HEART FAILURE AND RESPIRATORY MUSCLE STRENGTH

by

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Abstract

People with congestive heart failure (HF) frequently suffer from dyspnea. Transplantation offers a treatment for heart failure. To investigate the role of the respiratory muscles in dyspnea, respiratory muscle strength ($P_I$max, P_E max), maximal exercise capacity (peak VO_2), six-minute walk test (6-MWT) performance, quadriceps strength, and quality of life (QOL) were evaluated in subjects with severe HF (n=15) and post heart transplantation (TX, n=16). Peak VO_2, 6-MWT distance, and QOL were all significantly higher in the TX group. There was no significant difference between the groups for either $P_I$max (HF:113% predicted vs TX:103% predicted) or $P_E$max (HF:90% predicted vs TX:94% predicted). No significant correlations were detected between the outcome measures and $P_I$max or P_E max. These results suggest that while heart transplantation is associated with improved exercise capacity, functional mobility, and quality of life, respiratory muscle strength remains unchanged, and thus may not be a mechanism for dyspnea in HF.

Key Words: *respiratory muscle strength, heart failure, heart transplant*

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List of Abbreviations

Abbreviation	Long Form
6-MWT	six-minute walk test
AMC	age-matched control
ANOVA	analysis of variance
CHF	congestive heart failure
CI	cardiac index
CPAP	continuous positive airway pressure
DCM	dilated cardiomyopathy
DI	Dyspnea Index
FVC	forced vital capacity
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
HF	heart failure
IHD	ischemic heart disease
LVEF	left ventricular ejection fraction
MSVC	maximal sustainable ventilatory capacity
MVV	maximal voluntary ventilation
NYHA	New York Heart Association
Pdi	transdiaphragmatic pressure
Pe	esophageal pressure
Pg	gastric pressure
P_Emax	maximal expiratory pressure
P_Imax	maximal inspiratory pressure
$\dot{V}O_2$	oxygen consumption
QOL	quality of life
RPB	rating of perceived breathlessness
RV	residual volume
TLC	total lung capacity
TTIdi	tension-time index of the diaphragm
TTMUS	tension-time index of the inspiratory muscles
TX	post heart transplantation

Chapter 1

Introduction

Congestive heart failure (CHF) is a common clinical syndrome characterized by a progressive decline in myocardial contractility such that the cardiac output becomes inadequate to meet the body's metabolic requirements (Klainer, 1965). Exertional dyspnea and fatigue are common complaints in patients with CHF, limiting exercise capacity and potentially decreasing quality of life (McKelvie et al., 1995). The mechanism underlying these symptoms however, remains unclear (Mancini, 1995). Several investigators have suggested that respiratory abnormalities in CHF, including respiratory muscle weakness, may result in dyspnea (Hammond et al., 1990; McParland et al., 1992). The histochemical, metabolic and vascular abnormalities found in the limb muscles of CHF patients may also exist in the respiratory muscles and thereby cause dysfunction (Harrington and Coats, 1997). Whether these abnormalities are a consequence of impaired cardiac output resulting in muscle ischemia is uncertain.

Due to pulmonary edema, CHF patients often present with restrictive ventilatory deficits and decreased diffusion capacity of the lung (Naum et al., 1992; Bussières et al., 1995). Respiratory muscle weakness has also been reported in several studies (Hammond et al., 1990; McParland et al., 1992; Ambrosino et al., 1994; Nishimura et al., 1994; Evans et al., 1995; Nanas et al., 1999). Interpretation of these latter results is difficult since most of the investigators report comparisons of absolute rather than normalized values which fail to

account for the influence of age, gender and height on the outcomes measured. A few investigators (Evans et al., 1995; Nanas et al., 1999) have demonstrated a significant decrease in both maximal inspiratory ($P_I$max) and maximal expiratory pressure ($P_E$max) in HF when normalizing the values while a study by Mancini et al. (1992) reported no difference. Some of the controversy in the literature may be explained by the recent understanding that the degree of heart failure (New York Heart Association (NYHA) class III or IV) may be a determining factor in respiratory muscle strength (Ambrosino et al., 1994; Nishimura et al., 1994).

A relationship between dyspnea and respiratory muscle function may exist, although once again the available studies are not consistent. Mancini et al. (1992a) demonstrated a close relationship between the sensation of dyspnea as measured by the Borg scale and $P_I$max, $P_E$max, the forced expiratory volume in one second (FEV_1), and tension-time index of the diaphragm (TTIdi). Likewise, McParland et al. (1992) demonstrated a relationship between both $P_I$max and $P_E$max and dyspnea in heart failure subjects as scored by the Dyspnea Index (DI). When the DI was used to assess dyspnea during activity, further significant correlations were demonstrated with $P_I$max and P_E max (McParland et al., 1992). Conversely, Evans et al. (1995) demonstrated no relationship between a Borg breathlessness score and either $P_I$max or $P_E$max.

The relationship between respiratory muscle strength and exercise capacity or indices of heart failure remains unclear. Most investigators (Nishimura et al., 1994; Chua et al., 1995; Dimopoulou et al., 1999; Nanas et al., 1999) have demonstrated a significant relationship

between $P_I$max at rest and peak oxygen consumption (peak $\dot{V}O_2$) although one study (Witt et al., 1997) reported no relationship. No relationship however was established between $P_E$max and peak $\dot{V}O_2$ (Chua et al., 1995; Witt et al., 1997; Dimopoulou et al., 1999; Nanas et al., 1999). One study (Nishimura et al., 1994) also demonstrated a relationship in heart failure between cardiac index (CI) and $P_I$max as a percent predicted value although no relationship was reported by Ambrosino et al. (1995) between CI and $P_I$max when expressed as an absolute measure. Investigators (Ambrosino et al., 1995; Witt et al., 1997) have been unable to demonstrate a relationship between either $P_I$max or $P_E$max and NYHA class or left ventricular ejection fraction (LVEF).

Investigations into the relationship between skeletal muscle weakness and respiratory muscle function in patients with CHF, have also produced variable results (Chua et al., 1995; Evans et al., 1995; Mancini et al., 1992c). Evans et al. (1995) demonstrated that hand grip strength was significantly related to Pdi and cardiac output but not to exercise capacity in this population. McParland et al. (1995) also reported no significant relationship between respiratory muscle strength and hand grip strength, with the exception of $P_E$max measured at functional residual capacity in CHF. Likewise, Walsh et al. (1996) reported no relationship between respiratory muscle endurance and grip strength. Additionally, quadriceps strength, although significantly reduced in patients with heart failure, was not correlated with $P_I$max (Chua et al., 1995).

Orthotopic cardiac transplantation for end-stage heart failure is now a routine alternative form of therapy for some patients with CHF. Mancini et al. (1995b) have taken advantage

of this unique therapy to assess respiratory muscle strength of subjects pre- and post-transplantation in comparison to age-matched controls. They reported no significant differences between any of the groups. In a further study in which subjects with heart failure were followed post-transplantation, Tsai and Ahmad (1997) confirmed that no significant changes in respiratory muscle strength occur post cardiac transplantation in spite of dramatic improvements in both cardiac function and symptomatology. In fact, in several of the subjects, respiratory muscle strength decreased post cardiac transplantation even though significant improvements were documented in both NYHA heart failure classification and LVEF.

Some studies have reported respiratory muscle weakness in heart failure and related this decreased strength to patient symptomatology, including dyspnea. Cardiac transplantation offers patients one form of treatment for end-stage heart failure. While resting lung abnormalities in most patients with heart failure (with the exception of the diffusing capacity) are reversible post heart transplantation, it is not clear whether resting respiratory muscle strength is altered. This study was designed to assess the differences in respiratory muscle strength in two different conditions: 1) heart failure and 2) the reversal of heart failure, post cardiac transplantation.

Purpose

The purposes of this study were to:

1. determine if there is a difference in respiratory muscle strength between subjects with heart failure and subjects post cardiac transplantation
2. determine if there is a difference in exercise capacity, skeletal muscle strength, breathlessness, and quality of life between subjects with heart failure and subjects post cardiac transplantation
3. assess the relationship between respiratory muscle strength, skeletal muscle strength, resting cardiac index, exercise tolerance, and quality of life in subjects with heart failure and subjects post cardiac transplantation.

Chapter 2

Methodology

General Outline

Respiratory muscle strength was compared in subjects with severe heart failure and subjects after heart transplantation. Quadriceps muscle strength, functional mobility, exercise capacity, and quality of life were also compared between the two groups. The relationship of each outcome measure to respiratory muscle strength was investigated.

Subjects

Thirty-one volunteers (sample size estimate, Appendix B) were recruited through the Heart Transplant Program at the University Campus of the London Health Sciences Centre (LHSC-UC, London, Canada). Subjects were screened and referred to the study by cardiologists on this service.

Inclusion Criteria

In order to participate in the study, the subjects had to meet the inclusion criteria detailed below.

Group 1, Heart Failure (HF)

Subjects must have severe congestive heart failure (class III to IV) as described by the NYHA classification system (Appendix C). This classification is based on a cardiologist's clinical assessment of the patient's status.

Group 2, Post Heart Transplantation (TX)

Subjects must have undergone orthotopic cardiac transplantation between one and five years prior to the study.

Groups 1 and 2

1. Subjects must be able to provide informed consent.
2. Subjects must be over the age of 17 years.
3. Subjects must be capable of reading, understanding and completing the quality of life questionnaire and carrying out the required tests.

Exclusion criteria

Subjects were excluded from the study if they:

1. had previous cardiac, thoracic or upper abdominal surgery within the year prior to testing.
2. had any medical thoracic or pulmonary impairment, other than heart failure, which would alter respiratory muscle function (e.g. chronic obstructive lung disease).
3. had any confounding medical condition, as determined by the cardiologist, that would affect performance on the walk and exercise capacity tests (e.g. orthopaedic conditions or moderate to severe peripheral vascular disease).
4. were medically unstable at the time of testing (e.g. unstable angina or an acute systemic illness).
5. had musculoskeletal or neuromuscular pathology of the lower extremity prohibiting them from performing a treadmill test or a quadriceps muscle strength test.

The subjects were informed about the study and all potential risks and benefits of testing were explained before provision of informed consent. The study was approved by The University of Western Ontario's Review Board for Health Sciences Research Involving Human Subjects (review number E6025; Appendix D).

Descriptive data were obtained on each subject including age, gender, height, mass, CI, LVEF as measured by cardiac wall motion study, etiology of heart failure, medication use, exercise, and smoking history.

Study Setting and Ethics Approval

All tests were performed at LHSC-UC over a one week period. Pulmonary function and respiratory muscle strength testing were performed in the pulmonary laboratory. Maximal exercise treadmill testing was performed in the cardiac investigation unit. Tests of functional mobility and quadriceps muscle strength, and administration of the quality of life questionnaire were carried out in the physiotherapy department. Tests were scheduled to allow appropriate rest periods between procedures in order to prevent any systematic effect of testing order with respect to fatigue.

Test Protocol/Procedures

Pulmonary Function

In order to rule out obstructive deficits in the subjects, routine pulmonary function testing was performed including measurements of forced expired volumes, lung volumes, and diffusing capacity. Spirometric indices were calculated from the best of three full efforts. FEV_1 and forced vital capacity (FVC) were evaluated using the predicted values of Knudson et al. (1983). TLC and RV were measured using the helium dilution determination of lung

volumes and the predicted values of Goldman and Becklake (1959). The carbon monoxide diffusion capacity (D_LCO) was determined using the single breath carbon monoxide technique and values corrected for hemoglobin concentration (Cotes et al., 1972).

Respiratory Muscle Strength

Respiratory muscle strength was assessed by measuring maximal inspiratory ($P_I$max) and expiratory pressures ($P_E$max) with a *Vmax 229* metabolic cart (*SensorMedics, Corporation, Yorba Linda, USA*). Measurements were taken with the subject seated, wearing a noseclip, and breathing through a mouthpiece connected to a cylinder and calibrated manometer. Pressure at the mouth was recorded while the subject performed maximal inspiratory and expiratory maneuvers with encouragement against an occluded airway. A small hole in the cylinder prevented glottic closure during $P_E$max testing.

$P_I$max and $P_E$max were measured at residual volume (RV) and total lung capacity (TLC) respectively, since the muscles are at the optimal length to produce a maximal effort at these volumes (Black and Hyatt, 1969). Replicate determinations were done until the two highest values agreed within 5 cm H_2O. The maximum effort was recorded. Prediction equations for maximal respiratory pressures as developed by Wilson et al. (1984) were applied to obtain percent predicted values (Appendix E). All tests were conducted by an experienced technician unaware of the purpose of the study.

Peak Exercise Capacity

Peak exercise capacity was measured by treadmill testing using a modified Naughton treadmill protocol. Heart rate and rhythm was monitored throughout the protocol by a 12-lead electrocardiogram monitor. Subjects wore a nose clip and breathed through a mouthpiece. The *Vmax 229* metabolic cart was used to measure oxygen consumption. Calibration pre-test was according to the manufacturer's guidelines. The test was performed by technicians unaware of the purpose of the study.

Functional Mobility

A six-minute walk test (6-MWT) was performed as a measure of functional mobility (Guyatt et al., 1985). There are a variety of protocols available for conducting a 6-MWT (Beaumont et al., 1985; Swerts et al., 1990). The one currently in practice at LHSC-UC was used. Subjects walked on a motorized treadmill, setting their own pace using the controls on the panel in front of them. They received the following simple, concise instructions.

> *"Walk as far as you are able in the six minutes. You may stop the treadmill at any time you wish and rest. This time will count as part of your six minutes. I want you to push yourself so that you walk as far as you possibly can in the six minutes. Rest when you need to."*

Subjects received verbal encouragement as they performed the test. They were not allowed to see either the on-going distance or speed readings. A rating of perceived breathlessness (RPB) was obtained using the new Borg scale (see Appendix F; Borg, 1982) at rest and peak

performance. Total distance walked during the test was recorded in metres. All subjects were familiar with the test from previous experience.

Quadriceps Muscle Strength

Quadriceps muscle strength was assessed on the subject's dominant leg (defined as the kicking leg) using the LIDO multi-joint isokinetic dynamometer (Chatanooga, Montréal, Canada). Subjects had one practice session on the LIDO, kicking at approximately 1/3 maximum effort to prevent fatigue. The test involved five maximal repetitions of knee extension at a velocity of 180°/sec, with the highest torque being recorded.

Quality of Life

The Minnesota Living with Heart Failure Questionnaire is a 21-item, self-administered questionnaire covering physical, socioeconomic, and psychologic impairments common to CHF patients. Subjects were asked to rank each question on a scale from 0 (no) to 5 (very much). A total quality of life score (QOL) was calculated with a higher score (a maximum of 105) relating to a poorer quality of life (Rector et al., 1987). Subjects were allowed as much time as necessary to complete the questionnaire.

Data Analysis

Data were analysed to obtain descriptive statistics for age, gender, height, mass, cause of heart failure, LVEF, CI, smoking history, and medication use. Descriptive statistics were also obtained for FVC, FEV_1, the FEV_1/FVC ratio, TLC and RV.

Differences in $P_I$max, $P_E$max, peak $\dot{V}O_2$, 6-MWT distance, peak RPB, quadriceps strength, and QOL between HF and TX were assessed using unpaired t-tests. When tests of normality or equal variance failed, a Mann-Whitney Rank Sum test was performed. To control for multiple comparisons, a Bonferroni correction was applied and the critical level of significance set at $p \leq 0.003$.

A two-way analysis of variance (ANOVA) was performed to assess differences between subjects with heart failure due to dilated cardiomyopathy (DCM) and ischemic heart disease (IHD) in HF and TX. The critical level of significance set at $p \leq 0.05$.

The relationships between respiratory muscle strength ($P_I$max and $P_E$max) and peak $\dot{V}O_2$, 6-MWT distance and peak RPB, quadriceps strength, and QOL in the two groups were determined for all subjects (both HF and TX combined) using Pearson product-moment correlation coefficients. Heart function as measured by CI was also assessed for relationships with peak $\dot{V}O_2$, 6-MWT distance and peak RPB, quadriceps strength, and QOL in the combined HF and TX (Pearson r). Independent determinations of the relationships between

respiratory muscle strength and peak $\dot{V}O_2$, 6-MWT distance and peak RPB, quadriceps strength, and QOL (Pearson r) were performed for the HF subjects alone.

Chapter 3

Results

Subjects

Descriptive information for the 15 subjects (12 men) in the HF group and 16 subjects (14 men) in the TX group is presented in Table 3.1. Eight (53%) HF subjects had IHD while 6 (38%) of TX subjects had IHD pre-transplantation. One subject in each group had congenital heart disease. In the HF group, major medication use was as follows: a diuretic, 15 (100%); angiotensin-converting enzyme inhibitor, 15 (100%); digoxin, 9 (60%); coumadin, 9 (60%); amiodarone, 7 (47%); and a beta-blocker, 4 (27%). In the TX group, major medication use was as follows: cyclosporine, 16 (100%); aspirin, 10 (63%); a calcium channel blocker, 9 (56%); prednisone, 8 (50%); azathioprine, 5 (31%); mycophenolate, 5 (31%); and an angiotensin converting-enzyme inhibitor, 3 (19%). All of the subjects in the TX group underwent a three month exercise program following transplantation. The routine pre transplant exercise program had been initiated with two of the HF subjects. Both LVEF (20.3% vs. 57.8%, $p<0.001$) and CI (1.8 $l \cdot min^{-1} \cdot m^{-2}$ vs. 3.8 $l \cdot min^{-1} \cdot m^{-2}$, $p<0.001$) were significantly lower in HF compared to TX.

Table 3.1: Descriptive data for the heart failure and post heart transplantation groups

	Heart Failure n=15	Post Heart Transplantation n=16
Age (y)	51.5 (11.0)	51.8 (12.0)
Height (cm)	175 (8.3)	168 (7.5)
Mass (kg)	78.2 (19.2)	78.7 (13.0)
LVEF (%)	20.3 (8.8)	57.8 (10.6)*
CI ($l \cdot min^{-1} \cdot m^{-2}$)	1.8 (0.3)	3.8 (0.8)*
Smoking History (pk/yrs)	16.0 (18.7)	16.7 (23.6)

values are mean (SD); LVEF = left ventricular ejection fraction; CI = cardiac index; pk/yrs = packs of cigarettes smoked per day times number of years smoked
*$p \leq 0.001$

Pulmonary Function Tests

Pulmonary function data are presented in Table 3.2. No significant differences were detected between HF and TX groups for static lung volumes, percent predicted RV and TLC. However, significant differences were found in the dynamic lung volumes, percent predicted FVC and percent predicted FEV_1 (HF: 87% vs. TX: 109%, $p<0.001$ and HF: 81% vs. TX: 103%, $p<0.001$ respectively). The FEV_1/FVC ratio was within normal limits in both groups.

Respiratory Muscle Strength

Respiratory muscle strength data are presented in Table 3.3. No significant differences were noted between groups whether values were expressed as an absolute number or a percent of the predicted value. No significant differences occurred within or between groups when a two-way ANOVA was used to assess the influence of the type of disease, IHD or DCM.

Exercise Capacity, Functional Mobility, Quadriceps Strength, and Quality of Life

Peak $\dot{V}O_2$, 6-MWT distance and RPB, QOL, and quadriceps muscle strength score are displayed in Table 3.4. Transplant subjects had a higher peak $\dot{V}O_2$ than HF subjects (20.8 $ml \cdot kg^{-1} \cdot min^{-1}$ vs. 11.1 $ml \cdot kg^{-1} \cdot min^{-1}$ respectively, $p<0.001$). During the 6-MWT, TX subjects were able to walk further (528 m vs. 205 m, $p<0.001$) and scored lower on the modified Borg with respect to shortness of breath than HF subjects (3.0, "*moderate*" respectively vs.

Table 3.2: Pulmonary function data for the heart failure and post heart transplantation groups

	Heart Failure n=15	Post Heart Transplantation n=16
FVC (*l*)	3.75 (1.12)	4.34 (0.82)
% predicted	87 (19)	109 (16)*
FEV_1 (*l*)	2.76 (0.93)	3.31 (0.62)
% predicted	81 (19)	103 (15)*
FEV_1/FVC (%)	73 (7.9)	76 (4.1)
TLC (*l*)	5.69 (1.48)	6.06 (0.91)
% predicted	86 (17)	95 (10)
RV (*l*)	1.89 (0.65)	1.58 (0.33)
% predicted	86 (23)	78 (20)
D_LCO (mm Hg·min $^{-1}$·kPa^{-1})	21.4 (6.4)	17.5 (3.5)
% predicted	71 (15)	63 (11)

values mean (SD); FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; FEV_1/FVC = ratio of forced expiratory volume in one second to forced vital capacity; TLC = total lung capacity; RV = residual volume, D_LCO = carbon monoxide diffusion capacity

*$p \leq 0.001$

Table 3.3: Respiratory muscle strength in the heart failure and post heart transplantation groups

	Heart Failure n=15	Post Heart Transplantation n=16
$P_I$max (cm H_2O)	97 (24.6)	88 (21.4)
% predicted	113 (27.8)	103 (25.7)
$P_E$max (cm H_2O)	113 (30.5)	120 (43.4)
% predicted	90 (23.1)	94 (32.3)

values are mean (SD); $P_I$max = maximal inspiratory pressure; $P_E$max = maximal expiratory pressure

Table 3.4: Peak oxygen uptake, six-minute walk test results, quality of life scores, and quadriceps strength in the heart failure and post heart transplantation groups

	Heart Failure n=15		Post Heart Transplantation n=16	
peak $\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	11.1	(3.7)	20.8	(5.2)*
6-MWT				
distance (m)	205	(100.0)	528	(61.1)*
RPB	5.6	(1.8)	3.0	(2.3)*
QOL	77	(21.8)	17	(15.1)*
Quadriceps strength (N·m)	73	(36.1)	86	(22.5)

values are mean (SD); peak $\dot{V}O_2$ = peak oxygen uptake during maximal exercise testing; 6-MWT = 6-minute walk test; RPB = rating of perceived breathlessness; QOL = Minnesota Quality of Life Questionnaire score
*$p \leq 0.001$

5.6, "*strong*", p=0.001). Transplant subjects also recorded lower scores (better QOL) than HF subjects (17 vs. 77 respectively, p<0.001). No significant difference occurred between TX and HF subjects for quadriceps muscle strength (86 N·m vs. 73 N·m, p=0.248).

Correlations

Pearson product-moment correlations are displayed in Table 3.5. No significant relationship was detected between respiratory muscle strength and peak $\dot{V}O_2$, 6-MWT distance or RPB, quadriceps strength, or QOL in the combined group (HF and TX). However, highly significant correlations were found between CI and peak $\dot{V}O_2$ (p<0.001; Figure 3.1), 6-MWT distance (p<0.001; Figure 3.2), 6-MWT RPB (p=0.005; Figure 3.3) and QOL (p<0.001; Figure 3.4) while no relationship was demonstrated between CI and quadriceps strength in the combined group. A significant relationship was demonstrated between quadriceps strength and both $P_I$max and P_E max, when the heart failure subjects were assessed independently (p=0.005 and p<0.001; Figures 3.5 and 3.6).

Table 3.5: Pearson product-moment correlations between respiratory muscle strength or cardiac index and exercise capacity, functional mobility, and quality of life

	peak $\dot{V}O_2$	6-MWT		QOL
		distance	RPB	
$P_I$max	0.028	-0.058	0.140	-0.030
$P_E$max	0.309	0.202	0.117	-0.217
CI	0.620†	0.792†	-0.489*	-0.722†

peak $\dot{V}O_2$ = peak oxygen uptake during maximal exercise testing; 6-MWT = 6-minute walk test; RPB = rating of perceived breathlessness; QOL = Minnesota Quality of Life Questionnaire score; $P_I$max = maximal inspiratory pressure; $P_E$max = maximal expiratory pressure; CI = cardiac index

* $p \leq 0.01$; † $p \leq 0.001$

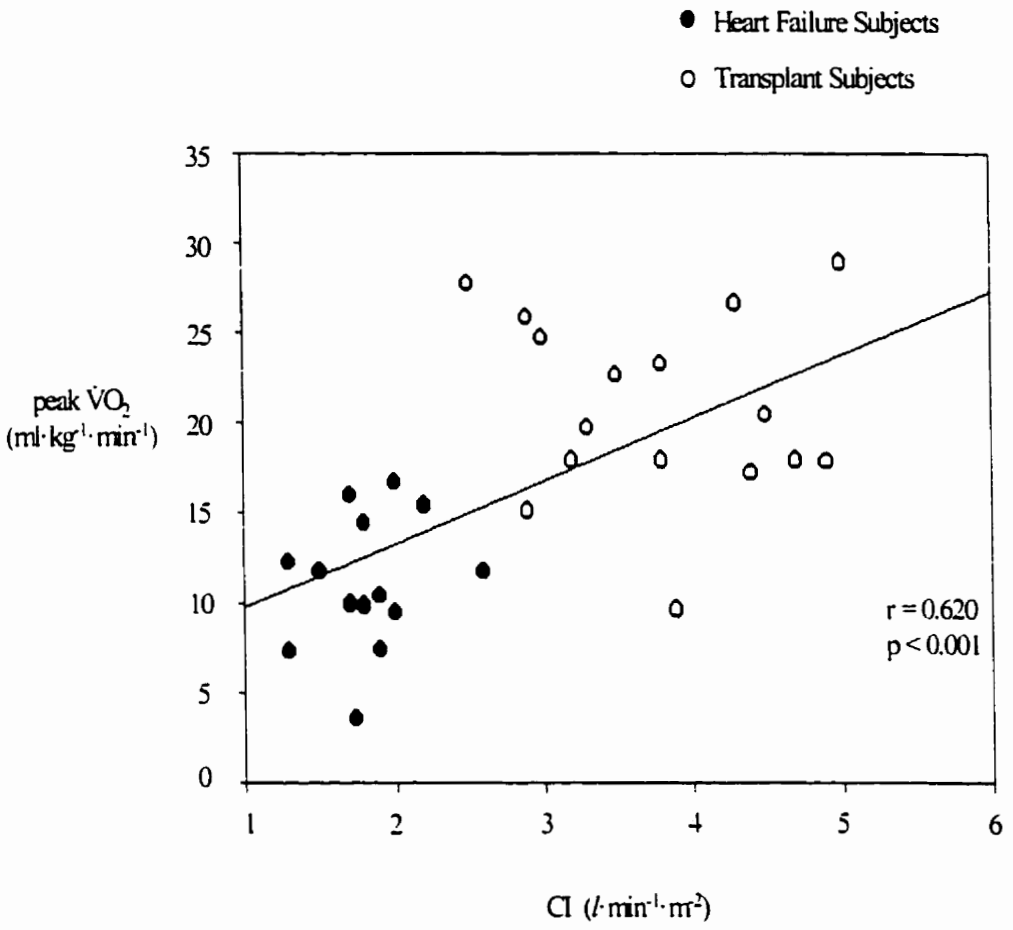

Figure 3.1 Relationship between cardiac index (CI) and peak oxygen uptake (peak $\dot{V}O_2$) in heart failure (n=14) and post heart transplantation (n=16) subjects

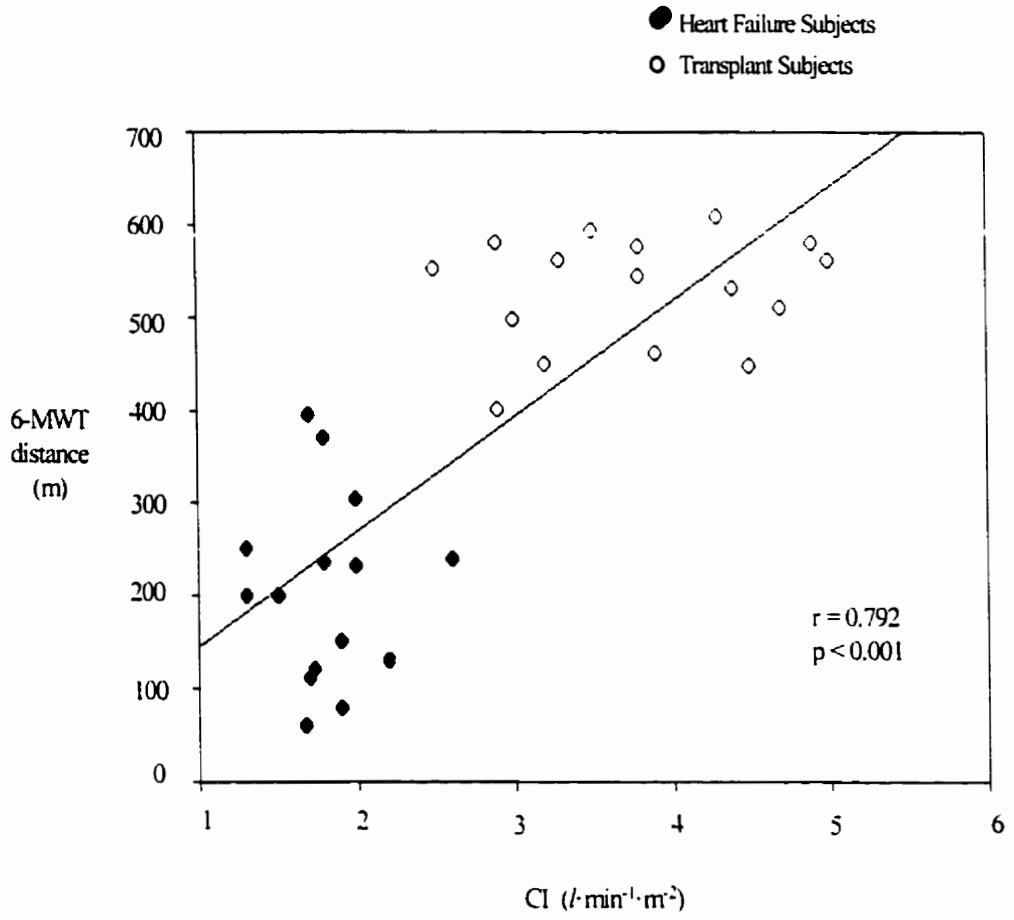

Figure 3.2 Relationship between cardiac index (CI) and six-minute walk test (6-MWT) distance in heart failure (n=15) and post heart transplantation (n=16) subjects

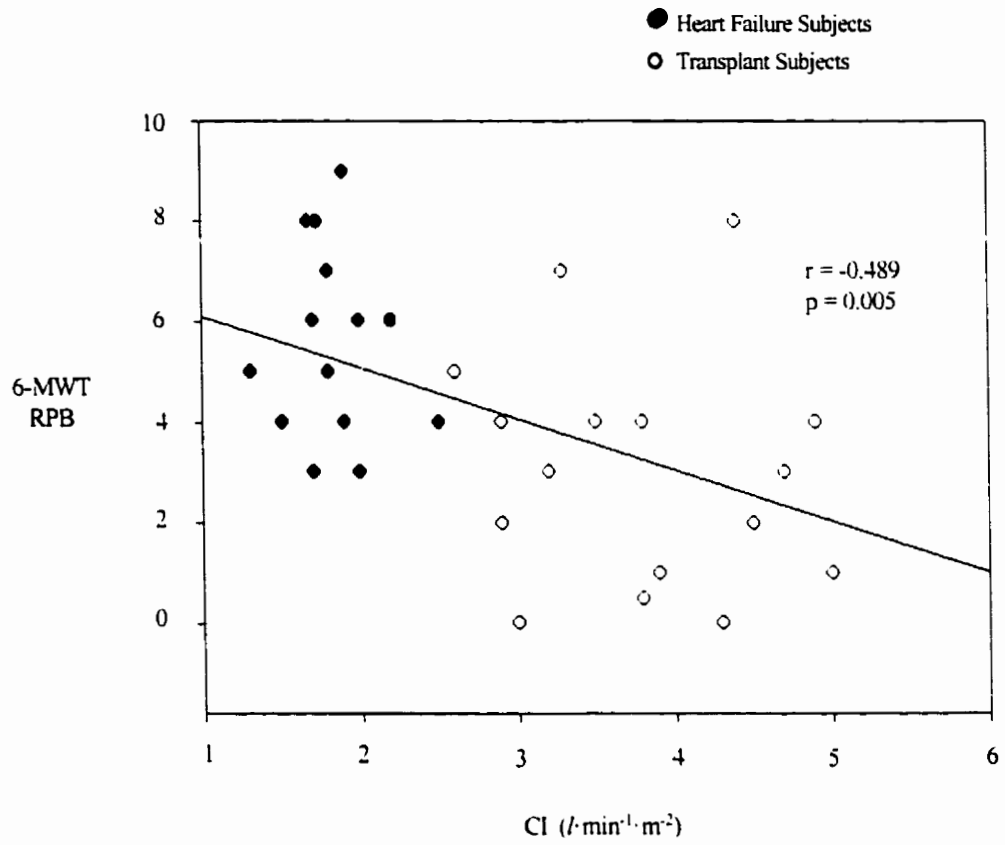

Figure 3.3 Relationship between cardiac index (CI) and six-minute walk test (6-MWT) rating of perceived breathlessness (RPB) in heart failure (n=15) and post heart transplantation (n=16) subjects

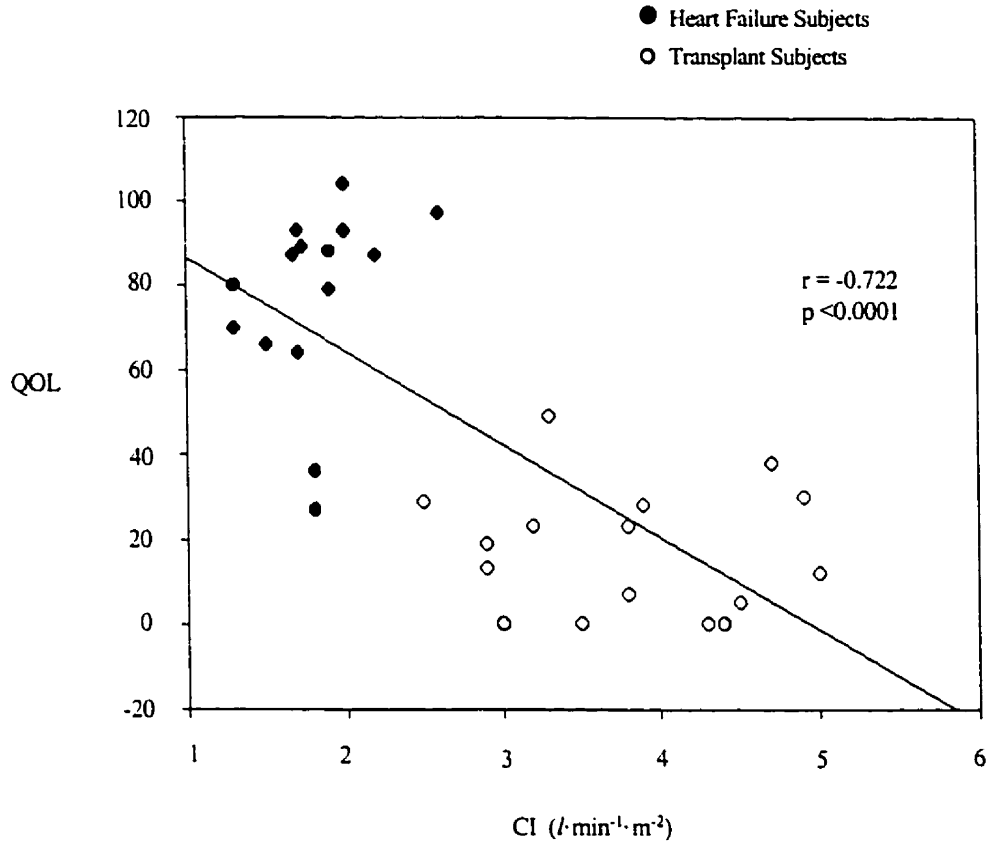

Figure 3.4 Relationship between cardiac index (CI) and quality of life score (QOL) in heart failure (n=15) and post heart transplantation (n=16) subjects

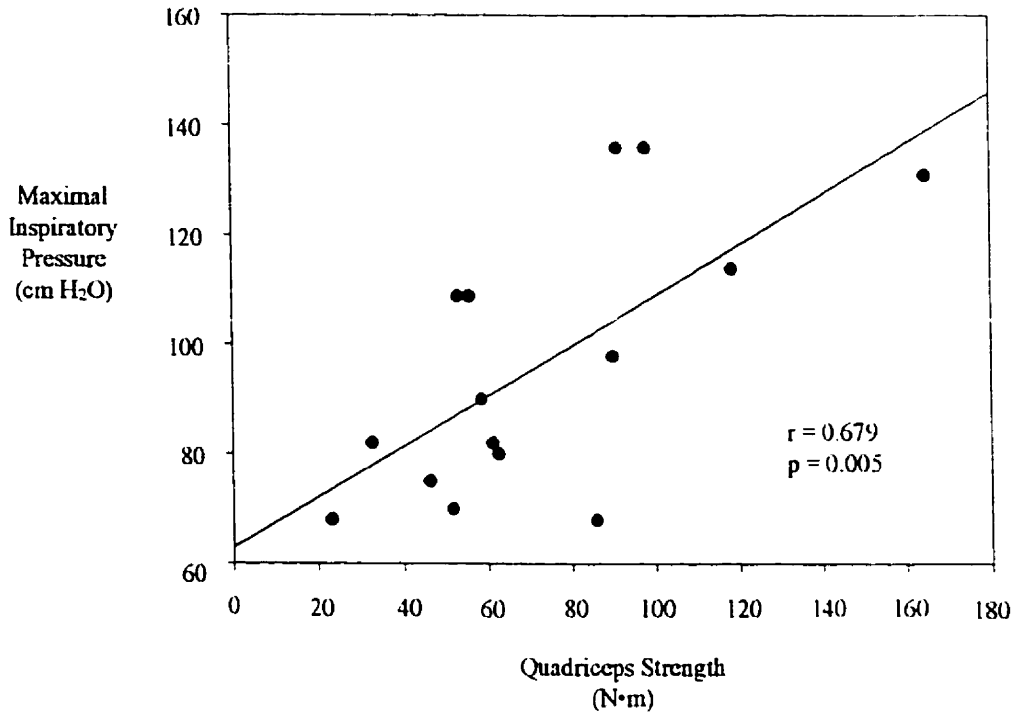

Figure 3.5 Relationship between quadriceps strength and maximal inspiratory pressure in heart failure subjects (n=15)

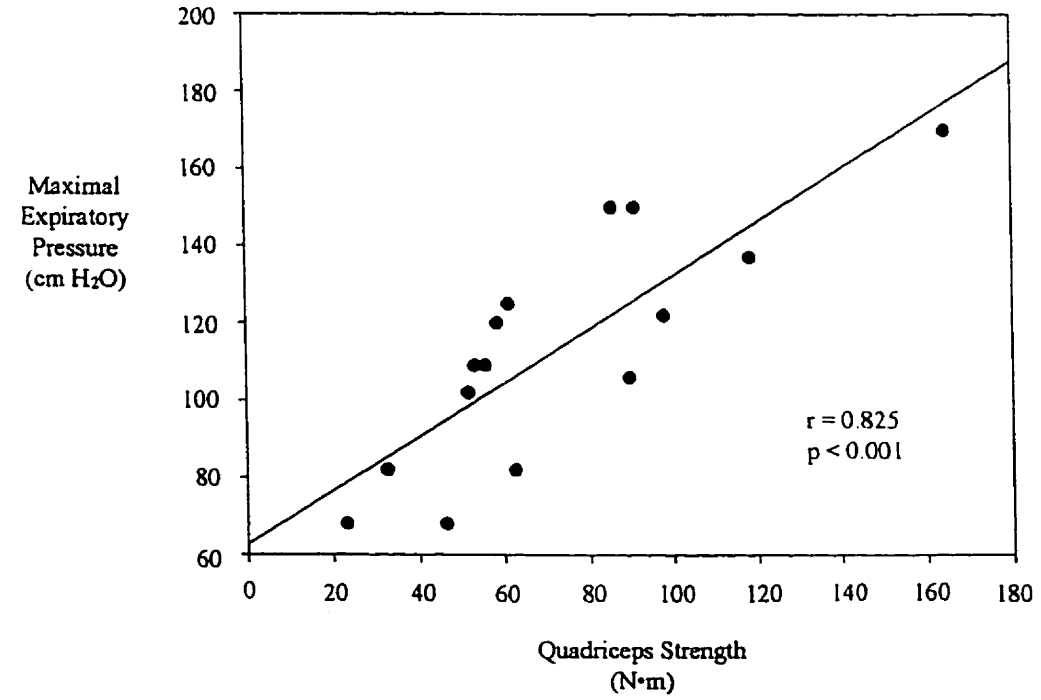

Figure 3.6 Relationship between quadriceps strength and maximal expiratory pressure in heart failure subjects (n=15)

Chapter 4

Discussion

This study has demonstrated that there was no difference in resting respiratory muscle strength between subjects with end-stage heart failure compared to subjects post heart transplantation. Peak $\dot{V}O_2$, walk test performance, and quality of life were noted to be significantly greater in the subjects having undergone transplantation. The strength of the respiratory muscles did not correlate with exercise capacity, perceived breathlessness during exercise, or assessment of quality of life. A relationship however, did exist between these parameters and CI suggesting that heart function (CI) is more closely associated with dyspnea and quality of life than respiratory muscle strength.

Respiratory Muscle Strength

Reliable measurements of respiratory muscle strength can be made by assessing maximal inspiratory and expiratory pressures (Black and Hyatt, 1969). Previous studies have suggested that respiratory muscle strength is decreased in heart failure at rest when directly measuring $P_I$max and $P_E$max (Hammond et al., 1990; McParland et al., 1992). Later studies have demonstrated that this decrease in fact only occurs in NYHA class III or IV heart failure patients with class I and II demonstrating normal strength (Ambrosino et al., 1994; Nishimura et al., 1994). For the purposes of this study therefore, only class III or IV heart failure patients were assessed.

As gender, age, and height may affect respiratory muscle strength when unpaired groups are assessed, normalized values should be reported (Wilson et al., 1984). Two previous studies (Nishimura et al., 1994, Evans et al., 1995) have reported a decrease in respiratory muscle strength in heart failure when percent predicted values are reported (Table 4.1). Conversely in this study, although no control group was used for comparison, $P_I$max was 113 and 103 percent of predicted and $P_E$max was 90 and 94 percent of predicted in HF and TX groups respectively.

A recent study by Daganou et al. (1999) has demonstrated a difference in respiratory muscle strength dependent on the type of heart failure. While subjects with either IHD or DCM demonstrated a decrease in $P_I$max when compared to controls, DCM subjects also demonstrated a significant decrease in inspiratory muscle strength when compared to IHD. Unfortunately, normalized values were not reported (Daganou et al., 1999). In the current study, there were no significant differences between subjects with IHD and DCM when comparing percent predicted $P_I$max or $P_E$max.

Skeletal Muscle Strength

Other studies have reported varying relationships between respiratory and skeletal muscle strength (Chua et al.1995, Evans et al.1995, Mancini et al., 1992c). There was no difference noted in skeletal muscle strength in subjects with heart failure when compared to subjects post transplantation in the current study. Furthermore, there was no relationship established

Table 4.1. Published data on maximal inspiratory ($P_I$max) and expiratory pressures ($P_E$max) in heart failure (HF) and age-matched control (AMC) subjects

Study	$P_I$max % predicted		$P_E$max % predicted	
	AMC	HF	AMC	HF
Mancini et al. (1992)	86(10) [6]	76(15) [10]	81(19) [6]	80(21) [10]
Nishimura et al. (1994)	106(24) [15]	107(34) [10]^{II}	102(29) [15]	90(24) [10]^{II}
	106(24) [15]	80(21)* [13]$^{III-IV}$	102(29) [15]	85(25) [13]$^{III-IV}$
Evans et al. (1995)	---	64(24)† [20]	---	70(17)† [20]
Nanas et al.[a] (1999)	88(18) [11]	73(24)* [45]	84(18) [11]	53(17)‡ [45]

values are mean (SD); [ ] = number of subjects; [a] = respiratory muscle strength measured post-exercise; ^{II} = class II heart failure; $^{III-IV}$ = class III or IV heart failure
* $p \leq 0.05$, † $p \leq 0.01$, ‡ $p \leq 0.001$ compared with AMC

between either $P_I$max or $P_E$max and skeletal muscle strength in heart failure and post heart transplantation group. However, a significant relationship was detected between quadriceps strength and both $P_I$max and $P_E$max in the heart failure group when assessed separately. This would suggest that there may be a threshold beyond which respiratory muscle strength and other skeletal muscle (quadriceps) strength may be related.

Skeletal Muscle Strength, Exercise Tolerance, and Quality of Life

Although no differences in respiratory muscle function were noted between HF and TX in this study, dramatic differences occurred in cardiac function (LVEF and CI). The TX subjects were also able to walk further in six minutes, felt less short of breath during exercise (new Borg scale), and reported an improved quality of life. A previous study by Mancini et al. (1995b) also found no difference in respiratory muscle strength between groups. (Table 4.2) Improvements were found in maximal voluntary ventilation (MVV) post-transplantation although both groups remained significantly impaired compared to normals. No difference was noted in either maximal sustainable ventilatory capacity (MSVC) or in dyspnea during (measured by the Borg scale; Mancini et al., 1995b). Similarly, Tsai and Ahmad (1997), reported no difference in respiratory muscle strength when comparing the same subjects pre- and post-transplant (Table 4.2). Contrary to Mancini et al. (1995b) however, no difference was reported in MVV while a significant improvement in dyspnea (measured by the DI at rest) was reported (Tsai & Ahmad, 1997). This would suggest that dyspnea is not likely related to respiratory muscle strength.

Table 4.2. Published data on maximal inspiratory ($P_I$max) and expiratory pressures ($P_E$max) in heart failure (HF), patients post heart transplantation (TX), and age-matched control (AMC) subjects

Study	$P_I$max			$P_E$max		
	CHF	TX	AMC	CHF	TX	AMC
Mancini et al. (1994)	29(14)[a] [15]	35(7) [8]	35(8) [8]	50(23) [15]	59(8) [8]	62(13) [8]
Tsai and Ahmad[c] (1997)	85(17)[b] [11]	82(19) [11]	---	105(28) [11]	103(32) [11]	---

values are means (SD); [a] = values in kPa; [b]= values in cm H_2O; [ ] = number of subjects in study; [c] same subjects pre- and post-transplantation; $P_I$max measured at residual volume; $P_E$max measured at total lung capacity

No statistical significance was reached in any of the group comparisons in either study.

Correlations

Although two previous studies have demonstrated a relationship between inspiratory muscle strength and dyspnea (McParland et al., 1992; Mancini et al., 1992a), no such relationship was detected in this study. This result would support the findings of Evans et al., (1995). McParland et al. (1992) assessed breathlessness while the patients were at rest using the DI. The index consists of three categories including the assessment of dyspnea associated with activity (Mahler et al., 1984). Subjects however, did not assess their dyspnea post-activity. Conflicting studies by Mancini et al. (1992a) and Evans et al. (1995) utilized the Borg scale and assessed breathlessness during activity. In the present study, dyspnea was also measured during activity. Dyspnea measured at rest might be more closely associated with respiratory muscle strength. It does not appear however that dyspnea during exercise is related to resting respiratory muscle strength.

No relationship was established between $P_I$max at rest and peak $\dot{V}O_2$. This finding supports the findings of Witt et al. (1997) although several other investigators have reported a significant relationship (Chua et al., 1995; Dimopoulou et al.; 1999, Nanas et al., 1999). Similar to all previous studies (Chua et al., 1995; Witt et al., 1997; Dimopoulou et al., 1999; Nanas et al., 1999), no relationship was demonstrated between $P_E$max and peak $\dot{V}O_2$ in this study. Nanas et al. (1999) also measured respiratory muscle strength following cardiopulmonary exercise stress testing but found no relationship with peak $\dot{V}O_2$ when this measure was used.

Although most previous studies (Ambrosino et al.; 1995, Witt et al., 1997) have demonstrated no relationship between inspiratory muscle strength and LVEF, CI, or peak $\dot{V}O_2$, one study reported a relationship between P $_{I}$max and CI (Nishimura et al., 1994). The present study found no relationship.

Rest versus Activity

The subjects in this study demonstrated a significant difference between groups in both percent predicted FVC and FEV_1. In previous studies comparing HF to controls, similar results were found (Hammond et al., 1990; Naum et al., 1992) although other studies have reported normal values for both FVC and FEV_1 (Sullivan et al., 1988; Hammond et al., 1990). The FEV_1/FVC ratio and static lung volumes were within normal limits for both groups in this study confirming that subjects in this study did not have an obstructive pulmonary deficit. A restrictive deficit in the HF group however, is evidenced by the decreased dynamic lung volumes in the presence of a normal FEV_1/FVC ratio. On review of the medications, all HF subjects were taking a diuretic suggesting that some degree of pulmonary edema may have been present leading to this restrictive pattern.

With a restrictive deficit, increases in minute ventilation associated with activity result in a disproportionate increase in the work of breathing. As work of breathing increases, respiratory muscle endurance is challenged (Mancini, 1995). As the muscles fatigue, a reduction in MVV and MSVC and an increase in TTIdi should be noted (Rochester, 1988). This trend has been demonstrated in heart failure (Mancini et al., 1992b; Mancini et al.,

1995b). Walsh et al. (1996) confirmed a decrease in respiratory muscle endurance using a threshold loading technique while Vibarel et al. (1998) demonstrated a reduction using a non-invasive index (tension-time index of inspiratory muscles).

This evidence suggests that when heart failure patients are challenged by an increased respiratory load, reserves are not available to compensate appropriately. In a recent study by Nanas et al. (1999) the relationship between respiratory muscle function and oxygen kinetics was examined. After 10 minutes of exercise, respiratory muscle strength was unchanged in most heart failure subjects. When a significant decrease in $P_I$max was noted however, there was a significant delay in the decline of $\dot{V}O_2$ during recovery following exercise. Brunner-La Rocca et al. (1999) have also demonstrated altered oxygen kinetics post-exercise in subjects with heart failure.

Limitations and Future Research

Severe heart failure patients were not followed through their post-transplantation course in this study due to time constraints. Only 15 to 20 transplants are performed each year at LHSC, with only approximately half those patients meeting the inclusion criteria for the study. Several patients wait in excess of one year for a transplant and some die during the waiting period. Death may also occur in the post-operative period and patients are sometimes lost to follow-up due to geography. Therefore several years would be required to realize an appropriate sample size.

Both HF and TX groups in this study included a mix of IHD and DCM patients. A recent paper has suggested that respiratory muscle strength in HF may vary depending on the etiology of disease (Daganou et al., 1999). Again, time would be a limiting factor if either group was excluded from the study or if numbers were increased to allow comparisons between IHD and DCM.

Severity of illness precluded some patients from entering the study as they were unable to perform the tests. Full assessment of exercise capacity is limited and often not possible in the class IV heart failure patient.

The current study examined respiratory muscle strength at rest. Future research should include measurements of dynamic respiratory muscle function as activity and increased work of breathing may impact on dyspnea.

Specific recommendations for future research include the following:

1. respiratory muscle strength and endurance be assessed before and after exercise
2. dyspnea be assessed before, during and after exercise
3. respiratory muscle endurance be examined to determine a relationship to work of breathing and exercise tolerance
4. dyspnea both at rest and exercise be assessed for a relationship with exercise tolerance, and respiratory muscle strength and endurance under exercise conditions.

Summary and Conclusions

The present study examined the respiratory muscle strength in individuals with heart failure and post cardiac transplantation. No difference was noted between the groups. However, there were functional differences post heart transplantation compared to severe heart failure, with subjects able to walk further, report less dyspnea and document an improved quality of life following transplantation. Differences in exercise capacity, shortness of breath and quality of life were not related to static measurements of respiratory strength although a highly significant relationship with CI was found. Thus the results of the study suggest that the contribution of respiratory muscle strength at rest to dyspnea is likely small. Dynamic respiratory muscle function therefore, needs to be more closely assessed and potential relationships with activity explored. This may provide greater insight into the mechanisms leading to dyspnea and fatigue in heart failure.

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APPENDIX A: Literature Review

Respiratory Muscle Function in Congestive Heart Failure

Introduction

Congestive heart failure (CHF) is a common clinical syndrome manifested by a decrease in myocardial contractility such that eventually, the cardiac output produced does not meet the body's metabolic demands (Klainer, 1965). Exertional dyspnea and fatigue are common complaints in patients with CHF, limiting exercise capacity and potentially decreasing quality of life. The mechanism underlying these symptoms however, remains unclear (Mancini, 1995). Recently, interest has turned toward the respiratory muscles as a possible cause (Hammond et al., 1990; McParland et al., 1992). The histochemical, metabolic and vascular abnormalities found in the limb muscles of CHF patients may also exist in the respiratory muscles and cause dysfunction (Harrington & Coats, 1997). Whether these abnormalities are a consequence of impaired cardiac output resulting in muscle ischemia is uncertain.

This review will outline relevant studies and discuss available research data in order to provide insight into CHF and its potential effect on respiratory muscle strength. It will also highlight areas lacking in research and potential for further studies.

Current Theories of Dyspnea and Fatigue in Heart Failure

In the past decade, many theories have been entertained as to the cause of dyspnea and fatigue in patients with heart failure. The initial thought was that the impaired cardiac output evident in these patients eventually results in poor oxygenation of the skeletal musculature

leading to muscular fatigue and a perceived shortness of breath (Wilson and Mancini, 1993; Macklem, 1980). It is most likely that the reasons for dyspnea in CHF patients may be multi-factorial with many hypotheses recently being tested (Mancini, 1995).

In patients with acute heart failure, changes in intrapulmonary vascular pressures are thought to cause dyspnea. This theory was investigated in patients with CHF by manipulating the pulmonary capillary wedge pressure acutely through pharmacological agents while measuring ventilation. There was no difference in the ventilatory response and no relationship was demonstrated between ventilation and either the resting or exercise induced pulmonary wedge pressure (Fink et al., 1986). Dyspnea has also been shown to be unrelated to alterations in arterial blood gas tensions, left ventricular performance, maximal exercise capacity or patient prognosis and survival (Sullivan et al., 1989). Current theories on the cause of exertional dyspnea in patients with chronic CHF include: 1) ventilation-perfusion abnormalities, chronic fibrotic changes, and activation of juxta-capillary receptors in the lungs; 2) an increased work of breathing; 3) early onset of lactic acidosis; and 4) possibly a change to the central control of ventilation by carbon dioxide (Mancini et al., 1992a). None, however have been adequately studied.

Patients with heart failure have a reduced leg blood flow during exercise which has been weakly related to the sensation of fatigue in this population (Sullivan et al., 1989). Again, the use of acute pharmacological agents, although increasing cardiac output and peripheral blood flow, did not produce an improvement in either peak exercise capacity or exertional fatigue in patients with CHF (Wilson et al., 1983a; Wilson et al., 1984). Although there may

be a reduced leg blood flow, other investigators demonstrated no abnormalities of muscle perfusion using ^{31}P magnetic resonance spectroscopy (Wilson et al., 1983a; Mancini et al., 1989). Further studies demonstrated impaired quadriceps muscle endurance in this population which was independent of blood flow (Minotti et al., 1991).

Several investigators have used ^{31}P magnetic resonance spectroscopy to study the skeletal muscle metabolism in patients with CHF (Wilson et al., 1983a; Mancini et al., 1989). Decreases in muscle pH and phosphocreatine levels were found to occur more quickly in patients with CHF than in normal subjects. Biopsy results confirmed suspected skeletal muscle abnormalities, including shifts from slow-twitch to fast-twitch type II fibres. decreased mitochondrial size and lower mitochondrial enzyme levels (Mancini et al., 1989; Drexler et al., 1992).

These histochemical, metabolic and vascular abnormalities of the limb muscles in heart failure may not be limited to the limb skeletal musculature. It has been proposed that such changes may fact, be more generalized, affecting all skeletal muscles, including the respiratory muscles (Mancini et al., 1995a). These intrinsic skeletal muscle abnormalities may contribute significantly to the symptoms of heart failure, particularly dyspnea. If the work of the respiratory muscles is increased or the muscles are weak, breathlessness could occur. Dyspnea may be the result of reduced cardiac output leading to respiratory muscle ischemia and eventually fatigue (Wilson and Mancini, 1993; See Figure A.1).

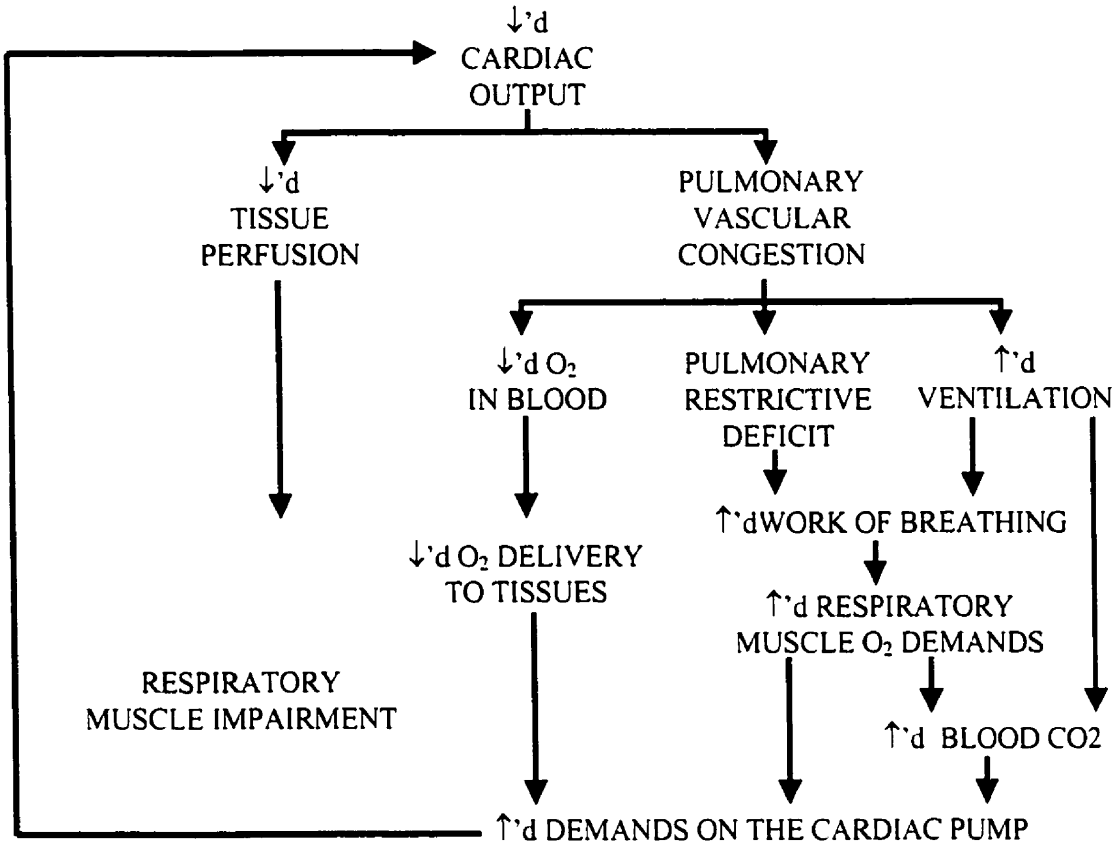

Figure A.1. Schematic demonstrating how decreased cardiac output may increase oxygen demands on the respiratory muscle resulting in potential respiratory muscle impairment. (modified from Macklem, Chest, 1980;78(5):753-8)

Respiratory Muscles

Respiratory muscles are skeletal muscles whose primary function is to rhythmically displace the chest wall in order to facilitate gas exchange within the lungs, ultimately maintaining arterial blood gases compatible with life (De Troyer & Estenne, 1988). Respiratory muscles are typically classified by function into either inspiratory or expiratory muscles. Some muscles have dual roles. The largest primary muscle of inspiration is the diaphragm. Although Goldman and Mead (1973) suggested that the diaphragm is the only significant muscle contracting to allow quiet inspiration, several other authors have clarified the importance of other chest wall muscles (Sampson & De Troyer, 1982; De Troyer & Estenne, 1988; Taylor, 1960). Both the internal and external intercostal muscles are also believed to have a role in inspiration, although their action remains controversial (De Troyer et al., 1983; De Troyer et al., 1985).

The internal intercostals include the internal interosseous intercostals and the parasternals (also referred to as the intercartilaginous intercostals ; Pick & Howden, 1974). The external intercostals and the parasternals are thought to be primarily muscles of inspiration, although at high lung volumes they may have a role in expiration, as stimulation of these muscles at these volumes results in a net rib movement downward (De Troyer et al., 1983; De Troyer & Estenne, 1988). Conversely, the internal interosseous intercostals which appear to have a role in expiration may participate in inspiration at low lung volumes as stimulation results in a net upward movement (De Troyer et al., 1983; De Troyer & Sampson, 1985).

The scalenes are considered to be primary muscles of inspiration and are constantly active during inspiration (De Troyer & Estenne, 1985). The accessory muscles of inspiration include the sternocleidomastoid, trapezius, pectoralis major and minor, serratus anterior, and latissimus dorsi (Campbell et al., 1970).

Expiration is generally considered to be passive (Celli, 1989). During increased activity and respiratory distress however, the abdominal wall (including the rectus abdominous, internal and external obliques and the transverse abdominous) contributes to both inspiration and expiration (Celli, 1989). The triangularis sterni is another muscle of expiration; it remains phasically active during quiet expiration and increases its activity with forced expiration (De Troyer et al., 1987). Finally, the quadratus lumborum assists in ventilation as a stabilizer of the lower rib cage (Basmajian & DeLuca, 1985).

Measurement

The simplest method of assessing respiratory muscle strength is to measure inspiratory and expiratory pressures at the mouth while the subject provides maximal efforts against a closed airway (Rochester, 1988). The technique generally used in the clinical and research setting is that established by Black and Hyatt (1969). These measurements have been shown to be both valid and reliable (Black & Hyatt, 1969). Maximal inspiratory pressure ($P_I$max) is assessed at residual volume (RV) or functional residual capacity (FRC), while maximal expiratory pressure ($P_E$max) is measured at total lung capacity (TLC) or FRC. Residual

volume and TLC are often chosen for $P_I$max and $P_E$max respectively as these volumes allow the muscles to be at an optimal length to produce a maximal effort.

Less commonly, respiratory muscle pressures may be measured within the pleural and abdominal cavities (Rochester, 1988). A balloon catheter is introduced through the nose and pharynx into the esophagus to measure pleural pressure. Similarly, a catheter is placed into the stomach to measure abdominal pressure. Esophageal (Pe) and gastric pressures (Pg) caused by active contraction of the respiratory muscles are estimated by subtracting end-expiratory or resting pressure from maximal inspiratory or expiratory efforts. Transdiaphragmatic pressure (Pdi) is calculated by subtracting Pe from Pg (Pdi = Pg - Pe). Pdi is usually measured when a subject performs a maximal inspiratory effort against a closed airway.

Respiratory muscle endurance is usually measured by use of the tension-time (pressure-time) index of the diaphragm (TTIdi) as proposed by Bellemare and Grassino (1982). This is the product of the contractile force (Pdi breath/ Pdi max) and duration (inspiratory duty cycle). In both normal human subjects and patients with chronic obstructive lung disease, the diaphragm becomes completely fatigued as the TTIdi exceeds 0.15 (Bellemare & Grassino, 1982).

Maximal voluntary ventilation (MVV) reflects airway resistance and respiratory muscle strength. Respiratory or ventilatory endurance is measured by determining the length of time during which maximal and submaximal levels of minute ventilation can be sustained

(Rochester, 1988). Endurance time is very short for ventilations greater than 90 % of MVV and prolonged for ventilations that are 60 to 70 % of MVV. The level of ventilation that can be sustained for 15 minutes, maximal sustainable ventilatory capacity (MSVC), follows a similar pattern. In normal subjects, the MSVC ranges from 60 to 80 % of MVV. Achieving levels of ventilation greater than MSVC requires increases in the neural drive. When the respiratory muscles shorten rapidly, the ability to produce force decreases. Therefore, breathing above MSVC will eventually produce inspiratory muscle fatigue (Rochester, 1988).

Dyspnea can be measured using the Dyspnea Index (DI) as described by Mahler et al. (1984). The index consists of three parts: the difficulty of the task producing the dyspnea, the extent of the effort required to produce dyspnea and the degree of functional impairment occurring as a result of the dyspnea. Each part is scored on a five point scale with the DI ranging from 0 to 12; the higher the dyspnea, the lower the score. This index has been shown to be valid and reliable in patients with cardiopulmonary limitations and correlates well with measures of functional ability such as the six-minute walk test. Dyspnea may also be measured by the modified Borg scale, a 10 point rating of perceived sensation of shortness of breath (Borg, 1982; Noble, 1982). This too, has been shown to be valid and reliable (Borg, 1982).

Respiratory Muscle Strength and Endurance

De Troyer et al. (1980) first reported reduced inspiratory muscle strength in patients with mitral stenosis using esophageal pressure measurements. Since then, several investigators have evaluated the impact of congestive heart failure on respiratory muscle strength using the methods proposed by Black and Hyatt (1969). The first published research on respiratory muscle strength in heart failure appeared at the beginning of the decade. In a well designed study, Hammond et al. (1990) assessed respiratory muscle strength in CHF patients by measuring each subject's maximal inspiratory and expiratory pressures at FRC, RV and TLC. Subjects with CHF as compared to normal subjects (Hammond et al., 1990) were found to have a reduced $P_I$max (61 cm H_2O at FRC, $p<0.001$; 59 cm H_2O at RV, $p<0.001$) and $P_E$max (62 cm H_2O at FRC, $p<0.001$; 69 cm H_2O at TLC, $p<0.001$). Since then several investigators have reported varying results. (Tables 1 and 2.)

Decreases in $P_I$max have been reported in several other studies (McParland et al., 1992; Nishimura et al., 1994; Ambrosino et al., 1994; Chua et al., 1995; Evans et al., 1995; McParland et al., 1995; Walsh et al., 1996; Vibarel et al., 1998; Daganou et al., 1999; see Table A.1). Unfortunately one of the investigators failed to report the $P_I$max values for the control group so analysis of this study is more difficult (Evans et al., 1995). Ambrosino et al. (1994) subdivided the heart failure group by degree of heart failure. They demonstrated no difference in $P_I$max in subjects with NYHA class II heart failure while demonstrating a significant decrease in $P_I$max in subjects with NYHA class III heart failure (70 cm H_2O) as compared to age-matched controls (104 cm H_2O, $p<0.01$; Ambrosino et al., 1994).

Table A.1. Published data on maximal inspiratory pressures ($P_I$max) in heart failure (HF) and age-matched control (AMC) subjects

Study	$P_I$max (cm H_2O)			
	FRC		RV	
	AMC	HF	AMC	HF
Hammond et al. (1990)	102(27) [18]	41(16)‡ [16]	106(28) [18]	47(20)‡ [16]
McParland et al. (1992)	98(?) [9]	80(20)* [9]	112(?) [9]	86(24)* [9]
Mancini et al. (1992)	101(14) [6]	81(23) [10]	---	---
Ambrosino et al. (1994)	104(28) [22]	88(27) [25][II]	---	---
	104(28) [22]	70(24)† [20][III]	---	---
Nishimura et al. (1994)	---	---	84(24) [15]	92(32) [10][II]
	---	---	84(24) [15]	60(15)* [13][III-IV]
Chua et al. (1995)	86(10) [7]	60(6)* [20]	89(13) [7]	77(7) [20]
Evans et al. (1995)	---	66(27)† [20]	---	---
McParland et al. (1995)	101(?) [15]	82(?)† [15]	111(?) [15]	91(?)† [15]
Walsh et al. (1996)	54(17) [10]	71(20)* [20]	---	---
	104(17) [10]	69(20)‡ [13]	---	---
Witt et al. (1997)	8.6(3.5)[a] [30]	6.7(2.4)† [47]	---	---
Daganou et al. (1999)	102(17) [16]	84(22)* [30][IHD]	---	---
	102(17) [16]	73(20)* [30][DCM]	---	—

values are mean (SD); [a] = values in kPa; [ ] = number of subjects; values measured at FRC (functional residual capacity), RV (residual volume), [II] = class II heart failure; [III] = class III heart failure; [III-IV] = class III to IV heart failure; [IHD] = ischemic heart disease; [DCM] = dilated cardiomyopathy

* $p \leq 0.05$, † $p \leq 0.01$, ‡ $p \leq 0.001$ compared with AMC

Table A.2. Published data on maximal expiratory pressures ($P_E$max) in heart failure (HF) and age-matched control (AMC) subjects

Study	$P_E$max (cm H_2O)			
	FRC		TLC	
	AMC	HF	AMC	HF
Hammond et al. (1990)	121(52) [18]	59(30)‡ [16]	143(56) [18]	74(31)‡ [16]
McParland et al.(1992)	131(?) [9]	114(33) [9]	173(?) [9]	133(38)* [9]
Mancini et al. (1992)	---	---	184(46) [6]	161(49) [10]
Ambrosino et al. (1994)	142(33) [22]	118(30) [25][II]	---	—
	142(33) [22	103(34)† [20][III]	---	---
Nishimura et al. (1994)	---	---	106(34) [15]	104(34) [10][II]
	---	---	106(34) [15]	84(18) [13][III-IV]
Chua et al. (1995)	135(9) [7]	95(6)* [20]	167(13) [7]	122(9)* [20]
Evans et al. (1995)	---	---	---	99(27)† [20]
McParland et al. (1995)	123(?) [15]	126(?) [15]	166(?) [15]	148(?)* [15]
Walsh et al. (1996)	---	---	---	---
	109(26) [10]	90(48) [13]	---	---
Daganou et al. (1999)	---	---	118(28) [16]	104(21) [30][IHD]
	---	---	118(28) [16]	90(20)* [30][DCM]

values are mean (SD); [ ] = number of subjects; values measured at FRC (functional residual capacity), TLC (total lung volume); [II] = class II heart failure; [III] = class III heart failure; [III-IV] = class III to IV heart failure; [IHD] = ischemic heart disease; [DCM] = dilated cardiomyopathy

* $p \leq 0.05$, † $p \leq 0.01$, ‡ $p \leq 0.001$ compared with AMC

Furthermore, there was a significant decrease in $P_I$max in class III subjects when compared to class II subjects ($p<0.05$). This finding was supported by Nishimura et al. (1994). Daganou et al. (1999) divided the heart failure subjects into groups based on cause of the failure. They reported a significant decrease in $P_I$max and in both the dilated cardiomyopathy group (DCM; 73 cm H_2O) and the ischemic heart disease group (IHD; 84 cm H_2O) as compared to controls (102 cm_2H O, $p<0.05$). The DCM group however, demonstrated a significant decrease in $P_I$max when compared to the IHD group ($p<0.05$). These studies suggest that type and degree of heart failure may influence inspiratory muscle strength (Ambrosino et al., 1994; Nishimura et al., 1994; Daganou et al., 1999).

Decreases in the strength of the expiratory muscles were also reported by several of these investigators (McParland et al., 1992; Ambrosino et al., 1994; Chua et al., 1995; Evans et al., 1995; McParland et al., 1995; Walsh et al., 1996; Vibarel et al., 1998; Daganou et al., 1999; see Table A.2). No difference was evident between class II and class III or class IV patients (Ambrosino et al., 1994; Nishimura et al., 1995). Similar to $P_I$max, Daganou et al. (1999) demonstrated a decrease in $P_E$max in DCM when compared to both age-matched controls and IHD ($p<0.05$).

Only four studies attempted to normalize the respiratory muscle strength values for age and gender differences by converting the measured value into a percent predicted (Mancini et al., 1992a; Nishimura et al., 1994; Evans et al., 1995; Nanas et al., 1999; Table A.3). Mancini et al. (1992a) and Nanas et al. (1999) used the formula of Black and Hyatt (1969) to predict respiratory pressures. This formula does not consider the effect of height on respiratory

muscle strength in women (Wilson et al., 1984), yet both studies included women. Evans et al. (1995) used the formulas developed by Wilson et al. (1984) which distinguish between men and women as well as considering the effects of both age and height on respiratory muscle strength. Nishimura et al. (1994) used formulas developed for the Japanese population which take into consideration the effects of aging on respiratory muscle strength. Mancini et al. (1992a) reported no difference in either the percent predicted $P_I$max or $P_E$max. Nishimura et al. (1994) demonstrated a difference in only $P_I$max in subjects with class III to IV heart failure when compared to controls (80% vs. 106%, $p<0.05$). While Evans et al. (1995) reported a significant decrease in both $P_I$max and $P_E$max ($p<0.01$), normal values were not provided for direct comparison. Nanas et al. (1999) demonstrated a similar decrease in $P_I$max ($p<0.05$) and $P_E$max($p<0.001$). With limited normalized data available, it is difficult to assess the decreases in $P_I$max and $P_E$max.

Orthotopic cardiac transplantation for end-stage heart failure is now a routine alternative for some patients with CHF. Mancini et al. (1995b) have taken advantage of this unique therapy to assess respiratory muscle strength of subjects pre- and post-transplantation in comparison to age-matched controls. (Table A.4.) There were no significant differences between any of the groups. In a study where subjects with heart failure were followed post-transplantation, Tsai and Ahmad (1997) confirmed that no significant changes in respiratory muscle strength occur post cardiac transplantation in spite of dramatic improvements in both cardiac function and symptomatology. In fact, in several of the subjects, respiratory muscle strength decreased post cardiac transplantation even though significant improvements were documented in both New York Heart Association (NYHA) classification ($p<0.001$) and left

Table A.3. Published data on inspiratory ($P_I$max) and expiratory pressures ($P_E$max) in heart failure (HF) and age-matched controls (AMC)

Study	$P_I$max (% predicted)				$P_E$max (% predicted)	
	FRC		RV		TLC	
	AMC	HF	AMC	HF	AMC	HF
Mancini et al. (1992)	86(10) [6]	76(15) [10]	---	---	81(19) [6]	80(21) [10]
Nishimura et al. (1994)	---	---	106(24) [15]	107(34) [10]^{II}	102(29) [15]	90(24) [10]^{II}
	---	---	106(24) [15]	80(21)* [13]$^{III-IV}$	102(29) [15]	85(25) [13]$^{III-IV}$
Evans et al. (1995)	---	64(24)† [20]	---	—	---	70(17)† [20]
Nanas et al. (1999)$^{\circ}$	---	---	88(18) [11]	73(24)* [45]	84(18) [11]	53(17)‡ [45]

values are mean (SD); [ ] = number of subjects; values measured at FRC (functional residual capacity), RV (residual volume), TLC (total lung volume); $^{\circ}$ = assessed post-exercise; ^{II} = class II heart failure; $^{III-IV}$ = class III or IV heart failure

* $p \leq 0.05$, † $p \leq 0.01$, ‡ $p \leq 0.001$ compared with AMC

Table A.4. Maximal inspiratory ($P_I$max) and expiratory pressures ($P_E$max) in heart failure (HF), in patients post heart transplant (TX) and in age-matched controls (AMC)

Study	$P_I$max			$P_E$max		
	CHF	TX	AMC	CHF	TX	AMC
Mancini et al. (1994)	29(14)[a] [15]	35(7) [8]	35(8) [8]	50(23) [15]	59(8) [8]	62(13) [8]
[1]Tsai and Ahmad (1997)	85(17)[b] [11]	82(19) [11]	---	105(28) [11]	103(32) [11]	—

values are means (SD); [a] = values in kPa; [b]= values in cm H_2O; [ ] = number of subjects in study; $P_I$max measured at residual volume; $P_E$max measured at total lung volume; [1] same subjects pre- and post-transplantation;
No statistical significance was reached in any of the group comparisons.

ventricular ejection fraction (LVEF; $p<0.001$). Tsai and Ahmad (1997) concluded that the impact of heart failure on respiratory muscle strength in CHF symptomatology is likely small.

Only two studies have attempted to assess the impact of heart failure on Pdi. Mancini et al. (1992a) measured Pdi at rest, during exercise, and after exercise in CHF and normal subjects. There was no difference in Pdi between groups at rest (HF: 5.8 cm H_2O, AMC: HF: 3.7 cm H_2O, p=NS). However, Pdi during exercise was significantly greater in heart failure (HF:18.6 cm H_2O, AMC: 12.1 cm H_2O, $p<0.05$; Mancini et al., 1992a). Evans et al. (1995) assessed Pdi at rest in heart failure and also found a significant increase ($p<0.01$). The tension-time index of the diaphragm was calculated by Mancini et al. (1992a) and demonstrated a similar pattern as Pdi. With increasing workloads, there was a greater increase in TTdi in heart failure than in controls ($p<0.05$). Absolute values were not given although a graph shows a steady increase in TTdi with an index of approximately 0.10 being reached at maximal workload when measured both at rest (Mancini et al., 1992a). This would indicate a trend toward diaphragmatic fatigue although Bellemare and Grassino (1982) stated that diaphragmatic fatigue occurs when the TTdi reaches 0.15.

In a recent study, investigators recognized that TTIdi only assesses the work done by the diaphragm (Vibarel et al., 1998). The work of the inspiratory muscles should be included to more accurately assess the complete work of inspiration. Using a formula previously validated (Ramonatxo et al., 1995), Vibarel et al. (1998) determined the tension-time index of the inspiratory muscles (TTMUS). If heart failure leads to a respiratory muscle

impairment, an increase in TTMUS should be noted. TTMUS was significantly increased in the heart failure group when compared to controls (HF: 0.08 vs. AMC: 0.04, $p<0.001$; Vibarel et al., 1998).

Maximal voluntary ventilation and MSVC have been examined in subjects with heart failure. Maximal voluntary ventilation is significantly reduced in this patient population as compared to age-, gender- and size-matched normal individuals (Mancini et al., 1992b; Mancini et al., 1995a; Mancini et al., 1995b). Maximal sustainable voluntary capacity has been similarly shown to be impaired in CHF patients (Mancini et al., 1995a; Mancini et al., 1995b). These results indicate that patients with heart failure may suffer from some degree of inspiratory muscle fatigue when an increased work of breathing occurs. Transplantation, although reversing the trend back towards normal, does not result in patients regaining normal values for either MVV or MSVC (Mancini et al., 1995b). It is not certain if this reversal is due to increased cardiac output or if histochemical, metabolic, and vascular abnormalities may be partly reversed (Mancini et al., 1995b).

Walsh et al. (1996) assessed inspiratory muscle endurance using a threshold loading technique. All subjects were required to breathe against a load (100 g) with an additional load (100 g) added at two minute intervals. The number of stages completed by the HF subjects (3.8) was significantly lower than that of the controls (7.5, $p<0.01$). The total test duration was also significantly less in HF (494 s) than AMC (996 s, $p<0.01$). Maximum tolerated threshold pressure was described as the maximum load a subject could tolerate for

a full two-minute period. This was also significantly reduced in HF (18.5 cm H_2O) when compared to controls (30.7 cm H_2O, $p \leq 0.01$; Walsh et al., 1996).

Skeletal Muscle Abnormalities

A prominent feature of CHF is skeletal muscle atrophy, with some patients progressing to a state of cardiac cachexia (Harrington & Coates, 1997). Mancini et al.(1992c) demonstrated severe muscle atrophy in over two-thirds of the subjects studied using mid arm muscle circumference and creatinine/height index. Muscle atrophy has likewise been demonstrated by computerized tomography and magnetic resonance imaging (Minotti et al., 1991; Minotti et al., 1993; Magnusson et al., 1994). As a result of muscle atrophy, decreases in muscle performance may be expected. Quadriceps strength in subjects with CHF has been studied by several groups (Magnusson et al., 1994; Minotti et al., 1991; Lipkin et al., 1981; Buller et al., 1991). Results vary among the groups with the larger studies demonstrating no significant changes in absolute strength.

Hand grip strength has also been assessed in heart failure (Davies et al., 1990; Evans et al., 1995; Walsh et al., 1996). Evans et al. (1995) documented a decreased grip strength to 43 percent of predicted in heart failure ($p<0.01$). Normal values were not presented. Walsh et al. (1996) however, found no difference in hand grip strength between heart failure and age-matched control subjects.

Changes in muscle histology may occur in the CHF population. An increase in the percentage of type II and type IIb muscle fibres has been reported although there is uncertainty as to which fibres are affected and to what degree (Lipkin et al., 1988; Mancini et al., 1989). Decreased mitochondrial density was demonstrated by Drexler et al.(1992). Vascularity may also play a role in skeletal muscle impairment. When capillary density was studied however, variable results were reported in the literature. Lipkin et al. (1988) showed no change, while Mancini et al. (1989) demonstrated an increase, and Drexler et al. (1992) documented a decrease in capillary density. In one histological study of the diaphragm in CHF, no significant change in fibre type distribution was found (Lindsay et al., 1992). Glycogen and lipid storage abnormalities as well as impaired lipid oxidation have been documented by a small number of investigators (Lipkin et al., 1988; Mancini et al., 1989; Drexler et al., 1992).

Relationships to Respiratory Muscle Impairment

Researchers have attempted to demonstrate a relationship between established limb skeletal muscle abnormalities and respiratory muscle function in patients with heart failure (Chua et al.1995; Evans et al.1995; Mancini et al., 1992c). Evans et al. (1995) demonstrated that hand grip strength was significantly related to Pdi in this population $r=0.527$, $p<0.05$) and cardiac output ($r=0.451$, $p<0.05$). In later studies by Evans et al.(1995), and McParland et al. (1995) however, no significant relationship was found between hand grip, exercise and CHF. Walsh et al. (1996) reported no relationship between maximal threshold pressure and grip strength.

When assessing quadriceps strength, although significantly reduced in patients with heart failure, there was no correlation with $P_I$max (Chua et al., 1995).

A relationship between dyspnea and respiratory muscle function may exist. Mancini et al. (1992a) demonstrated a close relationship between the sensation of dyspnea as measured by the Borg scale and $P_I$max, $P_E$max, FEV_1, and TTIdi. Likewise, McParland et al. (1992) demonstrated a relationship between both $P_I$max ($r=0.89$, $p=0.001$) and P_E max ($r=0.67$, $p=0.05$) and dyspnea in heart failure subjects as score by the DI. When the DI was assessed for dyspnea during activity, further significant correlations were demonstrated with $P_I$max and $P_E$max (McParland et al., 1992). Conversely, Evans et al. (1995) demonstrated no relationship between a Borg breathlessness score and either $P_I$max or $P_E$max.

Most investigators have demonstrated a significant relationship between $P_I$max at rest and peak $\dot{V}O_2$ (Nishimura et al., 1994; Chua et al., 1995; Dimopoulou et al., 1999; Nanas et al., 1999) although one study reported no relationship (Witt et al., 1997). No relationship however was established between $P_E$max and peak $\dot{V}O_2$ (Chua et al., 1995; Witt et al., 1997; Dimopoulou et al., 1999; Nanas et al., 1999). One study (Nishimura et al., 1994) also demonstrated a relationship in heart failure between CI and $P_I$max as a percent predicted although no relationship Ambrosino et al. (1995) between CI and $P_I$max expressed as an absolute measure. No relationships were demonstrated between either $P_I$max or $P_E$max and NYHA class (Witt et al., 1997) or LVEF (Ambrosino et al., 1995; Witt et al., 1997).

Respiratory Muscle Training

Mancini et al. (1995a) studied 14 patients with CHF to determine the effects of a respiratory muscle training program on respiratory muscle strength and exercise capacity. This program involving isocapnic hyperpnea, resistive breathing using the Threshold® inspiratory muscle trainer, strength training, and breathing 'calisthenics' was very selective, time-consuming and aggressive. Six of 14 subjects dropped out in the early stages of the study. In the remaining eight patients, training improved $P_I$max (↑ 14 cm H_2O, $p<0.01$), $P_E$max (↑ 39 cm H_2O, $p<0.001$), MVV (15 $l \cdot min^{-1}$, $p<0.05$) and MSVC (↑ 28.6 $l \cdot min^{-1}$, $p<0.05$). Post-training, the heart failure subjects were able to walk further during a six-minute walk test (↑ 320 ft, $p<0.001$) and had a higher peak $\dot{V}O_2$ during maximal exercise testing (↑ 1.9 $ml \cdot kg^{-1} \cdot min^{-1}$) was also demonstrated. The potential benefits of a respiratory muscle training program include remarkable improvements being shown in both MVV (greater than 50 %) and in sensation of perceived dyspnea (Mancini et al., 1995a). This should lead to improvements in activities of daily living in these patients. The results of this study however, need to be regarded with caution. The sample size was small and the convenience control group was likely less motivated as they did drop out of the original treatment program.

Cahalin et al. (1997) used a much less aggressive training program to assess the possible benefits of inspiratory muscle training. Whereas subjects in the Mancini et al. (1995a) study involved a number of training modalities including the Threshold® inspiratory muscle trainer set at 30% of $P_I$max, the Cahalin et al. (1997) study involved only the Threshold® inspiratory muscle trainer and prescribed training based on 20% of $P_I$max. Duration and frequency of

use also varied between the two groups. Mancini et al. (1995a) prescribed training for 20 minutes, three times a week compared to Cahalin et al. (1997) who trained their subjects for five to 15 minutes, three times a day. Like the Mancini et al. (1995a) study, the dropout rate was high with only eight of the fourteen subjects completing the eight week training program. Dropouts however, were not due to noncompliance. Subjects exited the study because they underwent surgery, had an intra aortic balloon pump inserted or in one case died. Thirteen of the 14 subjects completed 4 weeks of the program. Significant increases in both $P_I$max (12 cm H_2O, $p<0.05$), $P_E$max (11 cm H_2O, $p<0.05$) were reported. Dyspnea as measured by the modified Borg scale was also shown to improve significantly decreasing both at rest (↓0.7, p=0.0001) and during exercise (↓1.0, p=0.003). There were no significant relationships between respiratory muscle strength, dyspnea, NYHA classification, and LVEF after inspiratory muscle training.

Johnson et al. (1998) also used the Threshold® inspiratory muscle trainer to assess the impact of inspiratory muscle training in subjects with heart failure. Eighteen subjects were randomized into a training group (15 minutes, twice daily at 30% of $P_I$max) or a 'control' group (15 minutes, twice daily at 15% of $P_I$max). Sixteen of eighteen subjects completed the eight week training program with one dropout due to chest pain while breathing through the trainer, and one to death. $P_I$max increased significantly in the training group (25.4 cm H_2O) compared to the control (12.3 cm H_2O, p=0.04). It is important to note that the baseline mean $P_I$max in training group was lower than the control group (70 cm H_2O vs. 84 cm H_2O) although it is not stated whether the difference is significant or not. There were no reported

improvements in maximal exercise test performance, corridor walk performance, or in quality of life score post-training.

Continuous Positive Airway Pressure and Respiratory Muscles

Granton et al. (1996) demonstrated an improvement in inspiratory muscle strength with administration of nasal continuous positive airway pressure (CPAP). CPAP was slowly increased to a target pressure of 10 to 12.5 cm H_2O. Subjects used the CPAP for a minimum of six hours nightly over a three-month period. No dropouts occurred. $P_I$max increased from 65.5 percent predicted to 75.3 percent predicted ($p<0.005$). Significant improvements were also demonstrated in NYHA classification (pre-CPAP: 2.4 vs. post-CPAP: 1.6, $p<0.02$). Finally using the Chronic Heart Failure Questionnaire developed by Guyatt et al. (1989) in which a lower score is worse, significant improvements were also noted in dyspnea (pre-CPAP: 19.4 vs. post-CPAP:24.9, $p<0.01$) and fatigue (pre-CPAP: 15.4 vs. post-CPAP: 21.2, $p<0.005$; Granton et al., 1996).

Respiratory Muscle Function During Exercise

A limited number of investigators have recognized that the respiratory muscles and therefore perhaps dyspnea need to be assessed beyond the resting state in heart failure and have therefore examined the various pulmonary indices in the exercise state (Dimopoulou et al., 1999; Brunner-La Rocca et al., 1999; Nanas et al., 1999). $\dot{V}O_2$ has been demonstrated to be directly related to cardiac output and the extraction of oxygen at the tissue level.

Furthermore, oxygen kinetics, the rate of change of $\dot{V}O_2$ at the onset of exercise, is related to an increase in cardiac output (Koike et al., 1994). In patients with left ventricular dysfunction, there may be an inadequate increase of stroke volume during exercise and therefore a decreased cardiac output. This impairs $\dot{V}O_2$ (Mancini et al., 1991) and oxygen kinetics at the onset of exercise in heart failure (Koike et al., 1994). Although the research in this area needs to be further expanded, initial studies indicate a decrease in $P_I$max may be associated with a prolonged early recovery of oxygen kinetics during maximal exercise. This may lead to exercise intolerance in chronic heart failure (Brunner-La Rocca et al., 1999; Nanas et al., 1999).

In a study by Dimopoulou et al. (1999) maximal $\dot{V}O_2$ was shown to be correlated to FVC ($r=0.35$, $p=0.01$), FEV_1 ($r=0.45$, $p=0.001$), $FVEV_1$/FVC ratio ($r=0.37$, $p=0.009$), forced expiratory flow between 25 and 75 seconds ($r=0.047$, $p<0.001$), and $P_I$max ($r=0.46$, $p=0.001$). There was no correlation with $P_E$max, TLC, or the diffusing capacity of carbon monoxide. They concluded that lung function parameters influence exercise capacity in heart failure but only account for up to 30 percent of the variance noted in maximal exercise capacity (Dimopoulou et al., 1999).

Summary

Patients suffering with CHF generally complain of exertional fatigue and dyspnea. While the etiology of these symptoms remains unclear, several theories have been proposed. At the forefront of recent literature is the theory that poor cardiac output may result in impaired

oxygenation of body tissues including the respiratory muscles and this may result in weakness and consequently a sensation of dyspnea.

While some studies have demonstrated a decrease in both $P_I$max and $P_E$max, limited data is available when values have been normalized as a percent predicted. The evidence suggests that respiratory muscle weakness may occur in some heart failure patients but whether it occurs or not is likely multi-factorial with both the degree of failure and the type of disease considerations. While MVV is markedly decreased in these patients, diaphragmatic work of breathing is significantly increased. It is not clear whether these limitations improve after transplantation. Subjects may not have been followed long enough post-transplantation to determine the maximal gains. Required medications post-transplantation such as prednisone may also influence muscular performance, and this may account for an inability to fully normalize.

An early attempt to demonstrate training effects through a selective respiratory muscle training program has shown potential improvements in respiratory strength and dyspnea. Exercise tolerance, functional ability, or quality of life, however do not appear to be affected.

Respiratory muscle function may be impaired during exercise in heart failure with some evidence of altered oxygen kinetics. There appears to be a weak relationship between peak $\dot{V}O_2$ and inspiratory muscle strength as well as indices of pulmonary function. The research in this area is very limited however. It is well established that dyspnea limits activity in heart

failure patients. With the increased work of breathing during activity, perhaps the limited reserve capacity available in this population contributes to this often debilitating symptom.

Limitations to Current Literature

There are several limitations to the current literature. Patients with CHF are graded by the severity of their symptoms using the NYHA classification system. In this system, patients range from a class I (no symptoms but documented CHF) to a class IV (symptoms at rest). Most available studies have failed to discriminate between these groups although two did note that respiratory dysfunction may be greater in class III or IV CHF patients. Severity of symptoms in CHF needs to be considered when evaluating this population, as their primary limiting complaints are dyspnea and fatigue. The type of heart failure, dilated cardiomyopathy versus ischemic heart disease, may also bear consideration. Very few studies have distinguished between these two.

Difficulties in studying this patient population exist because of the wide variations in the clinical course. There are varying degrees of medical stability which are impossible to control for in an experimental situation. Furthermore, there are a wide variety of medications now available to assist in management of CHF including diuretics, beta-blockers, angiotensin converting enzyme inhibitors and inotropic agents. These may all affect dyspnea and exercise performance differently, yet are likewise difficult to control for in an experimental design.

Histological assessment of the respiratory muscles to determine histochemical, metabolic and vascular abnormalities could offer conclusive evidence of respiratory muscle abnormalities in patients with heart failure. Ethically however, research of the respiratory muscles is limited. Biopsy of these muscles in subjects compromised by heart failure has not been done.

Most of the literature assessing respiratory muscle function in heart failure reports only the measured values. Although age-matched controls have been included in many of the studies, other factors such as gender and height need to be considered in matching controls. When reporting pulmonary function data such as lung volumes, and FEV_1, predicted values are used for comparisons. Predicted values should be used when reporting $P_I$max and $P_E$max.

Finally, most of the literature to date has assessed respiratory muscle function during a resting state. As dyspnea tends to occur with activity, a closer examination of the impact of heart failure on the respiratory muscles during exercise is critical.

Future Research

The current published research poses several questions.

1. Although significant reductions in respiratory muscle strength and endurance have been demonstrated by a limited number of investigators, the question remains - is there respiratory muscle weakness associated with heart failure?
2. Does respiratory muscle weakness account for the dyspnea experienced by heart failure patients?
3. Is the degree of heart failure a factor in respiratory muscle weakness?
4. Is the type of heart failure a factor in respiratory muscle weakness?
5. What are the difference in respiratory muscle function in heart failure in a resting versus exercise state?
6. If respiratory muscle weakness exists in heart failure, can it be reversed?
7. Can dyspnea in heart failure be improved by maximizing respiratory muscle function?

Research in this area has only been published over the past decade. This research will need to be confirmed and expanded, while further research questions may be addressed. With CHF increasing in society, answers to many of these research questions become imperative in optimizing management of these patients.

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APPENDIX B: SAMPLE SIZE ESTIMATE

Sample Size Estimate

Using results from Ambrosino et al. (1995) on the breathing pattern, ventilatory drive and respiratory strength in patients with chronic heart failure and calculating for an unpaired t-test, the following figures were obtained (based on formulas supplied by Donner):

alpha (α) = .05, beta (β) = .20, power = .80, minimum detectable difference = 34 cmH_2O, standard deviation = 24

$$n = \frac{(Z_\alpha+Z_\beta)^2(2)(sd)^2}{(diff)^2}$$

$$n = \frac{(1.96+0.84)^2(2)(24)^2}{34^2}$$

$n = 7.8$

due to potential subject medical instability and inability to perform all tests, n was doubled

$n = 15$

Therefore sample size is 15 subjects per group.

$Z_\alpha = 1.96$ ($\alpha = 0.05$), $Z_\beta = 0.84$ ($\beta = 0.20$), sd=standard deviation, diff=minimal detectable difference

Ambrosino N, Opasich C, Crotti P, Cobelli F, Tavazzi L, Rampulla C: Breathing pattern, ventilatory drive and respiratory muscle strength in patients with chronic heart failure. Eur Respir J 1994;7:17-22.

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APPENDIX C:

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

New York Heart Association Classification

Class	Definition
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Braunwald E (ed): Heart disease: A textbook of cardiovascular medicine, Volume 1. WB Saunders Company, Philadelphia, 1997.

APPENDIX D: ETHICS REVIEW

The UNIVERSITY *of* WESTERN ONTARIO

Vice-President (Research)
Research Ethics Board - Medical Sciences Building

REVIEW BOARD FOR HEALTH SCIENCES RESEARCH INVOLVING HUMAN SUBJECTS

1997-98 CERTIFICATION OF APPROVAL OF HUMAN RESEARCH

ALL HEALTH SCIENCES RESEARCH INVOLVING HUMAN SUBJECTS AT THE UNIVERSITY OF WESTERN ONTARIO IS CARRIED OUT IN COMPLIANCE WITH THE MEDICAL RESEARCH COUNCIL OF CANADA "GUIDELINES ON RESEARCH INVOLVING HUMAN SUBJECT "

1997-98 REVIEW BOARD MEMBERSHIP

1) Dr B Borwein, Assistant Dean-Research - Medicine (Chairman) (Anatomy/Ophthalmology)
2) Ms S Hoddinott, Director of Research Services (Epidemiology)
3) Dr R Gagnon, St. Joseph's Health Centre Representative (Obstetrics & Gynaecology)
4) Dr F Rutledge, London Health Sciences Centre - Victoria Campus Representative (Critical Care - Medicine)
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6) Dr L Heller, Office of the President Representative (French)
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8) Ms S Fincher-Stoll, Office of the President Representative (Legal)
9) Dr D Freeman, Faculty of Medicine Representative (Clinical)
10) Dr D Sun, Faculty of Medicine Representative (Basic)(Epidemiology)
11) Dr M I Kavaliers, Faculty of Dentistry Representative (Dentistry-Oral Biology)
12) Dr H Laschinger, Faculty of Nursing Representative (Nursing)
13) Dr S Spaulding, Faculty of Applied Health Sciences Representative (Occupational Therapy)
14) Dr C Rice, Faculty of Kinesiology Representative (Kinesiology)
15) Dr D Rodenhiser, Research Institutes Representative (Paediatrics)
16) Mrs R Yohnicki, Administrative Officer
Alternates are appointed for each member

THE REVIEW BOARD HAS EXAMINED THE RESEARCH PROJECT ENTITLED
"Respiratory muscle strength pre-and-post-heart transplantation "

REVIEW NO E6025

SUBMITTED BY Dr C. Weermink, Transplant Unit, London Health Sciences Centre - University Campus

AND CONSIDERS IT TO BE ACCEPTABLE ON ETHICAL GROUNDS FOR RESEARCH INVOLVING HUMAN SUBJECTS UNDER CONDITIONS OF THE UNIVERSITY'S POLICY ON RESEARCH INVOLVING HUMAN SUBJECTS.

APPROVAL DATE 08 August 1997 (UWO Protocol, Letter of Information & Consent)

AGENCY HEART FAILURE RESEARCH FUND (Dr P Pflugfelder)

TITLE

Bessie Borwein, Chairman

c.c. Hospital Administration

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APPENDIX E:

PREDICTION EQUATIONS FOR RESPIRATORY MUSCLE STRENGTH

Prediction equations for maximal inspiratory ($P_I$max) and expiratory pressures ($P_E$max) in adults (over18 years)

Men: $P_I max = 142 - (1.03 \times age)$

$P_E max = 180 - (0.91 \times age)$

Women: $P_I max = -43 + (0.71 \times height)$

$P_E max = 3.5 + (0.55 \times height)$

Age is measured in years; height in cm; $P_I$max and $P_E$max in cm H_2O

Wilson SH, Cooke NT, Edwards RHT, Spiro SG: Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984;39:535-8.

APPENDIX F: THE NEW BORG SCALE

The Borg Category-Ratio Scale

RATING OF PERCEIVED BREATHLESSNESS

NEW BORG SCALE

0	Nothing at all	(just noticeable)
0.5	Very, very weak	
1	Very weak	
2	Weak	(light)
3	Moderate	
4	Somewhat strong	
5	Strong	(heavy)
6		
7	Very strong	
8		
9		
10	Very, very strong	(almost max)
●	Maximal	

Borg GA: Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-81.