{PPV} = \frac{TP}{TP + FP} \times 100\% \quad (5.3)$$

$$\text{NPV} = \frac{TN}{TN + FN} \times 100\% \quad (5.4)$$

Table 3.14 Terms Used to Demonstrate the Diagnostic Value of a Test

TP	True – Positive
TN	True – Negative
FP	False – Positive
FN	False – Negative

3.4.3 Study 3 (Mathematical Models of HR vs. VO₂ & HR vs. VCO₂)

As mentioned, Neder *et al.* (2001) described the importance of rate of change in the variables of interest for the continuous, dynamic cardiopulmonary responses. Hansen *et al.* (1984) reported that overweight individuals are expected to have a slightly higher VO_{2max} than subjects of normal weight and thus, adjustments are necessary. In CPET, obesity is assumed to be insignificant when VO₂ and VCO₂ are both divided by individual weight in the analysis (ml/min.kg).

Three scalar time series, y_i and x_{ij} , ($i = 1, \dots, N$ and $j = 1, 2$) are viewed from a dynamic physiological system during stress testing (Figure 3.10) with time interval of $t = 5s$, where y_i represents measured heart rate, x_{ij} represents measured VO₂ when $j = 1$ and measured VCO₂ when $j = 2$ for observation i , while N is the number of observations.

Figure 3.10 Physiological response during incremental exercise

A Pearson correlation research design (Mendenhall *et al.*, 2003) of the following form was then applied to examine the relationships between measured heart rate with measured oxygen consumption ($HR_{\text{measured}} : VO_{2\text{measured}}$), measured heart rate with measured carbon dioxide ($HR_{\text{measured}} : VCO_{2\text{measured}}$), and measured heart rate with predicted heart rate ($HR_{\text{measured}} : HR_{\text{predicted}}$).

Studies reported a steep increase of heart rate, as a function of metabolic demand, could be regarded as an indirect evidence of cardiac abnormalities or peripheral muscle impairment for oxygen utilization ($\Delta HR/\Delta VO_2$) (Fairbairn *et al.*, 1994; Jones, 1997; Jones *et al.*, 1998; Wasserman *et al.*, 1994).

Some studies claimed that the relationship between HR and VO_2 is linear, while others argued that the relationship is nonlinear. Therefore, there is a need to develop a general equation that allows this effective technique to be used in describing and predicting the dynamic physiological system accurately regardless of a linear or nonlinear relationship between HR and VO_2 .

Here, a function of the following form is proposed to calculate the predicted HR from measured VO_2 or VCO_2 as

$$\hat{y}_i = 10^{A_j} x_{ij}^{B_j} \quad (3.8)$$

where $\hat{y}_i$ is the predicted (fitted) value of y_i and; A_j and B_j are the unknown model parameters.

To determine the 2 unknown constants A_j and B_j , the least-square fitting method (Robert & Daniel, 1991) is employed to minimize the following cost function, which is the sum of the residuals between the measured and predicted HR.

$$\text{Minimize } F = \sum_{i=1}^N (y_i - \hat{y}_i)^2 \quad (3.9)$$

where $y_i - \hat{y}_i$ is defined as the deviation of the predicted HR from the measured HR at observation point i . To solve the above optimization problem (Equation 3.9), the Newton's Iteration method with a tolerance of 0.05 is used. Once the constants of the predicted equation are determined, they are classified into the range of normal and heart disease to identify demarcation and grey-region.

3.5 Statistical Analysis

Quantative variables were expressed as mean values and standard deviation (Mean $\pm$ S.D.) for easy comparison. Study subjects were divided into 2 groups according to health status (group 1, normals; group 2, abnormal patients). The logistic correlation analysis was performed with a commercial package (Statistical Package for the Social Sciences, SPSS ver. 9.0). In Study 3, bivariate association between heart rate with oxygen consumption and heart rate with carbon dioxide production was assessed by 2-tailed Pearson's coefficient of correlation (r). A p value < 0.01 was considered for statistical significance in all inferences (Elston & William, 1994).

CHAPTER 4: RESULTS

The results of this study are presented in the following sections: 1) Study 1 (Spirometry Data Interpretation & Representation) 2) Study 2 (Data Interpretation & Representation of Cardiopulmonary Exercise Testing) and 3) Study 3 (Mathematical Models of HR versus VO_2 & HR versus VCO_2).

4.1 Study 1 - Spirometry Data Interpretation & Representation

4.1.1 Subject Characteristics

62 subjects (45 males and 17 females) were randomly selected to undergo PFT prior to CPET in the Pulmonary Function Laboratory. The mean age was 41.9 years (SD, 15.2), the mean height was 163.7 cm (SD, 7.3), the mean weight was 69.0 kg (SD, 20.2), and the mean BMI was 25.6 kg/m^2 (SD, 6.5), which falls within the overweight group. Of these 62 subjects, 45 were normal control subjects with absence of pulmonary disease, and 17 were pulmonary (obstructive/restrictive) patients evaluated for pulmonary rehabilitation program (PRP). The distributions of gender, age, height, weight, and BMI were similar between normal and pulmonary patients (With reference to Table 4.1).

Table 4.1 Subject Characteristics for Study 1

	Total Group (n = 62)	Group 1 (Normals) (n = 45)	Group 2 (Pulmonary Patients) (n = 17)
Gender, % male	72.6	71.1	76.5
Age, yr	41.9 ± 15.2	40.2 ± 15.8	46.5 ± 12.9
Height, cm	163.7 ± 7.3	163.7 ± 7.8	163.9 ± 6.0
Weight, kg	69.0 ± 20.2	69.4 ± 21.6	67.9 ± 16.4
BMI, kg/m ²	25.6 ± 6.5	25.7 ± 6.7	25.3 ± 6.1

4.1.2 Graphical Presentation

The clinical interpretations of normal and the degree of obstructive and restrictive abnormalities are displayed in the following Table 4.2. The test diagnosis represents the graphical presentations illustrated in Appendix C. Next, the analysis compares this diagnosis test against the plethysmography results to classify the data. The results show that the number of patients with true positive was 24, true negative was 28, false positive was 10, and false negative was 0.

Table 4.2 Graphical Presentation for Study 1

#	P ₁	P ₂	P ₃	Test	Plethysmography	TP	TN	FP	FN
				Diagnosis	Diagnosis				
C01	1.08	1.64	0.03	Normal	Normal		1		
C02	1.13	1.30	0.84	Normal	Normal		1		
C03	1.17	0.47	0.31	Normal	Normal		1		
C04	1.07	2.58	0.86	Mild (R)	Normal			1	
C05	1.09	1.78	0.64	Normal	Normal		1		
C06	1.21	0.40	0.98	Normal	Normal		1		
C07	1.07	2.59	0.96	Mild (R)	Normal (IE)	1			
C08	1.22	1.96	3.86	Mild (R)	Normal			1	
C09	1.15	4.86	3.99	Moderate (R)	Moderate (R)	1			
C10	1.28	2.72	2.59	Mild (R)	Normal			1	
C11	1.32	6.27	6.31	Severe (R)	R	1			
C12	1.24	1.28	1.47	Normal	Normal		1		
C13	1.06	0.42	1.55	Normal	Normal		1		
C14	1.05	1.04	0.51	Normal	Normal		1		
C15	1.09	0.98	0.19	Normal	Normal		1		
C16	1.12	3.14	1.88	Mild (R)	Normal (IE)	1			
C17	1.15	2.81	1.55	Mild (R)	Normal			1	
C18	1.23	3.07	2.62	Mild (R)	R	1			
C19	1.23	1.54	0.71	Normal	Normal		1		
C20	1.13	0.41	0.20	Normal	Normal		1		
C21	1.13	1.77	0.73	Normal	Normal		1		
C22	1.23	0.81	0.62	Normal	Normal		1		
C23	1.63	4.16	5.48	Moderate (O&R)	Moderate	1			
C24	1.14	4.36	3.84	Moderate (R)	R + IE	1			
C25	1.03	4.23	3.27	Moderate (R)	Normal (IE)	1			
C26	1.19	1.44	0.19	Normal	Normal		1		
C27	1.53	2.81	3.73	Mild (O&R)	Moderate (O)	1			
C28	1.61	6.01	6.73	Severe (O&R)	Severe (O)	1			
C29	1.13	1.85	0.96	Normal	Normal		1		
C30	1.33	2.91	3.04	Mild (R)	R	1			
C31	2.26	1.52	2.78	Mild (O)	Mild (O)	1			
C32	1.17	3.44	2.42	Mild (R)	Normal (IE)	1			
C33	1.06	0.38	3.27	Normal	Normal		1		
C34	1.10	1.26	0.63	Normal	Normal		1		
C35	1.07	2.77	1.67	Mild (R)	Mild (R)	1			
C36	1.56	1.36	2.98	Mild (O)	Mild (O)	1			
C37	2.17	4.84	6.77	Severe (O) & Moderate (R)	Severe (O)	1			
C38	1.26	0.00	0.24	Normal	Normal		1		
C39	1.05	2.32	3.55	Mild (R)	Normal			1	
C40	1.10	1.41	0.14	Normal	Normal		1		
C41	1.27	2.42	2.25	Mild (R)	Normal			1	
C42	1.14	0.34	1.67	Normal	Normal		1		
C43	1.42	2.09	2.97	Mild (O&R)	Mild (O)	1			
C44	1.28	0.19	0.79	Normal	Normal		1		

4.2 Study 2 - Data Interpretation & Representation of CPET

4.2.1 Subject Characteristics

50 subjects (43 males and 7 females) were randomly selected to undergo CPET in the Pulmonary Function Laboratory. The mean age was 46.9 years (SD, 17.1), the mean height was 163.6 cm (SD, 8.2), the mean weight was 67.1 kg (SD, 19.4), and the mean BMI was 24.8 kg/m² (SD, 5.9). Of these 50 subjects, 26 were normal control subjects with absence of cardiomyopathy, and 24 were severe cardiomyopathy patients evaluated for heart transplant. The distributions of gender, age, height, weight, and BMI were similar between normal and cardiomyopathy patients (With reference to Table 4.5).

Table 4.5 Subject Characteristics for Study 2

	Total Group (n = 50)	Group 1 (Normals) (n = 26)	Group 2 (Cardiomyopathy Patients) (n = 24)
Gender, % male	86.0	84.6	87.5
Age, yr	46.9 ± 17.1	45.0 ± 21.7	49.0 ± 10.2
Height, cm	163.6 ± 8.2	166.0 ± 7.7	160.9 ± 8.0
Weight, kg	67.1 ± 19.4	64.1 ± 16.9	70.4 ± 21.7
BMI, kg/m ²	24.8 ± 5.9	23.0 ± 4.6	26.9 ± 6.5

4.2.2 Graphical Presentation

The clinical interpretations of normal and the possible presence of cardiomyopathy are displayed in Table 4.6. The test diagnosis represents the graphical presentations illustrated in Appendix D. The analysis then compares this diagnosis test against the exercise echocardiography results to classify the data. The results showed that the number of patients with true positive was 22, true negative was 24, false positive was 2, and false negative was 2.

Table 4.6 Graphical Presentation for Study 2

#	P ₁	P ₂	P ₃	Test Diagnosis	Echocardiography Diagnosis	TP	TN	FP	FN
B03	57	15	54	Cardiomyopathy	Cardiomyopathy	1			
B04	45	15	67	Cardiomyopathy	Cardiomyopathy	1			
B10	12	7	33	Normal	Normal		1		
B13	35	9	13	Normal	Normal		1		
B23	41	17	57	Cardiomyopathy	Cardiomyopathy	1			
B27	2	12	7	Normal	Normal		1		
B28	6	9	29	Normal	Normal		1		
B29	6	5	23	Normal	Normal		1		
B32	4	9	21	Normal	Normal		1		
B33	38	13	52	Cardiomyopathy	Cardiomyopathy	1			
B46	5	10	13	Normal	Normal		1		
B61	10	9	22	Normal	Normal		1		
B69	29	8	12	Normal	Normal		1		
B75	22	12	27	Cardiomyopathy	Normal			1	
B78	8	8	21	Normal	Normal		1		
B80	2	8	27	Normal	Normal		1		
B85	31	11	36	Cardiomyopathy	Cardiomyopathy	1			
B89	6	10	10	Normal	Normal		1		
B93	7	7	9	Normal	Normal		1		
B98	12	8	15	Normal	Normal		1		
C01	26	13	43	Cardiomyopathy	Cardiomyopathy	1			
C02	12	12	10	Normal	Normal		1		
C03	58	143	76	Cardiomyopathy	Cardiomyopathy	1			
C05	23	13	30	Cardiomyopathy	Normal			1	
C06	3	11	17	Normal	Normal		1		
C07	37	17	59	Cardiomyopathy	Cardiomyopathy	1			
C08	17	9	16	Normal	Normal		1		
C11	47	13	58	Cardiomyopathy	Cardiomyopathy	1			
C14	18	11	24	Normal	Normal		1		
C17	31	14	48	Cardiomyopathy	Cardiomyopathy	1			
C18	33	14	54	Cardiomyopathy	Cardiomyopathy	1			
C19	21	15	27	Cardiomyopathy	Cardiomyopathy	1			
C21	19	14	28	Normal	Cardiomyopathy				1
C25	9	11	22	Normal	Normal		1		
C29	23	12	41	Cardiomyopathy	Cardiomyopathy	1			
C32	30	13	50	Cardiomyopathy	Cardiomyopathy	1			
C33	36	11	13	Normal	Normal		1		
C34	1	13	25	Normal	Normal		1		
C35	38	11	51	Cardiomyopathy	Cardiomyopathy	1			
C38	25	13	49	Cardiomyopathy	Cardiomyopathy	1			
C40	11	10	16	Normal	Normal		1		
C43	3	7	20	Normal	Normal		1		
C44	41	21	52	Cardiomyopathy	Cardiomyopathy	1			
C45	11	18	35	Normal	Cardiomyopathy				1

C49	26	15	40	Cardiomyopathy	Cardiomyopathy	1			
C50	66	56	73	Cardiomyopathy	Cardiomyopathy	1			
C53	27	15	40	Cardiomyopathy	Cardiomyopathy	1			
C54	28	18	42	Cardiomyopathy	Cardiomyopathy	1			
C56	5	7	22	Normal	Normal		1		
C62	32	14	49	Cardiomyopathy	Cardiomyopathy	1			
Total						22	24	2	2

To complement the exercise echocardiography test from the above Table 4.6, the sensitivity and specificity of this graphical technique are both 92% (Table 4.7), where the predictive accuracies are 92% positive and 92% negative (Table 4.8).

Table 4.7 Sensitivity and Specificity of Graphical Presentation

Type	(%)	Formula
Sensitivity	92	$[TP/(TP+FN)]*100$
Specificity	92	$[TN/(TN+FP)]*100$

Table 4.8 Predictive Accuracy of Graphical Presentation

Predictive Accuracy		
Positive	92	$[TP/(TP+FP)]*100$
Negative	92	$[TN/(TN+FN)]*100$

The index interpretations of normal and the possible presence of cardiomyopathy are then displayed in the following Table 4.9. The test diagnosis represents the colored bar code illustrated in Appendix D. Again, the study compares this diagnosis against the exercise echocardiography results to classify the data. The results show that the number of patients with true positive results was 24, true negative was 21, false positive was 5, and false negative was 0.

Table 4.9 Cardiopulmonary Index (CPI) for Study 2

#	P ₁	P ₂	P ₃	(¹ 000) Cardio-Index	Index Diagnosis	Echocardiography Diagnosis	TP	TN	FP	FN
B03	57	15	54	45	Cardiomyopathy	Cardiomyopathy	1			
B04	45	15	67	44	Cardiomyopathy	Cardiomyopathy	1			
B10	12	7	33	3	Normal	Normal		1		
B13	35	9	13	4	Cardiomyopathy	Normal			1	
B23	41	17	57	40	Cardiomyopathy	Cardiomyopathy	1			
B27	2	12	7	0	Normal	Normal		1		
B28	6	9	29	2	Normal	Normal		1		
B29	6	5	23	1	Normal	Normal		1		
B32	4	9	21	1	Normal	Normal		1		
B33	38	13	52	26	Cardiomyopathy	Cardiomyopathy	1			
B46	5	10	13	1	Normal	Normal		1		
B61	10	9	22	2	Normal	Normal		1		
B69	29	8	12	3	Normal	Normal		1		
B75	22	12	27	7	Cardiomyopathy	Normal			1	
B78	8	8	21	1	Normal	Normal		1		
B80	2	8	27	0	Normal	Normal		1		
B85	31	11	36	13	Cardiomyopathy	Cardiomyopathy	1			
B89	6	10	10	1	Normal	Normal		1		
B93	7	7	9	0	Normal	Normal		1		
B98	12	8	15	1	Normal	Normal		1		
C01	26	13	43	14	Cardiomyopathy	Cardiomyopathy	1			
C02	12	12	10	1	Normal	Normal		1		
C03	58	143	76	630	Cardiomyopathy	Cardiomyopathy	1			
C05	23	13	30	9	Cardiomyopathy	Normal			1	
C06	3	11	17	1	Normal	Normal		1		
C07	37	17	59	36	Cardiomyopathy	Cardiomyopathy	1			
C08	17	9	16	2	Normal	Normal		1		
C11	47	13	58	35	Cardiomyopathy	Cardiomyopathy	1			
C14	18	11	24	5	Cardiomyopathy	Normal			1	
C17	31	14	48	21	Cardiomyopathy	Cardiomyopathy	1			
C18	33	14	54	24	Cardiomyopathy	Cardiomyopathy	1			
C19	21	15	27	8	Cardiomyopathy	Cardiomyopathy	1			
C21	19	14	28	7	Cardiomyopathy	Cardiomyopathy	1			
C25	9	11	22	2	Normal	Normal		1		
C29	23	12	41	11	Cardiomyopathy	Cardiomyopathy	1			
C32	30	13	50	19	Cardiomyopathy	Cardiomyopathy	1			
C33	36	11	13	5	Cardiomyopathy	Normal			1	
C34	1	13	25	0	Normal	Normal		1		
C35	38	11	51	22	Cardiomyopathy	Cardiomyopathy	1			
C38	25	13	49	16	Cardiomyopathy	Cardiomyopathy	1			
C40	11	10	16	2	Normal	Normal		1		
C43	3	7	20	0	Normal	Normal		1		
C44	41	21	52	44	Cardiomyopathy	Cardiomyopathy	1			
C45	11	18	35	7	Cardiomyopathy	Cardiomyopathy	1			

C49	26	15	40	16	Cardiomyopathy	Cardiomyopathy	1			
C50	66	56	73	268	Cardiomyopathy	Cardiomyopathy	1			
C53	27	15	40	17	Cardiomyopathy	Cardiomyopathy	1			
C54	28	18	42	21	Cardiomyopathy	Cardiomyopathy	1			
C56	5	7	22	1	Normal	Normal		1		
C62	32	14	49	22	Cardiomyopathy	Cardiomyopathy	1			
Total							24	21	5	0

To complement the exercise echocardiography test from the above Table 4.9, the sensitivity and specificity of this cardiopulmonary index (CPI) are 100% and 81 % respectively (Table 4. 10), where the predictive accuracies are 83% positive and 100% negative (Table 4.1 1).

Table 4.10 Sensitivity and Specificity of CPI

Type	(%)	Formula
Sensitivity	100	$[TP/(TP+FN)]*100$
Specificity	81	$[TN/(TN+FP)]*100$

Table 4.1 1 Predictive Accuracy of CPI

Predictive Accuracy		
Positive	83	$[TP/(TP+FP)]*100$
Negative	100	$[TN/(TN+FN)]*100$

4.3 Study 3 - Mathematical Models of HR vs. VO₂ & HR vs. VCO₂

4.3.1 Subject Characteristics

85 subjects (48 males and 37 females) were randomly selected to undergo CPET in the Pulmonary Function Laboratory. The mean age was 40.2 years (SD, 11.6), the mean height was 162.0 cm (SD, 8.2), the mean weight was 62.4 kg (SD, 13.1), and the mean BMI was 23.7 kg/m² (SD, 4.3). Of these 85 subjects, 65 were normal control subjects with absence of heart disease, and 20 were heart disease patients evaluated for heart transplant. The distributions of age, height, weight, and BMI were similar between normal and heart disease patients. However, there are significantly more males in the heart disease group than in normal subjects (With reference to Table 4.12).

Table 4.12 Subject Characteristics for Study 3

	Total Group (n = 85)	Group 1 (Normals) (n = 65)	Group 2 (Heart Patients) (n = 20)
Gender, % male	56.5	49.2	80
Age, yr	40.2 ± 11.6	40.3 ± 12.1	40.1 ± 9.9
Height, cm	162.0 ± 8.2	161.6 ± 8.3	163.3 ± 8.2
Weight, kg	62.4 ± 13.1	60.9 ± 11.5	67.3 ± 16.6
BMI, kg/m ²	23.7 ± 4.3	23.3 ± 3.7	25.1 ± 5.6

4.3.2 Correlation

The results for the correlation of heart rate are summarized in Table 4.13. The correlation of heart rate with VO₂ was 0.92 (SD, 0.05) in normal, and 0.76 (SD, 0.25) in heart disease groups. The correlation of heart rate with VCO₂ was 0.95 (SD, 0.03) in normal, and 0.80 (SD, 0.24) in heart disease groups. Hence, the subjects in both normal and heart disease groups had a higher significant correlation for VCO₂ than

for VO_2 in these 85 subjects ($p < 0.01$). At the same time, VCO_2 in both normal and heart disease groups had a smaller spread than VO_2 (With reference to the SD in Table 4.13).

Table 4.13 Correlation of Heart Rate in Normal and Heart Patients

	Group 1 (Normals) (n = 65)		Group 2 (Heart Patients) (n = 20)	
	r (Mean ± SD)	p Value	r (Mean ± SD)	p Value
VO_2	0.92 ± 0.05	< 0.01	0.76 ± 0.25	< 0.01
VCO_2	0.95 ± 0.03	< 0.01	0.80 ± 0.24	< 0.01

r = correlation coefficient

4.3.3 Mathematical Model (With reference to section 3.4.3)

The results for mathematical model of CPET are summarized in Table 4.14. The normal group for A_1 was 1.49 (SD, 0.15), B_1 was 0.50 (SD, 0.10), A_2 for was 1.61 (SD, 0.11), and B_2 was 0.39 (SD, 0.06). The heart patients group for A_1 was 1.66 (SD, 0.26), B_1 was 0.38 (SD, 0.21), A_2 was 1.73 (SD, 0.20), and B_2 was 0.30 (SD, 0.16).

Table 4.14 Mathematical Model Constants (A_j and B_j)

	Group 1 (Normal) (n = 65)	Group 2 (Heart Patients) (n = 20)
	Mean ± SD	Mean ± SD
$A_1 \text{ VO}_2$	1.49 ± 0.15	1.66 ± 0.26
$B_1 \text{ VO}_2$	0.50 ± 0.10	0.38 ± 0.21
$A_2 \text{ VCO}_2$	1.61 ± 0.11	1.73 ± 0.20
$B_2 \text{ VCO}_2$	0.39 ± 0.06	0.30 ± 0.16

CHAPTER 5: DISCUSSION

The discussion of the results are presented in the following sections: 1) Study 1 (Spirometry Data Interpretation & Representation) 2) Study 2 (Data Interpretation & Representation of Cardiopulmonary Exercise Testing) and 3) Study 3 (Mathematical Models of HR versus VO_2 and HR versus VCO_2).

5.1 Study 1 (Spirometry Data Interpretation & Representation)

In the graphical presentation (see sample in Figure 3.6), the skewness of the $P_1P_2P_3$ triangle towards any particular axis indicates the obstructive/restrictive nature of abnormality. At the same time, the area of this triangle is directly proportional to the severity stages of obstructive/restrictive lung disease. Thus, this graphical technique allows easy visualization of the disease progression during pulmonary rehabilitation. With reference to Tables 4.3 & 4.4, the technique can also be used to reinforce plethysmography in detecting pulmonary diseases as the sensitivity and negative predictive accuracy are observed to be 100%. These results show that the graphical presentation produces no false negative tests (With reference to equations 5.1 & 5.4).

In summary, this graphical presentation successfully employs FVC (Baur *et al.*, 1999; Hutchinson, 1846; Kannel *et al.*, 1980; Petty, 2002), FEV_1 (Macklem & Permutt, 1979; Petty, 2002), and normalized indices (Anthonsien *et al.*, 1994) to detect the presence of pulmonary disease.

5.2 Study 2 (Data Interpretation & Representation of CPET)

Results from Tables 4.7, 4.8, 4.10 & 4.11 show that CPI produces sensitivity of 8% higher than in the graphical technique. It also produces an excellent predictive value of 9% higher for positive result than in the graphical technique. The graphical technique produces specificity of 9% higher than in CPI. It similarly produces an excellent predictive value of 8% higher for negative result than in CPI. To optimize the accuracy of this diagnostic test, this study would apply both the graphical technique and CPI (Appendix D) simultaneously to reinforce the exercise echocardiography in detecting cardiomyopathy through easy visualization. CPI was used to analyze true positive (presence of abnormal) results from sensitivity and positive predictive value, and the graphical technique was used to analyze true negative (presence of normal) results from specificity and negative predictive value.

In summary, these graphical presentation and CPI successfully employ $VO_{2\max}$ (Cohn *et al.*, 1993; Gian *et al.*, 1995; Gibbons *et al.*, 2002; Linkoff *et al.*, 1987; Mancini *et al.*, 1991; Miller *et al.*, 1995; Myers *et al.*, 1998; Osada *et al.*, 1998; Pardaens *et al.*, 2000; Peters *et al.*, 1983; Stelken *et al.*, 1996; Stevenson *et al.*, 1995; Szlachcic *et al.*, 1985; Weiner *et al.*, 1995; Williams *et al.*, 1995), VO_2/P (Hanson *et al.*, 1987; Jones *et al.*, 1998; Koike & Wasserman, 1992; Neder *et al.*, 2001; Solal *et al.*, 1990), $O_2\text{pulse}_{\max}$ (Fairbairn *et al.*, 1994; Jones, 1997; Jones *et al.*, 1998; Wasserman *et al.*, 1994; Whipp *et al.*, 1996), and normalized indices (Cohen-Solal *et al.*, 1997; Ino *et al.*, 1996; Jones *et al.*, 1998; Pelliccia, 2000) to detect cardiomyopathy visually.

5.3 Study 3 (Mathematical Models of HR vs. VO_2 & HR vs. VCO_2)

5.3.1 Correlation

From Table 4.13, the heart rate in both normal and heart disease groups had a higher significant correlation for VCO_2 than for VO_2 . VCO_2 also had a smaller standard deviation (spread) than VO_2 . The body's priority to remove carbon dioxide may be the plausible reason to explain this phenomenon. During exercise, to avoid an accumulation of lactate acid in the exercised muscles, there is an exchange of increased venous blood in transporting carbon dioxide back to the lungs. This carbon dioxide is an important stimulus to respiration. Nerve receptors in the aorta near the heart and in the carotid artery send signals to the brain, which monitors carbon dioxide changes in the body system. If the amount of carbon dioxide in the blood increases, both the rate and depth of breathing increases for extraction. However, when the changes in oxygen levels are monitored, the nerve receptors may not be as sensitive as to carbon dioxide. This results in a lower correlation in oxygen. Unless there are serious disease complications in the aorta or in the carotid artery, which prohibit the nerve receptors from transmitting signals to the brain, significant correlations of oxygen and carbon dioxide are still guaranteed.

This phenomenon contributes towards the idea that usage of exercise peak VO_2 as a criterion for heart transplant candidate selection (as mentioned in Chapter 2) should be redefined. In contrast, VCO_2 may be a better criterion for candidate stratification. Also, identification with a cut-off VCO_2 value obtained from kinetic variables may even replace discrete VO_2 (David *et al.*, 1999; Edwards & Rodeheffer,

1992) in the assessment of heart transplant evaluation. Thus, optimal utilization of limited heart transplantation resource begins with an appropriate selection of new clinical variables where candidates can benefit from better management.

5.3.2 Mathematical Model

Unlike previous studies discussed in Chapter 2, this study has developed a mathematical model (Equation 3.8) that is flexible enough to describe and predict the dynamic physiological system accurately regardless of a linear (Astrand & Rhyming, 1954; Becklake *et al.*, 1965; Ekelund & Holmgren, 1967; Francis *et al.*, 1989; Higginbotham *et al.*, 1986; Jensen *et al.*, 1998) or nonlinear (Brooke & Hamley, 1972; Chapman *et al.*, 1960; Ekblom *et al.*, 1968; Hermansen *et al.*, 1970; Hofmann *et al.*¹, 1997; Jones, 1997; Pokan *et al.*, 1993; Wyndham *et al.*, 1959) relationship. This linear equation was developed by taking log from the mathematical model as follows:

From equation 3.8, $\hat{y}_i = 10^{A_j} x_{ij}^{B_j}$

Taking log on both sides, $\log \hat{y}_i = A_j + B_j \log x_{ij}$ (5.5)

where, A_j is the intercept and B_j is the gradient of a straight-line equation (Form: $y = mx + c$).

Neder *et al.* (2001) also observed similar regressed baseline value (intercept or constant) and the rate of change (slope or gradient) as an important physiological phenomenon. The results of A_j & B_j for normal and heart disease subjects are shown

in Table 4.14. These results successfully identify an important demarcation strategy of heart patients from normal. Furthermore, this study can make use of this linear equation 5.5 in normal subjects to indirectly predict kinetic VO_2 and VCO_2 from the measurement of heart rate (Astrand & Rhymin, 1954) as follows:

$$\text{Rearranging Equation 5.5,} \quad \log x_{ij} = \frac{1}{B}(-A + \log \hat{y}_j) \quad (5.6)$$

In summary, this demarcation trend from the mathematical model can be considered as a new important component in the interpretative strategy.

CHAPTER 6: CONCLUSION & FUTURE WORK

This chapter is divided into the following subsections: 1) Summary
2) Conclusion and 3) Recommendations.

6.1 Summary

The purpose of Study 1 and 2 was to assess the performance indices for monitoring disease progression and response to treatment (rehabilitation). They were then presented in flow charts and graphical presentations. The purpose of Study 3 was to examine the importance of carbon dioxide by comparing the correlation of heart rate with carbon dioxide against the correlation of heart rate with oxygen consumption. Also, a mathematical model of heart rate with oxygen and carbon dioxide in normal and heart disease to demarcate regions for clinical indications was developed.

In Study 1 and 2, the advantages of each parameter are consolidated, normalized these indices with reference values, and presented them in graphical presentations. The disease progression and response to treatment could be monitored from the areas and indices depicted in the graphical illustrations. In Study 3, the Pearson correlation was applied to discover and compare $HR:VCO_2$ against $HR:VO_2$. Then, a mathematical model of heart rate with oxygen and carbon dioxide was developed. Least-squared optimization using Newton's iteration method was used to solve the constants of the predicted equation. These constants then determine and demarcate the range of normal and heart diseases.

6.2 Conclusion

Based on the results in this study, the following conclusions were drawn:

6.2.1 Study 1 (Spirometry Data Interpretation & Representation)

The graphical technique successfully characterizes pulmonary disease from normal subjects, and allows the obstructive/restrictive nature of abnormality to be easily visualized.

6.2.2 Study 2 (Data Interpretation & Representation of CPET)

The oxygen parameters during CPET may be clinically relevant, as they have the ability to identify cardiomyopathy (severe cases for heart transplant evaluation) presence and differentiate them from normal subjects. At the same time, a graphical technique and non-dimensional cardiopulmonary index (CPI) were effectively introduced as a supplementary aid to demarcate cardiomyopathy from normal subjects. Hence, a supplement diagnostic test is established to complement the exercise echocardiography test.

6.2.3 Study 3 (Mathematical Models of HR vs. VO_2 & HR vs. VCO_2)

Heart rate significantly correlates better with carbon dioxide than oxygen. At the same time, a mathematical model successfully describes and predicts the dynamic physiological system accurately regardless of a linear or nonlinear relationship of heart rate with oxygen or carbon dioxide. Furthermore, this model provides more precise and valuable information about cardiopulmonary

physiological reactions in patients with heart diseases, demarcating them from normal subjects.

6.3 Recommendations

The following recommendations were made for future research studies:

6.3.1 Predicted Reference Values

This study has described local standard procedures of measurement for these clinically useful variables during non-invasive PFT and CPET. From the literature review in Chapter 2, the equations that estimate for primarily Caucasian population do not accurately predict the actual values of our subjects. Baur *et al.* (1999) strongly supports that these predicted values be used within Western countries only. More importantly, as these widely used predicated equations were based on studies performed more than 20 years ago, they might not represent the findings obtained in today's population (Baur *et al.*, 1999). Therefore, the future work can start off by setting up own local multicentre study using standardized procedures and rigorous quality control to develop appropriate PFT and CPET reference values based on Singapore population.

6.3.2 Study 1 (Spirometry Data Interpretation & Representation)

Forced expiratory volume in 6 s (FEV_6) can be recommended to replace FVC as normal lungs empty in six seconds (Petty, 2002). This has been shown to be an easier test and a good indicator of both obstructive and restrictive ventilatory disorders (Swanneyi *et al.*, 2000). At the same time, FEV_1/FEV_6 can replace FEV_1/FVC as another new parameter.

6.3.3 Study 2 (Data Interpretation & Representation of CPET)

The following parameters can be recommended to be included in the future development of graphical presentation and cardiopulmonary index (CPI).

Suggestion 1:

Vital capacity (VC) is not only a useful predictor of pulmonary disease but also of cardiac failure (Friedman *et al.*, 1976; Marcus *et al.*, 1989) and lung cancer (Skillrud *et al.*, 1986; Tockman *et al.*, 1987). It can also effectively select groups destined for premature death from all cause mortality (Bang *et al.*, 1993; Beaty *et al.*, 1982, 1985; Hole *et al.*, 1996; Krzyzanowski & Wysocki, 1986; Lange *et al.*, 1990; Neas & Schwartz, 1998; Schunemann *et al.*, 2000). Therefore, vital capacity predicts cardiovascular as well as non-cardiovascular mortality, which makes this pulmonary function measurement seems like a true measure of living capacity (Kannel *et al.*, 1980).

Suggestion 2:

It has been reported in a study that abnormal high minute ventilation for a given level of metabolism (high slope of V_E/VCO_2 relationship), was found to be an independent prognostic marker in patients with severe heart failure (Chua *et al.*, 1997). Also, this high slope is considered to be reflective of hyperventilation, an enlarged dead space fraction of the breath, or even both (Jones *et al.*, 1998; Milani *et al.*, 1996; O'Donnell & Webb, 1992; Reybrouck *et al.*, 1998; Wasserman *et al.*, 1979)

Suggestion 3:

Breathing factor may be an important factor, affecting the heart rate regulation, which should be specified in the CPET protocol (Swynghedauw *et al.*, 1997).

Suggestion 4:

Maximal heart rate (HR_{max}) may be included in the analysis as chronotropic incompetence defines a failure to reach 80 to 85% of the age-predicted maximum exercise heart rate or a low chronotropic index (heart rate adjusted to MET level). Chronotropic incompetence is associated with high risks of all-cause mortality (Lauer *et al.*, 1996,1999).

6.3.4 Study 3 (Mathematical Models of HR vs. VO_2 & HR vs. VCO_2)

The future work can extend the mathematical model into the recovery phase. Thus, further work on exercise recovery can be carried out to define the role of HR, VO_2 and VCO_2 in the association of risk stratification and mortality prognosis in heart failure patients using bicycle protocol. This may even prove to be useful when exercise to near-maximal levels (respiratory exchange ratio greater than 1) is not achieved (Cohen-Solal *et al.*, 1995; Daida *et al.*, 1996; Koike *et al.*, 1995; Pardaens *et al.*, 2000; Tanabe *et al.*, 2000).

Heart Rate (HR):

Studies have illustrated that abnormal heart rate recovery is associated with all-cause mortality (Cole *et al.*, 1999, 2000; Diaz *et al.*, 2001; Nishime *et al.*, 2000; Shetker *et al.*, 2001 ; Watanabe *et al.*, 2001)

Oxygen Consumption (VO_2):

The evaluation of the rate of decline in VO_2 kinetics during exercise recovery may provide additional information regarding the functional state in heart failure patients. Daida *et al.* (1996) reported a further increase in VO_2 during early active recovery in chronic heart failure patients following maximal exercise. He speculates that this response may be an indication of a very insufficient cardiopulmonary response to exercise. This can be further verified when study 3 is extended to recovery stages.

Studies have shown that delayed recovery in VO_2 kinetics may result in heart failure (Cohen-Solal *et al.*, 1993, 1995; Mancini *et al.*, 1991; Meakins *et al.*, 1927; Sietsema *et al.*, 1994). This delayed VO_2 recovery may explain the prolonged dyspnea or fatigue after exercise in heart failure patients (Daida *et al.*, 1996).

Carbon Dioxide Production (VCO_2):

Currently, studies have been focusing more on VO_2 in recovery (Hiroyuki *et al.*, 1996; Leandro *et al.*, 1999). It is the hope of this thesis that future work focuses more on VCO_2 as an important role in the recovery studies. As mentioned earlier, VCO_2 was used in V_E/CO_2 to assess patients suffering from breathlessness due to severe chronic airflow limitation (O'Donnell & Webb, 1992). At the same time, V_E/VCO_2 has already been established to be a prognostic significance in the heart failure population (Ross *et al.*, 2003). Therefore, VCO_2 can correlate with other CPET parameters in order to establish an important role in prognostic significance and mortality for heart disease population.

REFERENCES

1. AARC Clinical Practice Guideline Spirometry. (1996). *Respiratory Care* **41**(7), 629-636.
2. ACCP Scientific Section Recommendations. (1983). Statement on Spirometry. *Chest* **83**(3), 547-550.
3. American College of Sports Medicine. (2000). *ACSM's guidelines for exercise testing and prescription* (6th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.
4. Anthonisen, N.R., Connett, J.E., Kiley, J.P., Altose, M.D., Bailey, W.C., Buist, A.S., Conway, W.A. Jr., Enright, P.L., Kanner, R.E., & O'Hara, P. (1994). Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁: The Lung Health Study. *JAMA* **272**, 1497-1505.
5. Astrand, P., & Rhyming, I. (1954). A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *Journal of Applied Physiology* **7**, 218-221.
6. ATS (American Thoracic Society). (1986). Evaluation of impairment, disability secondary to respiratory disorders. *American Review of Respiratory Disease* **133**, 1205-1209.
7. ATS (American Thoracic Society). (1991). Lung function testing: selection of reference values and interpretative strategies. *American Review of Respiratory Disease* **144**, 1202-1218.

8. Baltopoulos, G., Fildisis, G., Karatzas, S., Georgiakodis, F., & Myrianthefs, P. (2000). Reference values and prediction equations for FVC and FEV₁ in the Greek Elderly. *Lung* 178, 201-212.
9. Bande, J., Clement, J., & Van De Woestijne, K.P. (1980). The influence of smoking habits and body weight on vital capacity and FEV₁ in male air force personnel: a longitudinal and cross sectional analysis. *American Review of Respiratory Disease* 122, 781-789.
10. Bang, K.M., Gergen, P.J., Kramer, R., & Cohen, B. (1993). The effect of pulmonary impairment on all-cause mortality in a national cohort. *Chest* 103, 536-540.
11. Baur, X., Isringhausen-Bley, S., & Degens, P. (1999). Comparison of lung-function reference values. *International Archives of Occupational & Environmental Health* 72, 69-83.
12. Beaty, T.H., Cohen, B.H., Newill, C.A., Menkes, H.A., Diamond, E.L., & Chen, C.J. (1982). Impaired pulmonary function as a risk factor of mortality. *American Journal of Epidemiology* 116, 102-113.
13. Beaty, T.H., Newill, C.A., Cohen, B.H., Tockman, M.S., Bryant, S.H., & Spurgeon, H.A. (1985). Effects of pulmonary function on mortality. *Journal of Chronic Diseases* 38, 703-710.
14. Becklake, M., Frank, H., Dagenais, G., Ostiguy, G., & Guzman, C. (1965). Influence of age and sex on exercise cardiac output. *Journal of Applied Physiology* 20, 938-947.
15. Bercklake, M.R. (1986). Concepts of normality applied to the measurement of lung function. *American Journal of Medicine* 80, 1158-1164.

References

16. Berger, J., Boczor, S., Nowak, D., Jorres, R., & Magnussen, H. (1996). *Relationship between bronchial reactions and methacholine, clinical parameters and case history symptoms* (Translated from German). Kunath H (ed.) Tagungsband "Medizin und Informatik". MMV Munich, 563-568.
17. Bishop, P.J. (1977). A bibliography of John Hutchinson. *Medical History* **21**, 384-396.
18. Borg, G.A. (1982). Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise* **14**, 377-381.
19. Braith, R.W. (1998). Exercise training in patients with CHF and heart transplant recipients. *Medicine & Science in Sports & Exercise* **30** (Suppl 10), S367-S368.
20. Brandli, O., Schindler, C.H., Kuenzli, N., Keller, R., Perruchoud, A.P., & Sapaldia team. (1996). Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. *Thorax* **51**, 277-283.
21. Brooke, J., & Hamley, E. (1972). The heart rate-physical work curve analysis for the prediction of exhausting work ability. *Medicine & Science in Sports* **4**, 23-26.
22. Buchfuhrer, M.J., Hansen, J.E., Robinson, T.E., Sue, D.Y., Wasserman, K., & Whipp, B.J. (1983). Optimizing the exercise protocol for cardiopulmonary assessment. *Journal of Applied Physiology* **55**, 1558-1564.
23. Cara, M., & Hentz, P. (1971). *Aide-mémoire of spirographic practice for examining ventilatory function* (2nd ed.). Industrial Health and Medicine series **11**, 1-130.

24. Cavanagh, P.R., & Kram, R. (1985). The efficiency of human movement: A statement of the problem. *Medicine & Science in Sports Science* 17,304-308.
25. Chapman, C., Fisher, J., & Sproule, B. (1960). Behavior of stroke volume at rest and during exercise in human beings. *Journal of Clinical Investigation* 30, 1208-1230.
26. Cherniak, R.M., & Raber, M.D. (1972). Normal standards for ventilatory function using an automated wedge spirometer. *American Review of Respiratory Disease* 106, 38-46.
27. Chia, S.E., Wang, Y.T., Chan, O.Y., & Poh, S.C. (1993). Pulmonary function in healthy Chinese, Malay and Indian adults in Singapore. *Annals Academy of Medicine Singapore* 22, 878-884.
28. Chua, T.P., Ponikowski, P., Harrington, D., Anker, S.D., Webb-Peploe, K., Clark, A.L., Poole-Wilson, P.A., & Coats, A.J. (1997). Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *Journal of the American College of Cardiology* 29, 1585-1590.
29. Cleland, J.G., Bulpitt, C.J., Falk, R.H., Findlay, I.N., Oakley, C.M., Murray, G., Poole-Wilson, P.A., Prentice, C.R., & Sutton, G.C. (1995). Is aspirin safe for patients with heart failure? *British Heart Journal* 74(3), 215-219.
30. Cleland, J.G., John, J., & Houghton, T. (2001). Does aspirin attenuate the effect of angiotensin-converting enzyme inhibitors in hypertension or heart failure? *Current Opinion in Nephrology & Hypertension* 10(5), 625-631.

31. Coats, A.J.S, Adamopoulos, S., Radaelli, A., McCance, A., Meyer, T.E., Bernardi, L., Solda, P.L., Davey, P., Ormerod, O., & Forfar, C. (1992). Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation* 85,2119-2131.
32. Cohen-Solal, A., Geneves, M., & Laperche, T. (1993). Kinetics of recovery of ventilation and oxygen uptake after maximal exercise test in heart failure: A new index of functional impairment? *Circulation* 88 (Suppl), 1-591.
33. Cohen-Solal, A., Laperche, T., Morvan, D., Geneves, M., Caviezel, B., & Gourgon, R. (1995). Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure: Analysis with gas exchange measurements and NMR epectroscopy. *Circulation* 91, 2924-2932.
34. Cohen-Solal, A., Barnier, P., Pessione, F., Seknadji, P., Logeart, D., Laperche, T., & Gourgon, R. (1997). Comparison of the long term prognostic value of peak exercise oxygen pulse and peak oxygen uptake in patients with chronic heart failure. *Heart* 78, 572-576.
35. Cohn, J.N. (1987). Quantative exercise testing for the cardiac patient: the value of monitoring gas exchange (Introduction). *Circulation* 76 (Suppl VI), VI-1-VI-2.
36. Cohn, J.N., & Rector, T.S. (1988). Prognosis of congestive heart failure and predictors of mortality. *American Journal of Cardiology* 22, 21-31.

37. Cohn, J.N., Johnson, G.R., Shabetai, R., Loch, H., Tristani, F., Rector, T., Smith, R., & Fletcher, R. (1993). Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. *Circulation* **87** (suppl VI), VI-5–VI-6.
38. Cole, C.R., Blackstone, E.H., Pashkow, F.J., Snader, C.E., & Lauer, M.S. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *The New England Journal of Medicine* **341**, 1351-1357.
39. Cole, C.R., Foody, J.M., Blackstone, E.H., & Lauer, M.S. (2000). Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascular healthy cohort. *Annals of Internal Medicine* **132**, 552-555.
40. Committee on Exercise Testing. (1997). ACC/AHA Guidelines for Exercise Testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* **30**, 260-311.
41. Constanzo, M.R., Augustine, S., Bourge, R., Bristow, M., O'Connell, J.B., Driscoll, D., & Rose, E. (1995). Selection and treatment of candidates for heart transplantation: a statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. *Circulation* **92**, 3593-3612.
42. Cotes, J.E. (1972). Response to progressive exercise: a three-index test. *British Journal of Diseases of the Chest* **66**, 169-184.

-
43. Cotes, J.E., Chinn, D.J., Quanjer, P.H., Roca, J., & Yernault, J.C. (1993). Standardisation of the measurement of transfer factor (diffusion capacity). Report of the Working Party on Standardisation of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *European Respiratory Journal* 6 (Suppl 16), 41-52.
 44. Crapo, R.O., Morris, A.H., & Gardner, R.M. (1981). Reference spirometric values using techniques and equipment that meet **ATS** recommendations. *American Review of Respiratory Disease* 123,659-664.
 45. Crapo, R.O. (1994). Pulmonary-function testing. *The New England Journal of Medicine* 331, 25-30.
 46. Curtis, J.R., Deyo, R.A., & Hudson, L.D. (1994). Pulmonary rehabilitation in chronic respiratory obstructive pulmonary disease. *Thorax* 49, 162-170.
 47. David, R.B., David, F., William, J.G., David, A.L., & Robert, D.L. (1999). Maximal exercise testing for the selection of heart transplantation candidates: Limitation of peak oxygen consumption. *Chest* 115,410-417.
 48. Dec, G.W., & Fuster, V. (1994). Idiopathic dilated cardiomyopathy. *The New England Journal of Medicine* 331, 1564-1575.
 49. Diaz, L.A., Brunken, R.C., Blackstone, E.H., Snader, C.E., & Lauer, M.S. (2001). Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. *Journal of the American College of Cardiology* 37, 1558-1564.
 50. Edwards, **B.S.**, & Rodeheffer, R.J. (1992). Prognostic features in patients with congestive heart failure and selection criteria for cardiac transplantation. *Mayo Clinic Proceedings* 67,485-492.
-

References

51. Ekblom, B., Astrand, P., Saltin, B., Stenberg, J., & Wallstron, B. (1968). Effect of training on circulatory response to exercise. *Journal of Applied Physiology* 24,518-528.
52. Ekelund, L., & Holmgren, A. (1967). Central hemodynamics during exercise. *CirculationResearch* 20 & 21 (Suppl 1), 33-44.
53. Elston, R.C., & William, D. (1994). *Essentials of biostatistics* (2nd ed.). Philadelphia, PA: FA Davis.
54. Enright, P.L., Kronmal, R.A., Higgins, M., Schenker, M., & Haponik, E.F. (1993). Spirometry reference values for women and men 65 to 85 years of age: Cardiovascular Health Study. *American Review of Respiratory Disease* 147, 125-133.
55. Epidemiology and Disease Control Department, Ministry of Health, Singapore. (1998). National Health Survey 1998. *Singapore: Ministry of Health, Singapore*.
56. Erdmann, E. (1998). Digitalis therapy. Relevance of heart rate reduction. *Basic Research in Cardiology* 93 (Suppl 1), 156-159.
57. ERS Task Force on Standardization of Clinical Exercise Testing. (1997). Clinical exercise testing with reference to lung diseases: Indications, standardization and interpretation strategies. *European Respiratory Journal* 10, 2662-2689.
58. European Respiratory Society. (1997). Clinical exercise testing with reference to lung diseases: indications, standardization, and interpretation strategies. *European Respiratory Journal* 10, 2662-2689.

References

59. Evians, R.W., Mannien, D.L., Garrison, L.P., & Maier, A.M. (1986). Donor availability as the primary determinant of the future heart transplantation. *JAMA* 255,1982-1988.
60. Fairbarn, M.S., Blackie, S.P., McElvaney, N.G., Wiggs, B.R., Pare, P.D., & Pardy, R.L. (1994). Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. *Chest* 105, 1365-1369.
61. Ferguson, D.W., Berg, W.J., Sanders, J.S., Roach, P.J., Kempf, J.S., & Kienzle, M.G. (1989). Sympathoinhibitory responses to digitalis glycosides in heart failure patients. *Circulation* **80**, 65-77.
62. Franciosa, J.A., Park, M., & Levine, T.B. (1981). Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *American Journal of Cardiology* **47**, 33-39.
63. Franciosa, J.A., Wilen, M., Ziesche, S., Cohn, J.N. (1983). Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *American Journal of Cardiology* 51, 831-836.
64. Francis, K., McClatchey, P., Sumison, J., & Hansen, D. (1989). The relationship between anaerobic threshold and heart rate linearity during cycle ergometry. *European Journal of Applied Physiology* 54,273-277.
65. Frazier, O.H., & Macris, M.P. (1994). Progress in cardiac transplant. *Surgical Clinics of North America* **74**, 1169-1182.
66. Friedman, G.D., Klatsky, A.L., & Siegelaub, A.B. (1976). Lung function and risk of myocardial infarction and sudden cardiac death. *The New England Journal of Medicine* **294**, 1071-1075.

-
67. Gian, C.M., Gianfranco, L., Marco, G., Giovanni, B.P., & Pier, G.A. (1995). Ultrafiltration in moderate heart failure: Exercise oxygen uptake as a predictor of the clinical benefits. *Chest* **108**, 94-98.
68. Gibbons, R.J., Balady, G.J., Bricker, J.T., Chaitman, B.R., Fletcher, G.F., Froelicher, V.F., Mark, D.B., McCallister, B.D., Mooss, A.N., O'Reilly, M.G., & Winters, W.L. Jr. (2002). ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *Journal of the American College of Cardiology* **30**, 260-315.
69. Gibson, G.J., William, W., & Nikolaos, S. (2002). ATS/ERS Statement on respiratory muscle testing. *American Journal of Respiratory & Critical Care Medicine* **166**, 518-624.
70. Glindmeyer, H.W., Lefante, J.J., McColloster, C., Jones, R.N., & Weill, H. (1995). Blue-collar normative spirometric values for Caucasian and African-American men and women aged 18 to 65. *American Journal of Respiratory & Critical Care Medicine* **151**, 412-422.
71. Griffin, B.P., Shah, P.K., Ferguson, J., Rubin, S.A. (1991). Incremental prognosis value of exercise hemodynamic variables in chronic congestive heart failure secondary to coronary artery disease or dilated cardiomyopathy. *American Journal of Cardiology* **67**, 848-853.
72. Groot, G., Welbergen, E., Clijsen, L., Cabri, J., & Antonis, J. (1994). Power, muscular work and external forces in cycling. *Ergonomics* **37**, 31-42.
73. ¹Guazzi, M. (1999). Hemodynamic interaction of aspirin with enalapril. *Circulation* **100(25)**, 141-142.
-

74. ²Guazzi, M., Pontone, G., & Agostoni, P. (1999). Aspirin worsens exercise performance and pulmonary gas exchange in patients with heart failure who are taking angiotensin-converting enzyme inhibitors. *American Heart Journal* **138**(2), 254-260.
75. Habedank, D., Reindl, I., Vietzke, G., Bauer, U., Sperfeld, A., Glaser, S., Wernecke, K.D., & Kleber, F.X. (1998). Ventilatory efficiency and exercise tolerance in 101 healthy volunteers. *European Journal of Applied Physiology* **77**, 421-426.
76. Hall, D. (2000). The aspirin-angiotensin-converting enzyme inhibitor tradeoff: To halve and halve not. *Journal of the American College of Cardiology* **35**(7), 1808-1812.
77. Hambrecht, R., Gielen, S., Linke, A., Fiehn, E., Yu, J., Walther, C., Schoene, N., & Schuler, G. (2000). Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. *JAMA* **283**, 3095-3101.
78. Hambrecht, R.P., Schuler, G.C., Muth, T., Grunze, M.F., Marburger, C.T., Niebauer, J., Methfessel, S.M., & Kubler, W. (1992). Greater diagnostic sensitivity of treadmill versus cycle exercise testing of asymptomatic men with coronary artery disease. *American Journal of Cardiology* **70**, 141-146.
79. Hamilton, A.L., Killian, K.J., Summers, E., & Jones, N.L. (1995). Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *American Journal of Respiratory & Critical Care Medicine* **152**, 2021-2031.
80. Hankinson, J.L. (1986). Pulmonary function testing in the screening of workers: guidelines for instrumentations, performance, and interpretation. *Journal of Occupational Medicine* **28**, 1081-1092.

References

-
81. Hankinson, J.L., Odencrantz, J.R., & Fedan, K.B. (1999). Spirometric reference values from a sample of the general U.S. population. *American Journal of Respiratory & Critical Care Medicine* **159**, 179-187.
 82. Hansen, J.E., Sue, D.Y., & Wasserman, K. (1984). Predicted values for clinical exercise testing. *American Review of Respiratory Disease* **129 (Suppl)**, S49-S55.
 83. Hansen, J.E., Casaburi, R., Cooper, D.M., & Wasserman, K. (1988). Oxygen uptake as related to work rate increment during cycle ergometer exercise. *European Journal of Applied Physiology* **57**, 140-145.
 84. Hanson, J.E., Sue, D.Y., Oren, A., & Wasserman, K. (1987). Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. *American Journal of Cardiology* **59**, 669-674.
 85. Hermansen, L., Ekblom, B., & Saltin, B. (1970). Cardiac output during submaximal and maximal treadmill and bicycle exercise. *Journal of Applied Physiology* **29**, 82-86.
 86. ¹Herzog, W., Guimaraes, A.C., Anton, M.G., & Carter-Erdman, K.A. (1991). Moment-length relations of rectus femoris muscles of speed skaters/cyclists and runners. *Medicine & Science in Sports Science* **23**, 1289-1296.
 87. ²Herzog, W., Hasler, E., & Abrahamse, S.K. (1991). A comparison of knee extensor strength curves obtained theoretically and experimentally. *Medicine & Science in Sports & Exercise* **23**, 108-114.
 88. Higginbotham, M., Morris, K., Williams, R., McHale, P., Coleman, R., & Cobb, F. (1986). Regulation of stroke volume during submaximal and maximal upright exercise in normal men. *Circulation Research* **58**, 281-291.
-

References

89. Hiroyuki, D., Thomas, G.A., Bruce, D.J., Ray, W.S., & Gerald, T.G. (1996). Further increase in oxygen uptake during early active recovery following maximal exercise in chronic heart failure. *Chest* **109**, 47-51.
90. Hofmann, P., Pokan, R., von Duvillard, S., Siebert, F., Zweiker, R., & Schmid, P. (1997). Heart rate performance curve during incremental cycle ergometer exercise in healthy young male subjects. *Medicine & Science in Sports & Exercise* **29**, 762-768.
91. Hofmann, P., Pokan, R., von Duvillard, S., Siebert, F., Zweiker, R., & Schmid, P. (1997). The Conconi test. *International Journal of Sports Medicine* **18**, 397-399.
92. Hole, D.J., Watt, G.C., Davey-Smith, G., Hart, C.L., Gillis, C.R., & Hawthorne, V.M. (1996). Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* **313**, 711-715.
93. Hsi, W.L., Lan, C., & Lai, J.S. (1998). Normal standards for cardiopulmonary responses to exercise using a cycle ergometer test. *Journal of the Formosan Medical Association* **97**, 315-322.
94. Hutchinson, J. (1846). On the capacity of the lungs, and on the respiratory functions, with view of establishing a precise and easy method of detecting disease by the spirometer. *Medico-Chirurgical Transactions (London)* **29**, 137-161.
95. Idelle, M.W., Darcy, M., Fernando, J.M., Frank, S., Darcy, S., & Jonathan, M. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory & Critical Care Medicine* **167**, 211-277.

96. Ino, T., Okubo, M., Nishimoto, K., Akimotot, K., Yabuta, K., & Okada, R. (1996). Clinicopathologic characteristics of hypertrophic cardiomyopathy detected during mass screening for heart diseases. *Pediatric Cardiology* **17**, 295-300.
97. Jensen, U.M., Bouvier, F., Nejat, M., Saltin, B., & Brodin, L. (1998). Left ventricular function in endurance runners during exercise. *Acta Physiologica Scandinavica* **164**, 167-172.
98. Jones, N.L., Campbell, E.J.M., Edwards, R.H.T, *et al.* (1975). *Clinical exercise testing*. Philadelphia PA, Saunders.
99. Jones, N.L., & Moran, E.J. (1982). *Clinical exercise testing*. W.B. Saunders.
100. Jones, N.L., Makrides, L., Hitchcock, C., Chypchar, T., & McCartney, N. (1985). Normal standards for an incremental progressive cycle ergometer test. *American Review of Respiratory Disease* **131**, 700-708.
101. Jones, N.L. (1997). *Clinical exercise testing* (4th ed.). Philadelphia **PA**, Saunders.
102. Jones, S., Elliot, P.M., Sharma, S., McKenna, W.J., & Whipp, B.J. (1998). Cardiopulmonary responses to exercise in patients with hypertrophic cardiomyopathy. *Heart* **80**, 60-67.
103. Kannel, W.B., Lew, E.A., Hubert, H.B., & Castelli, N.P. (1980). The value of measuring vital capacity for prognostic purposes. *Transactions of the Association of Life Insurance Medical Directors of America* **64**, 66-83.

104. Keteyian, S.J., Levine, A.B., Brawner, C.A., Kataoka, T., Rogers, F.J. Schairer, J.R., Stein, P.D., Levine, T.B., & Goldstein, S.T. (1996). Exercise training in patients with heart failure: a randomized, controlled trial. *Annals of Internal Medicine* 124, 1051-1057.
105. Killian, K.J., Leblanc, P., Martin, D.H., Summers, E., Jones, N.L., & Campbell, E.J. (1992). Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *American Review of Respiratory Disease* 146,935-940.
106. Knudson, R.J., Slatin, R.C., Lebowitz, M.D., & Burrows, B. (1976). The maximal expiratory flow-volume curve: normal standards, variability, and effects of age. *American Review of Respiratory Disease* 113,587-600.
107. Knudson, R.J., Lebowitz, M.D., Holberg, C.J., & Burrows, B. (1983). Changes in the normal maximal expiratory flow-volume curve with growth and aging. *American Review of Respiratory Disease* 127,725-734.
108. Kobashigawa, J.A., Leaf, D.A., Lee, N., Gleeson, M.P., Liu, H., Hamilton, M.A., Moriguchi, J.D., Kawata, N., Einhorn, K., Herlihy, E., Laks, H. (1999). A controlled trial of exercise rehabilitation after heart transplantation. *The New England Journal of Medicine* 340,272-277.
109. Koike, A., & Wasserman, J. (1992). Effect of acute reduction in oxygen transport on parameters of aerobic function during exercise. *Annals Academy of Medicine Singapore* 21, 14-22.
110. Koike, A., Yajima, T., & Adachi, H., Shimizu, N., Kano, H., Sugimoto, K., Niwa, A., Marumo, F., & Hiroe, M. (1995). Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. *Circulation* **91**, 1719-1724.

111. Krum, H., Bigger, T., Rochelle, L., Goldsmith, E.D.D., & Packer, M. (1995). Effect of long term digoxin therapy on automatic function in patients with chronic heart failure. *Journals of the American College of Cardiology* **25**, 189-294.
112. Krzyzanowski, M., & Wysocki, M. (1986). The relation of thirteen-year mortality to ventilatory impairment and other respiratory symptoms: the Cracow study. *International Journal of Epidemiology* **15**, 56-64.
113. Lange, P., Nyboe, J., Appleyard, M., Jensen, G., & Schnohr, P. (1990). Spirometric findings and mortality in never-smokers, *Journal of Clinical Epidemiology* **43**, 867-873.
114. Latini, R., Tognoni, G., Maggioni, A.P., Baigent, C., Braunwald, E., Chen, Z.M., Collins, R., Flather, M., Franzosi, M.G., Kjekshus, J., Køber, L., Liu, L.S., Peto, R., Pfeffer, M., Pizzetti, F., Santoro, E., Sleight, P., Swedberg, K., Tavazzi, L., Wang, W., & Yusuf, S. (2000). Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin. *Journal of the American College of Cardiology* **35**(7), 1801-1807.
115. Lauer, M.S., Okin, P.M., Larson, M.G., Evans, J.C., & Levy, D. (1996). Impaired heart rate response to graded exercise: Prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation* **93**, 1520-1526.
116. Lauer, M.S., Francis, G.S., Okin, P.M., Pashkow, F.J., Snader, C.E., & Marwick, T.H. (1999). Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA* **281**, 524-529.

117. Leandro, P., Jonathan, M., & Rusconi, C. (1999). Recovery kinetics of oxygen uptake and heart rate in patients with coronary artery disease and heart failure. *Chest* 116, 808-813.
118. Leor, J., Reicher-Reiss, H., Goldbourt, U., Boyko, V., Gottlieb, S., Battler, A., & Behar, S. (1999). Aspirin and mortality in patients treated with angiotensin-converting enzyme inhibitors. *Journal of the American College of Cardiology* 33(7), 1920-1925.
119. Linkoff, M.J., Chandler, S.L., & Kay, H.R. (1987). Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *American Journal of Cardiology* 59,634-638.
120. Macklem, P.T., & Permutt, S. (1979). The lung in transition from health to disease. *New York, NY Marcel Dekker*, 394-395.
121. Mancini, D.M., Eisen, H., Kussmaul, W., Mull, R., Edmunds, L.H. Jr., & Wilson, J.R. (1991). Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 83,778-786.
122. Mannino, D.M., Gagnon, R.C., Petty, T.L., & Lydick, E. (2000). Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. *Archives of Internal Medicine* 160, 1683-1689.
123. Marcus, E.B., Curb, J.D., MacLean, C.J., Reed, D.M., & Yano, K. (1989). Pulmonary function as a predictor of coronary heart disease. *American Journal of Epidemiology* 129, 97-104.

124. Massie, B.M., & Teerlink, J.R. (2000). Interaction between aspirin and angiotensin-converting enzyme inhibitors: Real or imagined. *American Journal of Medicine* **109**, 431-433.
125. Matthys, H., Zaiss, A.W., Theissen, J.L., Virchow, J.C.J.R., & Werner, P. (1995). Definition, normal reference and measured values to diagnose obstructive, restrictive and mixed ventilatory defects for clinical lung function evaluation (Translated from German). *Atemwege-lungenkrankheiten* **3**, 130-138.
126. McDonough, J., & Danielson, R. (1974). Variability in cardiac output during exercise. *Journal of Applied Physiology* **37**, 579-583.
127. Meakins, J., & Long, C.N.H. (1927). Oxygen consumption, oxygen debt and lactic acid in circulatory failure. *Journal of Clinical Investigation* **4**, 273-293.
128. Mendenhall, W., Beaver, R.J., & Beaver, B.M. (2003). *Probability and Statistics* (11th ed.). Brooke/Cole-Thomson Learning, Inc.
129. Milani, R.V., Mehra, M.R., Reddy, T.K., Lavie, C.J. & Ventura, H.O. (1996). Ventilation/carbon dioxide production ratio in early exercise predicts poor function capacity in congestive heart failure. *Heart* **76**, 393-396.
130. Milic-Emili, J., Marazzini, L., & D'Angelo, E. (1997). 150 years of blowing: since John Hutchinson. *Canadian Respiratory Journal* **4**, 239-245.
131. Miller, L.W., Kubo, S.H., Young, J.B., Stevenson, L.W., Loh, E., & Costanzo, M.R. (1995). *Medical management of heart and lung failure and candidate selection: report of the Consensus Conference on Candidate Selection for Heart Transplant* **14**, 562-571.

References

132. Morris, J.F., Koski, A., & Johnson, L.C. (1971). Spirometric standards for healthy non-smoking adults. *American Review of Respiratory Disease* **103**, 57-67.
133. Mulieri, L.A., Hasenfuss, G., Leavitt, B., Allen, P.D., & Alpert, N.R. (1992). Altered myocardial force-frequency relation in human heart failure. *Circulation* **85**, 1743-1750.
134. Myers, J., Buchanan, N., & Walsh, D., Kraemer, M., Mcauley, P., Hamiltonwessler, M., & Froelicher, V.F. (1991). Comparison of the ramp versus standard exercise protocols. *Journal of the American College of Cardiology* **17**, 1334-1342.
135. Myers, J., Gullestad, L., Vagelos, R., Do, D., Bellin, D., Ross, H., & Fowler, M.B. (1998). Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Annals of Internal Medicine* **129**, 286-293.
136. Nawarskas, J.J., & Spinler, S.A. (2000). Update on the interaction between aspirin and angiotensin-converting enzyme inhibitors. *Pharmacotherapy* **20**(6), 698-710.
137. Neas, L.M., & Schwartz, J. (1998). Pulmonary function levels as predictors of mortality in a national sample of US adults. *American Journal of Epidemiology* **147**, 1011-1018.
138. Neder, J.A., Nery, L.E., Castelo, A., Andreoni, S., Lerario, M.C., Sachs, A., Silva, A.C., & Whipp, B.J. (1999). Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: A randomised study. *European Respiratory Journal* **14**, 1304-1313.

139. Neder, J.A., Nery, L.E., Peres, C., & Whipp, B.J. (2001). Reference values for dynamic responses to incremental cycle ergometry in males and females aged 20 to 80. *American Journal of Respiratory & Critical Care Medicine* **164**, 1481-1486.
140. Nisco, S.J., & Reitz, B.A. (1994). Developments in cardiac transplantation. *Current Opinion in Cardiology* **9**, 237-246.
141. Nishime, E.O., Cole, C.R., Blackstone, E.H., Pashkow, F.J., & Lauer, M.S. (2000). Heart rate recover and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* **284**, 1392-1398.
142. Nohria, A., Eldrin, L., & Warner, S.L. (2002). Medical management of advanced heart failure. *JAMA* **287**, 628-639.
143. O'Donnell, D.E., & Webb K.A. (1992). Breathlessness in patients with severe chronic airflow limitation: physiologic correlations. *Chest* **102**, 824-831.
144. O'Donnell, D.E. (1994). Breathlessness in patients with chronic airflow limitation: mechanisms and management. *Chest* **106**, 904-912.
145. Osada, N., Chaitman, B.R., Miller, L.W., Yip, D., Cishek, M.B., Wolford, T.L., & Donohue, T.J. (1998). Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. *Journal of the American College of Cardiology* **31**, 577-582.
146. Pardaens, K., Van Cleemput, J., Vanhaecke, J., & Fagard, R.H. (2000). Peak oxygen uptake better predicts outcome than submaximal respiratory data in heart transplant candidates. *Circulation* **101**, 1152-1157.

147. Pechat, P. (1998). Beta-blocker treatment in heart failure. Role of heart rate reduction. *Basic Research in Cardiology* 93 (Suppl 1), 148-155.
148. Pelliccia, A. (2000). Athlete's heart and hypertrophic cardiomyopathy. *Current Cardiology Reports* 2(2), 166-171.
149. Peters, R.K., Cady, L.D. Jr., Bischoff, D.P., Bernstein, L., & Pike, M.C. (1983). Physical fitness and subsequent myocardial infarction in healthy workers. *JAMA* 249,3052-3056.
150. Peterson, J.G., Topol, E.J., Sapp, S.K., Young, J.B., Lincoff, A.M., & Lauer, M.S. (2000). Evaluation of the effects of aspirin combined with angiotensin-converting enzyme inhibitors in patients with coronary artery disease. *American Journal of Medicine* 109,371-377.
151. Petty, T.L. (2002). John Hutchinson's mysterious machine revisited. *Chest* 121, 219S-223S.
152. Piña, I.L. (1995). Optimal candidates for heart transplantation: is 14 the magic number? *Journal of the American College of Cardiology* 26,436-437.
153. Piña, I.L., Balady, G.J., Hanson, P., Labovitz, A.J., Madonna, D.W., & Myers, J. (1995). Guidelines for clinical exercise testing laboratories: A statement for healthcare professionals from the committee on exercise and cardiac rehabilitation, American Heart Association. *Circulation* 91, 912-921.
154. Pokan, R., Hofmann, P., Preidler, K., Leitner, H., Dusleag, J., Eber, B., Schwaberg, G., Fuger, G., & Klein, W. (1993). Correlation between inflection of heart rate/work performance curve and myocardial function in exhausting cycle ergometer exercise. *European Journal of Applied Physiology* 67, 385-388.

References

-
155. Quanjer, H., Tammeling, G.J., Cotes, J.E., Pederson, O.F., Peslin, R., & Yernault, J.C. (1993). Lung volumes and forced ventilatory flows. Report of the Working Party on Standardization of Lung Function Tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. *European Respiratory Journal* 6 (Suppl 16), 5-40.
 156. Ramos-Barbón, D., Fitchett, D., Gibbons, W.J., Latter, D.A., & Levy, R.D. (1999). Maximal exercise testing for the selection of heart transplant candidates: Limitation of peak oxygen consumption. *Chest* 115,410-417.
 157. Regina, A. (2000). *The circulatory system*. Chelsea House Publisher.
 158. Renzetti, A.D., Bleecker, E.R., Epler, G.R., Jones, R.N., Kanner, R.E., & Repsher, L.H. (1986). Evaluation of impairment/disability secondary to respiratory disorders. *American Review of Respiratory Disease* 133, 1205-1209.
 159. Reybrouck, T., Mertens, L., Schulze-Neick, I., Austenat, I., Eysken, B., Dumoulin, M., & Gewillig, M. (1998). Ventilatory inefficiency for carbon dioxide during exercise in patients with pulmonary hypertension. *Clinical Physiology* 18,337-344.
 160. Richard, C., Darcy, M., Ken, B., Jorge, Z., George, S., Jonathan, M., & Frank, S. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory & Critical Care Medicine* 167, 211-277.
 161. Robert, S.P., & Daniel, L.R. (1991). *Econometric models and economic forecasts* (3rd ed.). McGraw-Hill, Inc.
 162. Roberts, C.M., MacRae, K.D., Winning, A.J., Adams, L., & Seed, W.A. (1991). Reference values and prediction equations for normal lung function in a non-smoking white urban population. *Thorax* 46,643-650.
-

163. Roca, J., Sanchis, J., Agusti-Vidal, A., Segarra, F., Navajas, D., Rodriguez-Roisin, R., Casan, P., & Sans, S. (1986). Spirometric reference values for a Mediterranean population. *Bulletin Européen de Physiopathologie Respiratoire* 22,217-224.
164. Roca, J., Burgos, F., Sunyer, J., Saez, M., Chinn, S., Antó, J.M., Rodriguez-Roisin, R., Quanjer, P.H., Nowak, D., & Burney, P. (1998). Reference values for forced spirometry. *European Respiratory Journal* 11, 1354-1362.
165. Rodeheffer, R.J, & McGregor, C.G.A. (1992). The development of cardiac transplantation. *Mayo Clinic Proceedings* 67,480-484.
166. Ross, A., Jonathon, M., Syed, S.A., Elsa, B.V., & Mary, A.P. (2003). Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. *Chest* 124,720-727.
167. Ruhle, K.H., & Mattys, H. (1976). Critical selection of normal values for a computer program in the evaluation of lung function (Translated from German). *Pneumologie* 153,223-233.
168. Saltin, B., & Grimby, G. (1968). Physiological analysis of middle-aged and old former athletes. *Circulation* 38, 1104-1115.
169. Schlant, R.C., Friesinger, G.C. II, & Leonard, J.J. (1990). Clinical competence in exercise testing: A statement for physicians from the ACP/ACC/AHA Task Force on clinical privileges in cardiology. *Journal of the American College of Cardiology* 16, 1061-1065.
170. Schunemann, H.J., Dorn, J., Grant, B.J.B., Winkelstein, W. Jr., & Trevisan, M. (2000). Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 118, 656-664.

References

171. Sherman, C.B., Kern, D., Richardson, E.R, Hubert, M., & Fogel, B.S. (1993). Cognitive function and spirometry performance in the elderly. *American Review of Respiratory Disease* **148**, 123-126.
172. Shetler, K., Marcus, R., & Froelicher, V.F., Vora, S., Kalisetti, D., Prakash, M., Do, D., & Myers, J. (2001). Heart rate recovery: Validation and methodological issues. *Journal of the American College of Cardiology* **38**, 1980-1987.
173. Sietsema, K.E., Ben-Dov, I., Zhang, Y.Y., Sullivan, C., & Wasserman, K. (1994). Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. *Chest* **105**, 1693-1700.
174. Skillrud, D.M., Offord, K.P., & Miller, R.D. (1986). Higher risk of lung cancer in chronic obstructive pulmonary disease: a prospective, matched, controlled study. *Annals of Internal Medicine* **105**, 503-527.
175. Solal, A.C., Chabernaude, J.M., & Gourgon, R. (1990). Comparison of oxygen uptake during bicycle exercise in patients with chronic heart failure and normal subjects. *Journals of the American College of Cardiology* **16**, 80-85.
176. Song, K.H., Fedyk, R., & Hoover, R. (1999). Interaction of ACE inhibitors and aspirin in patients with congestive heart failure. *The Annals of Pharmacotherapy* **33(3)**, 375-377.
177. Spaulding, C., Charbonnier, B., Cohen-Solal, A., Juillière, Y., Kromer, E.P., Benhamda, K., Cador, R., & Weber, S. (1997). Acute hemodynamic interaction of aspirin and ticlopidine with enalapril: Results of a double-blind, randomized comparative trial. *Circulation* **96 (Suppl I)**, 1-523.
178. Spence, A.P., & Moran, E.B. (1992). *Human anatomy and physiology* (4th ed.). St Paul MN West.

179. Spiro, S.G., Juniper, E., Bowman, P., & Edwards, R.H. (1974). An increasing work rate test for assessing the physiological strain of submaximal exercise. *Clinical Science*
-

187. Sue, D.Y., & Wasserman, K. (1991). Impact of integrative cardiopulmonary exercise testing on clinical decision making. *Chest* 99, 981-992.
188. Sugrue, D.D., Rodeheffer, R.J., Codd, M.B., Ballard, D.J., Fuster, V., & Gersh, B.J. (1992). The clinical course of idiopathic dilated cardiomyopathy: a population-based study. *Annals of Internal Medicine* 117, 117-123.
189. Sullivan, M.J., Higginbotham, M.B., & Cobb, F.R. (1989). Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation* 79, 324-329.
190. Swanney, M.P., Jensen, R.L., Crichton, D.A., Beckert, L.E., Cardno, L.A., & Crapo, R.O. (2000). FEV₆ is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. *American Journal of Respiratory & Critical Care Medicine* 162, 917-919.
191. Swynghedauw, B., Jasson, S., Clairambault, J., Chevalier, B., Heymes, C., Medigue, C., Carre, F., & Mansier, P. (1997). Myocardial determinants in regulation of the heart rate. *Journal of Molecular Medicine* 75, 860-866.
192. Szlachcic, J., Masse, B.M., Kramer, B.L., Topic, N., & Tubau, J. (1985). Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *American Journal of Cardiology* 55, 1037-1042.
193. Tanabe, Y., Takahashi, M., Hosaka, Y., Ito, M., Ito, E., & Suzuki, K. (2000). Prolonged recovery of cardiac output after maximal exercise in patients with chronic heart failure. *Journal of the American College of Cardiology* 35, 1228-1236.
194. Teerlink, J.R., & Massie, B.M. (1999). The interaction of ACE inhibitors and aspirin in heart failure: torn between two lovers. *American Heart Journal* 138(2 Pt 1), 193-197.

195. Tockman, M.S., Anthonisen, N.R., Wright, E.C., & Donithan, M.G. (1987). Airways obstruction and the risk for lung cancer. *Annals of Internal Medicine* 106,512-518.
196. Ulmer, W.T., Reichel, G., Nolte, D., & Islam, M.S. (1991). *Lungfunction* (5th ed.) (Translated from German). Thieme, Stuttgart.
197. Waagstein, F., Hjalmarson, A., Varnauskas, E., & Wallentin, I. (1975). Effect of chronic beta-adrenergic receptor blockage in congestive cardiomyopathy. *British Heart Journal* 37, 1022-1036.
198. Wasserman, K., Whipp, B.J., Casaburi, R., Golden, M., & Beaver, W.L. (1979). Ventilatory control during exercise in man. *Bulletin Européen Physiopathologie Respiratoire* 15, 27-51.
199. Wasserman, K., Hansen, J.E., Sue, D.Y., Whipp, B.J., & Casaburi, R. (1994). *Principles of exercise testing and interpretation, and education*. Philadelphia, PA. Lea & Febiger.
200. Wasserman, K., Hansen, J.E., Sue, D.Y., Whipp, B.J., & Casaburi, R. (1999). *Principles of exercise testing and interpretation: including pathophysiology and clinical applications* (3rd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.
201. Watanabe, J., Thamilarasan, M., Blackstone, E.H., Thomas, J.D., & Lauer, M.S. (2001). Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: The cases of stress echocardiography. *Circulation* 104, 1911-1916.
202. Weber, K.T., & Janicki, J.S. (1986). *Cardiopulmonary exercise testing: physiologic principles and clinical applications*. Philadelphia, PA: W.B. Saunders.

203. Weiner, D.A., Ryan, T.J., Parsons, L., Fisher, L.P., Chaitman, B.R., Sheffield, L.T., & Tristani, F.E. (1995). Long-term prognostic value of exercise testing in men and women from the Coronary Artery Surgery Study (CASS) registry. *American Journal of Cardiology* **75**, 865-870.

 204. Weisman, I.M., & Zeballos, R.J. (1994). An integrated approach to the interpretation of cardiopulmonary exercise testing. *Clinics in Chest Medicine* 15,421-445.

 205. Weisman, I.M., & Zeballos, R.J. (1995). Cardiopulmonary exercise testing. *Pulmonary & Critical Care Update* **11**,1-9.

 206. Weisman, I.M., & Zeballos, R.J. (2001). Clinical exercise testing. *Clinics in Chest Medicine* 22,679-701.

 207. Whipp, B.J., Higgenbotham, M.B., & Cobb, F.C. (1996). Estimating exercise stroke volume from asymptotic oxygen pulse in humans. *Journal of Applied Physiology* 81,2674-2679.

 208. Wicks, J.R., Sutton, J.R., Oldridge, N.B., & Jones, N.L. (1978). Comparison of the electrocardiographic changes induced by maximum exercise testing with treadmill and cycle ergometer. *Circulation* **57**, 1066-1070.

 209. Williams, J.F. Jr., Bristow, M.R., & Fowler, M.B., Francis, G.S.,
-

References

210. Wilson, J.R., Rayos, G., Yeoh, T.K., Gothard, P., & Bak, K. (1995). Dissociation between exertional symptoms and circulatory function in patients with heart failure. *Circulation* **92**, 47-53.
211. Wilson, J.R., Rayos, G., Yeoh, T.K., & Gothard, P. (1995) Dissociation between peak exercise oxygen consumption and hemodynamic dysfunction in potential heart transplant candidates. *Journal of the American College of Cardiology* **26**, 429-435.
212. Winter, U.J., Fritsch, J., Gitt, A.K., Pothoff, G., Berger, P.G., & Hilger, H.H. (1994). Methodologic and clinical comparison of four different ergospirometry systems. *Zeitschrift für Kardiologie* **83**, 27-36.
213. Wyndham, C., Strydom, N., Maritz, J., Morrison, J., Peter, J., & Potgieter, Z. (1959). Maximum oxygen intake and maximum heart rate during strenuous work. *Journal of Applied Physiology* **14**, 927-936.
214. Zibrak, J.D., O'Donnell, C.R., & Marton, K. (1990). Indications for pulmonary function testing. *Annals of Internal Medicine* **112**, 763-771.

CONTRAINDICATIONS

Absolute:

1)	Acute febrile illness	Yes/No
2)	Acute ECG changes of myocardial ischemia	Yes/No
3)	Uncontrolled heart failure	Yes/No
4)	Pulmonary edema	Yes/No
	Unstable angina	Yes/No
	Acute myocarditis, pericarditis	Yes/No
	Uncontrolled hypertension (> 250mmHg systolic, 120mmHg diastolic)	Yes/No
	Uncontrolled asthma	Yes/No

Relative:

1)	Recent (<4 weeks) myocardial infarction	Yes/No
2)	Aortic valve disease	Yes/No
3)	Resting tachycardia (heart rate > 120/min)	Yes/No
4)	Severe electrolyte disturbances	Yes/No
5)	Thromboembolic disorders	Yes/No
6)	Poorly controlled diabetes	Yes/No
7)	Epilepsy	Yes/No
8)	Cerebrovascular disease	Yes/No
9)	Respiratory failure	Yes/No

210. Wilson, J.R., Rayos, G., Yeoh, T.K., Gothard, P., & Bak, K. (1995). Dissociation between exertional symptoms and circulatory function in patients with heart failure. *Circulation* **92**, 47-53.
211. Wilson, J.R., Rayos, G., Yeoh, T.K., & Gothard, P. (1995) Dissociation between peak exercise oxygen consumption and hemodynamic dysfunction in potential heart transplant candidates. *Journal of the American College of Cardiology* **26**, 429-435.
212. Winter, U.J., Fritsch, J., Gitt, A.K., Pothoff, G., Berger, P.G., & Hilger, H.H. (1994). Methodologic and clinical comparison of four different ergospirometry systems. *Zeitschrift für Kardiologie* **83**, 27-36.
213. Wyndham, C., Strydom, N., Maritz, J., Morrison, J., Peter, J., & Potgieter, Z. (1959). Maximum oxygen intake and maximum heart rate during strenuous work. *Journal of Applied Physiology* **14**, 927-936.
214. Zibrak, J.D., O'Donnell, C.R., & Marton, K. (1990). Indications for pulmonary function testing. *Annals of Internal Medicine* **112**, 763-771.

Evaluation Form

NAME:

REF NO:

DATE:

DIAGNOSES 1) _____
 2) _____

INDICATIONS FOR
EXERCISE TEST

A. Exercise Protocol

Ergometer	Cycle	Treadmill
Calculated Work Rate Increment	Watts/min	Gradient/min

B. Ratings of perceived exertion (0-9)

Time (min)	Scale	Time (min)	Scale	Time (min)	Scale
1		6		11	
2		7		12	
3		8		13	
4		9		14	
5		10		15	

C. BP & ECG recordings every 3 minutes

Time (min)	BP (mmHg)	ECG
0		
3		
6		
9		
12		
15		

D. CONSENT Y/N

E. RESTING DATA

- 1) FEV1 _____
FVC _____
FEV 1/FVC _____
MVV _____

2) 12-lead ECG (>40 years old) Normal/Abnormal

STUDY 1 (SPIROMETRY DATA INTERPRETATION & REPRESENTATION) RESULTS

Normal

Subject: C01

Subject: C02

Subject: C03

Subject: C05

Subject: C06

Subject: C12

Subject: C13

Subject: C14

Subject: C15

Subject: C19

Subject: C20

Subject: C21

Appendix C

Subject: C22

Subject: C26

Subject: C29

Subject: C33

Subject: C34

Subject: C38

Appendix C

Subject: C40

Subject: C42

Subject: C44

Subject: C46

Subject: C47

Subject: C54

Appendix C

Subject: C55

Subject: C56

Subject: C60

Subject: C61

Mild Obstructive

Subject: C31

Subject: C36

Mild Restrictive

Subject: C04

Subject: C07

Subject: C08

Subject: C10

Subject: C16

Subject: C17

Appendix C

Subject: C18

Subject: C30

Subject: C32

Subject: C35

Subject: C39

Subject: C41

Appendix C

Subject: C50

Subject: C51

Subject: C53

Subject: C57

Subject: C58

Subject: C62

Moderate Restrictive

Subject: C09

Subject: C24

Subject: C25

Subject: C59

Severe Restrictive

Subject: C11

Mild Obstructive & Restrictive

Subject: C27

Subject: C43

Subject: C45

Appendix C

Moderate Obstructive & Restrictive

Subject: C23

Severe Obstructive & Restrictive

Subject: C28

Severe Obstructive & Moderate Restrictive

Subject: C37

Moderate Obstructive & Severe Restrictive

Subject: C48

Possible Borderline Obstructive

Subject: C49

Subject: C52

STUDY 2 (DATA INTERPRETATION & REPRESENTATION OF CPET)
RESULTS

Normal

Subject: B10

Subject: B27

Subject: B29

Appendix D

Subject: B46

Subject: B61

Subject: B69

Subject: B78

Subject: B80

Subject: B89

Appendix D

Subject: B93

Subject: B98

Subject: C02

Subject: C06

Subject: C08

Subject: C14

Appendix D

Subject: C21

Subject: C25

Subject: C33

Subject: C34

Subject: C40

Subject: C43

Cardiomyopathy

Subject: B03

Subject: B04

Subject: B23

Subject: B33

Subject: B75

Subject: B85

Appendix D

Subject: C01

Subject: C03

Subject: C05

Subject: C07

Subject: C11

Subject: C17

Appendix D

Subject: C18

Subject: C19

Subject: C29

Subject: C32

Subject: C35

Subject: C38

Appendix D

Subject: C44

Subject: C49

Subject: C50

Subject: C53

Subject: C54

Subject: C62

CONFERENCE

IBEC (1st International BioEngineering Conference) 2004
in conjunction with
6th Annual NTU-SGH Biomedical Engineering Symposium 2004
BioEngineering: Challenges and Innovations
September 8, 9 and 10, 2004
Marina Mandarin, Singapore

Graphical Technique for Assessing Pulmonary Disease

K. C. Ang¹, J. H. Ong¹, D. N. Ghista¹, G. H. Lim¹, C. M. Loo²,

¹School of Mechanical and Production Engineering, Nanyang Technological University, Singapore

²Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore

Abstract— This paper introduces a simple graphical technique to facilitate the decision-making process for assessing pulmonary diseases. 62 patients (Mean age: 47 years, SD: 17 years) were randomly selected from patients who completed cardiopulmonary exercise test in the Pulmonary Function Laboratory of the Singapore General Hospital. 3 normalised respiratory data are plotted on a 3-axes planar space to form a triangle. The area of the triangle depicts the pulmonary state of the patient. At the same time, the skewness of the triangle towards particular axis is an indication of the obstructive/restrictive nature of the abnormality. In comparison to the doctor’s diagnosis, the sensitivity and specificity of this graphical technique is 100% and 74% respectively. The predictive accuracy is 71% positive and 100% negative. Hence, this graphical technique can successfully differentiate pulmonary diseases from normal subjects, and allows the obstructive/restrictive nature of the abnormality to be easily visualised.

Keywords—Spirometry, Vital Capacity, Pulmonary Disease

I. INTRODUCTION

Spirometry test is normally used for obtaining data on forced expired volume in 1 second (FEV₁) and forced vital capacity (FVC) as markers of pulmonary disease. These vital capacities are deemed to be the most powerful prognostic indicators of respiratory abnormalities [1]. Patients are assessed by comparing their spirometry measurements with predicted values [2,3]. These predicted values are formulated based on sex, age, height and weight. The predicted values of spirometry [4] were adjusted with Asian correction. Based on this comparison, a diagnostic flow chart (Fig. 1) enables designation of normal, possible borderline obstructive, mild obstructive, moderate obstructive, severe obstructive, mild restrictive, moderate restrictive, severe restrictive and mixed obstructive and restrictive conditions. However, clinicians may find that the decision process from the flow chart cumbersome and subjective. Therefore, a graphical way encompassing the decision process and analysis is required.

Fig. 1. Spirometry Flow Chart.

II. METHODOLOGY

The 3 normalised respiratory data, P_1 , P_2 , P_3 are defined as

$$P_1 = FVC \text{ (Measured)} / FEV_1 \text{ (Measured)} \quad (1)$$

$$P_2 = FEV_1 \text{ (Measured-Predicted)} / \text{Predicted} * 10 \quad (2)$$

$$P_3 = FVC \text{ (Measured-Predicted)} / \text{Predicted} * 10 \quad (3)$$

are plotted on a 3-axes planar space (Fig. 2). These 3 respiratory data form a triangle. Based on the classification of severity as defined in the flow chart (Fig. 1), the boundaries of normal, mild, moderate and severe can be illustrated as a series of triangles. Therefore, the area of the triangle depicts the pulmonary condition. At the same time, the skewness of the triangle towards particular axes indicates obstructive/restrictive nature of abnormality. To further enhance the visual representation, different colours, i.e. blue for normal, light blue for mild pulmonary problem, pink for moderate for moderate pulmonary problem, and red for severe pulmonary problem are incorporated. Fig. 3 illustrates the colours based on the boundaries of different classifications. Thus, the degree of severity of pulmonary disease is clearly discerned in the colour codes.

Fig. 2. Parametric Coordinates Triangle.

Spirometry (All Conditions)

Fig. 3. Parametric coordinate triangles for 'normal' and 'pulmonary diseases (Mild, Moderate and Severe)' subjects.

III. RESULTS

62 patients (Mean age: 47 years, SD: 17 years) were randomly selected having completed cardiopulmonary exercise test in the Pulmonary Function Laboratory of the Singapore General Hospital. All patients had their spirometry test as part of their assessment prior to the exercise stress test [5]. Spirometry was performed at rest with patient sitting and breathing room air using Jaeger GmbH CompactLab and MasterLab equipment. These subjects gave negative replies to simplified medical form regarding medication that might affect their results.

Subjects with obstructive problem have FEV_1/FVC index values range as 1.34 to 5.00; FEV_1 (normalised) values range as: 0.00 to 1.90 for possible borderline obstruction, 1.91 to 4.00 for mild condition, 4.01 to 5.90 for moderate condition, and 5.91 to 8.00 for severe condition.

Normal subjects (not having obstructive problems) have FEV_1/FVC index values ranging from 0.00 to 1.33, and FEV_1 (normalised) values ranging from 0.00 to 1.90. Subjects with restrictive problem have FVC (normalised) values ranging from: 1.91 to 4.00 for mild condition, 4.01 to 4.90 for moderate condition, and 4.91 to 8.00 for severe condition. Normal subjects not having restrictive problem have FVC (normalised) values ranging from 0.00 to 1.90. Examples of the graphical representation for normal and abnormal conditions are shown in Figs. 4-10.

In comparison to the doctor's diagnosis, the sensitivity and specificity of this graphical technique is 100% and 74% respectively. The predictive accuracy is 71% positive and 100% negative.

Fig. 4 : Parametric coordinates triangle for a 'normal' subject

Fig. 7 : Parametric coordinates triangle for a 'severe obstructive' subject

Fig. 5 : Parametric coordinates triangle for a 'mild obstructive' subject

Fig. 8 : Parametric coordinates triangle for a 'mild restrictive' subject

Fig. 6 : Parametric coordinates triangle for a 'moderate obstructive' subject

Fig. 9 : Parametric coordinates triangle for a 'moderate restrictive' subject

#C11

Fig. 10 : Parametric coordinates triangle for a 'severe restrictive' subject

IV. DISCUSSION

It is shown that the area of the $P_1P_2P_3$ (parametric) triangle is directly proportional to the severity of obstructive or restrictive subjects. The biggest $P_1P_2P_3$ triangle is associated with the most severe obstructive or restrictive problem in the given template. An advantage of this graphical technique is that the skewness of the particular axis indicates obstructive/restrictive nature of abnormality, whereby severity stages of that specific condition can be easily visualised at a glance. The skewness towards P_3 axis indicates obstructive abnormality, while the skewness towards P_2 axis indicates restrictive abnormality. Thereby, a simple graphical depiction of non-dimensional indices is employed to characterise pulmonary disease. Furthermore, this simple assessment can be employed in a progressive follow-up management of pulmonary disease. As pulmonary disease worsens from mild to moderate or moderate to severe, the $P_1P_2P_3$ grows noticeably and also changes colour. This depiction also makes it convenient for the patients to track their condition.

V. CONCLUSION

This graphical technique successfully differentiates pulmonary disease from normal subjects, and allows the obstructive/restrictive nature of the abnormality to be easily visualized. Hence, it facilitates the decision-making process from the flow chart.

REFERENCES

[1] X. Baur, S. Isringhausen-Bley, and P. Degens, *Comparison of lung-function reference values*. *Int Arch Occup Environ Health*, 72, pp. 69-83, 1999.

[2] G. Baltopoulos, G. Fildisis, G. Karatzas, F. Georgiakodis, and P. Myriantheis, *Reference values and predicted equations for FVC and FEV₁ in the Greek elderly*. *Lung*, 178, pp. 201-12, 2000.

[3] *Evaluation of impairment, disability secondary to respiratory disorders*, American Thoracic Society. *Am Rev Resp Dis*, 133, pp. 1205-9, 1986.

[4] R. J. Knudson, et al, *The Maximal Expiratory Flow-Volume Curve Normal Standards, Variability, and Effects of Age*. *Am Rev Resp Dis*, 113, pp. 589-90, 1976.

[5] N. L. Jones, and E. J. Moran, *Clinical exercise testing (2nd Ed.)*, W. B. Saunders, 1982.