INSPIRATORY MUSCLE STRENGTH IN ADULTS WITH STABLE CYSTIC FIBROSIS: CLINICAL PREDICTORS AND THE INFLUENCE OF DISEASE SEVERITY

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Dedications

To Jen, Brandon, and Nathan.

To all those affected by Cystic Fibrosis.
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Abstract

**Introduction:** The work of breathing (WOB) imposed on the inspiratory muscles (IM) is elevated in cystic fibrosis (CF). Impaired inspiratory muscle strength (IMS) may contribute to dyspnea and exercise intolerance. Literature favors the preservation of (IMS) in adults with CF; however, this may misrepresent IM involvement due to the heterogeneity of study participants. Impaired IMS cannot be fully ruled out as the influence of disease severity has not been investigated. Clinical predictors of IMS in adults with CF are needed to identify individuals at risk for inspiratory overload.

**Purpose:** The purpose of this study was to investigate the influence of disease severity on IMS and determine the potential for clinical measures to predict IMS in adults with stable CF.

**Methods:** Maximal inspiratory pressure expressed in cmH$_2$O (MIP) and percent of predicted (%MIP) was assessed to represent IMS in a cross-sectional sample of adults with stable CF. Between-group differences in MIP and %MIP were analyzed in adults with CF stratified by disease severity in comparison to healthy controls through general linear modelling. The ability for clinical measures to predict IMS was investigated through regression analysis.

**Results:** Fifty-eight adults with CF and 20 healthy controls completed the study. IMS was decreased in advanced pulmonary disease. Dyspnea was associated with MIP ($r=-0.48, p<0.001$) and %MIP ($r=-0.50, p<0.001$). Disease severity
accounted for 23% of the variance seen in MIP and %MIP after controlling for confounding variables (p<0.001). Resultant linear models explained 43% of the variance in MIP and 52% in %MIP.

**Conclusions:** Disease severity negatively influences IMS in adults with CF and impaired IMS can be missed when not controlling for the degree of airway obstruction. Decreased IMS is apparent in the presence of advanced CF-related lung disease though select individuals may be protected against this impairment. A combination of pulmonary, nutritional, and demographic factors may identify adults with CF at risk for inspiratory overload in need of IM testing. The clinical significance of these findings should be determined through prospective studies. Future research on the IM in CF must control for disease severity or risk misrepresenting the influence of CF lung disease.
Chapter I

Introduction and Background

Context and Background

Cystic fibrosis (CF) is an autosomal recessive genetic disorder affecting multiple body systems. It is generally considered a pulmonary disease as 90% of CF-related mortality is caused by respiratory failure (Flume, 2009). According to the Cystic Fibrosis Foundation (CFF) Annual Registry, there are over 27,000 individuals with CF in the United States. Survival has steadily increased with advances in medical care and early intervention. As of 2012, the median predicted age of survival equaled 41.1 years. Of the individuals in the CFF Registry, 49% were over the age of 18 (range= 0 – 82.7) indicating that CF is no longer just a pediatric disease (Cystic Fibrosis Foundation, 2013).

The comprehensive management of adults with CF deserves special attention. The importance of meeting the needs of this growing population is evident by the development of care guidelines specific to adults with CF in 2004 (Yankaskas, Marshall, Sufian, Simon, & Rodman, 2004). The interaction between the disease progression and its management over an increasing lifespan is leading to the emergence of secondary effects such as CF-related diabetes (CFRD), bone disease, and depression among others (Cystic Fibrosis Foundation, 2013). The relative novelty of this group necessitates research
specific to this population to identify chronic effects of the disease into adulthood and optimize therapeutic interventions.

Table 1.1

*Class of genetic mutations seen in cystic fibrosis*

<table>
<thead>
<tr>
<th>Mutation</th>
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<tr>
<td>I</td>
<td>Altered CFTR production</td>
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*Note.* This table was adapted from Koch et al, 2001.

The CF gene is found on the long arm of chromosome seven with over 1800 known mutations that impact the Cystic Fibrosis Transmembrane Regulator (CFTR) protein, which regulates chloride transport across cell membranes (Cystic Fibrosis Foundation, 2013; Salvatore et al., 2011; Yankaskas & Knowles, 1999). CFTR is also believed to play a role in inflammatory processes and the movement of other macromolecules (Divangahi et al., 2009). Five classes of mutations have been identified based on the resultant impact on the CFTR protein (Koch et al., 2001; Salvatore et al., 2011). The mutation class (Table 1.1) associated with CF, along with modifier genes, contribute to the various phenotypes seen with classes I through III associated with more severe
pulmonary disease (Koch et al., 2001; Salvatore et al., 2011). The delta F508 (ΔF508) class II mutation is present in 87% of individuals with CF (Cystic Fibrosis Foundation, 2013). The full function of CFTR is unknown.

The function of the airways, sweat glands, pancreas, and intestines are impaired as a result of the genetic defect associated with CF (O’Sullivan & Freedman, 2009). Research is emerging that potentially links CFTR mutations to skeletal muscle dysfunction and exercise intolerance (Lamhonwah et al., 2010; Selvadurai et al., 2002). In human skeletal muscle, CFTR has been identified within the sarcoplasmic reticulum and is believed to influence calcium regulation (Divangahi et al., 2009). In addition, deficiency in CFTR has been linked to diaphragmatic dysfunction in a CF mouse model (Divangahi et al., 2009). It is plausible that the CF-related alterations in human skeletal muscle function may extend to the muscles of inspiration. Inspiratory muscle (IM) dysfunction may have significant clinical consequences in CF as the imposed work of breathing is elevated due to progressive lung disease.

In newborns diagnosed with CF, pulmonary function is essentially normal but begins to deteriorate soon after birth (Linnane et al., 2008). Various theories exist to explain this progressive lung destruction (O'Sullivan & Flume, 2009). The production of abnormally viscous respiratory secretions is believed to predispose individuals with CF to chronic infections and recurrent pulmonary exacerbations (O’Sullivan & Freedman, 2009). The pathophysiologic effects associated with chronic infection lead to bronchiectatic changes (i.e. abnormal dilation and
scarring) within the airways and a progressive decline in pulmonary function (Davis, Drumm, & Konstan, 1996; O'Sullivan & Flume, 2009; Robinson & Bye, 2002). As a result, individuals with CF experience an increased work of breathing (WOB) and excessive dyspnea that is associated with decreased exercise capacity (Almajed & Lands, 2012; de Jong et al., 1997). As limited exercise capacity is linked to decreased quality of life and mortality, it is important to address its potential causes (Moorcroft, Dodd, & Webb, 1997; van de Weert-van Leeuwen et al., 2012).

CF-related pathologic changes within the respiratory system that contribute to exercise intolerance include progressive airflow limitation, excess WOB and impaired gas exchange (Almajed & Lands, 2012). These pulmonary limitations appear to effect exercise capacity to a greater extent in the presence of advanced CF as compared to individuals with milder disease (Moorcroft, Dodd, Morris, & Webb, 2005). Initial spirometric assessment in CF demonstrates obstructive patterns; however, restrictive patterns emerge in later stages of severity due to pulmonary fibrosis (Ziegler, Rozedder, Dalcin, & Menna-Barreto, 2009). These pulmonary impairments result in an increased ventilatory demand and resistive load imposed on the inspiratory pump for any level of metabolic activity. The pathologic changes of CF disease and subsequent ventilatory inefficiency elevate the WOB resulting in an increased oxygen cost of breathing (Bell, Saunders, Elborn, & Shale, 1996). “A majority of the muscular work required for breathing is performed during inspiration even in patients with chronic obstructive pulmonary disease (COPD)” (Mador, 1991, pg. 1430). An
imbalance in WOB relative to the strength of the IM may have significant clinical consequences. Impaired contractility of the IM could exaggerate this imbalance and contribute to the sensation of dyspnea, exercise intolerance, altered arterial blood gases and potentially respiratory failure in adults with CF.

Dyspnea has been defined as “a subjective experience of breathing discomfort that consists of qualitative distinct sensations that vary in intensity…derived from physiological, psychological, social, and environmental factors” (Parshall et al., 2012, pg. 436-437). The experience of dyspnea is typically described as an increased sensation of effort (Mahler, 2006). In pulmonary disease, this effort involves the inspiratory and expiratory phases of breathing (Mahler et al., 1996; O'Donnell, Bertley, Chau, & Webb, 1997). Many theories exist pertaining to the multi-factorial genesis of dyspnea in health and disease; however, “the descriptors of dyspnea support the concept that the inspiratory muscles play an important role” pertaining to its physiologic origin (Mahler, 2006, pg. 234). The influence of the inspiratory muscles on the sensation of dyspnea should be acknowledged and investigated as dyspnea may be useful in predicting survival in pulmonary disease (Nishimura, Izumi, Tsukino, & Oga, 2002). Interventions designed to enhance IM function may alleviate dyspnea and potentially transfer to improved survival in CF.

The perceived effort of breathing is influenced by the inspiratory pressure generated per breath ($P_{br}$) relative to the maximal pressure that can be generated by the IM (i.e. inspiratory muscle strength (IMS)). The “active muscle
force that occurs with breathing” influences the sensation of dyspnea (Parshall et al., 2012, pg. 438). As the ratio of $P_{br}$ to maximal inspiratory pressure (MIP) increases, the perceived breathing effort will increase and contribute to the sensation of dyspnea (Grazzini, Stendardi, Gigliotti, & Scano, 2005). Inspiratory workloads requiring muscle forces greater than 60% of the MIP or 40% of the maximal trans-diaphragmatic pressure are considered non-sustainable (Roussos, Fixley, Gross, & Macklem, 1979; Roussos & Macklem, 1977). However, the ability for the inspiratory muscles to sustain breathing is influenced by the $P_{br}/$MIP ratio and the inspiratory duty cycle ($T_i/T_{tot}$) represented as the inspiratory time ($T_i$) relative to the total time of the respiratory cycle ($T_{tot}$) (Bellemare & Grassino, 1982a, 1982b; Ramonatxo, Boulard, & Prefaut, 1995). This tension-time index (TTI) can be calculated as follows:

$$TTI = \left( \frac{P_{br}}{MIP} \right) \times \left( \frac{T_i}{T_{tot}} \right)$$

Critical values for the TTI above which the IM are prone to fatigue have been identified in the healthy population (Bellemare & Grassino, 1982a, 1982b; Ramonatxo et al., 1995). Inspiratory workloads nearing or in excess of these values may contribute to inefficient breathing patterns, enhance the perception of breathing, and/or contribute to IM fatigue (Mador, 1991; Mador & Acevedo, 1991). Excessive oxygen cost of breathing ($V_{O_2}$-breath) associated with fatiguing inspiratory workloads may decrease peripheral muscle performance due to a preferential perfusion of the IM at the expense of exercising limbs (Dempsey, Romer, Rodman, Miller, & Smith, 2006). This later phenomenon has
frequently been referred to as the “metaboreflex” and may result in peripheral muscle fatigue.

In 1997, Harms et al evaluated the effect of IM work during maximal exercise in healthy trained individuals (Harms et al., 1997). Through a controlled sequence of loading and unloading of the IM, the authors noted significant changes in physiologic responses during exercise on a cycle ergometer at similar absolute intensities. Inspiratory loading resulted in a significant decrease in lower extremity (LE) perfusion and oxygen consumption (VO₂-legs) with no change in whole body oxygen consumption (VO₂-tot) as compared to control situations. Unloading of the IM resulted in a significant increase in both LE perfusion and VO₂-legs with a lower VO₂-tot.

From these findings it is suggested that increased inspiratory loads can create a competition for blood flow between the IM and the exercising muscles. In response, a “metaboreflex” shunts perfusion away from the lower extremities and towards the IM to maintain their performance. It is reasonable to believe that this decreased perfusion may compromise the capacity of the peripheral exercising muscles. Interestingly, unloading the IM improved the VO₂-legs suggesting the WOB at maximal exercise alone may be sufficient to induce such a response. These findings were further supported by similar study by the same authors showing up to “14-16% of the cardiac output at maximal exercise is directed to the respiratory muscles” to meet their demand (Harms et al., 1998,
Excessive inspiratory work may indirectly limit exercise performance through the compromise of peripheral blood flow.

Ventilatory workloads resulting in inspiratory fatigue are rarely experienced in healthy populations due to the inherent ventilatory reserve, respiratory muscle capacity, and the low VO₂-breath. However, IM fatigue can be induced in controlled laboratory settings during near maximal exhaustive exercise (Johnson, Babcock, Suman, & Dempsey, 1993; Perret, Pfeiffer, Boutellier, Wey, & Spengler, 1999). Whether or not inspiratory fatigue occurs outside of the research setting is unclear as the body is believed to alter breathing patterns and employ physiologic responses to avoid fatigue of the IM even at the expense of effective gas exchange (Gandevia, Allen, Butler, Gorman, & McKenzie, 1998). These responses may represent the body’s attempt to maintain a TTI below its critical level in the presence of excessive loads and result in dyspnea, ventilatory inefficiency, and exercise intolerance. The relationship between MIP and TTI supports the importance of IMS as a major contributor to overall inspiratory muscle performance. Impaired IMS reflected as a decreased MIP would inherently elevate the P_{br}/MIP and influence the TTI and enhance dyspnea (Larson & Kim, 1987).

MIP is commonly decreased to 40 – 60% of predicted values in chronic obstructive pulmonary disease (COPD) and may contribute to dyspnea and exercise intolerance (Larson, Covey, & Corbridge, 2002). This impairment appears to result from hyperinflation, nutritional depletion, pulmonary
exacerbations, and use of systemic corticosteroids, all of which are also common in CF (Larson et al., 2002). Hyperinflation can depress the diaphragm placing the muscle in a shortened state. This positional change creates a mechanical inefficiency in the diaphragm limiting its contractile potential and is linked to diaphragmatic dysfunction in CF (Braun, Arora, & Rochester, 1982; Pradal et al., 1994). Energy expenditure is elevated in individuals with CF and disease related gastrointestinal abnormalities cause malabsorption of dietary nutrients (Matel & Milla, 2009). Chronic caloric deficits in individuals with CF frequently result in malnutrition characterized by the loss of lean body mass (LBM) which can negatively affect skeletal muscle function (Culhane, George, P earo, & Spoede, 2013; Olveira et al., 2012; Stallings, Stark, Robinson, Feranchak, & Quinton, 2008). The frequency of pulmonary exacerbations is also associated with LBM wasting and systemic corticosteroid use can contribute to skeletal muscle weakness in CF (Alicandro et al., 2013; Barry & Gallagher, 2003). All of these factors are related to disease severity which is associated with the decline in MIP seen in pulmonary disease (Kabitz, Walterspacher, Walker, & Windisch, 2007; Tudorache, Oancea, & Mladinescu, 2010).

In 1992, Mahler et al evaluated MIP, dyspnea, and lung function in individuals with symptomatic COPD (Mahler & Harver, 1992). A fair relationship was found between MIP and measures of dyspnea including the Medical Research Council scale and the Baseline Dyspnea Index (p<0.05). In addition, MIP was identified along with dyspnea and lung function as significant contributors to the physiologic presentation of COPD (Mahler & Harver, 1992).
Subjects with severe dyspnea as measured by the baseline dyspnea index presented with lower IMS than those with mild to moderate dyspnea. These findings further support the clinical relevance of MIP in pulmonary disease.

MIP also appears to impact exercise capacity in pulmonary disease. In 1994, Wijkstra et al reported a moderate relationship between MIP and the distance walked in six minutes \((r=0.58, p<0.001)\) and a fair relationship between MIP and the maximal work rate achieved on a lower extremity cycle ergometer \((r=0.45, p<0.001)\) (Wijkstra et al., 1994). The correlation between MIP and exercise capacity was greater than the correlation with dyspnea and similar to the correlation with lung function indicating the clinical value of this measure in pulmonary disease (Wijkstra et al., 1994). The potential influence of MIP on functional exercise capacity is further supported by the work of Gosselink et al (1996). Through stepwise multiple regression analysis, it was shown that quadriceps strength and MIP contributed to the distance walked in six-minutes explaining 45% of the variance \((p<0.001)\) (Gosselink, Troosters, & Decramer, 1996).

Non-invasive measurement of MIP at the mouth is a reliable assessment of global IMS and is easy to implement in the clinical setting (American Thoracic Society/European Respiratory, 2002). MIP may also serve as an index for the fatigability of the inspiratory muscles as the ability to sustain effective inspiratory work is influenced by the \(P_{br}/\text{MIP}\) ratio within the TTI (Bellemare & Grassino, 1982a; C. Roussos et al., 1979). The contractile force generated by the
inspiratory muscles relative to their strength can play a role in the development of inspiratory muscle fatigue (Mador, 1991).

Inspiratory workloads requiring the generation of large pressure relative to MIP may contribute to dyspnea, exercise intolerance, and potentially respiratory failure in adults with CF. An imbalance between the required $P_{br}$ and MIP may occur directly from the increased WOB associated with progressive pulmonary decline. In the presence of normal IMS, these elevated workloads may be within the capacity of the inspiratory muscles and have a negligible impact on exercise performance. However, adults with CF present with a progressive decline in pulmonary function, hyperinflation, decreased nutritional status, and frequent exacerbations requiring the use of systemic corticosteroids which have been suggested to impair the contractility of the IM in COPD (Larson et al., 2002). In the presence of impaired IMS, an imbalance may exist between the imposed inspiratory demand and the capacity of the IM to meet this demand. An imbalance may have serious clinical implications especially during exercise and/or acute pulmonary exacerbations when the WOB is further increased. Inspiratory muscle training (IMT) or other rehabilitation methods may attenuate these responses for some adults with CF.
Problem Statement and Goals

Increased WOB associated with the progressive pulmonary decline in CF is well known. Current literature may misrepresent inspiratory muscle involvement in CF and impaired IMS may be overlooked. This fact is due to the heterogeneity of subjects grouped together particularly pertaining to disease severity. Current research favors the preservation on MIP in adults with CF based on mean values of heterogeneous samples though individuals can have a variety of presentations ranging from below normal to supra-normal levels (Barry et al., 2008; Dunnink, Doeleman, Trappenburg, & de Vries, 2009; Mier, Redington, Brophy, Hodson, & Green, 1990). In the adult population, the influence of disease severity on MIP has not been investigated and the true impact of CF on global IMS unknown. Factors that negatively affect the inspiratory muscles in CF have been suggested; however, specific clinical identifiers of individuals with impaired IMS are needed.

Consistent with this problem statement, this project has two primary goals:

Goal #1:

Investigate the influence of disease severity on global inspiratory muscle strength in adults with stable cystic fibrosis.

Goal #2:

Investigate the ability of common clinical measures to predict global inspiratory muscle strength in adults with stable CF.
**Definitions**

Adults with cystic fibrosis: individuals 18 years of age or older with a confirmed diagnosis of CF through genotyping or sweat testing (sweat chloride levels $>60\text{mmol/L}$) (Farrell et al., 2008).

**Disease severity:** as classified by the guidelines set forth by the CF Foundation based on the percent predicted forced expiratory volume in one-second ($\%\text{FEV}_1$), where $\%\text{FEV}_1 > 70\%$ indicates mild lung disease, $40 – 69\%\text{FEV}_1$ indicates moderate lung disease, and $\%\text{FEV}_1$ less than $40\%$ indicates severe lung disease (Cystic Fibrosis Foundation, 2013).

**Disease stability:** the absence of any signs or symptoms associated with a pulmonary exacerbation.

**Hyperinflation:** determined by the ratio of residual volume (RV) to total lung capacity (TLC) assessed during routine pulmonary function tests (PFT) during period of disease stability. Significant hyperinflation shall be defined as an RV/TLC $> 50\%$. Alternate representations of hyperinflation will include RV in liters and percent-predicted.

**Ideal body weight:** the recommended body weight based on height and sex that is associated with optimal health using the Metropolitan Life Insurance height-weight tables (Metropolitan Life Insurance Company, 1983).

**Impaired inspiratory muscle strength:** mean values of MIP in cmH$_2$O or percent-predicted significantly lower than healthy matched controls (as determined by
statistical analysis) shall identify impaired IMS. To aid in determining clinical significance, impairments shall further be defined as MIP values < 80 cmH$_2$O (American Thoracic Society/European Respiratory, 2002). Alternately, values below 80% of predicted may reflect impaired IMS.

**Inspiratory muscle strength:** maximal inspiratory pressure measured at the mouth after the subject completes a maximal exhalation to residual volume. The measurement will be recorded in cmH$_2$O and percent-predicted.

**Lean body mass:** the weight of the individual's body that is not fat and measured as the difference between total body weight and fat weight expressed in kilograms (kg).

**Nutritional status:** represented as the ratio of LBM to ideal body weight (IBW) reflecting macro nutritional status. Nutritional depletion will be identified as a LBM/IBW <69% for males and <67% females as these values were associated with decreased MIP in adults with CF (Ionescu et al., 1998). Body mass index (BMI), lean body mass index (LBMI), and the percent of ideal body weight (%IBW) will also be used as alternate measures of macro nutrition.

**Percent of ideal body weight:** calculated as the ratio of the individual's whole body weight to the recommended IBW as per the Metropolitan Life Insurance height-weight tables (Metropolitan Life Insurance Company, 1983).

**Pulmonary exacerbation:** presence of signs and symptoms of pulmonary infection including increased shortness of breath, changes in sputum production
(increased quantity and/or viscosity), increased cough, decreased weight, abnormal respiratory examination, and/or decline in lung function (%FEV$_1$ decrease by 10% in the past four weeks) (Flume et al., 2009; Goss & Burns, 2007).

**Upper extremity muscle mass:** defined by the measurement of mid arm muscle circumference (MAMC) as calculated from the triceps skin fold measurement and the mid-arm circumference. Decreased upper extremity muscle mass (UEMM) shall be identified as MAMC < 70% of predicted as this value was associated with decreased MIP in adults with CF (Ionescu et al., 1998).

**Research Aim and Hypotheses**

The research aims of this study were to examine global IMS in adults with stable CF across a range of disease severities to infer the effect of progressive CF on IMS and investigate the potential for a set of clinical characteristics to predict MIP in this population.

Consistent with the aims and goals of this research project, the following hypotheses were proposed:

**Hypothesis 1a:** Inspiratory muscle strength would not significantly differ between adults with stable CF with mild lung disease as compared to healthy controls.

**Hypothesis 1b:** Inspiratory muscle strength would be significantly decreased in adults with stable CF with moderate to severe lung disease.
as compared to healthy controls and to those with less severe lung disease.

**Hypothesis 2:** The linear combination of disease severity, hyperinflation, nutritional status, and upper extremity muscle mass will predict inspiratory muscle strength in adults with stable CF.

**Significance and Need for the Study**

If present, impaired IMS may have significant clinical consequences in adults with CF and contribute to dyspnea, ventilatory inefficiency, and exercise intolerance. The decreased exercise capacity is of particular importance as it is associated with mortality (Moorcroft et al., 1997; Tantisira, Systrom, & Ginns, 2002; van de Weert-van Leeuwen et al., 2012). During pulmonary exacerbations, metabolism and WOB are both increased and MIP may decrease (Naon, Hack, Shelton, Gotthoffer, & Gozal, 1993; Wieboldt et al., 2012). Exacerbation-related declines in MIP accompanied by increased WOB may significantly elevate the $P_{Br}$/MIP ratio, influence the TTI, and potentially delay recovery. Impaired IMS at baseline may exaggerate this response and be offset by specific treatment interventions aimed at improving inspiratory muscle performance.

IMT can improve IM function in individuals with COPD; however, baseline inspiratory muscle weakness appears to be a perquisite for the transference to dyspnea, and exercise capacity (Geddes, O'Brien, Reid, Brooks, & Crowe, 2008; Geddes, Reid, Crowe, O'Brien, & Brooks, 2005; Gosselink et al., 2011; Lotters,
van Tol, Kwakkel, & Gosselink, 2002). The burden of additional interventions such as IMT should be considered prior to imposing them in CF as the demands and time commitments associated with disease management is already extreme (Sawicki, Sellers, & Robinson, 2009). The increased demands of added interventions may compromise aspects of quality of life in CF rather than enhance them (Schmidt et al., 2011). Additional treatment burdens may potentially infringe on adherence to other well-established treatments or time for simple leisure activities. Decreased IMS has not been confirmed nor adequately refuted to exist in individual adults with CF and should be investigated further prior to considering IMT as appropriate subject selection is likely imperative (Houston, Mills, & Solis-Moya, 2008; Reid, Geddes, O'Brien, Brooks, & Crowe, 2008).

The importance of confirming or refuting the existence of decreased IMS at baseline in adults with CF in this project cannot be understated. The results of this study can provide a foundation for future research in this area. If impaired IMS does not exist, then current theories on the potential efficacy of IMT, its mechanism of action, optimal training protocols, and the role of IMS in the clinical course of the disease should be challenged in this population. If decreased IMS does exist, the results of this study will aid the medical community in identifying individuals susceptible to this impairment, determine its clinical significance, and investigate interventions aimed at attenuating its effects. Through proper sequential research in this manner, the benefits of IMT in select adults with CF
may far outweigh the additional treatment burden as median life expectancy continues to increase.
References


Chapter II

Review of the Literature

Introduction

The ventilatory pump is comprised of the lungs, airways, thorax, and respiratory muscles. Of these elements, the muscles involved in inspiration handle a significant portion of the WOB even in the presence of pulmonary disease (Mador, 1991). These muscles rarely limit exercise performance in healthy individuals as the imposed WOB is normally well within their capacity (Aaron, Seow, Johnson, & Dempsey, 1992; Romer, Miller, Haverkamp, Pegelow, & Dempsey, 2007; Wasserman, Hansen, Sue, Stringer, & Whipp, 2005). However, “excessive” inspiratory work may indirectly limit exercise by increasing the sensation of dyspnea, inducing inefficient breathing patterns, and/or altering vascular responses.

Figure 2.1 was devised for this project to illustrate the theoretical physiologic consequences of excessive inspiratory demand on exercise (Dempsey, Harms, & Ainsworth, 1996; Dempsey, Romer, Rodman, Miller, & Smith, 2006). Increased inspiratory demands may contribute to the sensation of dyspnea by elevating the required pressure per breath relative to the MIP (i.e. the $P_{br}/MIP$ ratio). Excessive demands may further alter breathing patterns, and potentially contribute to diaphragmatic fatigue (Johnson, Babcock, Suman, &
In trained individuals, high intensity exercise may lead to increased inspiratory demand, which can result in elevated $P_{br}$: MIP ratio. This can lead to increased perception of breathing, alterations in breathing pattern to combat inspiratory fatigue, and alterations in perfusion to combat inspiratory fatigue. These changes can result in decreased exercise tolerance.

*Figure 2.1*. The theoretical effects of inspiratory demand on exercise performance. $P_{br}$ = inspiratory pressure generated per breath, MIP = maximal inspiratory pressure.
trigger preferential perfusion of the IM predisposing the peripheral exercising musculature to fatigue (Romer & Polkey, 2008). Such excessive demands rarely occur in healthy individuals except during near-maximal exercise but could exist in pulmonary populations at lower intensities. This “metaboreflex” has been identified in heart failure and its implications have been proposed to exist in pulmonary disease (Dempsey et al., 2006; Olson et al., 2010; Roseguini et al., 2008).

Restrictive and/or obstructive pulmonary pathology can result in increased inspiratory workloads secondary to an abnormally elevated ventilatory demand and limited ventilatory reserve. Extreme inspiratory demands can result in direct or indirect failure of the ventilatory pump. According to Bye et al:

“The respiratory system may fail directly or indirectly. Indirect failure would occur if the additional oxygen (O2) provided by increasing ventilation was used by the ventilatory muscles thus depriving the rest of the body of O2. Direct failure would result if the ventilatory pump would fail to provide sufficient ventilation to provide efficient gas exchange. Lastly, the ventilation may be temporarily adequate but respiratory muscle fatigue may eventually cause ventilatory insufficiency.” (Bye, Farkas, & Roussos, 1983, pg. 439).

The CF-related decline in respiratory physiology may increase the inspiratory demand and result in direct or indirect failure of the ventilatory pump as described above. Such demands may become evident at rest in advanced
disease and/or during acute periods of elevated WOB associated with exercise and/or pulmonary exacerbations. In the presence of impaired IMS these effects may have a pronounced impact on dyspnea, peripheral muscle function, and ventilatory efficiency that may be alleviated through therapeutic interventions.

Inspiratory muscle training (IMT) has demonstrated the ability to improve IMS, dyspnea, and functional capacity in individuals with COPD particularly in the presence of inspiratory muscle weakness (Beckerman, Magadle, Weiner, & Weiner, 2005; Covey et al., 2001; Gosselink et al., 2011). As impaired IMS is likely to be prerequisite to the physiologic consequences explained above, caution should be used when applying these research results in the adult CF population as alterations in IMS are less understood. Additional baseline knowledge on IMS specific to the adult CF population is essential to advance research in this area and help determine the potential efficacy of therapeutic interventions such as IMT.

Consistent with the research aims of this study, the purpose of this literature review is to:

1. Appraise aspects of inspiratory muscle function and their measurement.

2. Evaluate the current literature on the efficacy of IMT in CF in comparison to COPD.

3. Evaluate the current literature on IMS in adults with CF.
Methods

Primary areas of literature were identified to provide the framework for this study as outlined above. Individual literature searches were performed on the PubMed, Medline (1948 – present) and CINAHL (1982 – present) databases to locate relevant articles. Primary keywords included: cystic fibrosis and inspiratory muscle. A similar search strategy was used pertaining to COPD to locate articles addressing inspiratory muscle training for comparison to the CF literature. To locate articles pertaining to aspects of inspiratory muscle function and measurement the following keywords were utilized: inspiratory muscle, strength, endurance, and tension time index. Using Boolean logic, primary keywords were combined with “and” or “or” to locate articles specific to this search. Abstracts of the resultant articles were manually reviewed and relevant articles identified.

Articles were included if they addressed the topic areas of inspiratory muscles, inspiratory muscle training and the measurement of inspiratory muscle function. Relevant articles focusing on the measurement of inspiratory muscle function in health and pulmonary disease were retained for part 1 of this review. Articles evaluating inspiratory muscle training in both CF and COPD were included for comparison in part 2. In evaluating aspects of inspiratory muscle strength for part 3, the included articles were specific to adults with CF as identified by a mean age of 18 years or older in the study population.
Bibliographies of all included articles retrieved were cross-referenced to ensure key articles were relevant to each section were not omitted.

**Aspects of Inspiratory Muscle Function and their Measurement**

The diaphragm is the primary muscle of inspiration and bears the primary burden of the imposed WOB at rest. However, the diaphragm and the accessory muscles of inspiration collectively contract to perform inspiratory work which represents a majority the WOB as exhalation is aided by the elastic recoil of the lungs and chest wall in absence of disease. The collective IM possess similar characteristics to the peripheral skeletal muscles including aspects of muscular strength and muscular endurance. Muscular strength is the maximal tension a muscle can generate in a single isolated contraction whereas weakness is “a condition in which the capacity of the rested muscle to generate force is impaired” (NHLBI, 1990, pg. 474). Muscle endurance represents the ability of a muscle to sustain a given workload over time (American Thoracic Society/European Respiratory, 2002). Muscle fatigue is a transient decrease in the ability to generate tension, or perform work, which is recovered with rest (Mador, 1991). Fatigue may occur through central or peripheral mechanisms. Central mechanisms limit the ability of the central nervous system (CNS) to generate adequate stimuli relative to the demand (Mador, 1991). Peripheral mechanisms may occur anywhere during the CNS-to-muscle transmission or within the metabolic capacity of the muscle itself such as depletion of energy stores (Mador, 1991).
Muscular endurance is influenced by the physiologic and metabolic characteristics of the muscle and is related to the relative force of a given contraction. Nutritional depletion may decrease muscle mass and available macro and micro nutrients for energy transfer during muscular activity limiting the contractile processes. The ability for a muscle to sustain or repeat a contraction is inversely related to the force generated relative to the strength of that muscle. The greater the contractile force of a muscle relative to its maximal force-generating capacity the less time the muscle will be able to sustain/repeat the contraction. As this ratio increases within the inspiratory muscles, the perception of effort also increases and breathing patterns may be altered. These physiologic responses may limit the ability of the ventilatory pump to sustain a given workload resulting in either direct or indirect failure (Bye et al., 1983). In this manner, muscular strength, endurance, and overall performance are intimately related.

When the IM contract, tension is generated to increase intrathoracic volume and create adequate negative pressure for inspiration to occur. As such, IMS is typically measured in terms of negative pressure recorded as absolute values represented in units of cmH₂O (American Thoracic Society/European Respiratory, 2002). In order to isolate the diaphragm, costly invasive procedures are implemented to quantify trans-diaphragmatic pressure (T\text{di}). One of the earliest introductions of this technique was done in 1960 (Agostoni & Rahn, 1960). Measurement of T\text{di} is performed through the insertion of balloon catheters into the esophageal and gastric regions connected to pressures
transducers. “Pressure within the esophagus ($P_{es}$) is a reflection of pleural pressure ($P_{pl}$), whereas the gastric pressure reflects abdominal pressure ($P_{abd}$). The difference between these two measurements is the $T_{di}$” (Troosters, Gosselink, & Decramer, 2005, pg. 64). Pressure generated during maximal diaphragmatic contractions ($T_{di\max}$) represents diaphragmatic strength (American Thoracic Society/European Respiratory, 2002).

The benefit of measuring the $T_{di}$ is its ability to isolate diaphragmatic performance and provide specific information pertaining to this muscle. However, the procedure is invasive and uncomfortable for the subject making it unsuitable for clinical use. $T_{di}$ measurements have also been criticized due to the significant variability reported between studies in the literature (Laporta & Grassino, 1985). The transducers are accurate but expensive and reliable measurements are dependent on, and specific to, balloon placement and procedural techniques (Laporta & Grassino, 1985; Troosters et al., 2005). As the diaphragm works collectively with the accessory muscles of inspiration, this measure may not reflect the overall “strength” of the global inspiratory pump nor translate to functional performance.

As a reasonable alternative, inspiratory pressure at the mouth can be measured non-invasively and is considered a representation of the contractile force of the collective inspiratory muscles. Mouth pressures generated during a maximal forceful inspiration is an acceptable measure of global IMS (American Thoracic Society/European Respiratory, 2002). This maximal inspiratory mouth
pressure has been correlated to the $T_{di}$ supporting its validity as a representation of inspiratory strength (Braun, Arora, & Rochester, 1982; Kabitz, Walker, Walterspacher, & Windisch, 2007; Ramonatxo, Boulard, & Prefaut, 1995). In 1995, Ramonatxo found a correlation coefficient of 0.94 (p<0.001) between MIP and $T_{di}$ in healthy subjects and those with chronic COPD. Reliability of MIP has been established in COPD, bronchiectasis, and CF (Enright, Unnithan, & Davies, 2006; Larson, Covey, & Corbridge, 2002; Larson & Kim, 1987; Moran, Piper, Elborn, & Bradley, 2005).

Detailed procedures on the assessment of MIP can be found in the literature (American Thoracic Society/European Respiratory, 2002). Subjects should receive proper coaching and instructions prior to testing to ensure proper testing performance. Briefly, the subject should be seated wearing nose clips. After completely exhaling to residual volume (RV) or after a normal relaxed exhalation to functional residual capacity (FRC), a maximal inspiratory effort (i.e. a Mueller Maneuver) is performed through either a tube or flanged mouthpiece against an occluded airway. The mouth piece is connected to an inspiratory circuit with a 2mm air leak imposed to limit the influence of the buccal muscles on pressure generation. Debate exists related to the ideal mouthpiece used during measurement of MIP (Koulouris, Mulvey, Laroche, Green, & Moxham, 1988; Wohlgemuth, van der Kooi, Hendriks, Padberg, & Folgering, 2003). In individuals with neuromuscular weakness involving the facial muscles, the flanged mouthpiece may afford a better seal (American Thoracic Society/European Respiratory, 2002). In the absence of this weakness, either
mouthpiece is considered acceptable with little measurement differences between the two as long as an adequate seal is in place (Troosters et al., 2005; Wohlgemuth et al., 2003). Type of mouthpiece used is most important to standardize procedures and to consider when selecting reference values. A flanged mouthpiece is recommended according to the 2002 American Thoracic Society (ATS) Statement on Respiratory Muscle Testing.

The inspiratory circuit used to assess MIP should be connected to a pressure transducer capable of measuring negative pressures with an adequate range based on the subject’s capabilities. Various devices exist ranging from simple handheld pressure gauges to more elaborate computer systems. Portable handheld pressure devices make the measurement of MIP in the clinic reasonable when indicated (American Thoracic Society/European Respiratory, 2002; Hamnegard et al., 1994). The maximal pressure sustained for one-second during the Mueller Maneuver described above is recorded as the MIP. This measurement is typically expressed in nominal values (i.e. -80 cmH₂O) and as a percent of predicted according to established normal values available in the literature (Black & Hyatt, 1969; Neder, Andreoni, Lerario, & Nery, 1999; Wilson, Cooke, Edwards, & Spiro, 1984). However, it is suggested that a group of healthy volunteers may serve as a better comparison as large variability exists between the published normal values (Troosters et al., 2005). Frequently, the negative pressure is reported as a positive value for ease of data interpretation.
The number of trials, subject effort, and the lung volume from which the Mueller maneuver was performed can influence the measurement results for MIP. Initial measurements may be artificially depressed due to poor technique especially in naïve subjects. Repeated testing will increase the results as the individual is familiarized with the testing procedures. To control for this learning effect, sub-maximal “warm up” inspiratory maneuvers may be useful just prior to performing the maneuver (Volianitis, McConnell, & Jones, 2001). In addition, practice tests are recommended for the subject to become familiar with the technique. After the subject can satisfactorily perform the maneuver, the best of five measurements with less than 5 - 10% variability should be recorded as the individual’s MIP (Dimitriadis, Kapreli, Konstantinidou, Oldham, & Strimpakos, 2011; Larson et al., 1993; Troosters et al., 2005). A minimum of one to two minutes of rest should be allowed between trials to prevent the effects of fatigue associated with repeated contractions.

The measurement of MIP as described is a volitional maneuver that is influenced by subject effort. Non-volitional forms to stimulate the IM do exist and include electric or magnetic stimulation of the phrenic nerve (American Thoracic Society/European Respiratory, 2002). As with the measurement of T_{di}, these techniques are not easily implemented in the clinic and do not represent global inspiratory efforts. To overcome the effect of patient effort, consistent and maximal verbal encouragement is recommended during the volitional tests. Evaluator assessment of the subject’s technique and quality of the generated pressure curve can aid in determining the test effort and should be considered
when interpreting the test quality. These procedures should help recognize the effects of subject effort during volitional maneuvers and confirm acceptable techniques.

Lung volume and the elastic properties of the thorax can affect pressure generation during the assessment of MIP. As with all skeletal muscle, the contractile ability of the diaphragm is related to the length of the individual fibers. Lung volume will impact diaphragmatic length and is related to its force-generating capabilities (Braun et al., 1982). Alterations in pressure generation may reflect a mechanical disadvantage of the diaphragm based on lung volume rather than a true weakness of physiologic origin. For this reason, MIP is generally measured from either RV or FRC as these volumes are reproducible in repeated measures. Starting at RV is attained by having the subject maximally exhale to completely empty his/her lungs just prior to performing the MIP maneuver. However, when measuring from this volume the elastic recoil of the thorax may contribute to the pressure generated. In this manner, measurement from FRC may better isolate global IMS but result in lower values as the effect of the thoracic recoil is absent. Initiation from FRC is attained by having the subject perform a simple relaxed tidal exhalation just prior to the MIP maneuver. In light of the potential effect of lung volume on pressure generation, either RV or FRC are acceptable starting points when assessing MIP as long as diaphragmatic position and the potential influence of thoracic recoil are considered when interpreting results. ATS recommends MIP to be measured from RV for the

In contrast to the measurement of IMS, various protocols and procedures exist in attempt to quantify IME. Significant debate exists over the best method to quantify IME making the literature difficult to interpret. Tests of IME are criticized because they are task-specific and may not reflect day-to-day inspiratory muscle performance (American Thoracic Society/European Respiratory, 2002). The true ability for the inspiratory muscles to sustain a given load is most related to the overall work endured by these muscles as represented in the TTI.

IME may be quantified as the time the inspiratory muscles can sustain an imposed workload until task failure (American Thoracic Society/European Respiratory, 2002). This conceptually has been abbreviated as T$_{lim}$ and is influenced by multiple factors including the strength of the inspiratory muscles. In 1977, Roussos and Macklem evaluated diaphragmatic fatigue in healthy individuals (Roussos & Macklem, 1977). Subjects were asked to breathe against resistive loads of increasing levels ranging from 40% to 90% of their T$_{dilimax}$ and were allowed to choose their own rate and tidal volume. The end-point of each breathing trial was identified when the subject “could no longer tolerate the procedure and came off the apparatus” and represents the “endurance time” or T$_{lim}$ (Roussos & Macklem, 1977, pg. 190). As a result, the authors noted a “critical value” of 40% T$_{dilimax}$ above which T$_{lim}$ was finite with eventual task
failure. It was noticed that the duration of inspiration at the given $T_{di}/T_{di\text{max}}$ ratio decreased as the individual reached $T_{\text{lim}}$ during fatiguing runs and the “ventilatory pattern became irregular and disorganized” (Roussos & Macklem, 1977, pg. 191). These later findings may represent alterations in breathing pattern to combat the impending fatigue at the cost of ventilatory efficiency.

As a follow up, the authors repeated a similar study utilizing mouth pressure measurements and identified a critical value of 60% MIP above which $T_{\text{lim}}$ would be finite (Roussos, Fixley, Gross, & Macklem, 1979). This level equated to a critical work rate of 6.6 kgm/min. The tests were repeated at one-half of the subject’s inspiratory capacity to determine the impact of hyperinflation. Under the simulated hyperinflation, the critical value for fatiguing runs occurred at 30% MIP equating to a work rate of 2.6 kgm/min. The authors noted significant reports of dyspnea during fatiguing runs and the absence of dyspnea below these levels (Roussos et al., 1979).

The results reported by Roussos et al in 1977 and 1979 suggest a relationship between IMS and IME as the ability to sustain the task was affected by the $P_{br}/\text{MIP}$ ratio. However, the notion that the IME was solely determined by the relative intensity of the contraction was challenged. It was suggested that the inspiratory muscles could in fact sustain a range of relative resistances if allowed to alter inspiratory time relative to total breathing time (i.e. the inspiratory duty cycle; $T_i/T_{\text{tot}}$).
In 1982, Bellemare and Grassino evaluated the relationship between $T_{di}/T_{di\text{max}}$ ratio and $T/T_{tot}$ in influencing the ability of the diaphragm to sustain a given inspiratory task. In their work, the authors measured $T_{lim}$ in healthy subjects while breathing against resistive loads while varying the individual duty cycles. The imposed work was represented as the “diaphragmatic tension-time index” (TTI$_{di}$) calculated as the product of $T_{di}/T_{di\text{max}}$ and $T/T_{tot}$. It was shown that the $T_{lim}$ of the diaphragm was determined by TTI$_{di}$. Decreasing the inspiratory duty cycle increased the $T_{lim}$ for a given constant resistive load. Regression analysis revealed a strong linear relationship between TTI$_{di}$ and $T_{lim}$ ($r=0.93$, $p<0.05$). A critical TTI$_{di}$ of 0.15 (range 0.12 – 0.20) was identified below which the breathing pattern could be sustained indefinitely. Inspiratory work above this critical TTI$_{di}$ was associated with a finite $T_{lim}$ associated with electromyographic evidence of diaphragmatic fatigue (Bellemare & Grassino, 1982).

The methods of measuring $T_{di}$ in the studies by Bellemare et al (1982) are extremely difficult to implement in the clinical environment and may not be necessary. Ramonaxto et al (1995) validated a non-invasive measurement of the TTI using mouth pressures in both healthy subjects and a cohort of individual with COPD (Ramonatxo et al., 1995). The authors measured the TTI$_{di}$ in a similar manner as Bellemare et al (1982) and compared it to a non-invasive measure of the TTI at the mouth for the collective inspiratory muscles (TTI$_{mouth}$). By substituting the $P_{br}$ measured at the mouth for $T_{di}$ and MIP for $T_{di\text{max}}$, the authors calculated the TTI$_{mouth}$ by the following equation:
\[ TTI_{\text{mouth}} = \left( \frac{P_{br}}{\text{MIP}} \right) \times \left( \frac{T_i}{T_{\text{tot}}} \right) \]

Analysis revealed significant relationships between all invasive diaphragmatic measures and their corresponding non-invasive measures at the mouth \((p<0.001)\). This resulted in “highly significant correlations between \(TTI_{\text{mouth}}\) and \(TTI_{\text{di}}\) for the healthy subjects \((TTI_{\text{mouth}} = 2.1 \ TTI_{\text{di}} + 0.012; r=0.97, p<0.001)\) and those with COPD \((TTI_{\text{mouth}} = 2.0 \ TTI_{\text{di}} + 0.024; r=0.97, p<0.001)\)” (Ramonatxo et al., 1995). These findings support the validity of a non-invasive measurement of the TTI and mouth pressures as a representation of inspiratory workloads and breathing patterns encompassing the collective inspiratory muscles. A critical \(TTI_{\text{mouth}}\) value of 0.33 was identified as the fatigue threshold corresponding to the critical \(TTI_{\text{di}}\) of 0.15 found by Bellamare and Grassino in 1982.

The relationship between the TTI and inspiratory muscle fatigue thresholds illustrate the dynamic capability of the body to manipulate the breathing pattern. In doing so, performance of these critical muscles can be sustained in the presence of excessive inspiratory resistive loads. In the work by Ramonatxo et al (1995), only one subject with COPD demonstrated a resting TTI slightly above the critical threshold for fatigue. This suggests first that there may be some individual variability with these thresholds or the results in this individual did not represent true resting breathing. More importantly, this indicates that individuals can manipulate breathing patterns to maintain an adequate TTI. Based on the components of the TTI, this can be achieved by lowering the
generated pressure per breath or decreasing the inspiratory time to compensate. Either of which may contribute to ventilatory inefficiencies especially in the presence of pulmonary pathology.

The presence of a decreased MIP at baseline can have obvious implications in creating a natural elevation of $P_{br}/MIP$ ratio within the $TTI_{mouth}$. In the presence of this impairment, the body would need to lower the $P_{br}$ and/or the $T_i$ to keep the $TTI_{mouth}$ below the fatigue threshold. Each of these accommodations could negatively impact ventilatory efficiency unless accompanied by an increase in inspiratory flow rates. Unfortunately, impaired IMS may limit the ability to increase flow rates to adequate levels. At rest, the ventilatory pump system may be able to compensate in the earlier stages of the pulmonary disease. However, problems may arise when an elevated WOB associated with progressive pulmonary decline, exercise demand, or acute pulmonary exacerbations is thrust upon the individual.

In 1997, Hayot et al measured the $TTI_{mouth}$ at rest in children with CF with mild to moderate lung disease as compared to a group of healthy volunteers (Hayot, Guillaumont, Ramonatxo, Voisin, & Prefaut, 1997). The individuals with CF demonstrated a greater $TTI_{mouth}$ as compared to the controls though this value was well below the fatigue threshold ($TTI_{mouth}=0.087 \pm 0.030$ vs. $0.056 \pm 0.014$; p<0.001). The results and components of the $TTI_{mouth}$ at rest are summarized in Table 2.1.
Table 2.1

*Non-invasive tension-time index at rest in children with CF*

<table>
<thead>
<tr>
<th>Value</th>
<th>CF (n=16)</th>
<th>Controls(n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – yr.</strong></td>
<td>11.0 ± 2</td>
<td>11.0 ± 2</td>
</tr>
<tr>
<td><strong>LBM - kg</strong></td>
<td>29.3 ± 5</td>
<td>29.3 ± 4.3</td>
</tr>
<tr>
<td><strong>FEV\textsubscript{1} - % predicted</strong></td>
<td>81.0 ± 16*</td>
<td>107.0 ± 11</td>
</tr>
<tr>
<td><strong>FRC/TLC - %</strong></td>
<td>54.0 ± 5**</td>
<td>45.0 ± 8</td>
</tr>
<tr>
<td><strong>P\textsubscript{0.1} - cmH\textsubscript{2}O</strong></td>
<td>3.2 ± 0.9***</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td><strong>P\textsubscript{br} - cmH\textsubscript{2}O</strong></td>
<td>17.5 ± 4.6</td>
<td>15.3 ± 3.3</td>
</tr>
<tr>
<td><strong>MIP - cmH\textsubscript{2}O</strong></td>
<td>86.0 ± 32***</td>
<td>124.0 ± 26</td>
</tr>
<tr>
<td><strong>P/MIP - %</strong></td>
<td>22.7 ± 8.4**</td>
<td>13.8 ± 2.3</td>
</tr>
<tr>
<td><strong>T\textsubscript{i}/T\textsubscript{tot}</strong></td>
<td>0.39 ± 0.06</td>
<td>0.4 ± 0.05</td>
</tr>
<tr>
<td><strong>TTI\textsubscript{mouth}</strong></td>
<td>0.087 ± 0.030**</td>
<td>0.056 ± 0.014</td>
</tr>
</tbody>
</table>

*Note: The above table was adapted from Hayot et al (1997). LBM=lean body mass; FEV\textsubscript{1}=forced-expiratory volume in one-second; FRC=functional residual capacity; TLC=total lung capacity; P\textsubscript{0.1}=mouth occlusion pressure; P\textsubscript{br}=mean inspiratory mouth pressure; T\textsubscript{i}=inspiratory time; T\textsubscript{tot}=total breathing time; TTI\textsubscript{mouth}=tension-time index at the mouth.*

* p<0.001, between group difference, **p<0.01, between group difference, ***p<0.05, between group difference

The elevated TTI\textsubscript{mouth} appears to be resultant from an increased P\textsubscript{br}/MIP ratio resulting from an increased inspiratory effort in the presence of a decreased MIP. At rest, the T\textsubscript{i}/T\textsubscript{tot} did not differ between groups suggesting that the individuals with CF were able to sustain the P\textsubscript{br}/MIP and supported by the
TTI$_{mouth}$ being below the fatigue threshold. However, a negative linear correlation was noted in the CF group between P$_{br}$/MIP and T$_i$/T$_{tot}$ ($r = -0.53; p<0.05$). This finding suggests individuals compensate for an elevated P$_{br}$/MIP by decreasing the time spent in inspiration to combat fatigue. Both lean body mass (LBM) and FRC were correlated to TTI$_{mouth}$ ($r = -0.70, p<0.05; r = 0.77, p<0.05$ respectively) and were shown to be determinants of the TTI$_{mouth}$ through regression analysis with LBM being the strongest measure. This finding is likely explained by the effect of pulmonary hyperinflation on diaphragmatic function and the negative influence of LBM depletion on skeletal muscle contractility contributing to the decreased MIP.

Breathing patterns associated with the TTI$_{mouth}$ in response to maximal exercise were evaluated in children with CF (Keochkerian et al., 2005). Similar to the work by Hayot et al (1997), subjects with CF presented with an elevated TTI$_{mouth}$, P$_{br}$, and P$_{br}$/MIP accompanied by a decreased MIP ($p<0.001$). In contrast, these subjects presented with a significantly lower T$_{i}$/T$_{tot}$ ($p<0.05$) suggesting an altered breathing pattern at rest. In agreement with Hayot (1997), the TTI$_{mouth}$ remained below the fatigue threshold. In response to graded aerobic exercise, individuals with CF demonstrated a significantly elevated TTI$_{mouth}$ and P$_{br}$/MIP compensated by a significantly decreased T$_{i}$/T$_{tot}$ ($p<0.001$) for any equivalent intensity as compared to healthy controls. A negative correlation was found between P$_{br}$/MIP and T$_{i}$/T$_{tot}$ ($r = -0.93, p <0.0001$). Again, the TTI$_{mouth}$ remained below the critical level associated with fatigue. Work by Keochkerian et al (2005) also suggests the influence of hyperinflation and lean
body mass in determining the $TTI_{mouth}$ and particularly the $P_{br}/MIP$. Significant correlations were found between the ratio of RV to total lung capacity (TLC) and $P_{br}/MIP$ as well as the $T_i/T_{tot}$ ($r = 0.92$, $p<0.001$; $r = -0.94$, $p<0.01$ respectively). MIP also was correlated to the weight to height ratio ($r = 0.89$, $p<0.001$) and to RV/TLC ($r = -0.87$, $p<0.009$).

In 2008, the $TTI_{mouth}$ was evaluated in children with CF ($n=47$) as compared to controls ($n=47$) (Hahn et al., 2008). As a group, $%FEV_1$ ranged from 50 – 83% in the subjects with CF suggesting mild to moderate disease according to the CF Foundation standards. When stratified by disease severity based on the pulmonary function score (PFS), MIP appeared to decrease with increasing severity though this difference failed to reach a level of statistical significance. The observed decrease was accompanied by an elevated $P_{br}/MIP$ and $TTI_{mouth}$ with no difference in $T_i/T_{tot}$. The resultant findings showing an elevated $TTI_{mouth}$ at rest were in agreement of those by Hayot et al (1997) and Keochkerian (2005). In contrast, however, the authors failed to show an inverse relationship between $P_{br}/MIP$ and $T_i/T_{tot}$. Only weak relationships were found between MIP represented as percent of predicted with $%FEV_1$ ($r = 0.34$, $p=0.02$) and hyperinflation measured by the ratio of FRC to TLC ($r = -0.30$, $p=0.04$).

These discrepancies may be due to the relatively small number of subjects with severe lung disease ($n=6$) in addition to the age of the subjects. In the preceding work by Hayot (1995) and Keochkerian (2005), the mean age of subjects was 11 ± 2 and 13.1 ± 1.5 yrs. respectively. Where the mean age of the entire group included by Hahn et al (2008) was 14 yrs., the mean age of the group with
severe lung disease was 23 yrs. The small number of subjects in the severe
category accompanied by the mixing of children with adults may have impacted
the results.

These findings suggest that children with CF may adapt breathing
strategies to combat inspiratory fatigue but have not been fully investigated in the
adult population. Children with CF appear to decrease inspiratory time to
compensate for an elevated $P_{br}/MIP$ due to a decreased MIP associated with
hyperinflation and decreased macro nutritional status. Though not assessed in
the CF literature, the altered breathing patterns may have protective benefits by
maintaining the $TTI_{mouth}$ at a sub-threshold level relative to fatigue at the cost of
ventilatory efficiency as suggested in the literature (Bye et al., 1983; Rochester,
1993). The resultant metabolic effects would naturally limit the ability to sustain
exercise thus avoiding excessive inspiratory work. Allowing the $P_{br}/MIP$ to
elevate at the expense of the $T_{i}/T_{tot}$ may also have secondary benefits to ward off
fatigue by limiting exercise. An elevated $P_{br}/MIP$ will contribute to the sensation
of dyspnea (Grazzini, Stendardi, Gigliotti, & Scano, 2005). These effects could
result in self-imposed limitations in exercise again protecting the inspiratory
muscles from the fatiguing workloads.
Efficacy of Inspiratory Muscle Training in Cystic Fibrosis

Table 2.2 summarizes the four original research studies published on IMT in CF (Asher, Pardy, Coates, Thomas, & Macklem, 1982; W. de Jong, W. M. van Aalderen, J. Kraan, G. H. Koeter, & C. P. van der Schans, 2001a; Enright, Chatham, Ionescu, Unnithan, & Shale, 2004; Sawyer & Clanton, 1993). Mean age of the subjects studied ranged from 11.46 – 24.8 years of age. Only one study was specific to the adult population (Enright et al., 2004). Three studies reported disease severity in terms of the %FEV\textsubscript{1}. One author utilized the National Institute of Health Score (NIHS) (Sawyer & Clanton, 1993). Subjects presented with mild to severe pulmonary disease (mean %FEV\textsubscript{1}= 35 – 72%, mean NIHS=87.7%) though the majority of individuals had only mild to moderate lung dysfunction. A significant degree of heterogeneity existed in terms of disease severity within the groups studied with some subjects presenting minimal to no impairments in pulmonary function. Authors did not control for disease severity or the level of IMS at baseline. The TTI and breathing patterns have not been assessed in adults with CF at rest, during exercise, or in response to IMT. Two systematic reviews on IMT in CF were also identified as part of this literature review (Houston, Mills, & Solis-Moya, 2008; Reid, Geddes, O'Brien, Brooks, & Crowe, 2008).
Table 2.2

*Inspiratory muscle training in cystic fibrosis*

<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>Age of subjects</th>
<th>Disease Severity</th>
<th>Baseline MIP(^a)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asher, 1982 n=11</td>
<td>16.0 %FEV(_1)=35%</td>
<td>85 cmH(_2)O-RV</td>
<td>↑ IME ↑ IMS ↓PFT ↓Peak exercise ←Sub-max exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>74 cmH(_2)O-FRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sawyer, 1993 n=10</td>
<td>11.5 NIHS=88%</td>
<td>107 cmH(_2)O-FRC</td>
<td>IME not tested ↑IMS ↑PFT ↑Peak exercise</td>
<td></td>
</tr>
<tr>
<td>De Jong, 2001a n=7</td>
<td>17.0 %FEV(_1)=72%</td>
<td>105 %pred-RV</td>
<td>↑ IME ↑IMS ↑PFT ↑Peak exercise ←Dyspnea ←QOL</td>
<td></td>
</tr>
<tr>
<td>Enright, 2004 n=9</td>
<td>24.8 %FEV(_1)=64%</td>
<td>134 cmH(_2)O-RV</td>
<td>↑IME ↑IMS ↑PFT ↑Peak exercise ←QOL</td>
<td></td>
</tr>
</tbody>
</table>

Note. Values are reported as the means for the training group only. MIP=maximal inspiratory pressure; MSVC=maximum sustainable ventilatory capacity; RV=measurement taken from residual volume; FRC=measurement taken from functional residual capacity; IME=inspiratory muscle endurance; IMS=inspiratory muscle strength; PFT=pulmonary function tests; NIHS=National Institute of Health Score; %FEV\(_1\)=forced expiratory volume in one-second expressed as percent predicted; QOL=quality of life.

\(^a\) Potential criteria to identify inspiratory muscle weakness include MIP < 80 cmH\(_2\)O, or MIP \(\leq 80\%\) of predicted.

Baseline measurements of global IMS represented by MIP were considered within normal limits. According to the ATS statement on respiratory
muscle testing, MIP values of at least 80 cmH₂O measured at RV excludes clinically significant inspiratory muscle weakness (IMW) (American Thoracic Society/European Respiratory, 2002). In a meta-analysis evaluating the efficacy of IMT in COPD, MIP < 60 cmH₂O was a suggested threshold level to identify the presence of IMW that may respond to IMT (Gosselink et al., 2011; Lotters, van Tol, Kwakkel, & Gosselink, 2002). MIP < 70% of predicted has been used by researchers to identify IMW in patients with chronic heart failure amendable to IMT (Chiappa et al., 2008; Dall'Ago, Chiappa, Guths, Stein, & Ribeiro, 2006). Based on these criteria, IMW did not exist as represented by the mean value of MIP in the samples evaluated as a group. Ranges and individual subject values were not provided.

Protocols used for IMT in individuals with CF were developed based on existing literature in the COPD population (see Table 2.3). Modes of training included flow-based (F-IMT) and threshold-based (T-IMT) protocols performed up to 30 minutes per day on most days of the week. Threshold devices utilize a spring-loaded inspiratory valve to control the inspiratory resistance applied to the subject. Once set to the desired level, the subject needs to generate the “threshold” inspiratory pressure to open the valve for inspiration to occur. The valve remains open as long as the pressure is maintained. Flow-based devices require subjects to freely inhale through apertures of various diameters. Inspiratory flow rate needs to be controlled during F-IMT as it directly influences the resistance applied to the inspiratory muscles. Research suggests that either mode is effective at increasing IMS and IME as long as the load is controlled.
As can be seen in Table 2.3, the time and scheduling commitments of these protocols are quite demanding. This fact could result in non-compliance outside of the research environment as both time constraints and perceived burden of care are identified influences on adherence to therapies in the CF population (Bregnballe, Schiotz, Boisen, Pressler, & Thastum, 2011; George et al., 2010). The standard demands of CF care in the adult population include complex daily medication and airway clearance routines, intricate nutritional monitoring due to pancreatic insufficiency and malabsorption of fats, regular physical activity, and frequent visits to medical specialist (Sawicki, Sellers, & Robinson, 2009). The resultant burden associated with the management of this

(Geddes, Reid, Crowe, O’Brien, & Brooks, 2005). T-IMT has a clinical advantage as the inspiratory pressure generated is easier to control.

### Table 2.3

**Inspiratory muscle training protocols in cystic fibrosis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Mode</th>
<th>Intensity</th>
<th>Duration</th>
<th>Frequency</th>
<th>Length</th>
<th>Total Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asher (1982)</td>
<td>Flow</td>
<td>Max tolerable</td>
<td>15 min</td>
<td>2x/day</td>
<td>4 wks.</td>
<td>840 min</td>
</tr>
<tr>
<td>Sawyer (1993)</td>
<td>Threshold</td>
<td>50-60% MIP</td>
<td>30 min</td>
<td>1x/day</td>
<td>10 wks.</td>
<td>2100 min</td>
</tr>
<tr>
<td>De Jong (2001)</td>
<td>Threshold</td>
<td>40% MIP</td>
<td>20 min</td>
<td>5x/wk.</td>
<td>6 wks.</td>
<td>600 min</td>
</tr>
<tr>
<td>Enright (2004)</td>
<td>Flow</td>
<td>80% MIP</td>
<td>6 sets of 6 reps</td>
<td>3x/wk.</td>
<td>8 wks.</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>

*Note.* MIP=maximal inspiratory pressure
chronic illness creates intense challenges to balance other life responsibilities for the adult with CF (Sawicki et al., 2009). Additional treatment burdens such as the proposed IMT protocols may infringe on time available for established therapies. In addition, the effects of IMT are believed to reverse upon cessation (Weiner, Magadle, Beckerman, Weiner, & Berar-Yanay, 2004). The ongoing maintenance of such training interventions may not be a reasonable expectation in adults with CF unless strong evidence suggests a beneficial effect. Careful subject selection is warranted when prescribing protocols in clinical and/or research scenarios.

Though limited, the literature appears to support the ability of IMT to increase measures of IME and global IMS with either F-IMT or T-IMT in CF (see Table 3). All studies demonstrated an improvement in both these variables with the exception of de Jong et al (2001). In their work, the authors demonstrated an increase in IME but not IMS when training at an intensity of 40% MIP (de Jong et al., 2001a). The need for higher intensities to increase measures of muscular strength is consistent with basic exercise training principles (ACSM, 2010). A minimal intensity of 50% MIP may be required to increase IMS especially in the presence of normal strength (Enright et al., 2004; Sawyer & Clanton, 1993). However, care must be taken when making this interpretation as de Jong (2001) had insufficient power due to the small sample size (n=7). The authors noted positive trends in IMS as a result of their protocol that fell short of statistical significance (p=0.064) and acknowledged that significant differences may have emerged in the presence of a larger sample. In addition, the training stimulus
used by de Jong (2001) may have been inadequate. Frequency, intensity, and duration of training may be varied to adjust the overall exercise dosage (ACSM, 2010). Enright et al (2004) demonstrated significant findings in both IME and IMS training only 3x/wk. but at 80% MIP. Asher et al (1982) suggested improvements in IME and IMS in as little as 4 weeks when training at the “maximal load tolerated”. It appears an inverse relationship may exist between the training intensity and the prescribed frequency/duration. This fact is consistent with basic principles of exercise prescription where the overall training stimulus for a given mode of exercise is a function of intensity, frequency, and duration. Increases in IMS may emerge at lower intensities but require higher training frequency as seen by Sawyer et al (1993).

The ideal IMT prescription has not been established as no studies have compared various IMT protocols; however, the limited available research suggests IMT can improve measures of inspiratory muscle function in individuals with CF (Asher et al., 1982; de Jong et al., 2001a; Enright et al., 2004; Reid et al., 2008; Sawyer & Clanton, 1993). From this literature, it also appears that increases in IMS may be accompanied by increases in IME but not vice versa. This observation suggests a relationship between these two measures that may be explained by the contribution of MIP to the TTI_{mouth}. The effect of IMT on inspiratory muscle function is promising but the potential for these improvements to transfer to clinically relevant outcome measures in CF is less clear.
The potential for IMT to enhance peak exercise capacity and/or measures of pulmonary function in CF cannot be determined based on the current literature. The effect of IMT on functional exercise measures such as the six-minute walk test has not been evaluated in the CF population. Improvement in peak work achieved on a lower extremity cycle ergometer test and treadmill time during a Bruce protocol was noted in response to F-IMT and T-IMT respectively (Enright et al., 2004; Sawyer & Clanton, 1993). Interestingly, these ergogenic effects were also accompanied by improvements in PFT. In contrast, results by Asher (1982) and de Jong (2001) failed to show improvements in either PFT or peak exercise capacity as a result of IMT. Variations in protocol and/or extraneous factors may explain these conflicting results as explained below.

The exercise dosage prescribed by Asher (1982) and de Jong (2001) may have been insufficient to result in ergogenic improvements. Both studies used lower exercise dosages (see Table 2.3) in comparison to Sawyer (1993) and Enright (2004). The transference of IMT to exercise may simply require higher intensities (i.e. > 50% MIP) and/or longer durations (8 – 10 weeks) of training. Such protocols may favor improvements in IMS versus IME illustrating the potential importance of MIP and allow adequate time for training effects to occur. Interestingly, de Jong (2001) demonstrated a 35% increase in IME yet failed to show improvements in peak exercise suggesting that enhanced IME alone may not transfer to exercise tolerance. A recent review on the use of IMT in COPD supports this theory as IME training is suggested to be less effective as
compared to IMS training for optimal effects but this theory requires validation in the CF population (Gosselink et al., 2011).

The improvements noted in PFTs by both Sawyer (1993) and Enright (2004) may have occurred from extraneous factors as IMT is not associated with improved lung function in pulmonary disease (Gosselink et al., 2011). Sawyer (1993) reported “subjective observation of the experimental subjects demonstrated increased coughing and sputum production as compared to the controls” (Sawyer & Clanton, 1993, pg. 1495). The potential for resistive inspiratory maneuvers to aid in mucus clearance has been suggested in individuals with CF with a similar device as that used by Enright (2004) and in non-CF bronchiectasis using a threshold trainer (Chatham, Ionescu, Nixon, & Shale, 2004; Chatham, Nixon, Ionescu, & Shale, 1999; Naraparaju, Vaishali, Venkatesan, & Acharya, 2010). Though conflicting reports exist on their influence on PFT, improvements have been noted in response to airway clearance techniques in CF (McIlwaine et al., 2013). This finding may suggest that a possible airway clearance mechanism associated with IMT separate from the training-related improvements in IMS resulted in enhanced lung function. In addition, possible airway clearance effects associated with IMT may partially explain the improvements noted in exercise performance.

One proposed mechanism of dyspnea is an imbalance between IMS and the imposed WOB (Grazzini et al., 2005; Parshall et al., 2012). It is believed that gradual deconditioning results from dyspnea-related inactivity and contributes to
the development of exercise limitations in pulmonary disease (Lahaije, van Helvoort, Dekhuijzen, & Heijdra, 2010; Victorson, Anton, Hamilton, Yount, & Cella, 2009). IMT may lead to dyspnea relief by decreasing the $P_{br}/MIP$ ratio and allow a gradual increase in activity to reverse the impact of deconditioning. Logic would dictate that additional time would be needed to reverse dyspnea-related deconditioning to enhance exercise capacity after improvements in dyspnea post-IMT. The longer intervention period used by Sawyer (1993) and Enright (2004) may have allowed some reversal of dyspnea-related deconditioning over the length of the study as a result of dyspnea relief. Alternatively, dyspnea alleviation would likely increase symptom-limited performance. The fact that de Jong et al. (2001) failed to alleviate dyspnea could explain the lack of exercise improvements in their study. Unfortunately, neither Sawyer (1992) nor Enright (2004) reported dyspnea measures adequately to determine its relationship to exercise improvements.

The impact of IMT on dyspnea and quality of life (QOL) has not been adequately researched in CF. Dyspnea was included as an outcome measure in only one study resulting in no effect (de Jong et al., 2001a). This study was performed at a lower intensity for only 6 weeks and had a small number of subjects with normal IMS. Aspects of QOL were assessed through questionnaires in response to IMT on two occasions and found no effect (de Jong et al., 2001a; Enright et al., 2004). Caution should be taken in ruling out this particular effect as the subjects in both of these studies had only a mild degree of pulmonary dysfunction. These aspects of QOL may not have been
impacted by ventilatory parameters in these individuals. In addition, the added burden of the IMT program could have negated overall some benefits. Finally, de Jong et al (2001a) used the Fatigue Index 20 and Enright et al (2004) used a hospital anxiety and depression scale along with the Chronic Respiratory Disease Questionnaire (G. H. Guyatt, Berman, Townsend, Pugsley, & Chambers, 1987; Smets, Garssen, Bonke, & De Haes, 1995; Zigmond & Snaith, 1983). Use of QOL measures specific to individuals with CF such as the Cystic Fibrosis Questionnaire may have resulted in different findings (Quittner et al., 2012).

The potential benefit of IMT in CF is evident but its overall efficacy is neither well supported nor refuted in the literature (Houston et al., 2008; Reid et al., 2008). The general IMT protocols implemented in the CF research were based on current literature pertaining to IMT in COPD. These protocols appear to increase measures of inspiratory muscle performance in CF with inconsistent transference to other clinically relevant outcomes. Both CF and COPD present with obstructive changes in pulmonary function characterized by increased airway resistance and hyperinflation. In addition, mucus retention, chronic inflammation, and frequent pulmonary exacerbations contribute to a progressive decline in lung function in both diseases. Malnutrition, excess dyspnea, increased WOB, and exercise intolerance are common in both CF and COPD. Given their pathophysiologic similarities, a closer look at the literature in COPD as compared to CF is warranted to fully understand the potential efficacy of IMT in adults with CF.
Nineteen original studies evaluating IMT alone in COPD were utilized in this review to compare to the results seen in CF (Beckerman et al., 2005; Covey et al., 2001; Falk, Eriksen, Kolliker, & Andersen, 1985; Flynn et al., 1989; Garcia, Rocha, Pinto, Lopes, & Barbara, 2008; G. Guyatt, Keller, Singer, Halcrow, & Newhouse, 1992; Harver, Mahler, & Daubenspeck, 1989; Hill et al., 2006; Kim et al., 1993; Koppers, Vos, Boot, & Folgering, 2006; Larson, Kim, Sharp, & Larson, 1988; Lisboa, Munoz, Beroiza, Leiva, & Cruz, 1994; Lisboa et al., 1997; Ramirez-Sarmiento et al., 2002; Sanchez Riera et al., 2001; Scherer, Spengler, Owassapian, Imhof, & Boutellier, 2000; Seron et al., 2005; Villafranca, Borzone, Leiva, & Lisboa, 1998; Weiner et al., 2004). The results of these studies are summarized in Appendix A.

As in CF, a properly constructed IMT program can increase IMS and IME in individuals with COPD. This interpretation is confirmed in multiple systematic reviews and meta-analyses of current literature (Geddes, O'Brien, Reid, Brooks, & Crowe, 2008; Geddes et al., 2005; Gosselink et al., 2011; Lotters et al., 2002; Shoemaker, Donker, & Lapoe, 2009). F-IMT and T-IMT are believed to be equally effective (Geddes et al., 2008; Geddes et al., 2005; Lotters et al., 2002). Based on the current literature, the ergogenic potential of IMT in COPD appears more promising than in CF. This difference may be explained by the outcomes assessed, the mode of training, and/or the characteristics of the subjects studied.

Peak exercise performance was measured on a lower extremity cycle ergometer (3 studies) and a treadmill (1 study) in response to either F-IMT or T-
IMT in CF. Sub-maximal exercise performance was assessed in one instance on a cycle ergometer (Asher et al., 1982). No study evaluated measures of functional exercise capacity such as the six-minute walk test, shuttle test, or step tests in CF in response to IMT. Voluntary isocapnic hyperpnea (VIH) has been studied on one occasion in an extremely small sample (n=4) of children with CF (Keens et al., 1977). It should be noted that the efficacy of IMT in COPD appears specific to its ability to decrease dyspnea and/or increase measures of functional exercise capacity (FEC) which are often symptom limited. IMT alone has not consistently resulted in increased maximal exercise capacity in individuals with COPD as a result of F-IMT or T-IMT. However, maximal exercise has been increased after VIH as a mode of IMT on two occasions (Koppers et al., 2006; Scherer et al., 2000). Ergogenic effects of T-IMT or F-IMT may have been seen in the CF literature had measures of FEC been included or VIH was used. However, the use of VIH is complicated, requires expensive equipment, and is not clinically applicable.

To evaluate the feasibility and potential for IMT to increase measures of FEC in adults with CF, pilot data was collected as part of this dissertation process (Dekerlegand, Hadjiliadis, Myslinski, Holsclaw, & Ferrin, 2011). Five adults with CF (age=22 – 36yrs, mean=28.2 +/- 6.3yrs; %FEV₁=23 - 104%, mean = 66.8 +/- 32.7%, BMI=19.1 – 26.1, mean BMI=21.76) were recruited from the CF clinic at the Hospital of the University of Pennsylvania (HUP) and enrolled in an evidence based T-IMT home program (30 minutes/day, 6 days/ week, at 50-60% MIP). One subject completed only 54% of the prescribed protocol because of
Table 2.4

**Pilot data summary**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Group Valuesa</th>
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<tr>
<td>Gender</td>
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<td>M</td>
<td>F</td>
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<td>36</td>
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<td>BMI</td>
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<td>26.1</td>
<td>19.1</td>
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<table>
<thead>
<tr>
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<td>Post-IMT</td>
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<td>%Change</td>
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<tr>
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<td>93</td>
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<td>143</td>
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<td>104</td>
<td>117</td>
<td>13</td>
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<td></td>
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<td>22.75(7.5)*</td>
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<table>
<thead>
<tr>
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<td>129.00(23.1)</td>
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<td>Post-IMT</td>
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<td>%Change</td>
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<td>63.75(36.9)</td>
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<td>Post-IMT</td>
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<td>%Change</td>
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<td>562.1</td>
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<td>38.7</td>
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<td>527.3</td>
<td>-54.9</td>
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<td></td>
<td></td>
<td>514.10(93.5)</td>
<td>-9.83(39.78)</td>
<td>-2.00</td>
</tr>
</tbody>
</table>

*Note. BMI=body mass index; MIP=maximal inspiratory pressure; IMT=inspiratory muscle training; FEV₁=forced expiratory volume in one-second; 6MWD=six-minute walk distance.*

*a. Values listed as mean (SD)*

*p<0.05*
time commitments and was excluded from the analysis. The remaining four subjects completed the study with a compliance rate of 92%. After training, MIP improved in all subjects with a mean increase of 24.75% (104.25 to 129 %predicted; 100 cmH$_2$O to 122.75 cmH$_2$O, p<0.01).

Primary outcome measures included FEC as assessed by the distance walked in 6 minutes (6MWD) and %FEV$_1$. No significant group changes were noted in 6MWD (514m to 505m) or %FEV$_1$ (64% to 67%) after the intervention period. Subject data and results are illustrated in Table 2.4. The results of this pilot study suggest that the prescribed T-IMT training protocol may be safely and effectively implemented in an outpatient adult CF clinic. The feasibility of recruiting subjects and collecting data at an outpatient adult CF center was confirmed though difficult due to the imposed time burden of the protocol. This is the only data to date evaluating the effect of IMT on FEC in individuals with CF and is in contrast to the COPD literature. T-IMT appears to increase IMS but did not result in an increase in FEC as represented by the 6MWD. However, in looking at the individual data in case series, subject 3 demonstrated a 10% increase in 6MWD and an improved FEV$_1$ after IMT (387m to 426m, 44 to 55 %predicted respectively). Interestingly, this individual demonstrated lower IMS at baseline (MIP=76% predicted, 60 cmH$_2$O) than the others. Impaired IMS is believed to be a prerequisite baseline characteristic for the beneficial effects of IMT in COPD (Gosselink et al., 2011; Lotters et al., 2002; Nici et al., 2006). Specifically, Lotters (2002) and Gosselink (2011) each suggest a baseline MIP $\leq$ 60 cmH$_2$O as criteria to identify clinical responders to IMT which was present in
this subject. Numerous extraneous variables could explain the isolated improvement in FEC in this subject; however, given the existing research in COPD, the probability that inspiratory muscle weakness is a prerequisite for therapeutic benefits related to IMT in CF is a plausible explanation and should be considered.

Differences in subject characteristics between the COPD and CF populations may explain discrepancies in the outcomes of T-IMT and F-IMT in the literature. Table 2.5 summarizes key patient characteristics of the subjects studied with CF as compared to COPD. Values were calculated from the means provided in individual studies as listed in Table 2.2 for CF and Appendix A for COPD. Missing or insufficient data were excluded from this calculation. In distinct contrast to CF, the subjects with COPD were older, had an advanced degree of disease severity, and presented with lower IMS at baseline. It should be noted that the mean %FEV\textsubscript{1} listed for the CF studies is skewed from mild towards moderate pulmonary disease as one study that included subjects with very mild lung disease did not report their %FEV\textsubscript{1} (Sawyer & Clanton, 1993).

The ergogenic effects of IMT alone may be limited to individuals with impaired IMS which may be unique to COPD as compared to adults with CF. The presence of this impairment may alter breathing patterns based on the TTI\textsubscript{mouth} and be alleviated by IMT though this theory has not been evaluated. The decline in IMS seen in COPD may be due to age-related deterioration in conjunction with the disease as IMS has been shown to decline with age (Britto,
Zampa, de Oliveira, Prado, & Parreira, 2009). IMT may be beneficial in the geriatric population in the absence of COPD and can potentially increase exercise performance (Watsford & Murphy, 2008). Impaired IMS may not exist in the younger CF population but may appear in adult subjects living with the chronic effects of the disease.

Table 2.5

*Comparison of subject characteristics from IMT literature COPD and CF*

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of studies</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63.9 (n=19)</td>
<td>17.3 (n=4)</td>
</tr>
<tr>
<td>FEV$_1$ %pred</td>
<td>40.8 (n=16)</td>
<td>57.1 (n=3)</td>
</tr>
<tr>
<td>MIP-RV (cmH$_2$O)</td>
<td>66.7 (n=9)</td>
<td>109.5 (n=2)</td>
</tr>
<tr>
<td>MIP-FRC (cmH$_2$O)</td>
<td>53.7 (n=8)</td>
<td>90.5 (n=2)</td>
</tr>
</tbody>
</table>

*Note.* The number of studies included in the calculations for each variable is given in parentheses. COPD=chronic obstructive pulmonary disease; CF=cystic fibrosis; FEV$_1$=forced expiratory volume in one-second; MIP-RV=maximal inspiratory pressure measured from residual volume; MIP-FRC=maximal inspiratory pressure measured from functional residual capacity.
Disease severity and course may also explain differences in the presentation of IMS between the CF and COPD populations. COPD is typically discovered much later in life after the disease had progressed to the moderate to severe stages (Hill, Jenkins, Hillman, & Eastwood, 2004; O'Brien, Geddes, Reid, Brooks, & Crowe, 2008). In addition, the most common complaint that leads to the discovery of COPD is dyspnea on exertion (Hill et al., 2004). This suggests an already limited FEC due to ventilatory constraints. In contrast, the diagnosis of CF is typically made early on in the disease when there is minimal pulmonary dysfunction. The immediate focus on disease management in CF, such as physical activity and pulmonary hygiene, may influence the response to the increased WOB over time creating a divergent trajectory of inspiratory muscle adaptations as compared to COPD. Based on these findings, further literature review on IMS in adults with CF is warranted to determine if alterations in IMS exist in this population.

**Inspiratory muscle strength in adults with cystic fibrosis**

Seventeen articles published between 1993 and 2011 evaluating IMS in adults with CF (mean age > 18 years of age) were identified. Six articles assessed IMS represented by MIP measured from functional residual capacity (MIP-FRC) (Barry et al., 2008; Barry & Gallagher, 2003; Chatham et al., 1994; Dufresne et al., 2009; Lands, Heigenhauser, & Jones, 1993; Leroy, Perez, Neviere, Aguilaniu, & Wallaert, 2011). Nine articles measured MIP from residual volume (MIP-RV) (Bradley et al., 1999; W. de Jong, W. M. C. van Aalderen, J.
Kraan, G. H. Koeter, & C. P. van der Schans, 2001b; Dunnink, Doeleman, Trappenburg, & de Vries, 2009; Enright, Chatham, Ionescu, Unnithan, & Shale, 2007; Ionescu et al., 1998; Mier, Redington, Brophy, Hodson, & Green, 1990; Szeinberg, England, Mindorff, Fraser, & Levison, 1985; Troosters et al., 2009; Ziegler, Lukrafka, de Oliveira Abraao, Rovedder, & de Tarso Roth Dalcin, 2008). The remaining two articles assessed diaphragmatic strength alone (Pinet et al., 2003; Pradal et al., 1994). Inspiratory muscle endurance was assessed in only two studies (Lands et al., 1993; Leroy et al., 2011). Sustained maximum inspiratory pressure (SMIP) from RV to TLC was measured in three instances as a representation of inspiratory work capacity (Chatham et al., 1994; Enright et al., 2007; Ionescu et al., 1998).

Tables 2.6 and 2.7 summarize the overall results pertaining to IMS represented by MIP measured from RV and FRC respectively. Values listed represent the mean value ± standard deviation for included subjects with CF. In instances where subjects with CF were divided into sub-groups based on patient characteristics (i.e. gender), the mean value of the subjects combined were manually calculated and listed as mean value only. Global IMS was decreased, normal, or above normal when group means were represented as percent-predicted and/or compared to a healthy control group. Eight articles suggest a possible decreased IMS in adults with CF when looking at mean values and/or individual variations (Barry et al., 2008; Barry & Gallagher, 2003; Chatham et al., 1994; Ionescu et al., 1998; Leroy et al., 2011; Mier et al., 1990; Szeinberg et al., 1985; Ziegler et al., 2008). Group mean MIP expressed in cmH₂O.
<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>MIP(^a) (cmH(_2)O)</th>
<th>MIP(^a) (%-pred)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley (1999) n=14</td>
<td>99.4 ± 27.1</td>
<td>NR</td>
<td>MIP did not differ as compared to healthy controls based on absolute values (95.3±22.9 cmH(_2)O)</td>
</tr>
<tr>
<td>De Jong (2001) n=22</td>
<td>107± 29</td>
<td>118 ± 23 (82 – 176)</td>
<td>MIP is preserved based on calculated %-pred</td>
</tr>
<tr>
<td>Dunnink (2009) n=27</td>
<td>113 ± 30 (58 – 160)</td>
<td>125 ± 32 (82 ± 226)</td>
<td>MIP is increased based on calculated %-pred (p=0.00)</td>
</tr>
<tr>
<td>Enright (2007) n=40</td>
<td>116</td>
<td>NR</td>
<td>MIP did not differ as compared to healthy controls based on absolute values (124 cmH(_2)O)</td>
</tr>
<tr>
<td>Ionescu (1998) n=25</td>
<td>93.1 ± 31.7</td>
<td>NR</td>
<td>MIP is decreased as compared to healthy controls based on absolute values (107.3±21.9 cmH(_2)O, p&lt;0.05)</td>
</tr>
<tr>
<td>Mier (1990) n=25</td>
<td>67.9</td>
<td>64 ± 24%</td>
<td>MIP is decreased based on calculated %-pred</td>
</tr>
<tr>
<td>Szeinberg (1985) n=23</td>
<td>115.57 (66 – 160)</td>
<td>NR</td>
<td>MIP is decreased in individuals with CF with hyperinflation or nutritional compromise as compared to healthy controls (137 ± 15 cmH(_2)O) and individuals with CF without hyperinflation or nutritional compromise (p&lt;0.05)</td>
</tr>
<tr>
<td>Troosters (2009) n=64</td>
<td>NR</td>
<td>98.7%</td>
<td>MIP did not differ as compared to healthy controls based on %-pred (102.5%)</td>
</tr>
<tr>
<td>Ziegler (2008) n=39</td>
<td>97.2</td>
<td>85%</td>
<td>MIP is preserved based on calculated %-pred. 46.3 % of subjects with CF had values below normal.</td>
</tr>
</tbody>
</table>

Note. Values in the table reflect subjects with CF as calculated from the information provided in each study and expressed group mean ± SD (range) where able. MIP=maximal inspiratory pressure; %-pred=percent of predicted; NR=not reported; CF=cystic fibrosis

\(^a\) Potential criteria to identify impaired inspiratory muscle strength include MIP < 80 cmH\(_2\)O or MIP\(<\) 80% of predicted.
Table 2.7

Maximal inspiratory pressure from functional residual capacity in adults with CF

<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>MIP(^a) (cmH(_2)O)</th>
<th>MIP(^a) (%-pred)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barry, S. (2003) n=23</td>
<td>NR</td>
<td>94.0 ± 34.3 (39.8 – 175)</td>
<td>MIP is preserved based on mean calculated %-pred but ranged from severe weakness to above normal.</td>
</tr>
<tr>
<td>Barry, P. (2008) n=15</td>
<td>NR</td>
<td>80.0 ± 17.5</td>
<td>MIP is on the low end of normal based on the calculated %-pred</td>
</tr>
<tr>
<td>Chatham (1994) n=17</td>
<td>87.5 ± 22.7 (37 – 117)</td>
<td>NR</td>
<td>MIP is decreased as compared to healthy controls based on absolute values (107.2±21.9 cmH(_2)O, p&lt;0.02)</td>
</tr>
<tr>
<td>Dufresne (2009) n=38</td>
<td>100.0 ± 29</td>
<td>NR</td>
<td>MIP is increased as compared to healthy controls based on absolute values (83±28 cmH(_2)O, p&lt;0.002)</td>
</tr>
<tr>
<td>Lands (1993) n=14</td>
<td>96.4 ± 23.2</td>
<td>123.5 ± 70.7</td>
<td>MIP did not differ as compared to healthy controls based on absolute value (114.4±33.2 cmH(_2)O) or %-pred (118.2±28.4%)</td>
</tr>
<tr>
<td>Leroy (2011) n=18</td>
<td>69.8 ± 28.7 (29 – 129)</td>
<td>78.4 ± 34.1 (23.4 – 148)</td>
<td>MIP is decreased based on mean calculated %-pred and absolute values and ranged from severe weakness to above normal.</td>
</tr>
</tbody>
</table>

*Note.* The values given in the table were calculated based on the information provided in each study are subjects with CF and expressed group means ± SD (range) where able. MIP=maximal inspiratory pressure; %-pred=percent of predicted value; NR=not reported; CF=cystic fibrosis.

\(^a\) Potential criteria to identify impaired inspiratory muscle strength include MIP < 80 cmH\(_2\)O or MIP≤ 80% of predicted.
or %-predicted was considered within normal limits in four of these studies (Barry et al., 2008; Barry & Gallagher, 2003; Chatham et al., 1994; Ionescu et al., 1998).

These findings suggest variability in IMS in the adult CF population with a tendency to favor its preservation as compared to normal predicted values. However, criteria for impaired IMS were not considered nor known for this population. Caution should be used when evaluating MIP based on predicted values given the variability of these equations (Troosters et al., 2005). Closer inspection of the data is warranted given the heterogeneous nature of this population as individual subject data ranged from severe “weakness” to supernormal values when this information was provided in some studies.

In 2008, Ziegler et al evaluated MIP in a sample of 39 subjects with CF. The authors reported a mean MIP of the entire group of 85% predicted. At first glance, this suggests normal IMS in this population. However, the authors noted 17 of the 39 subjects (43.6%) presented with IMS below the lower limits of normal indicating impairment. Barry, S. et al (2003) reported a mean MIP %-predicted of 94 +/- 34.3% in a sample of 23 individuals with CF which suggests preserved IMS in this population. In the study by Barry et al (2003), inter-subject variability in MIP ranged from 39.8 to 175% predicted leading the authors to conclude “some patients have preserved inspiratory muscle strength whereas others have markedly reduced or supernormal levels of respiratory strength” (Barry & Gallagher, 2003, pg. 1382). Leroy et al (2011) reported a mean value for MIP of 78.4 +/- 34.1% predicted in their sample of 18 subjects with CF with a
range of 23.4 – 148% predicted. The mean MIP was 64% predicted as reported by Mier (1990). In contrast, no subject presented with a MIP below 80% predicted in the studies by de Jong (2001) and Dunnink (2009).

The MIP data are difficult to interpret in terms of cmH₂O as adequate values have not been established specific to the CF population. The clinical impact of this number should also be considered relative to the inspiratory pressure required per breath (i.e. the P_{br}/MIP ratio) imposed by the WOB to sustain ventilation which is increased in CF. “Normal” IMS may still be insufficient. However, according to ATS Guidelines for Respiratory Muscle Testing a “MIP value of 80 cmH₂O will generally exclude clinically important inspiratory muscle weakness” in adults with normal pulmonary mechanics (American Thoracic Society/European Respiratory, 2002, pg. 532). Research on IMT in COPD suggests IMT is most effective when MIP is ≤ 60 cmH₂O (Lotters et al., 2002). Based on this criteria, and given the increased WOB in moderate to severe CF, it may be reasonable to consider MIP values of 60 – 80 cmH₂O as mild impairment with values below 60 cmH₂O suggestive of moderate to severe impairment in adult populations though further investigation is required.

The mean values for MIP in cmH₂O illustrated in the groups studied do not suggest the presence of impaired IMS in CF. However, wide inter-subject variability is noted when looking at the ranges provided with some individuals as low as 29 and 37 cmH₂O (Chatham et al., 1994; Leroy et al., 2011). Collectively, these data suggests that some individuals with CF will demonstrate severe
impairments in IMS. These impairments disappear or significantly diminish when looking at mean values of heterogeneous samples. The characteristics of the subjects studied may explain these discrepancies and need further evaluation. Tables 2.8 and 2.9 summarize the group characteristics of the subjects included in the studies suggesting decreased MIP and those suggesting preserved or supernormal MIP in adults with CF respectively.

One particular limitation of these data is the large range of disease severity and degree of malnutrition of the subjects included. Both of these variables are believed to impact IMS in COPD and in CF (Barry & Gallagher, 2003; Kabitz, Walterspacher, Walker, & Windisch, 2007; Nishimura et al., 1995; Szeinberg et al., 1985). In addition, not all studies considered hyperinflation which negatively impacts IMS (Braun et al., 1982). Individual variations in MIP within and between studies may be explained by an interaction of differences in subject characteristics including age, disease severity, level of hyperinflation, macro nutritional status, and the use of systemic corticosteroids.
Table 2.8

*Baseline subject characteristics in studies suggesting preserved or supranormal MIP in adults with CF*

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (yrs)</th>
<th>FEV₁</th>
<th>Hyperinflation</th>
<th>BMI</th>
<th>Other Nutrition</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley, 1999</td>
<td>25.9 ± 3.5</td>
<td>1.55 ± 0.48L</td>
<td>RV/TLC 53.0 ± 8.1%</td>
<td>20.4 ± 2.9</td>
<td>LBM (kg) 44.5 ± 12.2</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dufresne 2009</td>
<td>29.1 ± 6.6</td>
<td>49 ± 25 %pred (15-113%)</td>
<td>RV %pred 215.0 ± 65%</td>
<td>19.8 ± 2.8</td>
<td>LBM (kg) 40.0 ± 11.0</td>
<td>No</td>
</tr>
<tr>
<td>DeJong 2001</td>
<td>19.0 ± 5.0 (12 - 30)</td>
<td>62 ± 28 %pred (21-111%)</td>
<td>NR</td>
<td>19.5 ± 2.8 (15.4-25.6)</td>
<td>LBM (kg) 46.4 ± 10 (31.1-66.4)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dunnick 2008</td>
<td>26.0 ± 7.0 (18 - 40)</td>
<td>63 ± 25 %pred (20-105%)</td>
<td>NR</td>
<td>21.0 ± 3 (16-29)</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Enright, 2007</td>
<td>22.4 (18 – 32)</td>
<td>47 %pred</td>
<td>RV/TLC 38.0%</td>
<td>22.0</td>
<td>LBM (kg) 44.6</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lands, 1993</td>
<td>21.0 ± 8.4</td>
<td>73 ± 25 %pred</td>
<td>RV/TLC 37.8 ± 13%</td>
<td>24.0</td>
<td>LBM (kg) 44.5 ± 9.01</td>
<td>Unknown</td>
</tr>
<tr>
<td>Troosters 2009</td>
<td>26.0 ± 8.0</td>
<td>65 ± 19 %pred</td>
<td>NR</td>
<td>20.9</td>
<td>NR</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Note.* FEV₁=forced expiratory volume in one-second; BMI=body mass index; RV/TLC=ratio of residual volume to total lung capacity; LBM=lean body mass in kg; %pred=percent of predicted value; NR=not reported; IBW=ideal body weight.
Table 2.9

*Baseline subject characteristics in studies suggesting decreased MIP in adults with CF*

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (yrs)</th>
<th>FEV$_1$</th>
<th>Hyperinflation</th>
<th>BMI</th>
<th>Other Nutrition</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barry, 2003</td>
<td>23.3 ± 15.1 (18 - 39)</td>
<td>48.7 ± 24 %pred (25 - 108)</td>
<td>NR</td>
<td>20.6 ± 2.5 (16.4 - 25.5)</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Barry, 2008</td>
<td>23.9 (19 – 40)</td>
<td>68.3 ± 22 %pred (31 - 113)</td>
<td>NR</td>
<td>21.3 ± 1.9</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Chatham, 1994</td>
<td>23.8 (17 - 40)</td>
<td>44.3 %pred (15 - 95)</td>
<td>NR</td>
<td>19.5 (17.5 - 22.5)</td>
<td>NR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ionescu, 1998</td>
<td>22.9 ± 3.8 (18 - 113)</td>
<td>61.1 %pred (18 - 113)</td>
<td>NR</td>
<td>21.3 ± 3.8</td>
<td>NR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Leroy, 2011</td>
<td>32.0 ± 12.6 (20 – 67)</td>
<td>44.1 ± 19 %pred (21 – 82%)</td>
<td>RV/TLC 57+/-8%</td>
<td>19.8 ± 1.9 (17.2 - 22.7)</td>
<td>LBM% 82.3 ± 8.6 (70.5 – 97)</td>
<td>No</td>
</tr>
<tr>
<td>Mier 1990</td>
<td>21.0 (16 - 28)</td>
<td>46.0 ± 21 %pred (21 – 82%)</td>
<td>RV %pred 216.0 ± 85</td>
<td>19.1</td>
<td>NR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Szeinberg, 1985</td>
<td>22.1 ± 3.7 (16 - 29)</td>
<td>59.2 %pred (18 - 96%)</td>
<td>RV/TLC 49.2</td>
<td>20.8</td>
<td>BWR 98.3 (73 - 116)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ziegler, 2008</td>
<td>23.7 ± 6.4 (16 - 47)</td>
<td>53.2 %pred</td>
<td>NR</td>
<td>20.3</td>
<td>NR</td>
<td>No</td>
</tr>
</tbody>
</table>

*Note.* FEV$_1$=forced expiratory volume in one-second; BMI=body mass index; RV/TLC=ratio of residual volume to total lung capacity; LBM=lean body mass; %pred=percent of predicted value; NR=not reported; LBM%=lean body mass to total body weight ratio; BWR=weight to ideal body weight ratio.
Disease severity and age

IMS decreases as a result of the aging process in healthy individuals and has been shown to be related to disease severity in individuals with COPD and children with CF (Britto et al., 2009; Hahn et al., 2008; Kabitz, Walterspacher, et al., 2007; Tudorache, Oancea, & Mladinescu, 2010). In 2001, de Jong et al demonstrated a positive correlation between disease severity as measured by FEV$_1$ with MIP %-predicted in adults with CF ($r=0.53$, $p=0.011$). These findings were supported by the results of Barry, S. et al (2003) who also demonstrated a positive correlation between these two variables ($r=0.64$, $p<0.01$). The subjects enrolled in the later study were slightly older and in a more advanced stage of disease severity. The stronger correlations seen by Barry et al (2003) suggest that age and FEV$_1$ may have a stronger influence on MIP as the individual ages and/or the disease progresses.

All studies evaluating MIP in adults with CF are limited because of their inclusion of individuals with a large range of disease severity (see Tables 2.8 and 2.9). This degree of heterogeneity in subject characteristics is a major design fault. The grouping of individuals with severe pulmonary disease with individuals with mild or no pulmonary disease can skew the results when looking at the group means of a sample. This limitation in inclusion criteria may distort the true effect of living with this progressive disease on IMS especially if those with severe disease are underrepresented. To date, the specific influence of disease severity on IMS has not been investigated.
The notion that impaired IMS may develop in the later stages of the disease course is supported by the results of Barry, S. (2003), Ziegler (2008), Mier (1990), Leroy (2001), and Chatham (1994) that suggests decreased IMS in adults with CF. Each of these studies included subjects that were older and had more advanced disease as measured by %FEV$_1$ as compared to studies demonstrating normal or supernormal IMS. An interaction between the disease progression and chronic effects of disease management over the increasing life span may impact IMS in CF rather than the aging process itself given the younger nature of the subjects studied. The impact of CF on IMS may be relative to the severity of disease progression over time, the associated intensity and duration of required medical treatments, adherence to complicated treatment regimes, and the emergence of secondary impairments leading to impaired IM contractility.

**Hyperinflation**

MIP measures the combined effort of the accessory muscles of inspiration along with the diaphragm and represents global IMS. This measure is a functional representation of the inspiratory pump as these muscles work in a synergistic nature to meet the imposed WOB rather than in isolation. Lung volume is known to impact diaphragmatic position, its contractile ability, and its contribution to MIP in health and disease (Braun et al., 1982; Larson et al., 2002; Szeinberg et al., 1985). Hyperinflation causes the diaphragm to assume a flattened position within the thoracic cavity placing the individual fibers in a
shortened state negatively affecting their tensile properties. This hyperinflation is known to occur in CF from pulmonary obstruction and increases to varying amounts as the disease progresses. Hyperinflation is measured by indirectly assessing FRC and/or RV through body plethysmography. In addition, these values may be expressed as a percentage relative to TLC.

In 1994, Pradal et al evaluated diaphragmatic strength in 15 adults with CF. In their analysis, diaphragmatic strength was associated with hyperinflation (r= -0.55, p<0.05) and poor nutritional status (r=0.76, p<0.001) (Pradal et al., 1994). Hyperinflation was quantified by the FRC/TLC ratio. Nutritional status was measured by the ratio of body weight to ideal body weight. "Multiple linear regression analysis was significant for these factors (R²=0.70, p<0.05) however, the partial regression coefficient was only significant for nutritional status (p<0.01)" (pg. 167). It should be noted that heterogeneity of disease severity was observed in the sample (%FEV₁ = 19 – 102, mean=59 +/- 28). This methodological flaw, in addition to a small sample size, may have influenced the conclusions pertaining to the contribution of hyperinflation if individuals with severe disease were underrepresented.

The impact of hyperinflation on MIP has been evaluated in adults with CF (Szeinberg et al., 1985). In this study, MIP was measured in 23 individuals with CF (%FEV₁ =18 – 96%, mean=59.2%) and in 33 healthy individuals. The subjects with CF were divided into two groups based on hyperinflation and compared to the healthy controls. Table 2.10 summarizes the findings of MIP
Table 2.10

*Impact of hyperinflation on maximal inspiratory pressure in adults with CF*

<table>
<thead>
<tr>
<th></th>
<th>CF with Hyperinflation (RV/TLC &gt; 50%)</th>
<th>CF without Hyperinflation (RV/TLC ≤ 50%)</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>11</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>MIP (cmH₂O)</td>
<td>102 ± 21 *</td>
<td>128 ± 39</td>
<td>137 ± 42</td>
</tr>
<tr>
<td>FEV₁ (%pred)</td>
<td>42 ± 13 *</td>
<td>76 ± 14</td>
<td>NR</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>62 ± 8 *</td>
<td>38 ± 9</td>
<td>NR</td>
</tr>
<tr>
<td>MVV</td>
<td>53 ± 17 *</td>
<td>88 ± 20</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Note.* Table adapted from Szeinberg et al (1985, pg. 768). RV = residual volume; TLC = total lung capacity; MIP = maximal inspiratory pressure; FEV₁ = forced expiratory volume in one-second; MVV = maximal voluntary ventilation, %pred = percent of predicted value; NR = not reported.

* p<0.05

across these three groups. Adults with CF and pulmonary hyperinflation (RV/TLC>50%) demonstrated a significantly decreased MIP as compared to those without hyperinflation and compared to the healthy controls. In the absence of hyperinflation, MIP was not significantly different than those without CF (Szeinberg et al., 1985). Adults with CF and hyperinflation presented with more advanced pulmonary disease as measured by %FEV₁, and decreased maximal voluntary ventilation (MVV) (p<0.05). This later statement suggests a potential interaction of hyperinflation and disease severity negatively effecting MIP. In addition, it is possible that MIP may contribute to IME as represented by MVV though this analysis was not performed.
The extraneous variable of hyperinflation may contribute to the conflicting results pertaining to MIP in adults with CF. The phenotypic presentation of hyperinflation is variable in this population. Four studies suggesting preserved MIP in adults with CF also measured hyperinflation (Bradley et al., 1999; Dufresne et al., 2009; Enright et al., 2007; Lands et al., 1993). In their reports, both Enright (2007) and Lands (1993) showed MIP did not differ as compared to healthy controls. The subjects in each of the studies had only a mild degree of hyperinflation (RV/TLC = 38 and 37.8% respectively). The absence of hyperinflation may preserve global IMS. The authors did not analyze the effect or relationship of hyperinflation and MIP. An RV/TLC above 50% was associated with decreased MIP while those with RV/TLC below 50% did not differ from healthy controls (Szeinberg et al., 1985). The mean value of RV/TLC of the subjects recruited by Enright (2007) and Lands (1993) were both below 50%, making their findings in line with that of Szeinberg (1985) when comparing to healthy individuals.

The results of Bradley et al (1999) and Dufresne et al (2009) suggest preserved IMS in adults with CF. Similar degrees of hyperinflation were noted in the work by Bradley (1999) when looking at entire group means as compared to Szeinberg (1985) (RV/TLC = 53 versus 49.2 respectively). However, the authors did not analyze the results based on the degree of hyperinflation and used a smaller sample size which may have influenced their findings. Dufresne et al (2009) reported MIP values that did not significantly differ as compared to healthy controls. In their study, subjects presented with hyperinflation as measured by
RV percent-predicted equal to 215% +/- 65% (mean +/- SD). It is difficult to compare these results with those of Szeinberg as the RV/TLC ratio was not provided and it is possible that they had a lower degree of hyperinflation relative to TLC which may have preserved diaphragmatic length. In addition, the large standard deviation (+/- 65%) of the RV percent-predicted indicates a large range in their measurement and the authors did not control for this variable.

Two additional studies measured hyperinflation and reported decreased levels of MIP in adults with CF (Leroy et al., 2011; Mier et al., 1990). MIP was shown to be decreased in terms of percent-predicted and absolute values in a sample of 18 adults with CF presenting with hyperinflation (RV/TLC=57 +/- 8%) (Leroy et al., 2011). The results of Leroy et al (2011) in combination with those of Szeinberg (1985) support the potential impact of hyperinflation (RV/TLC > 50%) on MIP in adults with CF.

In contrast, Mier et al (1990) suggested decreased MIP (64% predicted) in their sample. Hyperinflation was represented as RV percent-predicted (RV = 216 +/- 85%pred). The findings by Mier (1985) are in direct contrast to those mentioned earlier by Dufresne (2009) in subjects with similar characteristics in terms of hyperinflation and disease severity. A comparison cannot be made based on RV/TLC ratios, as this measure was not reported by either of these authors. This discrepancy is difficult to interpret but suggests additional variables beyond disease severity and hyperinflation may influence the MIP.
Nutritional Status

Measures of nutrition such as BMI, LBM (kg), percent of IBW (%IBW), and the ratio of LBM to IBW represent macro nutrition. The impact of micro nutritional status on IM function has not been evaluated in adults with CF. For the purposes of this discussion, the term “nutritional status” shall refer to measures of macro nutrition.

Poor nutritional status has been suggested to influence MIP and linked to both peripheral muscle and diaphragmatic dysfunction in adults with CF. Dufresne (2009) measured MIP as compared to healthy controls and reported nutritional status as LBM expressed in kilograms (kg). The subjects with CF presented with a mean LBM of 40.0 +/- 11.0 kg, which did not significantly differ from the healthy comparison group indicating a preserved level of nutrition. Mier (1990) measured MIP in a group of adults with CF presenting with nutritional depletion as indicated by a body mass index (BMI) equal to 19.1 kg/m². The preserved LBM of the subjects evaluated by Dufresne (2009) may have maintained the strength of the peripheral accessory muscles of inspiration (i.e. sternocleidomastoid, scalenes, and external intercostals) in the presence of hyperinflation. This preservation could compensate for diaphragmatic weakness resulting from hyperinflation and appear as a preserved MIP. The malnourishment seen in the subjects recruited by Mier (1990) may have involved the accessory muscles of inspiration limiting their ability to compensate for a mechanically disadvantaged diaphragm.
In addition to stratifying based on hyperinflation, Szeinberg et al compared MIP in adults with CF with and without nutritional depletion. In their study, nutritional status was measured as the %IBW. Nutritionally compromised individuals with CF (%IBW <90%) were compared to those with normal nutritional status (%IBW >90%) and healthy controls. MIP was significantly lower in the malnourished group as compared to those with normal nutrition (p<0.05). As compared to healthy controls, MIP in the individuals with CF and normal %IBW was not significantly different. The overall results of Szeinberg, suggest that both macro nutrition and hyperinflation will influence MIP in adults with CF and should be controlled for when evaluating IMS in this population. The combined effect of these two variables was not evaluated.

BMI is a standard measurement to assess nutritional status and has been shown to moderately correlate to MIP (r=0.55, p<0.01) in adults with CF and contribute to 9% of its variance (Barry & Gallagher, 2003). Adults with CF and a BMI < 20kg/m$^2$ were shown to have a lower MIP as compared to those with BMI > 20kg/m$^2$ (Ionescu et al., 1998). In terms of survival, both IMS (MIP %predicted: 64 versus 85.5 %) and nutritional status (BMI: 16.5 versus 19.8 kg/m$^2$) were significantly lower in adults with CF who later died or received transplant (Ionescu et al., 1998). In contrast, Ziegler et al (2008) failed to show a difference in MIP when comparing adults with CF with and without nutritional depletion based on BMI. MIP did not significantly differ in those subjects with normal nutrition (BMI > 20kg/m$^2$, n=24) as compared to malnourished individuals (BMI < 20kg/m$^2$, n=15). BMI did not correlate to MIP in this study.
This discrepancy may be explained by extraneous variables or the inherent limitations in BMI to accurately reflect nutritional status. Interestingly, 10 subjects with normal nutrition (BMI > 20kg/m²) presented with MIP below the lower limits of normal in the study by Ziegler (2008). This would have lowered the mean value of MIP in this group to a similar level as those with nutritional depletion. Either extraneous variables other than macro nutrition contributed to the decreased MIP in these 10 subjects, or BMI did not accurately capture all individuals with macro nutritional depletion. As other contributing factors (i.e. hyperinflation) were not adequately addressed, the effect of extraneous variables cannot be determined. BMI has known limitations in assessing nutritional status as it does not consider all constituents of body composition (ACSM, 2010). Specifically, individuals with CF and a normal BMI have been shown to have evidence of decreased LBM (Ionescu et al., 2003). This suggests that BMI may not capture skeletal muscle wasting in adults with CF and may not be the most appropriate measure relative to IMS. Decreased LBM may have been present in the individuals with impaired IMS in the normal nutrition group identified by Ziegler (2008). If present, decreased LBM could explain a decreased MIP in these subjects and the lack of difference noted between groups based on BMI.

Lean body mass and/or the %IBW may be better measures of nutritional status related to MIP as compared to BMI due to their ability to capture muscle wasting. Representation of LBM as a function of IBW may also have advantages as it may capture LBM depletion in individuals with normal weight (Engelen, Schols, Baken, Wesseling, & Wouters, 1994). As illustrated in Table 2.8, five
studies suggest normal or supernormal MIP in adults with CF that measured both BMI and LBM (Bradley et al., 1999; de Jong et al., 2001b; Dufresne et al., 2009; Enright et al., 2007; Lands et al., 1993). Interestingly, all of these studies reported similar values for mean LBM (kg) for their subjects. Two of these studies indicated that these values did not differ as compared to their healthy controls suggesting LBM was preserved (Bradley et al., 1999; Dufresne et al., 2009). All had varying degrees of nutritional status based on BMI. Enright (2007) further analyzed their findings and noted a decreased MIP was present in individuals with LBM below the 5th percentile of normal. Lands (1993) also reported %IBW for their subjects in addition to LBM (kg). In their study, MIP was not decreased. LBM (kg) was significantly lower than their comparison group but the subjects with CF were normal in terms of %IBW (%IBW=94.3 +/-9.64). The subjects included by Lands (1993) had very mild disease (%FEV1 = 74 +/-24.8%) and minimal hyperinflation (RV/TLC=37.8 +/- 13).

Measures of body mass relative to IBW may identify significant nutritional depletion resulting in decreased muscle strength. It may also exclude individuals with “low” LBM simply due to their smaller body size. If skeletal muscle wasting extends to the accessory muscles of inspiration, these muscles may be unable to assist the diaphragm adequately in terms of global IMS. The resultant finding would be a decreased MIP that may negatively impact the performance of the inspiratory pump. The results discussed earlier by Szeinberg (1985) support this assumption as individuals with CF who were below 90% IBW had a lower MIP.
In further support, Ionescu (1998) showed decreased MIP in adults with CF with compromised nutritional status as measured by the ratio of LBM to IBW.

The potential interaction between the chronic effects of CF over the lifespan, disease severity, hyperinflation, and nutritional status on MIP may be illustrated by examining the conflicting results between Leroy et al (2011) and Lands et al (1993). The results by Leroy (2011) suggest a decreased MIP in adults with CF whereas Lands (1993) suggest preservation of MIP. In comparing patient characteristics, there is a stark contrast between these studies in terms of the variables discussed. As can be seen in Tables 2.8 and 2.9, the subjects recruited by Leroy et al were older, had more severe pulmonary disease, greater hyperinflation, and were in a greater state of nutritional depletion, and thus had a lower MIP. The absence of these characteristics in the subjects recruited by Lands et al is consistent with the expected finding of normal MIP.

The pattern of LBM wasting may also influence inspiratory muscle function. Muscle wasting in adults with CF has been suggested to follow a “distal to proximal” pattern initiating at the legs progressing to the arms and finally involving the trunk over time (Bolton, Ionescu, Evans, Pettit, & Shale, 2003, pg. 885). “The arm, leg, and trunk FFM were individually related to physical activity” (Bolton et al., 2003, pg. 886). Finally, this pattern of muscle wasting was also related to FEV₁ in the presence of severe disease (Bolton et al., 2003). These findings suggest that inactivity as a result of disease progression, along with poor nutrition, may lead to muscular deconditioning. Non-compliance with disease
management plans may also influence this sequence. In the early stages, individuals with CF may limit their walking activity due to dyspnea but continue to use their upper extremities for basic self-care while the inspiratory muscles are used to maintain ventilation. This sequence would preserve the function of these later muscles while resulting in disuse atrophy of the low extremities. Progressive inactivity and malnourishment associated with advancing disease severity may then extend this deconditioning to the arms and lastly impact the vital inspiratory muscles of the thorax. Proximal muscle wasting of the upper extremities may extend to the accessory muscles of inspiration and potentially cause impaired IMS in adults with CF.

Multiple studies considered peripheral muscle strength in relation to MIP. In 2003, Barry et al demonstrated a positive correlation between knee extensor strength and MIP ($r=0.76$, $p<0.05$). Interestingly, elbow flexor strength demonstrated an even greater correlation coefficient ($r=0.87$, $p<0.05$). In a study by de Jong et al (2001), MIP correlated to elbow flexor strength ($r=0.44$, $p=0.041$) whereas no correlation was found with knee extensor strength. Handgrip was also shown to correlate to MIP in some instances but the relationship was not as strong as the proximal upper extremities (Barry & Gallagher, 2003; Dunnink et al., 2009). The stronger relationship between MIP and upper extremity strength suggests that inspiratory muscle impairments may be preceded by upper extremity weakness associated with a preferential pattern of muscle wasting.
As part of their anthropometric measurements, Ionescu et al (1998) measured the mid-arm muscle circumference (MAMC) as a measure of proximal upper body muscle wasting. In their analysis, the authors demonstrated a “MAMC<70% predicted was associated with a reduction in MIP (p<0.05)” (pg. 1273). “The LBM/IBW and MAMC were related (r=0.45, p<0.05)” (pg. 1274).

Szeinberg et al (1985) also measured MAMC which was significantly decreased in their malnourished group (%IBW < 90%). Though a decreased MIP accompanied this finding, care must be taken when making the assumption that decreased MAMC precedes inspiratory muscle impairments as Ziegler et al (2008) failed to show a significant relationship between MAMC and MIP. This weak relationship is consistent with a multi-factorial cause of decreased MIP including disease severity, hyperinflation, and macro nutritional status. In the case of Ziegler et al, hyperinflation was not reported. It is possible that diaphragmatic strength was maintained and compensated for any muscle wasting that was present in the accessory muscles of inspiration. In addition, the muscle wasting may not have been associated with impaired muscle function at that time.

**Corticosteroids**

Inhaled and systemic corticosteroid use is a standard intervention in the management of CF to control pulmonary inflammation over the disease course (Yankaskas, Marshall, Sufian, Simon, & Rodman, 2004). The effect of inhaled corticosteroids and other pulmonary medications on the inspiratory muscles specifically has not been evaluated. Barry et al (2003) evaluated the influence of
systemic corticosteroids use on MIP. In their study, the authors calculated the average daily dose (ADD) of corticosteroid usage (converted to an equivalent dose of prednisolone) over the previous 12 months in a sample of 23 adults with CF. The ADD was calculated as 5.1 mg/day and was strongly related to MIP ($r = -0.73$, $p<0.01$). In addition, stepwise multiple regression analysis revealed that ADD accounted for 54% of the variance seen in MIP in their sample. This indicates that systemic corticosteroid use plays a significant role in determining IMS; however, the methods employed to determine the ADD in this study are not clinically applicable.

Systemic steroid usage was inconsistently controlled for in the included studies evaluating IMS in adults with CF. This oversight is most likely due to the difficulty in gathering accurate data about this variable further illustrating the lack of clinical feasibility. The fact that decreased IMS was suggested in the absence of steroid usage implies that other factors play a role (Barry & Gallagher, 2003; Leroy et al., 2011; Ziegler et al., 2008). Use of systemic corticosteroids may represent the chronic effects of the disease management and/or directly contribute to muscle wasting. However, advancing disease severity, hyperinflation, and declining LBM may ultimately represent the effect of systemic corticosteroids. As these measures are easily assessed in the clinic, their combination may serve as a surrogate representation for chronic systemic corticosteroid use when considering the effect on IMS.
Physical Activity

Physical activity levels and chronic exercise may in itself produce training effects in the inspiratory muscles resulting in improved IMS from the imposed ventilatory demands. In addition, activity levels can combat the deleterious effects of deconditioning. Recently, Dassios et al (2013) compared measures of inspiratory muscle function in adolescents with CF who regularly participate in aerobic exercise as compared to a matched sedentary group. In this cross-sectional study, a significantly greater MIP was observed in the physically active group (mean MIP = 92 cmH₂O vs. 62 cmH₂O, p<0.001). Similar results have been found in the COPD population where significant increases in IMS has been observed as a result of pulmonary rehabilitation or a comprehensive exercise program (Cortopassi et al., 2009; Reis et al., 2013).

To date, the study by Dassios (2013) is the only published data investigating the potential effect of regular physical activity and/or exercise on IMS in CF (Dassios, Katelari, Doudounakis, & Dimitriou, 2013). However, exercise capacity has been associated with MIP on separate occasions. Dunnink et al (2009) found a positive relationship (r=0.59, p=0.001) between MIP and the distance walked on the modified shuttle test where Bradley et al (1999) demonstrated a positive relationship (r=0.68, p<0.05) with the peak workload achieved on a lower extremity ergometer (Bradley et al., 1999; Dunnink et al., 2009). Though a cause and effect relationship cannot be confirmed, these findings suggest that physical activity may provide a protective response on the
inspiratory muscles to combat the deleterious effect of disease-related factors in CF.

Summary

IMS can potentially affect exercise performance indirectly via its relationship to the TTI within the $P_{br}/MIP$ ratio. A combination of increased WOB in the presence of decreased MIP may be seen in pulmonary disease and alter the $P_{br}/MIP$ ratio. Elevation of this ratio can result in an increased load perception and altered breathing patterns to avoid inspiratory muscle fatigue. As a result, functional exercise capacity may be limited by dyspnea and/or ventilatory inefficiency. IMT may alleviate this sequence.

Insufficient research exists to support or refute the efficacy of IMT in adults with CF though it does demonstrate the ability to improve MIP. The heterogeneous nature of the progression and clinical manifestation in CF complicates research methods in this population. Care must be taken when suggesting such a laborious intervention to individuals already burdened by the management of their disease. Multiple systematic reviews and meta-analyses emphasize the need for impaired IMS at baseline as a prerequisite for ergogenic benefits in populations similar to CF such as COPD. In the absence of this impairment, the benefits of IMT may not outweigh the additional burden of the intervention.
Alterations in IMS in adults with CF have not been adequately investigated in the literature. Research favors the preservation of IMS as measured by MIP but closer inspection suggests a variable presentation including decreased, normal, and above normal values. The literature is limited by the extreme heterogeneity of the populations studied and small sample size used in many of the studies reviewed. In addition, studies basing their findings on percent-predicted may be faulted as there is extreme variability within these predicted values. As with the majority of phenotypic presentations in CF, the impact of the disease on MIP appears variable. Select individuals with CF can present with a significantly decreased MIP but clinical characteristics to positively identify these individuals are unclear. A combination of hyperinflation, decreased macro nutrition, and severity of pulmonary disease may result in impaired IMS but has not yet been confirmed. Subgroups of adults with CF may exist that present with a unique set of clinical characteristics resulting in decreased IMS amendable to IMT. The need for this type of investigation has been suggested in the literature (Dunnink et al., 2009; Houston et al., 2008; Reid et al., 2008).

**Synthesis of the Literature Relevant to this Project**

As a result of this literature review, it is apparent that further research is warranted to investigate potential alterations in IMS in adults with CF to advance research in this area. The present study investigated the influence of disease severity on global inspiratory muscle strength in adults with stable CF. The potential for common clinical characteristics to predict global inspiratory muscle
strength in adults with stable CF was also analyzed. This knowledge is imperative to design future studies on the inspiratory muscles in adults with CF to determine the efficacy of IMT in this population. The results may enable clinicians and researcher to identify select individuals that may respond to IMT.
References


Chapter III

Methods

Research Design

This was a cross-sectional study investigating global inspiratory muscle strength (IMS) in adults with cystic fibrosis (CF). Differences in IMS were assessed in adults with stable CF grouped by disease severity in comparison to healthy controls. Possible relationships between disease severity and IMS were analyzed in adults with CF. The ability for select clinical measures to predict IMS was determined through a multiple regression model.

Variables and Operational Definitions

Within this research model, the dependent variable represented the construct of inspiratory muscle strength. Independent variables represented four primary constructs including disease severity, nutritional status, hyperinflation, and upper extremity muscle mass. This section operationally defines each of these constructs. Specific procedural methods, instrumentation, validity, and reliability for each measurement are described in the data collection section of this chapter.

Dependent variables

1. **Global Inspiratory Muscle Strength** was operationalized as the maximal inspiratory pressure (MIP) measured at the mouth measured from residual volume (RV) according to guidelines set forth by the American
Thoracic Society (ATS) (American Thoracic Society/European Respiratory, 2002). MIP was reported in centimeters of water pressure (cmH₂O) and as percent-predicted (%MIP) according to Black and Hyatt (Black & Hyatt, 1969). Both MIP and %MIP served as dependent variables in this study. “Impaired IMS” was defined as values significantly below that of age-matched healthy controls. MIP was used to identify differences in absolute IMS whereas %MIP was used to compare values relative to established norms to further help in identifying impairments. To aid in determining clinical significance, impairments in the adult population were further be defined as MIP values < 80 cmH₂O (American Thoracic Society/European Respiratory, 2002). Alternately, values below 80% of predicted may reflect impaired IMS.

**Independent Variables**

1. **Disease Severity** was operationalized as the percent of predicted forced expiratory volume in one second (%FEV₁) (Yankaskas, Marshall, Sufian, Simon, & Rodman, 2004). Predicted values were taken according to Hankinson et al (1999) (Hankinson, Odencrantz, & Fedan, 1999). Severity of disease was categorized according to guidelines set forth by the CF Foundation (CFF) whereas %FEV₁ ≥ 70% indicates mild lung disease, 40 – 69 %FEV₁ indicates moderate
lung disease, and \( \%FEV_1 < 40\% \) indicates severe lung disease (Cystic Fibrosis Foundation, 2013).

2. **Nutritional Status** was operationalized as the ratio of lean body mass (LBM) to ideal body weight (IBW) to reflect macro nutrition (Engelen, Schols, Baken, Wesseling, & Wouters, 1994; Ionescu et al., 1998). The presence or absence of significant nutritional depletion was noted (Y/N) to aid interpreting the results. A LBM/IBW ratio < 69% for males and 67% for females was used to identify individuals with significant nutritional depletion as these cut-off values are associated with decreased MIP in adults with CF (Ionescu et al., 1998). Lean body mass index (LBMI), body mass index (BMI), and the percent of IBW (%IBW) were used as alternate measures to help identify the best representation of nutritional status to predict inspiratory muscle strength.

3. **Hyperinflation** was operationalized as the ratio of RV to total lung capacity (TLC) and recorded as a percent (Pellegrino et al., 2005). The presence or absence of significant hyperinflation was noted (Y/N) to aid interpreting the results. An RV/TLC ratio > 50% was used to identify individuals with significant hyperinflation as this cut-off value was associated with decreased MIP in adults with CF (Szeinberg, England, Mindorff, Fraser, & Levison, 1985). To help identify the best
representation of hyperinflation to predict inspiratory muscle strength, this construct was also operationalized as RV expressed in liters as well as percent of predicted.

4. **Upper Extremity Muscle Mass (UEMM)** was operationalized as the percent of predicted mid-arm muscle circumference (%MAMC). The presence or absence of decreased UEMM was noted (Y/N) to aid interpreting the results. A %MAMC < 70% was used to identify individuals with decreased UEMM to as this cut-off value was associated with decreased MIP in adults with CF (Ionescu et al., 1998).

**Subjects**

Subjects with CF were recruited from the Adult CF Clinic located at the Hospital of the University of Pennsylvania (HUP). A sample of convenience was used and potential subjects were identified during routine clinic visits. Children and adolescents were excluded from this study as the aims were specific to the adult CF population $\geq 18$ years of age. No individual was excluded on the basis of gender, race, religious background, sexual preference, or ethnicity. To ensure proper understanding of the research protocol, tests, and procedures, eligible subjects were limited to English speaking individuals.

Initial contact was made during routine clinic visits to inform adults with CF of the study opportunity. Upon arrival to the clinic, potential volunteers were educated in the purpose of the study, the general protocol, and associated risks
and benefits. Interested subjects were screened for eligibility and provided with a detailed explanation of the study procedures. Eligible subjects were enrolled after completing the informed consent process. Each subject that completed the study was compensated with a $20 gift card.

The following inclusion criteria were applied to subjects with CF:

- Age greater than or equal to 18 years.
- English speaking
- Diagnosis of cystic fibrosis identified through past genetic testing and/or sweat chloride (Cl\(^-\)) concentration >60mmol/L and confirmed through past medical records
- Stable lung function with no change in medical status in the past 4 weeks

Subjects with CF were excluded in the presence of any of the following criteria:

- Current active smoker
- Secondary pulmonary comorbidity other than asthma
- Orthopedic condition involving the thorax that may interfere with testing performance
- Recent thoracic or abdominal surgery that may interfere with testing performance
- Neuromuscular disease
- Pregnancy
- Signs and symptoms of a pulmonary exacerbation
- Unresolved pneumothorax
- Positive colonization with species of *burkholderia*
- Prior lung transplant
- Cardiac pacemaker

A group of healthy controls were recruited as a control group to assist in interpretation of the results as recommended in the literature (Troosters, Gosselink, & Decramer, 2005). Healthy adult English speaking control subjects (age ≥ 18) were recruited from the Stratford campus of Rutgers, the State University of New Jersey, School of Health Related Professions and at HUP with the use of flyers. Attempts were made to obtain an equal distribution of male and female healthy subjects within a similar age range as those subjects recruited with CF as both gender and age may influence IMS (Black & Hyatt, 1969; Bradley et al., 1999; Britto, Zampa, de Oliveira, Prado, & Parreira, 2009; Lands, Heigenhauser, & Jones, 1993). Healthy individuals were excluded if they were current smokers, pregnant, diagnosed with pre-existing pulmonary disease (i.e. asthma), diabetes, heart failure, active respiratory infection, or any condition that could affect their ability to perform testing procedures as confirmed during interview. Eligible control subjects were educated on the purpose of the study, its protocol, and associated risks and benefits. After completing the informed consent process, basic demographic data including age and gender were
obtained followed by a complete assessment of body composition, pulmonary function, and MIP as described below.

**Data Collection and Instrumentation – Subjects with Cystic Fibrosis**

Select data was collected from the subjects’ medical records from the results of medical tests associated with routine clinical care including pulmonary function tests (PFT), demographic data, and medical history. Data collected by the primary investigator that was not part of routine care included non-invasive measurement of MIP, assessment of LBM, and UEMM.

Primary pulmonary function measurements used in this analysis included FEV$_1$, RV, and TLC and recorded from the medical record as recorded in the HUP pulmonary function lab. All pulmonary function testing equipment and procedures utilized at this lab were in accordance to ATS guidelines (Miller et al., 2005; Wanger et al., 2005). As part of routine care, adults with CF undergo basic spirometry testing measured by a licensed respiratory therapist skilled in the performance of PFTs immediately prior to each clinic visit at the HUP Adult CF clinic. Measurement of FEV$_1$ was completed according to standard guidelines, including routine calibration, on the same day as the measurements of MIP and body composition (Miller et al., 2005). The progression of hyperinflation has been suggested to change at a similar rate as compared to airway obstruction in CF (Kraemer, Baldwin, Ammann, Frey, & Gallati, 2006). Given this relationship, RV and TLC were extrapolated from the most recent body plethysmography test completed within 12 months of MIP testing as long as the %FEV$_1$ measured at
that time was within 10% of current values. Inspiratory capacity was also extrapolated from these tests and recorded in liters and as percent of predicted.

Demographic information obtained from the medical record and/or subject interview to characterize the adults with CF included: age (yrs.), genotype (if available), sex (M/F), height (cm), weight (kg), percent of IBW (%IBW), body mass index, presence of CF-related diabetes (Y/N), pancreatic insufficiency(Y/N), sputum colonization, general medications, and the presence of concurrent systemic corticosteroid use (mg/day). Baseline dyspnea was assessed by the Modified Medical Research Council Dyspnea Scale (Mahler & Wells, 1988). The complete data collection form used in the study for adults with CF is included in Appendix B. Given the extensive number of genetic defects associated with CF and that delta F508 (ΔF508) mutation is the most common, genotype was categorized as ΔF508/ΔF508, ΔF508/other, or other/other. Similar classification systems have been effectively used in the literature to describe CF populations (King, Wilson, Kotsimbos, Bailey, & Nyulasi, 2005; Selvadurai et al., 2002). Results of the individual’s most recent sputum culture were used to document current pulmonary bacterial colonization. Subjects were excluded in the presence of any species of *burkholderia* secondary to infection control issues.

**Global inspiratory muscle strength**

Inspiratory muscle strength was assessed via non-invasive measurement of MIP using a commercially available handheld mouth pressure meter
(MicroRPM® (RPM01), CareFusion Ltd., San Diego, CA, USA). Per the manufacturer specifications “the calibration is factory set and should remain stable indefinitely” (CareFusion, 2010). Measurement of MIP via such portable pressure meters is a valid and reliable representation of global inspiratory muscle strength commonly used in clinical and research environments (American Thoracic Society/European Respiratory, 2002; Hamnegard et al., 1994; Larson & Kim, 1987).

The validity of this technique to reflect IMS is supported by strong correlations with transdiaphragmatic pressure ($T_{di}$). Braun et al (1982) demonstrated a correlation coefficient of 0.93 ($p<0.001$) between these two measures and Ramonaxto et al (1995) demonstrated supporting results with a correlation coefficient of 0.94 ($p<0.001$) (Braun, Arora, & Rochester, 1982; Ramonatxo, Boulard, & Prefaut, 1995). Similar portable pressure devices have been shown to reliably measure MIP in adults with CF with a coefficient of reliability equal to 0.89 and an intra-class coefficient (ICC) of 0.88 (Enright, Unnithan, & Davies, 2006). The repeatability and reliability of the specific Micro-Medical® mouth pressure meter has been established in individuals with non-CF bronchiectasis who are similar to the adult CF population (Moran, Piper, Elborn, & Bradley, 2005). In this population, the limits of agreement from MIP between two testing procedures separated by 10 – 14 days was found to be $-3.50 \pm 20 cm H_2O$ with an ICC of 0.93 ($95\%CI 0.82$ to 0.97) (Moran et al., 2005). Recently, the reliability of the MicroRPM has been established in healthy individuals resulting in
an ICC of 0.86 – 0.90 (SEM=9 – 10, SDD=18 – 22) (Dimitriadis, Kapreli, Konstantinidou, Oldham, & Strimpakos, 2011).

Data measurements were recorded and saved using associated software through a laptop interface (Puma® (PU1000), Micro-Medical). Figure 3.1 illustrates a healthy subject performing the maneuver. Testing procedures followed the American Thoracic Society (ATS) guidelines for assessing IMS at the mouth (American Thoracic Society/European Respiratory, 2002). Prior to testing, subjects were educated on the procedure, including the importance of maintaining a tight mouth seal, and the primary investigator demonstrated the maneuver. Subjects were seated wearing nose clips. A rubber flanged mouthpiece was attached to the portable mouth pressure meter in line with a bacterial filter and an inspiratory valve. The inspiratory valve contained a small leak to prevent the influence of the buccal muscles. Each subject performed static maximal inspiratory efforts (i.e. a Mueller maneuver) from RV for at least 2 seconds as per standard protocols. MIP was defined as the mean maximal pressure sustained for one-second as this has been shown to be an acceptable measure of IMS comparable to peak pressure and is thought to be more reliable (American Thoracic Society/European Respiratory, 2002; Windisch, Hennings, Sorichter, Hamm, & Crieie, 2004). Standardized instructions and strong verbal encouragement were provided during the maneuvers. Biofeedback was provided by allowing the subject to visualize the computer interface to ensure maximal volitional efforts. Subjects completed a minimum of two practice trials demonstrating appropriate technique prior to initiating the testing sequence.
Subsequently, the maximum pressure of at least five satisfactory inspiratory maneuvers that presented with less than 5-10% variability was recorded as per ATS guidelines. All subjects refrained from using a bronchodilator for at least 2 hours prior to MIP testing. Measurement trials were separated by one to two minutes of rest to negate the potential effect of fatigue.

*Figure 3.1.* Healthy subject performing a maximal inspiratory pressure maneuver using the MicroMedical®, mouth pressure meter. For this study, the subject was allowed to view the computer screen for visual feedback during the maneuver.

**Anthropometrics**

Height (Ht.) was measured using a standard stadiometer and recorded in centimeters (cm). Weight (Wt.) was recorded in kilograms (kg) measured while wearing light clothing with shoes and socks removed during bioelectrical
impedance analysis (BIA) assessment. Prior to weighing, each subject emptied his/her pockets and removed any items (i.e. belts or keys) that may add weight to the scale. To accommodate for the light clothing, 4.4 kg (2 pounds) was deducted as a standard for all subjects. LBM was derived from measurements of percent body fat (%BF), fat mass (FM), and Wt. calculated as follows:

\[ \text{FM} = (\%BF) \times (\text{Wt}) \]
\[ \text{LBM} = \text{Wt} - \text{FM} \]

Percent body fat was measured via BIA and also estimated from BMI and skin fold (SF) measurements described below. Results from each measure were substituted for the analogous results obtained from BIA to determine their clinical utility to predict MIP in the absence of expensive BIA equipment. Ideal body weight was based on the Metropolitan Life Insurance height-weight tables (Metropolitan Life Insurance Company, 1983). The LBM to IBW ratio (LBM/IBW) was represented nutritional status as it has been used to detect LBM depletion in the presence of normal weight (Engelen et al., 1994). The presence of significant nutritional depletion was identified by a LBM/IBW ratio < 69% for males and 67% for females and are associated with decreased MIP in adults with CF (Ionescu et al., 1998). The %IBW was calculated as the ratio of Wt. to IBW. The lean body mass index (LBMI) was calculated as the LBM (kg) divided by the Ht (m²) (King et al., 2010; VanItallie, Yang, Heymsfield, Funk, & Boileau, 1990).

Body mass index was calculated as the Wt (kg) divided by the Ht (m²) (ACSM, 2010). The Deurenberg equation was then used to estimate %BF based
on BMI (%BF<sub>BMI</sub>) and is illustrated below. This equation has been validated in healthy populations ($R^2 = 0.79$, SEE=4.1%) (Deurenberg, Weststrate, & Seidell, 1991).

$$\%BF_{BMI} = (1.20 \times BMI) + (0.23 \times age) - (10.8 \times sex^*) - 5.4$$

*sex= 1(male) and 0 (female)

In adults with CF, the %BF<sub>BMI</sub> significantly correlates to whole-body bioimpedance analysis in both males ($r=0.76$) and females ($r=0.87$) supporting its validity (Hollander, De Roos, De Vries, & Van Berkhout, 2005). Fat mass from BMI measurements (FM<sub>BMI</sub>) was calculated as the product of the resultant %BF<sub>BMI</sub> and weight. LBM from BMI (LBM<sub>BMI</sub>) was then calculated as the difference between weight and FM<sub>BMI</sub>.

To assess LBM from SF (LBM<sub>SF</sub>), measurements were taken at two sites using Lange Calipers (Beta Technology, Santa Cruz, CA). The use of Lange calipers is considered a valid method to assess body composition in the general adult population (Beam & Szymanski, 2010; Durnin & Womersley, 1974; Gruber, Pollock, Graves, Colvin, & Braith, 1990; Orphanidou, McCargar, Birmingham, Mathieson, & Goldner, 1994). Calipers were calibrated with a gauge block (code 010729) as per the manufacturer recommendations. The mean value of three vertical SF measurements taken at the right triceps and biceps at a midway point between the acromion and olecranon processes was recorded in millimeters (mm). Body density (Db<sub>SF</sub>) was calculated from these measurements according
to standard equations derived from this technique (Durnin & Womersley, 1974). The standard error of the estimate of body density with this method is reported as 0.0124 for males and 0.0118 for females (Durnin & Womersley, 1974).

The Siri equation was then applied to calculate the %BF from $\text{Db}_{\text{SF}}$ where $\%\text{BF}_{\text{SF}} = \frac{495}{\text{Db}_{\text{SF}}} - 450$. The product of the $\%\text{BF}_{\text{SF}}$ and weight was used to calculate fat mass from SF measurements. Lean body mass ($\text{LBM}_{\text{SF}}$) was ultimately calculated as the difference between weight and fat mass from SF measurements. This simple two-site skin-fold measurement technique to assess $\text{LBM}_{\text{SF}}$ has been evaluated in adults with CF and significantly correlated to measurements by whole body BIA in both adult males ($r=0.72$) and females ($r=0.75$) with CF (Hollander et al., 2005).

For the primary statistical analyses in this study, %BF and LBM were derived from whole body BIA (%BF$_{\text{BIA}}$ and LBM$_{\text{BIA}}$) using the Tanita BC-418 body composition analyzer (50kHz, 500 μA) as seen in Figure 3.2. Measurements were taken in a temperature controlled environment. Subjects refrained from ingesting caffeine or alcohol for at least two hours prior to testing and voided their bladder within 30 minutes prior to testing. The Tanita BC-418 utilizes an eight electrode contact system with the subject standing on bilateral foot plates and holding bilateral hand grips with the arms in a dependent relaxed position. The Tanita BC-418 has an accuracy of 12Ω according to the manufacturer specifications. Subjects wore light clothing with shoes and socks removed. Data provided by BIA included whole body impedance as well as segmental analysis.
for the trunk and each extremity. Body composition was determined based on the measured whole body impedance utilizing the manufacturers' pre-programmed protocols.

Measuring body impedance is a simple non-invasive procedure that involves passing a small electrical current through the body via skin electrodes. This current conducts slower through fat tissues as compared to fat-free tissues (Lukaski, 1987). The resistance to current flow through the body is used to calculate conductance (\(Ht^2/R\)) and then to predict LBM (Lukaski, 1987). The validity of BIA to assess LBM has been validated in the healthy population (Lukaski, Johnson, Bolonchuk, & Lykken, 1985; Segal, Van Loan, Fitzgerald, Hodgdon, & Van Itallie, 1988).

*Figure 3.2 Tanita BC-418 body composition analyzer.*
In small cohorts of individuals with CF, $LBM_{\text{BIA}}$ was correlated to LBM measurements via skinfold calipers ($r=0.96$) and dual energy x-ray absorptiometry ($r=0.83 – 0.86$) (Holt et al., 1994; Pichard, Kyle, & Slosman, 1999). Specifically in adults with CF, a strong relationship exists between LBM measured via dual energy x-ray absorptiometry (DEXA) and $LBM_{\text{BIA}}$ utilizing predictive equations by Lukaski (1987) and Segal (1988) ($r=0.95$ and 0.94 respectively) (King et al., 2005). Significant correlations were found between body composition measurements using DEXA, BIA, and skinfold measurements ($p<0.001$) (Beaumesnil et al., 2011; Ziai et al., 2014). Bioimpedance analyzers similar to that in the present study have been used in the literature and these methods are considered acceptable representations of body composition in adults with CF (Hollander et al., 2005).

The MAMC was measured to reflect upper extremity muscle mass and calculated as follows (Ionescu et al., 1998):

$$\text{MAMC (cm)} = \text{Mid-arm circumference (cm)} – (3.14 \times \text{triceps skinfold (cm)})$$

Mid-arm circumference was measured with a standard spring-loaded soft tape measure. The measurement was made at a mid-point between the acromion and olecranon processes on the right side of the body with the arm in a dependent relaxed position. The MAMC was documented in both absolute values (cm) and represented as percent of predicted according to Bishop et al (1981) (Bishop, Bowen, & Ritchey, 1981). Significantly decreased MAMC was
identified as values below 70% predicted as this has been associated with decreased MIP in adults with CF (Ionescu et al., 1998).

Data Collection and Instrumentation – Healthy Controls

Demographic information (age and gender) along with medical history as applicable to confirm study eligibility was obtained through subject interview. Procedures for the measurement of IMS and anthropometrics in the healthy controls were identical to those performed in the CF group. Lung volumes were not assessed in the healthy population and assumed to be within normal limits based on the absence of underlying lung pathology and normal spirometry values. The complete data collection form used in this study for healthy control subjects is provided in Appendix C.

Forced vital capacity (FVC) and FEV$_1$ were assessed in healthy subjects by the primary investigator using Micro Plus handheld turbine spirometer (CareFusion Ltd., San Diego, CA) according to standard guidelines (Miller et al., 2005). Such handheld turbine spirometers have demonstrated acceptable levels of agreement with standard spirometers (Korhonen, Remes, Kannisto, & Korppi, 2005; Liistro et al., 2006). According to the manufacturer specifications, the Micro Plus spirometer has an accuracy of +/- 3% which meets ATS requirements (Miller et al., 2005). Routine calibration checks were performed using a 3 liter calibration syringe according to the manufacturer’s recommendations to confirm accuracy of the spirometer. The primary investigator provided thorough instructions and demonstrated the technique prior to testing. Each subject
performed a maximal forceful exhalation from total lung capacity through a cylindrical mouthpiece attached to the spirometer by an antimicrobial filter. Verbal encouragement was provided to ensure a maximal effort where each subject completely emptied his/her lungs. Testing was performed with the subject in the standing position while wearing nose clips and the best of three acceptable maneuvers was recorded. %FEV₁ was determined according to the same reference values used for the CF group (Hankinson et al., 1999).

**Study Protocol**

Expedited Institutional Review Board (IRB) approvals were obtained from Rutgers, the State University of New Jersey and HUP prior to commencing study-related activities (Appendices D and E). All data collected from the subjects with CF occurred at the HUP Adult CF Clinic in Philadelphia, PA, during routine clinic visits. Inclusion criteria were confirmed in discussion with the attending physician and review of the medical record. The absence of exclusion criteria was identified in a similar manner and re-confirmed by subject interview. Prior to enrolment, informed consent was obtained after each subject had his/her questions answered to a satisfactory level. All data collection was performed the investigator (RLD) in the order listed below. In the event that a subject had recently consumed caffeine and/or alcohol, measurement of BIA was performed last after minimum of 2 hours past ingestion.

1. Height and weight measurements
2. Bio impedance analysis
3. Mid-arm circumference and skin fold measurements

4. Maximal inspiratory mouth pressure

Other required data as discussed above was extrapolated from the subject's medical record. Calculated data (i.e. LBM, LBMI, BMI and MAMC) was performed using an electronic spreadsheet. Prior to utilization, the spreadsheet calculations were manually cross-checked for accuracy. Calculations were completed for each subject by the investigator after data collection was completed to minimize subject time.

Data from the healthy subjects were collected on the Stratford Campus of Rutgers, the State University of New Jersey, School of Health Related Professions and at the HUP in Philadelphia, PA. Prior to enrollment, informed consent was obtained after each healthy subject had his/her questions answered to a satisfactory level. Eligibility criteria were confirmed through subject interview after subjects were thoroughly educated on the study protocol, procedures, risks, and benefits. All data collection for healthy subjects was completed by the investigator and followed the identical sequence as in the CF population.

Data was initially recorded in hard copy format using IRB approved data collection forms. Data was then transferred into an electronic spreadsheet. Each entry was double checked against the hard copy form prior to importing into SPSS statistical software. Accuracy of data transfer was then reconfirmed by manually checking every fifth entry in the SPSS program.
Data Analysis Plan

All statistical analyses were performed using SPSS statistical software v. 21. Descriptive statistics were used to calculate means, ranges, standard deviations, and 95% confidence intervals for data recorded as continuous variables as appropriate. Nominal variables (i.e. sex, genotype, CF-related diabetes, pancreatic insufficiency, and sputum colonization) were summarized with frequency distributions. The number of subjects presenting with significant nutritional depletion, hyperinflation, or decreased UEMM (as defined earlier) was calculated. Prior to analysis, data was assessed for normality using the Kolmogorov-Smirnov (with the applied Lilliefors’ significance correction) and Shapiro-Wilks tests in combination with visual inspection of histogram and box plots. Levene’s test was used to test the hypothesis of equal variance. Differences between all subjects with CF and the healthy control group for baseline demographics recorded as continuous data were determined as indicated with independent t-tests. A Mann-Whitney U test was utilized in the event that parametric assumptions were violated. Differences in categorical data between groups were assessed using Chi-square analyses. Fisher’s exact test was used if the assumptions for Chi-square analyses were not met. Significance level for all statistical tests was set at \( \alpha = 0.05 \).

Research goal #1: hypotheses 1a and 1b

To investigate the potential effect of disease severity on global IMS, subjects were grouped into four levels based on diagnosis and disease severity.
based on %FEV$_1$ (healthy controls, mild CF, moderate CF and severe CF). MIP and %MIP were set as dependent variables. Between group differences were analyzed by a one-way analysis of variance (ANOVA) as the level of normality was acceptable. The Brown-Forsythe statistic was calculated and used to interpret data in the presence of unequal variances. Post hoc analysis was performed using Bonferroni multiple comparison test to minimize the risk for a type I error. ANOVA procedures were then used to assess for between-group differences in baseline characteristics to identify potential confounding variables that could influence MIP. In the presence of non-normal data distributions, a Kruskal-Wallis ANOVA was utilized. The overall effect of disease severity on MIP was ultimately determined through general linear modeling (GLM) procedures while controlling for identified confounding variables.

**Research goal #2: hypothesis 2**

The potential for disease severity, nutritional status, upper extremity muscle mass, and hyperinflation to predict MIP and %MIP was determined through multiple linear regression analysis in the subject with CF only. Figure 3.3 illustrates the general algorithm used during factor selection. Similar modelling procedures have been described in the literature (Byham-Gray, Parrott, Ho, Sundell, & Ikizler, 2014). The initial set of factors evaluated was based on a combination of statistical, clinical, and theoretical criteria. Prior to running this analysis, statistical assumptions were evaluated. Pearson product-moment correlations were performed to identify relationships between each dependent
variable (MIP and %MIP) and the proposed independent variables and to identify other potential predictors from the data collected in this study. Spearman’s Rho was used in the presence of a non-normal distribution. Based on the acquired sample size, the total number of independent variables was limited to a maximum of 5 (Field, 2009). Variables demonstrating significant associations (p<0.05) with MIP or %MIP were retained as potential predictors in their respective models and screened for collinearity. This conservative cut off point of p<0.05 was selected given the limited room in the proposed models. In the presence of significant collinearity (r≥0.70), the variable with the strongest relationship with MIP was retained for the model unless theoretical and/or clinical rationale justified the other variable. Factors with a known influence on IMS in CF and/or the general population as identified in the current literature were also considered as potential predictors. The final models were evaluated using collinearity diagnostics. Homoscedasticity, linearity, and normality of errors were assessed by visual analysis of residual plots.
Figure 3.3. The general algorithm for factor selection during regression modelling.
Power Analysis

To estimate required sample size, a priori power analyses were performed for primary statistical tests outlined above. Calculations were completed using G*Power 3 power analysis program (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). Given the relatively large standard deviation and variability of MIP seen in the normal populations, Cohen’s d was set to detect a large effect size in order to identify clinically significant differences (Black & Hyatt, 1969; Wilson, Cooke, Edwards, & Spiro, 1984). Specific values for Cohen’s d were determined based on the individual statistical test as recommended within the G*Power 3 program.

Table 3.1 summarizes the input parameters for each a-priori power analysis and the resultant recommended sample size. Level of significance was set at $\alpha=0.05$ with an acceptable power level $(1 - \beta)$ of 0.80 for each. Based on this analysis a minimum sample of 76 subjects (19 per group) was needed for the ANOVA analysis and a minimum of 40 subjects was needed for the regression analysis.
Table 3.1

*Power analysis summary per statistical test*

<table>
<thead>
<tr>
<th>Statistical Test</th>
<th>Input</th>
<th>Sample</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-way ANOVA</td>
<td>Effect size: 0.40</td>
<td>76</td>
<td>0.82</td>
</tr>
<tr>
<td>(effect of disease severity)</td>
<td># groups: 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Regression</td>
<td>Effect size: 0.35</td>
<td>40</td>
<td>0.81</td>
</tr>
<tr>
<td>(%FEV₁, LBM/IBW, MAMC, RV/TLC)</td>
<td># predictors: 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* ANOVA=analysis of variance; %FEV₁=percent predicted forced expiratory volume in one-second; LBM/IBW=ratio of lean body mass to ideal body weight; RV/TLC=ratio of residual volume to total lung capacity; MAMC=mid-arm muscle circumference.
References


Chapter IV

Manuscripts

ALTERATIONS IN INSPIRATORY MUSCLE STRENGTH IN ADULTS WITH STABLE CYSTIC FIBROSIS: THE INFLUENCE OF DISEASE SEVERITY

Manuscript 1 of 2
Abstract

Background: Current literature favors the preservation of inspiratory muscle strength (IMS) in CF; however, the heterogeneity of disease severity in the subjects studied limits the applicability of these findings and impaired IMS cannot be ruled out. The effect of advanced CF lung disease on IMS has not been evaluated. If present, inspiratory muscle dysfunction may contribute to both dyspnea and exercise intolerance. The purpose of this study was to evaluate the influence of disease severity on IMS in adult with CF.

Methods: Maximal inspiratory pressure was assessed in a cross-sectional sample of adults with stable CF and recorded in cmH₂O (MIP) and as %-predicted (%MIP). Differences in MIP and %MIP in were analyzed between groups based on disease severity according to their %-predicted forced expiratory volume in one-second (%FEV₁) and in comparison to healthy controls without CF.

Results: Fifty-eight adults with CF with mild (n=20, %FEV₁≥70%), moderate (n=20, %FEV₁= 40 – 69%) and severe (n=18, %FEV₁<40%) lung dysfunction and 20 healthy control subjects completed the study. Significant differences in MIP in cmH₂O (p=0.001) and %-predicted (p<0.001) were noted between groups based on disease severity. Both MIP and %MIP were significantly decreased in adults with CF in the presence of advanced pulmonary disease as compared to those with mild disease and healthy controls. An influence of disease severity
remained after controlling for identified confounding variables (partial \( \eta^2 = 0.23 \), \( p < 0.001 \)).

**Conclusions:** Alterations in IMS exist in adults with CF that are evident only after controlling for the degree of lung dysfunction. Disease severity negatively influences IMS in adults with CF. These alterations may contribute to dyspnea and altered breathing patterns that could feasibly limit exercise performance in advanced CF. Additional research is needed to determine the clinical significance of these findings and evaluate appropriate interventions to address identified deficits. Future studies on the inspiratory muscles in adults with CF must control for disease severity for accurate interpretation.
Introduction

Airway inflammation and recurrent exacerbations lead to progressive lung dysfunction and disease severity in cystic fibrosis (CF). Impaired exercise capacity from pulmonary disease is well-documented in CF and linked to quality of life (QOL) and mortality (de Jong et al., 1997; van de Weert-van Leeuwen et al., 2012). Causes of impaired exercise in CF include dyspnea and impaired gas exchange associated with excess work of breathing (WOB) particularly in severe pulmonary disease (de Jong et al., 1997; Moorcroft, Dodd, Morris, & Webb, 2005). A majority of this WOB is believed to fall on the inspiratory muscles even in the presence of pulmonary disease (Mador, 1991). Excess inspiratory work may contribute to exercise intolerance in adults with CF and inspiratory muscle dysfunction may compound the problem if present.

Perceived WOB is influenced by the inspiratory pressure per breath ($P_{br}$) and the maximal inspiratory pressure (MIP) of the inspiratory muscles (i.e. inspiratory muscle strength (IMS)). Individuals with CF demonstrate an elevated $P_{br}$ to MIP ratio ($P_{br}/\text{MIP}$) at rest and during exercise that may contribute to dyspnea (Dassios, Katelari, Doudounakis, Mantagos, & Dimitriou, 2012; Grazzini, Stendardi, Gigliotti, & Scano, 2005; Hahn et al., 2008; Keochkerian et al., 2005). Inspiratory fatigue is believed to occur with a $P_{br}/\text{MIP}$ above 0.60 which suggests a link between IMS and inspiratory muscle endurance (IME) (Roussos, Fixley, Gross, & Macklem, 1979). However, breathing patterns may change at the
expense of ventilatory efficiency in response to elevated workloads avoiding inspiratory fatigue (Gandevia, Allen, Butler, Gorman, & McKenzie, 1998). Finally, preferential perfusion of the diaphragm over peripheral musculature in response to excess inspiratory work may indirectly limit exercise performance (Dempsey, Romer, Rodman, Miller, & Smith, 2006). Figure 4.1 illustrates theoretical effects of excess inspiratory demand on exercise. Indeed, MIP has demonstrated
significant relationships with the modified shuttle test, lung function, dyspnea, and leg discomfort in CF (Dunnink, Doeleman, Trappenburg, & de Vries, 2009).

In the presence of normal IMS, resistive loads rarely exceed levels of physiologic consequence. However, MIP is commonly decreased to 40 – 60% of predicted values in chronic obstructive pulmonary disease (COPD) and contributes to dyspnea and exercise intolerance (Larson, Covey, & Corbridge, 2002). This impairment appears to result from hyperinflation, malnutrition, pulmonary exacerbations, and systemic corticosteroid use which are common to CF and relative to disease severity (Larson et al., 2002). In contrast, research on IMS is conflicting and studies suggest normal or above normal MIP secondary to a training effect from the elevated WOB (Dunnink et al., 2009; Heinzmann-Filho, Marostica, & Donadio, 2012). Conversely, others suggest decreased MIP (Dassios et al., 2012; Ionescu et al., 1998; Leroy, Perez, Neviere, Aguilaniu, & Wallaert, 2011; Szeinberg, England, Mindorff, Fraser, & Levison, 1985). However, the research is faulted as interpretations are based on mean values from heterogeneous groups with significant ranges of disease severity. Impaired IMS may be missed when looking at such samples which typically underrepresent severe disease. For example, Ziegler et al reported a mean MIP percent of predicted (%MIP) in the 80th percentile; however, “in 17 subjects (43.6%), MIP was below the lower limit of normal” (Ziegler, Lukrafka, de Oliveira Abraao, Rovedder, & de Tarso Roth Dalcin, 2008, pg.444). Barry et al (2003) reported a mean %MIP of 94% but with a range of 40 – 175% (Barry & Gallagher, 2003). Leroy et al (2011) reports a range for %MIP of 23 – 148%
(Leroy et al., 2011). These findings suggest significant alterations in IMS exist in adults with CF warranting further investigation.

Literature exists pertaining to IMS as measured by MIP in adults with CF; however, individual variability in MIP in adults with CF has not been completely explained and the impact of disease severity has not been evaluated. If present, impaired IMS may have significant clinical consequences given the elevated WOB and may contribute to dyspnea, ventilatory inefficiency, and exercise intolerance. Inspiratory muscle weakness (IMW) could feasibly contribute to hypoventilation and even respiratory failure (Taylor-Cousar, 2009). Consistent with these premises the aim of this study is to investigate the influence of disease severity on IMS in adults with stable CF.
Methods

A cross-sectional sample of English speaking adults (age ≥ 18yrs) with CF, stable lung function, and no medical status changes in the prior 4 weeks were recruited from a hospital-based outpatient CF clinic (Hospital of the University of Pennsylvania (HUP), Philadelphia, Pa.). Exclusion criteria were: 1. Signs or symptoms of a pulmonary exacerbation 2. Active smoker, 3. Secondary pulmonary condition other than asthma, 4. Thoracic or abdominal condition interfering with testing, 5. Neuromuscular disease, 6. Pregnancy, 7. Unresolved pneumothorax, 8. *Burholderia sp.*, 9. Lung transplant and 10. Cardiac pacemaker. A control group of English speaking subjects (age ≥ 18) without CF were recruited from HUP and a local University (Rutgers, the State University of New Jersey, Stratford, NJ). Healthy subjects were excluded in the presence of current smoking, pregnancy, pre-existing pulmonary disease, diabetes, heart failure, active respiratory infection, allergy flare, or any condition that could affect testing performance. All procedures were approved by the Institutional Review Boards of Rutgers, The State University of New Jersey and HUP prior to initiating study-related activities. Eligible volunteers completed the informed consent process prior to enrollment were offered a $20 gift card upon study completion.

Demographics

Basic demographics including age, ethnicity, sex, and genotype were recorded to characterize the subjects. Genotype was categorized as
ΔF508/ΔF508, ΔF508/other, or other/other. The presence of pancreatic insufficiency, CF-related diabetes (CFRD), and colonization of pseudomonas was also documented. Baseline dyspnea was assessed by the Modified Medical Research Council Dyspnea Scale (Mahler & Wells, 1988).

**Pulmonary Function**

Pulmonary function measurements including the forced expiratory volume in one-second (FEV\(_1\)), forced vital capacity (FVC), the FEV\(_1\)/FVC ratio, residual volume (RV), total lung capacity (TLC) and the RV/TLC ratio were extracted from the medical records of subjects with CF. These measurements were performed as part of routine care by a licensed respiratory therapist according to standard guidelines (Miller et al., 2005; Wanger et al., 2005). Simple spirometry was assessed in the healthy subjects to ensure normal lung function using the Micro Plus (CareFusion Ltd., San Diego, CA) handheld spirometer by the primary investigator according to standard guidelines (Miller et al., 2005). The best of three trials was recorded and routine equipment calibration checks were performed.

Spirometry was completed the same day as IMS testing and expressed as liters and percent predicted in all subjects (Hankinson, Odencrantz, & Fedan, 1999). Lung volumes were recorded in the subjects with CF only and extrapolated from body plethysmography tests performed within 12 months of IMS testing provided the FEV\(_1\) percent predicted (%FEV\(_1\)) was within 10% of current values. Hyperinflation was defined as the ratio of residual volume (RV) to
total lung capacity (TLC). Disease severity was categorized as mild (%FEV$_1$ $\geq$ 70%), moderate (%FEV$_1$ 40 – 69%), and severe (%FEV$_1$ < 40%) (Cystic Fibrosis Foundation, 2013).

**Anthropometrics**

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared and percent of ideal body weight (%IBW) was documented (Cystic Fibrosis Foundation, 2013; Metropolitan Life Insurance Company, 1983). Lean body mass (LBM) was derived from body composition measurements using the Tanita BC-418 bioelectrical impedance analyzer (Tanita Corporation of America, Arlington Heights, IL, USA) taken in a temperature controlled environment. Subjects refrained from ingesting caffeine and/or alcohol for at least two hours and voided their bladder within 30 minutes before testing.

Mid-arm circumference (MAC) was measured with a spring-loaded soft tape measure at the mid-point between the acromion and olecranon processes on the right side of the body with the arm in a relaxed dependent position. The average of three triceps skinfold measurements at the same site using Lange calipers (Beta Technology, Santa Cruz, CA) was recorded. The mid-arm muscle circumference (MAMC) was then calculated and expressed as percent-predicted to reflect upper extremity muscle mass (Bishop, Bowen, & Ritchey, 1981; Ionescu et al., 1998).
Inspiratory Muscle Strength

Maximal inspiratory pressure (MIP) was measured with a handheld mouth pressure meter (MicroRPM® (RPM01), CareFusion Ltd., San Diego, CA, USA) interfaced with a laptop computer (Puma® (PU1000), Micro-Medical). Testing procedures followed standard guidelines (American Thoracic Society/European Respiratory, 2002). Subjects were seated wearing nose clips. A rubber flanged mouthpiece was used with an in-line bacterial filter. The inspiratory circuit contained a small leak to prevent the influence of the buccal muscles. Subjects refrained from using bronchodilators for at least 2 hours prior to testing. Each subject performed a maximal static inspiratory maneuver from RV for at least 2 seconds. Standardized instructions were provided. Participants were allowed to see the computer screen reflecting their performance and received strong verbal encouragement to ensure maximal efforts. A minimum of two practice attempts were allowed prior to testing. Subsequently, the maximum pressure sustained for one-second of at least five satisfactory maneuvers with less than 5-10% variability was recorded in centimeters of water pressure (MIP) and percent of predicted (%MIP) (Black & Hyatt, 1969). Maneuvers were separated by two minutes of rest. MIP was converted to absolute values for ease of data interpretation.

Statistical Analysis

Statistical procedures were performed using SPSS statistical software v. 21. Means, ranges, and standard deviations were calculated for continuous
variables. Categorical variables were summarized with frequency distributions. Parametric assumptions were assessed prior to analysis. Differences between subjects with CF and healthy subjects were determined using independent t-tests for continuous variables. A Mann-Whitney U test was utilized where parametric assumptions were violated. Differences in categorical data between groups were assessed using Chi-square analyses.

After grouping by disease severity, differences were determined by a one-way analysis of variance (ANOVA). In the presence of parametric violations, a Kruskal-Wallis ANOVA was utilized. The overall effect of disease severity on IMS was determined through general linear modeling (GLM) procedures while controlling for confounding variables. Post hoc analysis was performed using Bonferroni multiple comparison test. A priori power analysis determined a minimum of 19 subjects per group was needed to detect a large effect size with a power level of 0.80 (α=0.05).
Results

Subjects

One hundred thirty adults with CF were screened. Seventy-two were excluded for the following reasons: 51 were ineligible, 17 had scheduling conflicts, and 4 declined. A total of 58 subjects with CF between the ages of 20 and 60 (mean ± SD= 32.3 ± 9.3 yrs.) were enrolled with a %FEV$_1$ ranging from 20 - 130% (mean ± SD= 59.57 ± 26.9%). Lung volumes were unavailable in two of the subjects with severe and one with moderate pulmonary disease. Twenty-one healthy subjects enrolled; however, one subject unable to perform a satisfactory MIP maneuver was excluded. Twenty healthy subjects between the ages of 23 and 61 (mean ± SD= 32.9 ± 10.9 yrs.) with a %FEV$_1$ between 85 and 119% (mean ± SD= 100.1 ± 10.3%) completed the study.

Correlations and differences prior to grouping by disease severity

%FEV$_1$ was related to both MIP ($r= 0.43; p<0.001$) and %MIP ($r= 0.61; p=0.001$) in the group with CF but not in the healthy group. %MIP demonstrated significant relationships with sex ($r= -0.42, p=0.001$), dyspnea ($r= -0.50, p<0.001$), %IBW ($r=0.33, p=0.012$), BMI ($r=0.29, p=0.034$), %MAMC ($r=0.37, p=0.004$), and RV/TLC ($r= -0.59, p<0.001$). MIP demonstrated significant relationships with dyspnea ($r= -0.48, p<0.001$), %IBW ($r=0.35, p=0.007$), BMI ($r=0.39, p=0.003$), LBM ($r= 0.28, p=0.037$), and RV/TLC ($-0.42, p=0.002$). No significant differences
Table 4.1

Characteristics of Participants Prior to Grouping by Disease Severity

<table>
<thead>
<tr>
<th></th>
<th>Cystic Fibrosis (n=58)</th>
<th>Non-CF (n=20)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age – yrs.</td>
<td>32.31 ± 9.27</td>
<td>32.9 ± 10.89</td>
<td>0.991a</td>
</tr>
<tr>
<td>White ethnicity – no. (%)</td>
<td>58 (100)</td>
<td>20 (100)</td>
<td>NAd</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>28 (48)</td>
<td>9 (45)</td>
<td>1.00b</td>
</tr>
<tr>
<td><strong>Nutritional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height – cm</td>
<td>164.34 ± 8.41</td>
<td>170.28 ± 9.82</td>
<td>0.011c</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>58.57 ± 10.23</td>
<td>71.13 ± 13.21</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>%IBW</td>
<td>94.71 ± 10.44</td>
<td>105.55 ± 12.04</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>BMI</td>
<td>21.59 ± 2.67</td>
<td>24.36 ± 2.81</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>LBM – kg</td>
<td>47.04 ± 9.15</td>
<td>55.39 ± 13.46</td>
<td>0.011a</td>
</tr>
<tr>
<td>MAMC - %predicted</td>
<td>91.59 ± 8.82</td>
<td>107.00 ± 12.38</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP – cmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>105.72 ± 26.80</td>
<td>114.80 ± 20.56</td>
<td>0.172a</td>
</tr>
<tr>
<td>MIP – cmH&lt;sub&gt;2&lt;/sub&gt;O/kg</td>
<td>1.82 ± 0.46</td>
<td>1.64 ± 0.31</td>
<td>0.050c</td>
</tr>
<tr>
<td>MIP - %predicted</td>
<td>102.22 ± 27.64</td>
<td>112.70 ± 22.17</td>
<td>0.130c</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; – L</td>
<td>2.05 ± 0.80</td>
<td>3.74 ± 0.85</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; - %predicted</td>
<td>59.57 ± 26.92</td>
<td>100.05 ± 10.25</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC - %</td>
<td>63.59 ± 13.96</td>
<td>86.20 ± 4.87</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>RV – L</td>
<td>2.47 ± 1.01</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RV - %predicted</td>
<td>155.38 ± 48.90</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RV/TLC - %</td>
<td>42.36 ± 12.91</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Note. Values are presented as mean ± SD for continuous data. NA=not assessed; LBM=lean body mass; %IBW=percent of ideal body weight; BMI=body mass index; MAMC=mid-arm muscle circumference; MIP=maximal inspiratory pressure; FEV<sub>1</sub>=forced expiratory volume in one-second; FVC=forced vital capacity; RV=residual volume; TLC=total lung capacity

*P-value listed for independent samples Mann Whitney U test. b P-value listed for Pearson Chi-square. c P-value listed from independent t-test. d Statistic not computed as variable was constant.
were noted in age, ethnicity, sex, or IMS between the healthy subjects and those with CF prior to grouping by disease severity (Table 4.1).

**Influence of disease severity on inspiratory muscle strength**

Differences emerged after grouping by disease severity for both MIP (F=5.90; p=0.001) and %MIP (F=16.99; p<0.001). Tables 4.2 and 4.3 summarize the study population by disease severity. Box plots for MIP and %MIP are shown in figure 4.2. Grouping by severity accounted for 19% of the variance in MIP and 41% of the variance in %MIP (partial $\eta^2 = 0.193$ and 0.408 respectively). MIP was lower in the group with severe CF compared to the healthy controls (mean difference= -20.74; 95% CI= -41.36 to -0.13; p=0.048) and those with mild CF (mean difference= -27.99; 95% CI= -48.61 to -7.38; p=0.003). The group with moderate CF had a significantly lower MIP compared to those with mild CF (mean difference= -22.15; 95% CI= -42.21 to -2.09; p=0.022) but a non-significantly decreased MIP compared to the healthy controls (p=0.286). When expressed as %MIP, IMS was decreased in the group with moderate CF in comparison to the healthy controls (mean difference= -19.36; 95% CI= -37.25 to -1.45; p=0.027) and the group with mild CF (mean difference= -34.30; 95% CI= -52.20 to -16.40; p<0.001). A decreased %MIP was noted in the group with severe CF as compared to the healthy control (mean difference= -28.87; 95% CI= 47.26 to -10.47; p<0.001) and those with mild CF (mean difference= -43.82; 95% CI= -62.21 to -25.42; p<0.001). There were no
Table 4.2

**Characteristics of Participants after Grouping by Disease Severity**

<table>
<thead>
<tr>
<th></th>
<th>Non-CF (n=20)</th>
<th>Mild CF (n=20)</th>
<th>Moderate CF (n=20)</th>
<th>Severe CF (n=18)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yrs.</td>
<td>32.90 ± 10.89</td>
<td>27.95 ± 7.02</td>
<td>33.90 ± 10.67</td>
<td>35.39 ± 8.38</td>
<td>0.051&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>9 (45)</td>
<td>4 (20)</td>
<td>12 (60)</td>
<td>12 (67)</td>
<td>0.019&lt;sup&gt;be&lt;/sup&gt;</td>
</tr>
<tr>
<td>Genotype&lt;sup&gt;f&lt;/sup&gt; – no. (%)</td>
<td>-</td>
<td>10/7/3 (50/35/15)</td>
<td>7/11/2 (35/55/10)</td>
<td>8/10/0 (44/56/0)</td>
<td>0.394&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CFRD – yes (%)</td>
<td>-</td>
<td>9 (45)</td>
<td>9 (45)</td>
<td>9 (50)</td>
<td>1.00&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PI – yes (%)</td>
<td>-</td>
<td>17 (85)</td>
<td>18 (90)</td>
<td>17 (94)</td>
<td>0.864&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pseudomonas – yes (%)</td>
<td>-</td>
<td>13 (65)</td>
<td>18 (90)</td>
<td>13 (76)*</td>
<td>0.168&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Corticosteroids&lt;sup&gt;g&lt;/sup&gt; – yes (%)</td>
<td>0</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>5 (28)</td>
<td>0.003&lt;sup&gt;ce&lt;/sup&gt;</td>
</tr>
<tr>
<td>Corticosteroids&lt;sup&gt;g&lt;/sup&gt; - mg/d</td>
<td>0</td>
<td>0</td>
<td>1.00 ± 4.47</td>
<td>2.69 ± 5.38</td>
<td>0.004&lt;sup&gt;ae&lt;/sup&gt;</td>
</tr>
<tr>
<td>Height – cm</td>
<td>170.28 ± 9.82</td>
<td>161.64 ± 6.47</td>
<td>164.30 ± 8.97</td>
<td>167.40 ± 9.05</td>
<td>0.015&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>71.13 ± 13.21</td>
<td>59.03 ± 6.89</td>
<td>57.95 ± 9.50</td>
<td>58.75 ± 14.01</td>
<td>0.001&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>IBW - %predicted</td>
<td>105.55 ± 12.04</td>
<td>100.10 ± 7.73</td>
<td>92.95 ± 9.22</td>
<td>90.67 ± 12.18</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI</td>
<td>24.36 ± 2.81</td>
<td>22.59 ± 2.35</td>
<td>21.34 ± 1.82</td>
<td>20.76 ± 3.47</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LBM – kg</td>
<td>55.39 ± 13.46</td>
<td>43.94 ± 7.00</td>
<td>48.09 ± 8.94</td>
<td>49.31 ± 10.88</td>
<td>0.030&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>MAMC - %predicted</td>
<td>107.00 ± 12.38</td>
<td>94.95 ± 8.49</td>
<td>91.60 ± 7.73</td>
<td>87.83 ± 9.25</td>
<td>&lt;0.001&lt;sup&gt;de&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;h&lt;/sup&gt; – no. (%)</td>
<td>18/2/0/0/0</td>
<td>12/7/0/1/0</td>
<td>6/10/4/0/0</td>
<td>1/7/6/3/0&lt;sup&gt;i&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;de&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Note.* Values are presented as mean ± SD for continuous data. CF=cystic fibrosis; CFRD=cystic fibrosis related diabetes; PI=pancreatic insufficiency; IBW=ideal body weight; BMI=body mass index; LBM=lean body mass; MAMC=mid-arm muscle circumference.

<sup>a</sup>P-value for Kruskal Wallis analysis between all groups. <sup>b</sup>P-value listed for Pearson Chi-square analysis. <sup>c</sup>P-value listed for Fisher’s exact test. <sup>d</sup>P-value for ANOVA analysis between all groups. <sup>e</sup>Significant at p<0.05 between the CF groups. <sup>f</sup>Genotype listed as frequency counts for ΔF508/ΔF508, ΔF508/other, other/other. <sup>g</sup>Systemic corticosteroids. <sup>h</sup>Dyspnea reported as frequency counts for the categorical grades in the MMRC dyspnea scale (0/1/2/3/4) where the higher number indicates a greater dyspnea burden. <sup>i</sup>One subject with missing data (n=17).
Figure 4.2. Box plots for MIP (A) and %MIP (B) relative to disease severity prior to controlling for covariates. %MIP= maximal inspiratory pressure (percent-predicted); MIP= maximal inspiratory pressure (cmH₂O).
Table 4.3

Pulmonary characteristics of participants grouped by disease severity

<table>
<thead>
<tr>
<th></th>
<th>Non-CF (n=20)</th>
<th>Mild CF (n=20)</th>
<th>Moderate CF (n=20)</th>
<th>Severe CF (n=18)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP – cmH₂O</td>
<td>114.80±20.56</td>
<td>122.05±22.09</td>
<td>99.90±23.06</td>
<td>94.06±27.77</td>
<td>0.001&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>MIP – cmH₂O/kg</td>
<td>1.64±0.31</td>
<td>2.05±0.30</td>
<td>1.77±0.51</td>
<td>1.64±0.46</td>
<td>0.005&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>MIP - %pred.</td>
<td>112.70±22.17</td>
<td>127.65±20.09</td>
<td>93.35±22.77</td>
<td>83.83±17.86</td>
<td>&lt;0.001&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEV₁ – L</td>
<td>3.74±0.85</td>
<td>2.93±0.61</td>
<td>2.04±0.42</td>
<td>1.09±0.32</td>
<td>&lt;0.001&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEV₁ - %pred.</td>
<td>100.05±10.25</td>
<td>88.95±17.09</td>
<td>57.60±7.72</td>
<td>29.11±5.94</td>
<td>&lt;0.001&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEV₁/FVC - %</td>
<td>86.20±4.87</td>
<td>77.20±7.34</td>
<td>64.00±7.02</td>
<td>48.00±7.45</td>
<td>&lt;0.001&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>RV – L</td>
<td>-</td>
<td>1.65±0.42</td>
<td>2.50±0.62</td>
<td>3.46±1.03</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>RV - %pred.</td>
<td>-</td>
<td>118.05±28.50</td>
<td>159.11±35.97</td>
<td>197.63±47.42</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>RV/TLC - %</td>
<td>-</td>
<td>30.45±6.09</td>
<td>42.79±6.66</td>
<td>56.75±9.48</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note. Values are presented as mean ± SD. MIP=maximal inspiratory pressure; FEV₁=forced expiratory volume in one-second; FVC=forced vital capacity; RV=residual volume; TLC=total lung capacity; %pred=percent of predicted.

<sup>a</sup> P-value listed from ANOVA analysis for differences between all groups. <sup>b</sup> Significant at p<0.05 for between group differences in CF subjects only. <sup>c</sup> P-value listed is from ANOVA for differences between CF groups only.

Between group differences were noted for age, sex, corticosteroids and measures of nutritional status (Table 4.2). To better isolate the influence of disease severity on IMS, between-group differences were re-assessed while controlling for these variables. Nutritional status was represented by BMI as it is the preferred measure in CF (Stallings, Stark, Robinson, Feranchak, & Quinton, 2008). Hyperinflation was not included as a covariate secondary to extreme
collinearity between RV/TLC and %FEV\(_1\) \((r=-0.86; \ p<0.001)\). The estimated means for MIP and %MIP after controlling for these covariates are illustrated in table 4.4 and figure 4.3. Between group differences remained for both MIP (\(F=7.02; \ p<0.001\)) and %MIP (\(F=7.10; \ p<0.001\)) with the disease severity accounting for 23% of the variance seen in both MIP and %MIP (partial \(\eta^2=0.231\) and 0.233 respectively).

Table 4.4

*Estimated means for MIP and %MIP after controlling for age, sex, corticosteroids, and BMI*

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mean</th>
<th>SE</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>MIP Healthy</td>
<td>113.05</td>
<td>4.9</td>
<td>103.23</td>
</tr>
<tr>
<td>Mild CF</td>
<td>126.56</td>
<td>5.0</td>
<td>116.59</td>
</tr>
<tr>
<td>Moderate CF</td>
<td>99.20</td>
<td>4.7</td>
<td>89.82</td>
</tr>
<tr>
<td>Severe CF</td>
<td>91.77</td>
<td>5.4</td>
<td>81.03</td>
</tr>
<tr>
<td>%MIP Healthy</td>
<td>109.78</td>
<td>4.8</td>
<td>100.17</td>
</tr>
<tr>
<td>Mild CF</td>
<td>122.99</td>
<td>4.9</td>
<td>113.23</td>
</tr>
<tr>
<td>Moderate CF</td>
<td>96.98</td>
<td>4.6</td>
<td>87.80</td>
</tr>
<tr>
<td>Severe CF</td>
<td>88.22</td>
<td>5.3</td>
<td>77.70</td>
</tr>
</tbody>
</table>

*Note.* CF: cystic fibrosis, MIP: maximal inspiratory pressure in cmH\(_2\)O, %MIP: maximal inspiratory pressure percent of predicted, SE: standard error

MIP was significantly decreased in the groups with moderate and severe CF as compared to the group with mild CF (mean difference= -27.36; 95% CI= -46.92 to -7.76; \(p=0.002\), and mean difference= -34.79; 95% CI= -56.46 to -13.12; \(p<0.001\) respectively). There was no significant difference noted in MIP between
groups with moderate and severe CF (p=1.000). As compared to the healthy controls, there was no significant difference in MIP for the subjects with CF regardless of severity. However, MIP was notably decreased in the severe group to a level falling just short of significance as compared to the healthy controls (mean difference= -21.28; 95% CI= -42.60 to 0.049 to; p=0.051).

After controlling for the identified covariates, %MIP remained decreased in the group with severe CF as compared to the healthy controls (mean difference= -21.56; 95% CI= -42.44 to – 0.68; p=0.039) and those with mild CF (mean difference= -34.77; 95% CI= -55.98 to -13.55; p<0.001). No significant difference was noted in %MIP between the groups with moderate and severe CF (p=1.000). The group with moderate CF demonstrated a significantly decreased %MIP in comparison to those with mild CF (mean difference= -26.01; 95% CI= -45.20 to -6.81; p=0.003). There was no significant difference in %MIP between the healthy group in comparison to those with mild CF (p=0.290) or moderate CF (p=0.428).
Figure 4.3a. Graphical representation of the estimated marginal means for MIP and %MIP between groups after controlling for age, gender, corticosteroids, and body mass index. MIP was significantly decreased in the groups with moderate and severe CF as compared to mild CF (p<0.001). There was no significant difference in MIP in CF as compared to the healthy controls regardless of disease severity; however, MIP was decreased in the group with severe CF to a level just short of significance as compared to healthy controls (p=0.051). %MIP was significantly decreased in severe CF as compared to both mild CF (p<0.001) and healthy controls (p=0.039). %MIP was significantly decreased in moderate CF as compared to mild CF only (p=0.003). MIP=maximal inspiratory pressure (cmH2O); %MIP=maximal inspiratory pressure (percent-predicted)

a. Covariates appearing in the model are evaluated at the following values: Gender = .47, Steroids (mg/d) = 0.88, BMI = 22.300, Age = 32.46
Discussion

This study identified alterations in IMS in adults with stable CF emerging only after grouping for disease severity. The groups with moderate and severe-CF demonstrated lower %MIP than those with mild-CF and the healthy controls. Absolute values of MIP were lower in the presence of moderate and severe-CF as compared to mild CF; however, only in the presence of severe-CF was MIP significantly lower than the healthy controls. After controlling for confounding variables, both MIP and %MIP remained significantly decreased in the groups with moderate and severe-CF as compared to those with mild-CF. However, these values remained significantly decreased only in the group with severe-CF as compared to the healthy controls. The decreased MIP in the group with severe CF versus the healthy controls fell just short of significance (p=0.051) likely due to a type II error. No significant differences in IMS were noted between those with mild-CF as compared to healthy controls or between those with moderate and severe-CF.

Existing research suggests IMS is preserved in CF secondary to a WOB-induced training effect (Heinzmann-Filho et al., 2012). Our data suggests an evolutionary pattern may exist where IMS is elevated in mild disease but declines with advancing severity. As the WOB would be lowest in the presence of mild lung disease, it is possible that this stimulus alone may not explain the elevated IMS we observed in this cohort. In 2013, Dassios identified enhanced IMS in individuals with CF who regularly participate in aerobic exercise (Dassios,
Katelari, Doudounakis, & Dimitriou, 2013). We did not measure physical activity in the present study; however, as physical activity is positively related to FEV$_1$ in CF, it is possible that our group with mild CF was more active (Hebestreit et al., 2006). Physical activity alone, or in conjunction with minor pulmonary dysfunction, may provide a protective training stimulus on the inspiratory muscles and contribute to the beneficial effect of exercise in CF. Unfortunately, these gains appear to reverse in moderate and severe CF where exercise is influenced by respiratory factors and activity may decline (Hebestreit et al., 2006; Moorcroft et al., 2005). Potential causes and effects should be investigated.

Malnutrition and systemic corticosteroid use can negatively influence IMS (Barry & Gallagher, 2003; Ionescu et al., 1998; Szeinberg et al., 1985). Positive relationships between nutritional indices and IMS in our sample support the role of nutrition. The impact of systemic corticosteroids on IMS cannot be determined from our data. Though the influence of disease severity remained after controlling for concurrent corticosteroid use only a small number (n=6) of subjects were using this medication. Results may have been different if chronic use was measured due to their known effect on IMS (Barry & Gallagher, 2003). As chronic systemic corticosteroid use is common in advanced CF, their contribution may be partially reflected in the influence of disease severity seen here.

Hyperinflation places the diaphragm at a mechanical disadvantage limiting its contractility. Decreased MIP has been shown in adults with CF with an RV/TLC >50% (Szeinberg et al., 1985). We did not control for hyperinflation due
to its high association with our measure of disease severity (%FEV$_1$) and theoretically could be considered a direct effect of the disease. In addition, RV/TLC is not always available whereas %FEV$_1$ is routinely measured and may capture hyperinflation in the majority of CF patients. Nonetheless, the effect of disease severity on IMS was most prominent in the severe-CF group who demonstrated significant hyperinflation (RV/TLC=56.75 ± 9.48%). CF-related hyperinflation likely explains at least part of the effect of disease severity on IMS; however, additional factors such as inflammation and genetic influences on skeletal muscle should be investigated.

Our groups with moderate and severe CF presented with weaker inspiratory muscles as represented by %MIP compared to those with mild CF and the healthy controls; nonetheless, the mean values for IMS may be considered “within normal limits” for the general population. However, literature is yet to adequately define minimal thresholds for IMS and “normal” strength may present as relative weakness when accompanied by the excess WOB associated with advanced CF. In fact, MIP was strongly correlated to the maximal work rate achieved on a cycle ergometer (r=0.68, p<0.05) in a group of adults with CF and apparently normal IMS (Bradley et al., 1999). The authors suggest that even normal IMS was inadequate relative to the imposed airway resistance and contributed to dyspnea indirectly limiting exercise performance (Bradley et al., 1999). In addition, a high degree of variability was noted for IMS in our study with %MIP ranging from 63% to 151% and 63% to 134% in the groups with moderate and severe-CF respectively. Fifteen (39%) of the 28 combined
subjects with moderate and severe CF presented with MIP below 80% of predicted similar to Ziegler et al (2008) (Ziegler et al., 2008). Interestingly, all subjects with mild-CF presented with %MIP above 89%. The degree of heterogeneity noted in IMS within the present study is in agreement with existing research but suggests impaired IMS cannot be identified by disease severity alone (Barry & Gallagher, 2003; Leroy et al., 2011). However, the absence of moderate or severe disease may prove to exclude inspiratory muscle weakness (IMW).

To date, only one study attempted to assess respiratory muscle function in CF relative to disease severity making it difficult to compare our results with existing research. In 2008, Hahn et al measured the tension time index (TTI) in a primarily pediatric sample of subjects with CF at rest and compared differences after grouping by the disease severity based on a “pulmonary function score” (Hahn et al., 2008). A healthy comparison group without CF was not used. When looking at the individual components of the TTI, Hahn et al (2008) reported a decreased MIP and %MIP in the presence of advanced pulmonary disease. Though these differences failed to reach significance, statistical power was likely inadequate given the small number of individuals in the severe category (n=6). In contrast, the decreased MIP and %MIP that we observed in the presence of advanced CF reached a level of statistical significance. These differences likely emerged secondary to our larger sample size with adequate representation of disease severities that was specific to the adult population. These findings
support the potential negative impact of CF on IMS and the need to control for disease severity when researching the inspiratory muscles in this population.

Our study procedures were not without limitations and were specific to adults. The results may not apply to the pediatric population. The cross-sectional design with a sample of convenience from a single clinic could create a “cohort” effect, resulting in a non-representative sample of the target population. As such, the results here may be specific to our sample. The clinical impact of these findings on exercise capacity requires further research as we did not measure this variable. As it was not feasible to control for all medications, the influence of pharmaceuticals on IMS could not be determined. This study focused on one aspect of inspiratory muscle function. Though literature supports the potential importance of IMS, future research in CF should compare other measures of inspiratory muscle function including inspiratory muscle endurance. Finally, our volitional measure of IMS is dependent on patient effort. Consistent instructions, adequate practice, verbal encouragement, and visual biofeedback were provided by a single tester and we believe maximal efforts were performed. Still, the specific cause of the observed alterations in IMS cannot be determined and the influence of subject effort cannot be completely ruled out.
Conclusion

Inspiratory muscle strength is decreased in adults with CF with advanced lung disease but maintained in the presence of mild disease and in select individuals with moderate and severe lung dysfunction. The absence of advanced lung disease may rule out significant inspiratory muscle weakness. The elevated IMS observed in mild CF can mask alterations in IMS when looking at heterogeneous groups in terms of disease severity. To our knowledge, this is the only study investigating the specific influence of disease severity on IMS in adults with CF with equal representation of disease categories and in comparison to a healthy control group. The decreased MIP observed could contribute to increased inspiratory work, dyspnea, alterations in breathing patterns, and possibly increase the risk for inspiratory fatigue in severe disease (Hahn et al., 2008; Keochkerian et al., 2005). Indirect effects of disease severity (i.e. malnutrition) appear to play a role in the earlier disease stages while direct effects (i.e. hyperinflation) are predominant in advanced severity. Future research should investigate interactions between disease severity, MIP, and other indices of breathing mechanics, and their potential effect on ventilatory efficiency and dyspnea perception.

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References


CLINICAL PREDICTORS OF INSPIRATORY MUSCLE STRENGTH IN ADULTS WITH STABLE CYSTIC FIBROSIS

Manuscript 2 of 2
**Abstract**

**Background:** Inspiratory muscle strength (IMS) can range from below normal to supernormal levels in adults with cystic fibrosis (CF). Decreased IMS can contribute to dyspnea, alter breathing patterns and may indirectly limit exercise capacity particularly in advanced disease. Identification of impaired IMS in CF may detect individuals in need of therapeutic interventions to enhance or aid the inspiratory pump. Direct measurement of IMS is difficult in the clinic and not routinely indicated at this time; however, commonly used clinical measures may predict IMS. The purpose of this study was to evaluate the ability of routine measures to predict IMS in the adult CF population.

**Methods:** Maximal inspiratory pressure measured in both cmH$_2$O (MIP) and percent of predicted (%MIP) was assessed in 58 adults with stable CF with a range of disease severities (FEV$_1$ = 20 – 130% of predicted). Body composition was estimated from body mass index, skinfold measurements, and assessed using bioelectrical impedance analysis. The ability these measures along with routine demographic, nutritional, and pulmonary clinical outcomes to predict MIP and %MIP was evaluated through linear regression modelling.

**Results:** Dyspnea rating on the Modified Medical Research Council Dyspnea Scale was significantly associated with both MIP (r= -0.48, p<0.001) and %MIP (r= -0.50, p<0.001). The linear combination of the percent of predicted forced expiratory volume in one-second (%FEV$_1$), percent of predicted residual volume
(%RV), lean body mass index from skinfold measurements (LBMI_{SF}) and age(yrs.) explained 43% of the variance in MIP [MIP = 26.449 + 0.182 (%FEV_{1}) − 0.132 (%RV) + 6.495 (LBMI_{SF}) - 0.649 (age), R^2=0.428, SEE=21.06, p<0.001]. The linear combination of percent of predicted inspiratory capacity (%IC), %RV, and body mass index (BMI) explained 52% of the variance in %MIP [%MIP=64.523 +0.422(%IC) – 0.164(%RV) + 1.229(BMI), R^2=0.522, SEE=19.66, p<0.001].

**Conclusions:** Adults with CF present a wide range of values of IMS that are associated with dyspnea. A combination of commonly used pulmonary, nutritional and demographic factors can explain some of the variability in IMS in adults with CF but not all. Poor nutritional status and hyperinflation appear to have the greatest influence. In the absence of lung volumes, %FEV_{1} may still predict portions of the variance in IMS. The results of this study may help the clinician identify adults with CF who warrant a direct assessment of IMS or who benefit from interventions aimed at enhancing inspiratory muscle function. Further research is needed to improve the identified predictive models and validate their use.
Introduction

A defect in the cystic fibrosis transmembrane regulator (CFTR) gene creates an airway environment that leads to infection and inflammation in cystic fibrosis (CF) (O’Sullivan & Flume, 2009; Ratjen, 2009). Recurrent pulmonary exacerbations, chronic infection, and bronchiectatic changes lead to progressive destruction of lung tissue (Amadori et al., 2009; O’Sullivan & Freedman, 2009). Pulmonary impairments elevate the demand and resistive load imposed on the ventilatory pump and contribute to exercise intolerance from excess work of breathing (WOB), dyspnea, and dead space ventilation (Almajed & Lands, 2012). Causes of exercise intolerance are of particular importance as exercise capacity is linked to mortality and quality of life (QOL) in CF (de Jong et al., 1997; van de Weert-van Leeuwen et al., 2012). The majority of the WOB is believed to fall on the inspiratory muscles in pulmonary disease (Mador, 1991). In healthy individuals, inspiratory resistive loads rarely exceed the capacity of the inspiratory muscles; however, problems may arise in CF and contribute to dyspnea and exercise intolerance.

Many theories exist pertaining to the genesis of dyspnea, however, the inspiratory muscles are believed to play a significant role (Grazzini, Stendardi, Gigliotti, & Scano, 2005; Mahler, 2006). Particularly, inspiratory muscle strength (IMS) measured as maximal inspiratory pressure (MIP) can contribute to the perceived effort of breathing. As the individual pressure per breath (P\text{br}) increases relative to MIP, the sense of dyspnea will increase (Grazzini et al.,
2005; Rochester, 1993). Indeed, enhancing IMS can decrease the perception of loaded breathing in healthy individuals (Kellerman, Martin, & Davenport, 2000). An elevated $P_{br}$ to MIP ratio ($P_{br}/MIP$) has been observed during exercise testing which may contribute to dyspnea and indirectly limit exercise (Keochkerian et al., 2005; Rochester, 1993). In the presence of such inspiratory loads, individuals with CF alter their breathing patterns by decreasing inspiratory time to potentially avoid inspiratory fatigue (Hahn et al., 2008; Keochkerian et al., 2005). These altered breathing patterns are believed to limit tidal volume, elevate respiratory rate, and potentially compromise gas exchange (Rochester, 1993). Impaired contractility of the inspiratory muscles would compound these problems in CF and may become evident as individuals age into adulthood and/or in the presence of progressive lung disease.

Decreased IMS is related to altered nutritional indices, hyperinflation, and disease severity in adults with CF (Ionescu et al., 1998; Leroy, Perez, Neviere, Aguilaniu, & Wallaert, 2011). The elevated $P_{br}/MIP$ associated with altered breathing patterns in CF may be partly due to decreased MIP (Keochkerian et al., 2005). Nonetheless, research has shown normal or above normal IMS in adults with CF due to training-induced adaptations from the chronically elevated WOB (Dufresne et al., 2009; Dunnink, DOELEMAN, TRAPPENBURG, & de Vries, 2009; Heinzmann-Filho, Marostica, & Donadio, 2012). However, closer inspection of available data suggests that adults with CF can present with a range from severe weakness to supernormal strength of the inspiratory muscles. For example, Leroy et al (2010) documented IMS ranging from 23% to 148% of predicted
values (Leroy et al., 2011). Other authors report IMS ranging from 40 – 175% of predicted (Barry & Gallagher, 2003). In the presence of normal or supernormal IMS, the CF-related WOB may not overload the inspiratory muscles to a critical point that they significantly contribute to dyspnea or exercise capacity. However, these findings suggest the inspiratory muscles do not adapt favorably in all adults with CF and impaired IMS could have significant consequences.

Heterogeneity in the clinical presentation of adults with CF may explain the variability in IMS and influential factors have been suggested. Altered IMS is of clinical importance as it can potentially contribute to dyspnea, hypoventilation, and exercise intolerance (Grazzini et al., 2005; Mahler, 2006; Taylor-Cousar, 2009). In a small study, IMS was noted to be lower in adults with CF who either died or received lung transplant 20 months later (Ionescu et al., 1998). Rehabilitation interventions such as inspiratory muscle training (IMT) may be of benefit; however, research is limited and IMT is recommended on a case by case basis in CF (Houston, Mills, & Solis-Moya, 2008). A better understanding of clinical determinants of IMS may identify subsets of adults with CF at risk for inspiratory overload who may respond to IMT or similar interventions (Reid, Geddes, O'Brien, Brooks, & Crowe, 2008). Consistent with this premise, the primary aim of the present study was to assess the ability for common clinical measures to predict IMS in adults with CF. Alternate models were created for use based on the clinical availability of the identified measures.
Methods

English speaking adults with CF (age > 18 yrs.) and stable lung function without changes in medical status in the prior 4 weeks were recruited from a hospital-based outpatient clinic (Hospital of the University of Pennsylvania (HUP), Philadelphia, PA). A sample of convenience was used and potential subjects were identified during routine visits. CF diagnosis was confirmed through past genetic testing. Exclusion criteria were: 1. Signs or symptoms of a pulmonary exacerbation 2. Active smoker, 3. Secondary pulmonary condition other than asthma, 4. Thoracic or abdominal condition that may interfere with testing, 5. Neuromuscular disease, 6. Pregnancy, 7. Unresolved pneumothorax, 8. Positive for *Burholderia sp.*, 9. Lung transplant and 10. Cardiac pacemaker. Study procedures were approved by the Institutional Review Boards of Rutgers, The State University of New Jersey and HUP. Eligible volunteers completed the informed consent process prior to enrollment and awarded a $20 gift card upon study completion. Demographics including age, sex, ethnicity, genotype (if available), presence of CF-related diabetes and/or pancreatic insufficiency, sputum colonization, and current systemic corticosteroid use was recorded from the medical record.

Pulmonary Function

Pulmonary function tests (PFT) results were extracted from the subject’s medical record. Measurements were performed by a licensed respiratory therapist as part of routine care. All PFT equipment and procedures were in
accordance to standard guidelines (Miller et al., 2005; Wanger et al., 2005). Spirometry, including FEV$_1$, forced vital capacity (FVC) the FEV$_1$/FVC ratio, and mid-inspiratory flow rate (FIF$_{50%}$), was performed on the same day as IMS testing. Lung volumes, including inspiratory capacity (IC), residual volume (RV), total lung capacity (TLC) and the RV/TLC ratio were extrapolated from the most recent body plethysmography tests performed within 12 months of MIP testing. Values were considered an acceptable representation of current volumes provided the %FEV$_1$ was within 10% of present values as hyperinflation and airway obstruction are suggested to progress at similar rates (Kraemer, Baldwin, Ammann, Frey, & Gallati, 2006). Subjects were referred for updated testing if this criterion was not met. Results were recorded as absolute values as well as percent of predicted according to Hankinson (1999) (Hankinson, Odencrantz, & Fedan, 1999)

**Anthropometrics and Nutritional Status**

Nutritional status was represented as the ratio of lean body mass (LBM) to ideal body weight (IBW) to optimally detect depletion of fat-free mass (Engelen, Schols, Baken, Wesseling, & Wouters, 1994; Ionescu et al., 1998). In addition, the LBM index (LBMI) was calculated as the LBM (kg) divided by the height (m) squared as an alternate method to normalize LBM (King et al., 2010; VanItallie, Yang, Heymsfield, Funk, & Boileau, 1990). Measurements were taken in a temperature controlled room on the same day as MIP testing with light clothing worn but shoes and socks removed. Height (cm) was measured on a standard
stadiometer and weight (kg) was recorded during bioelectrical impedance analysis (BIA). To accommodate for the light clothing, 4.4 kg was deducted from the measured weight for each subject. Body mass index (BMI) was calculated as kg/m$^2$ (Cystic Fibrosis Foundation, 2013). Percent of ideal body weight (%IBW) was documented according to the Metropolitan Life Insurance height-weight tables (Metropolitan Life Insurance Company, 1983).

Mid-arm circumference (MAC) was measured at the mid-point between the acromion and olecranon processes on the right side of the body with the arm in the dependent position. A soft spring-loaded tape measure was used. The triceps skinfold was recorded as described below. The mid-arm muscle circumference (MAMC) was calculated as illustrated below and expressed in absolute values and as a percent of predicted (Bishop, Bowen, & Ritchey, 1981; Ionescu et al., 1998):

$$MAMC\ (cm) = \text{Mid-arm circumference}\ (cm) - (3.14 \times \text{triceps skinfold}\ (cm))$$

Percent body fat (%BF) was obtained from BIA, skin fold (SF) measurements, and estimated from BMI. LBM was derived from each technique as the difference between weight and the calculated fat mass. Results from BIA were used as a representation of LBM ($LBM_{BIA}$) as BIA has demonstrated a strong relationship with dual energy x-ray absorptiometry (DEXA) in CF (Beaumesnil et al., 2011; King, Wilson, Kotsimbos, Bailey, & Nyulasi, 2005; Ziai et al., 2014). LBM estimates from SF ($LBM_{SF}$) and BMI ($LBM_{BMI}$) were substituted
for LBM\textsubscript{BIA} to determine their potential as alternate factors to predict MIP in the absence of BIA equipment.

The Tanita BC-418 body composition analyzer (Tanita Corporation of America, Arlington Heights, IL, USA) was used to assess whole body BIA with subjects in a relaxed standing position. Similar analyzers have been used in the CF literature (Hollander, De Roos, De Vries, & Van Berkhout, 2005; Ziai et al., 2014). Subjects refrained from ingesting caffeine and/or alcohol at least two hours and voided their bladder within 30 minutes prior to testing. SF measurements were taken at two sites using Lange Calipers (Beta Technology, Santa Cruz, CA). This simple two-site technique has been used in adults with CF and results correlate to measurements from BIA (Hollander et al., 2005). The mean value of three vertical SF measurements (mm) taken at the right triceps and biceps midway between the acromion and olecranon processes was recorded (ACSM, 2010). %BF was calculated from these SF measurements according to standard equations (Durnin & Womersley, 1974). The Deurenberg equation was used to estimate %BF from BMI as previously used in the CF and illustrated in the equation below (Deurenberg, Weststrate, & Seidell, 1991; Hollander et al., 2005).

\[
\%BF_{\text{BMI}} = (1.20 \times \text{BMI}) + (0.23 \times \text{age}) - (10.8 \times \text{sex}^*) - 5.4
\]

* sex= 1(male) and 0 (female)
**Inspiratory Muscle Strength**

MIP at the mouth was measured with a handheld respiratory pressure meter (RPM) (MicroRPM®, CareFusion Corporation, San Diego, CA, USA) by a single tester according to standard guidelines (American Thoracic Society/European Respiratory, 2002). Subjects were seated, wearing nose clips, and refrained from using bronchodilators for at least 2 hours prior to testing. The inspiratory circuit contained a small leak to limit the influence of the buccal muscles. A rubber flanged mouthpiece with an inline bacterial filter was connected to the RPM interfaced with a laptop and associated software (PUMA®, CareFusion Corporation, San Diego, CA, USA). Subjects performed a maximal static inspiratory maneuver from residual volume (RV) for at least two seconds. MIP was identified as the mean pressure sustained for one second and recorded in centimeters of water pressure (MIP) and percent of predicted (%MIP) (Black & Hyatt, 1969). Standardized instructions were provided and a minimum of two practice trials were allowed to ensure proper technique. Subsequently, the best of at least five satisfactory maneuvers varying by less than 5-10% was recorded. Strong verbal encouragement was provided and subjects visualized the computer screen to elicit a maximal volitional effort. A two-minute rest period separated each trial.

**Statistical Analysis**

Mean values, ranges, and standard deviations were calculated for continuous data. Categorical variables were summarized with frequency
distributions. For ease of data interpretation, negative inspiratory pressures were converted to their positive values. Prior to analysis, parametric assumptions were assessed. A predictive model for IMS was developed through linear regression with MIP as the dependent variable. Analysis proceeded to first identify the best-fitting model using nutritional measures and $\text{LBM}_{\text{BIA}}$. Subsequently alternate versions of the primary model were assessed to expand its clinical utility. Figure 4.4 illustrates the general modelling procedures followed in this study. Similar processes have been previously described in the literature (Byham-Gray, Parrott, Ho, Sundell, & Ikizler, 2014). All analyses were performed using SPSS statistical software v. 21.

The selection of clinical predictors was based on statistical, clinical, and theoretical criteria. Pearson correlations identified linear relationships between independent variables and MIP. Spearman’s Rho was used when parametric assumptions were violated. Given the small sample size, the total number of independent variables was limited to a maximum of 5 (Field, 2009). Only variables demonstrating significant linear relationships with MIP as identified by a conservative $p$-value of $< 0.05$ were considered. In the presence of significant collinearity ($r > 0.70$) between possible predictors, the variable with the strongest relationship with MIP was retained unless theoretical and/or clinical rationale justified the other. Final models were evaluated using collinearity diagnostics. Homoscedasticity, linearity, and normality of errors were assessed by visual analysis of residual plots. Casewise diagnostics identified potential outliers and
Cooks distance assessed their influence. Processes were repeated with %MIP set as the dependent variable.
Figure 4.4. General algorithm for factor selection during regression modelling.
Results

Subjects

Fifty-eight adults with CF (28 males) completed the study. Participant characteristics are summarized in table 4.5. There was an even distribution of pulmonary disease severity. Twenty subjects presented with mild disease (%FEV$_1$ $\geq$ 70%), 20 with moderate disease (%FEV$_1$ 40 – 69%), and 18 with severe disease (%FEV$_1$ < 40%) (Cystic Fibrosis Foundation, 2013). Lung volumes were unavailable for 3 subjects (2 severe, 1 moderate). The remaining volumes were measured within a mean of 2.1 months of MIP testing. Twenty-five (43%) subjects were ΔF508 homozygous, 28(48%) were ΔF508 heterozygous and the remaining 5(9%) were ΔF508 negative. CFRD was present in 27(47%) subjects and 52(90%) were pancreatic insufficient. Sputum cultures were unavailable for one subject. Forty-four (77%) of the remaining subjects were positive for pseudomonas. Only 6 (10%) used concurrent systemic corticosteroids with a mean dose of 1.18 ± 4.06 mg/day (range 0 – 20 mg/day). Variables demonstrating significant linear associations (p<0.05) with MIP and %MIP were categorized as pulmonary or nutritional factors and ranked by their strength of association (tables 4.6 and 4.7). Dyspnea was recorded as a categorical variable with 5 levels. As such, dyspnea was not considered as a potential predictor due to limited space in our model.
### Table 4.5

**Characteristics of the sample population (N=58)**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age - yrs</strong></td>
<td>32.31 ± 9.27</td>
<td>20 – 60</td>
</tr>
<tr>
<td><strong>Height – cm</strong></td>
<td>164.34 ± 8.41</td>
<td>147.32 – 180.34</td>
</tr>
<tr>
<td><strong>Weight – kg</strong></td>
<td>58.57 ± 10.23</td>
<td>37.73 – 94.00</td>
</tr>
<tr>
<td><strong>IBW - %predicted</strong></td>
<td>94.71 ± 10.44</td>
<td>69 – 125</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>21.59 ± 2.69</td>
<td>14.7 – 30.4</td>
</tr>
<tr>
<td><strong>LBM&lt;sub&gt;BIA&lt;/sub&gt; - kg</strong></td>
<td>47.04 ± 9.15</td>
<td>34.80 – 73.41</td>
</tr>
<tr>
<td><strong>LBM&lt;sub&gt;BIA/IBW&lt;/sub&gt; - %</strong></td>
<td>75.74 ± 8.04</td>
<td>63 – 93</td>
</tr>
<tr>
<td><strong>LBMI&lt;sub&gt;BIA&lt;/sub&gt;</strong></td>
<td>17.27 ± 2.03</td>
<td>12.9 – 22.6</td>
</tr>
<tr>
<td><strong>MAMC - %predicted</strong></td>
<td>91.59 ± 8.82</td>
<td>71 – 121</td>
</tr>
<tr>
<td><strong>MIP – cmH₂O</strong></td>
<td>105.72 ± 26.80</td>
<td>48 – 175</td>
</tr>
<tr>
<td><strong>MIP - %predicted</strong></td>
<td>102.22 ± 27.64</td>
<td>63 – 167</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; – L</strong></td>
<td>2.05 ± 0.88</td>
<td>0.63 – 4.40</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; - %predicted</strong></td>
<td>59.57 ± 26.92</td>
<td>20 – 130</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC - %</strong></td>
<td>63.59 ± 13.96</td>
<td>33 – 92</td>
</tr>
<tr>
<td><strong>FIF&lt;sub&gt;50%&lt;/sub&gt; - L/min</strong></td>
<td>4.23 ± 1.69</td>
<td>1.03 – 8.63</td>
</tr>
<tr>
<td><strong>FIF&lt;sub&gt;50%&lt;/sub&gt; - %predicted</strong></td>
<td>93.25 ± 35.08</td>
<td>20 – 183</td>
</tr>
<tr>
<td><strong>RV&lt;sup&gt;a&lt;/sup&gt; – L</strong></td>
<td>2.47 ± 1.01</td>
<td>1.02 – 5.21</td>
</tr>
<tr>
<td><strong>RV&lt;sup&gt;a&lt;/sup&gt; - %predicted</strong></td>
<td>155.38 ± 48.90</td>
<td>69 – 249</td>
</tr>
<tr>
<td><strong>RV/TLC&lt;sup&gt;a&lt;/sup&gt; - %</strong></td>
<td>42.36 ± 12.91</td>
<td>21 – 71</td>
</tr>
<tr>
<td><strong>IC&lt;sup&gt;a&lt;/sup&gt; – L</strong></td>
<td>2.26 ± 0.64</td>
<td>1.05 – 3.74</td>
</tr>
<tr>
<td><strong>IC&lt;sup&gt;a&lt;/sup&gt; - %predicted</strong></td>
<td>86.82 ± 32.28</td>
<td>40 – 179</td>
</tr>
</tbody>
</table>

*Note.* IBW=ideal body weight; BMI=body mass index; LBM<sub>BIA</sub>=lean body mass assess by body impedance analysis; LBMI<sub>BIA</sub>/IBW=lean body mass index calculated with bioelectrical impedance analysis; MAMC=mid-arm muscle circumference; MIP=maximal inspiratory pressure; FEV<sub>1</sub>=forced expiratory volume in one-second; FVC=forced vital capacity; FIF<sub>50%</sub>=mid-inspiratory flow rate; RV=residual volume; TLC=total lung capacity; IC=inspiratory capacity.

<sup>a</sup>Data missing for 3 subjects. Mean values reported on 55 subjects.
Table 4.6

Factors with significant linear associations with MIP ranked by strength of association

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>R value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Dyspnea</td>
<td>-0.48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.47&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td>0.46&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>%FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.43&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>FIF&lt;sub&gt;50%&lt;/sub&gt;</td>
<td>0.43&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>RV/TLC</td>
<td>-0.42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>RV</td>
<td>-0.38&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>%RV</td>
<td>-0.37&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>%IC</td>
<td>0.34&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>%FIF&lt;sub&gt;50%&lt;/sub&gt;</td>
<td>0.30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>0.29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.029</td>
</tr>
<tr>
<td>Nutritional</td>
<td>LBMI&lt;sub&gt;BIA&lt;/sub&gt;</td>
<td>0.40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.39&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>LBM&lt;sub&gt;BIA&lt;/sub&gt;/IBW</td>
<td>0.35&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>%IBW</td>
<td>0.35&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>MAMC</td>
<td>0.33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>0.29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>LBM&lt;sub&gt;BIA&lt;/sub&gt;</td>
<td>0.28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Note. MIP=maximal inspiratory pressure; FEV<sub>1</sub>=forced expiratory volume in one-second; IC=inspiratory capacity; %FEV<sub>1</sub>=FEV<sub>1</sub> percent predicted; RV/TLC=ratio of residual volume to total lung capacity; FIF<sub>50%</sub>=mid-inspiratory flow rate; RV=residual volume; %RV=residual volume percent predicted; %IC=inspiratory capacity percent predicted; %FIF<sub>50%</sub>=mid-inspiratory flow rate percent predicted; FEV<sub>1</sub>/FVC=ratio of FEV<sub>1</sub> to forced vital capacity; LBMI<sub>BIA</sub>=lean body mass index from bioelectrical impedance analysis (BIA); BMI=body mass index; LBM<sub>BIA</sub>/IBW=ratio of LBM<sub>BIA</sub> to ideal body weight; %IBW=percent of ideal body weight; MAMC=mid arm muscle circumference; LBM<sub>BIA</sub>=lean body mass from BIA.

<sup>a</sup> Spearman’s Rho correlation coefficient
<sup>b</sup> Pearson’s correlation coefficient
**Table 4.7**

*Factors with significant linear associations with %MIP ranked by strength of relationship*

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>R value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>%IC</td>
<td>0.65^a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>%FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.61^a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RV</td>
<td>-0.59^b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RV/TLC</td>
<td>-0.55^b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>%RV</td>
<td>-0.55^b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>0.51^b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>-0.50^a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.47^a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>%FIF&lt;sub&gt;50%&lt;/sub&gt;</td>
<td>0.44^b</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td>0.31^b</td>
<td>0.024</td>
</tr>
<tr>
<td>Nutritional</td>
<td>%BF&lt;sub&gt;BIA&lt;/sub&gt;</td>
<td>0.49^b</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>%MAMC</td>
<td>0.43^b</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Ht</td>
<td>0.38^a</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>%IBW</td>
<td>0.37^b</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.32^b</td>
<td>0.034</td>
</tr>
<tr>
<td>Demographic</td>
<td>Sex</td>
<td>-0.42^a</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Note. %MIP= maximal inspiratory pressure percent predicted; %IC= inspiratory capacity percent predicted; RV= residual volume in liters; %FEV<sub>1</sub>= forced expiratory volume in one-second percent predicted; RV/TLC= ratio of residual volume to total lung capacity; FEV<sub>1</sub>/FVC= ratio of FEV<sub>1</sub> to forced vital capacity; %RV= residual volume percent predicted; FEV<sub>1</sub>= forced expiratory volume in one-second in liters; %FIF<sub>50%</sub>= forced mid-inspiratory flow rate percent predicted; IC= inspiratory capacity in liters; %BF<sub>BIA</sub>= percent of body fat as determined through bioelectrical impedance analysis (BIA); Ht= height; %MAMC= mid arm muscle circumference percent predicted; %IBW= percent of ideal body weight; BMI= body mass index.

^a Spearman’s Rho correlation coefficient

^b Pearson’s correlation coefficient
Clinical predictors of MIP

%FEV\textsubscript{1} was selected as the initial pulmonary factor as it is considered the “single most useful objective measure of pulmonary status” in adults with CF (Yankaskas, Marshall, Sufian, Simon, & Rodman, 2004, pg. 4S). Collinearity screening with %FEV\textsubscript{1} excluded IC, RV/TLC, RV, IC percent of predicted (%IC), and FEV\textsubscript{1}/FVC as potential pulmonary predictors ($r \geq 0.70$). Inspiratory flow rates ($\text{FIF}_{50\%}$ and $\%\text{FIF}_{50\%}$) were excluded on the theoretical basis that they are likely an effect of MIP rather than a determinant. RV expressed as percent predicted (%RV) was retained to represent hyperinflation given its known influence on IMS (Szeinberg, England, Mindorff, Fraser, & Levison, 1985).

Of the nutritional factors, LBMI\textsubscript{BIA} was retained as it demonstrated the strongest association with MIP. Collinearity screening excluded LBM\textsubscript{BIA}/IBW, MAMC, weight, and LBM\textsubscript{BIA} as potential nutritional predictors ($r \geq 0.70$). BMI was excluded as it can hide depletion of LBM which can impact muscle strength (Bolton, Ionescu, Evans, Pettit, & Shale, 2003). %IBW was also excluded as it does not consider differences in body composition. Age and sex were considered as potential predictors though sex was excluded due to its collinearity with LBMI\textsubscript{BIA} ($r=0.74$, $p<0.001$). Systemic corticosteroid use was selected to fill the model based on its known influence on MIP in CF but was removed as an insignificant ($p=0.275$) positive coefficient for was noted in direct disagreement with its expected effect (Barry & Gallagher, 2003).
The linear combination of %FEV₁, %RV, LBMI_{BIA}, and age accounted for 40% of the variance seen in MIP ($R^2=0.395$; SEE=21.67; $F=8.151$; $p<0.001$). Using %IBW and BMI in place of LBMI_{BIA} significantly weakened the model ($R^2=0.260$ and 0.297 respectively) and were determined inadequate alternates; however, substituting with LBMI_{SF} improved the model accounting for 43% of the variance in MIP ($R^2=0.428$; SEE=21.06; $F=9.369$; $df = 4, 50$; $p<0.001$).

Substituting with LBMI_{BMI} resulted in a model similar to using LBMI_{BIA} and accounted for 39% of the variance in MIP ($R^2=0.391$; SEE=21.529; $F=10.902$; $p<0.001$). The linear combination of %FEV₁, %RV, LBMI_{SF}, and age was identified as the best predictive model. The linear combination of %FEV₁, %RV, LBMI_{BMI}, and age was retained as an alternate model in the event that skinfold measurements are unavailable in the clinic as its predictive ability was similar to using the more expensive LBMI_{BIA}. The initial model using LBMI_{BIA} was discarded.

To accommodate the clinical situation where lung volume measurements are unavailable, the predictive models above with LBMI_{SF} and LBMI_{BMI} were reassessed after removing %RV. The linear combination of %FEV₁, LBMI_{SF} and age still accounted for 40% of the variance seen in MIP ($R^2 = 0.396$; SEE=21.406; $F=11.790$; $p<0.001$) whereas the linear combination of %FEV₁ and LBMI_{BMI} accounted for only 35% ($R^2=0.353$; SEE=21.956; $F=14.974$; $p<0.001$). The identified predictive equations for MIP are summarized in table 4.8.
Table 4.8

**Summary of the developed models for predicting MIP in adults with stable CF**

<table>
<thead>
<tr>
<th>Predictive Equation(^a)</th>
<th>(R^2)</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.449 + 0.182 (%FEV(<em>1)) – 0.132 (%RV) + 6.495 (LBMI(</em>{SF})) – 0.649 (age)</td>
<td>0.428</td>
<td>21.060</td>
</tr>
<tr>
<td>Alternates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-6.165 + 0.347 (%FEV(<em>1)) + 6.510 (LBMI(</em>{SF})) – 0.587 (age)</td>
<td>0.396</td>
<td>21.406</td>
</tr>
<tr>
<td>6.540 + 0.168 (%FEV(<em>1)) – 0.142 (%RV) + 6.704 (LBMI(</em>{BMI}))</td>
<td>0.391</td>
<td>21.529</td>
</tr>
<tr>
<td>-22.832 + 0.339 (%FEV(<em>1)) + 6.529 (LBMI(</em>{BMI}))</td>
<td>0.353</td>
<td>21.956</td>
</tr>
</tbody>
</table>

Note. The table summarizes the ideal models identified from this analysis to predict MIP. The best predictive model was able to explain the largest portion of the variance in the dependent variable. The alternate models may be used based on the available data in the clinic. MIP=maximal inspiratory pressure; %FEV\(_1\)=forced expiratory volume in one-second percent predicted; %RV=residual volume percent predicted; LBMI=lean body mass index; LBMI\(_{SF}\)=LBMI derived from skinfolds; BMI=body mass index; LBMI\(_{BMI}\)=LBMI from BMI.

\(^a\)%FEV\(_1\) and %RV are each represented as a whole percent and not converted to a decimal, age is measured in yrs.
Clinical predictors of %MIP

%IC was selected as the initial pulmonary factor as it had the greatest association with %MIP (r=0.65, p<0.001). Collinearity screening excluded %FEV\textsubscript{1}, RV/TLC, FEV\textsubscript{1}, and IC. %RV was selected next as it would detect a degree of hyperinflation not captured by RV in absolute terms. FEV\textsubscript{1}/FVC, %BF\textsubscript{BIA}, and sex were used to fill the model due to their level of associations with %MIP and the absence of collinearity problems. The coefficients both FEV\textsubscript{1}/FVC and sex were not significant (p=0.416 and 0.683 respectively) and were excluded to allow additional room in the model. FIF\textsubscript{50\%}, height, %MAMC, %IBW, BMI, and corticosteroids were each subsequently analyzed for their potential model contributions; however, none of these variables improved the model and were insignificant. The linear combination of %IC, %RV, and %BF\textsubscript{BIA} was the best predictive model accounting for 53\% of the variance in %MIP (R\textsuperscript{2}=0.531; SEE=19.468; p<0.001). Substituting %BF\textsubscript{SF}, %BF\textsubscript{BMI}, %IBW, and BMI for %BF\textsubscript{BIA} in a sequential manner resulted in models with similar predictive ability. Regression coefficients for the nutritional indices included in the present study fell short of significance with %BF\textsubscript{BIA} trending closest (p=0.127). However, the effect of nutrition on IMS is well-accepted and removing measures of nutrition would likely compromise the external application of the model given our small sample size. BMI was retained over %BF\textsubscript{BIA} secondary to its clinical applicability and recommended use in CF (Stallings, Stark, Robinson, Feranchak, & Quinton, 2008). The linear combination of %IC, %RV, and BMI was identified as the best...
predictive and clinical model accounting for 52% of the variance in %MIP ($R^2=0.522$; $\text{SEE}=19.659$; $p<0.001$).

To accommodate the situation where lung volumes were unavailable, the modelling procedures for %MIP were repeated with %FEV$_1$ substituted for %IC and %RV. The initial 5 factors included %FEV$_1$, %BF$_\text{BIA}$, sex, %FIF$_{50\%}$, and Height. Neither sex nor %FIF$_{50\%}$ was found to be significant contributors. The linear combination of %FEV$_1$, %BF$_\text{BIA}$, and height accounted for 43% of the variance seen in %MIP ($R^2=0.437$; $\text{SEE}=21.306$; $p<0.001$). After substituting %BF$_\text{SF}$, %BF$_\text{BMI}$, %IBW, and BMI for %BF$_\text{BIA}$ in a sequential fashion, the use of %IBW was able to account for 46% of the variance in %MIP ($R^2=0.463$; $\text{SEE}=0.813$; $p<0.001$) whereas substituting with BMI accounted for 44% of the variance in %MIP ($R^2=0.439$; $\text{SEE}=21.260$; $p<0.001$). The identified predictive equations for %MIP are summarized in table 4.9.
Table 4.9

Summary of the developed models for predicting %MIP in adults with stable CF

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictive Equation</th>
<th>$R^2$</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best</td>
<td>64.523 +0.422(%IC) – 0.164(%RV) + 1.229(BMI)</td>
<td>0.522</td>
<td>19.659</td>
</tr>
<tr>
<td>Alternates</td>
<td>174.457 + 0.415(%FEV$_1$) + 0.727(%IBW) – 1.009(Ht)</td>
<td>0.463</td>
<td>20.813</td>
</tr>
<tr>
<td></td>
<td>171.160 + 0.468(%FEV$_1$) + 2.044(BMI) – 0.858(Ht)</td>
<td>0.439</td>
<td>21.260</td>
</tr>
</tbody>
</table>

Note. The table summarizes the ideal models identified from this analysis to predict %MIP. Best predictive model was able to explain a larger portion of the variance in the dependent variable. The alternate models may be used based on the available data in the clinic. %MIP=maximal inspiratory pressure percent predicted; %IC=inspiratory capacity percent of predicted; %RV=residual volume percent predicted; BMI=body mass index; %FEV$_1$=forced expiratory volume in one-second percent predicted; %IBW=percent of ideal body weight; Ht=height.

*%IC, %RV, and %IBW are each represented as a whole percent and not converted to a decimal, height is measured in cm.
Discussion

Nutritional status, hyperinflation, and disease severity were identified clinical predictors of inspiratory muscle strength (IMS) in our cohort of adults with CF. Height and age also contributed to the models. Overall, IMS ranged from below normal to above normal levels and the identified predictive models accounted for 43% and 52% of the variance seen in MIP and %MIP respectively. Nutritional status appears to have the greater influence on MIP whereas lung volumes appear exert a greater influence on %MIP. Simple estimates of LBM and other nutritional indices may be adequate representations of nutritional status to estimate IMS. Relative representations of LBM (i.e. LBMI or the LBM/IBW) were better determinants of MIP as opposed to absolute values. Measures reflecting overall nutritional status (i.e. %IBW and BMI) were better predictors of %MIP. To the author’s knowledge, this is the first study to focus on specific models to predict IMS in the adults with CF that clinicians can easily incorporate into routine clinic visits.

In the present study, %MIP ranged from 63 – 167% (mean ±SD=102.22 ± 27.64). This degree of variability is consistent with the literature and supports the presence of decreased IMS in some adults with CF. Leroy et al (2010) and Barry et al (2003) reported %MIP in adults with CF ranging from 23 – 148% and 40 – 175% respectively (Barry & Gallagher, 2003; Leroy et al., 2011). The subjects assessed by Leroy (2010) and Barry (2003) demonstrated more advanced disease severity and malnutrition than our sample (mean %FEV$_1$= 44.1% and
48.7% versus 59.6%, and BMI=19.8 and 20.6 versus 21.6 respectively). Hyperinflation was not reported by Barry (2003); however, the subjects included by Leroy (2010) had a greater degree of hyperinflation as compared to our subjects (mean RV/TLC=57.0% versus 42.4%). These differences in subject characteristics may explain the lower values for %MIP seen in these studies. In contrast, other authors have reported higher values for %MIP in adults with CF ranging from 82 – 176% and 82 – 226% respectively suggesting preserved IMS but in less severe cohorts (de Jong, van Aalderen, Kraan, Koeter, & van der Schans, 2001; Dunnink et al., 2009). These observations support the negative influence of disease severity, malnutrition, and hyperinflation on IMS in the adult CF population. However, these factors only accounted for approximately half of the variance in IMS in our sample. Other potential factors should be identified to enhance the predictive model.

Sex, BMI, and the average daily dose of systemic corticosteroids over the preceding 12 months (ADD) has been suggested to explain 76% of the variance seen in %MIP in sample of 23 adults with CF (Barry & Gallagher, 2003). These findings support our inclusion of BMI as a predictor of %MIP but require validation in a larger sample. Without lung volumes, BMI and %IBW were identified as significant predictors in our model along with %FEV₁ and height further supporting the need to include nutritional measures. ADD alone was reported by Barry et al (2003) to explain 54% of the variance in their small sample (Barry & Gallagher, 2003). Though impressive, the methods employed to measure ADD are not clinically feasible. We measured concurrent systemic
corticosteroid use (mg/day) to enhance the clinical application of our model but this variable was insignificant. It is difficult to ascertain the true influence of concurrent systemic corticosteroid use from our data as only a small number of subjects (n=6) were using this medication. It is plausible that the ADD could explain some of the remaining variance in IMS. However, methods to efficiently monitor this data should first be developed to enhance its clinical applicability.

The influence of sex on IMS is unclear. Lands et el (1993) suggests a greater preservation of MIP in females whereas Bradley et al (1999) noted the opposite (Bradley et al., 1999; Lands, Heigenhauser, & Jones, 1993). Dunnink (2009) found greater absolute values of MIP in males but no sex-related differences in %MIP. A negative correlation existed between sex and %MIP in our study though sex did not contribute to our models. Additional analysis of our data showed a non-significantly lower MIP in females but significantly greater %MIP (p<0.05) suggesting females are less affected. Care must be taken when interpreting this data, however, as the females in our sample presented with milder disease and could bias results. Still, the potential influence of sex cannot be discarded.

Sex differences in thoracic adaptations to hyperinflation have been noted suggesting a greater role of ribcage muscles during inspiration in females (Bellemare & Jeanneret, 2007). As MIP does not isolate the diaphragm but assesses global IMS, the increased contribution of the thoracic accessory muscles of inspiration in females may be detected in this maneuver.
Alternatively, MIP may capture an altered breathing strategy in females with CF and the increased contributions of these muscles may create a preferred training effect in females. Though stronger, reliance on these muscles could negatively influence posture and alter breathing patterns that become problematic with disease progression. As female gender is associated with decreased survival in CF, potential interactions between sex, alterations in inspiratory muscle function, breathing strategies, and survival should be investigated while controlling for disease severity (Saint-Criq & Harvey, 2013).

Airway obstruction and hyperinflation influence IMS in adults with CF; however, these measures may not capture all aspects of CF disease. Genetic factors may alter fitness levels and calcium regulation of human skeletal muscle independent of lung function (Lamhonwah et al., 2010; Selvadurai et al., 2003; Selvadurai et al., 2002). Though no association was found between genotype and IMS in our study, the potential for genetic factors to affect the inspiratory muscles cannot be ruled out from our small sample. MIP has been noted to be decreased upon admission for acute pulmonary exacerbations and gradually increase over the course of hospitalization and post discharge (Naon, Hack, Shelton, Gotthoffer, & Gozal, 1993; Wieboldt et al., 2012). Based on this evolution, IMS appears to decrease secondary to acute exacerbations. Whether or not IMS returns to pre-exacerbation levels is unclear as it was not assessed prior to admission. Pulmonary exacerbations can lead to a decline in %FEV₁ and LBM which may affect IMS (Alicandro et al., 2013). In addition, inflammation associated with pulmonary exacerbations can affect skeletal muscle strength
potentially including the inspiratory muscles (Langen et al., 2006). Specifically, pseudomonas infection and inflammation were associated with diaphragmatic weakness in CFTR deficient mice (Divangahi et al., 2009).

The presence of pseudomonas colonization did not correlate with IMS in our study; however, we did not measure inflammatory markers. In 2009, Dufresne investigated the effect of systemic inflammation on LBM and IMS in adults with CF (Dufresne et al., 2009). In their model, LBM, airway resistance, and logIL-8 accounted for 43% of the variance seen in MIP. Our model showed similar predictive ability with much simpler measures. However, Dufresne (2009) reported that systemic inflammation did not contribute to diaphragmatic strength and MIP was actually greater than healthy controls (Dufresne et al., 2009). Interestingly, FFM was also maintained in the presence of elevated inflammation. Protective factors may exist to combat the catabolic effects of inflammation.

Dunnink (2009) showed a modest relationship between MIP and performance on the modified shuttle test ($r=0.59$, $p=0.001$) as well as dyspnea in males ($r=0.63$, $p<0.05$) and females ($r=0.58$, $p<0.05$). In other instances, physically active individuals with CF demonstrated greater MIP than their sedentary counterparts (Dassios, Katelari, Doudounakis, & Dimitriou, 2013). These findings indicate a relationship between MIP and exercise though cause and effect cannot be determined. It is feasible that the increased activity levels have a protective effect on the inspiratory muscles resulting in greater MIP. Conversely, decreased MIP may negatively influence exercise performance.
Likely, a combination is true and the interaction between exercise capacity and IMS in CF warrants further detailed investigation with advanced physiologic measures.

Though decreased in some individuals, it is unclear that the degree of impairment in IMS is sufficient to have clinical consequences. MIP above 80 cmH$_2$O is believed to rule out impaired IMS in healthy adults (American Thoracic Society/European Respiratory, 2002). Alternatively, values below 80% of predicted is commonly used to identify impairments in other clinical measures. In our study, only 10 (17.2%) of the subjects presented with MIP levels below 80 cmH$_2$O and 15 (26%) were below 80% of predicted. Interestingly, all subjects below this threshold presented with either moderate or severe pulmonary disease where respiratory factors play a greater role in exercise performance. However, “normal” IMS may present as “weakness” in the presence of excess work of breathing associated with advanced CF and indirectly limit exercise.

Bradley et al (1999) reported a non-significant difference in MIP as compared to healthy controls suggesting “normal” levels. However, MIP was significantly related to the peak work rate achieved on a cycle ergometer test ($r=0.68$, $p<0.05$) which appeared limited by dyspnea (Bradley et al., 1999). The authors concluded the “subjective reports of dyspnea may be due to the inability of the inspiratory muscle to overcome airway resistance rather than a true level of weakness” (Bradley et al., 1999, pg. 652). The authors did not report on relationships between dyspnea and MIP; however, MIP is suggested to play a
role in the genesis of dyspnea (Grazzini et al., 2005). It is feasible that the required pressure per breath \( P_{br} \) to overcome airway resistance was a greater percentage of MIP and contributed to an increased perception of breathing. Such “functional weakness” may indirectly limit exercise.

Indeed, increased \( P_{br} \) to MIP ratios have been reported in the CF literature at rest and during exercise apparently secondary to an elevated \( P_{br} \) and decreased MIP (Hahn et al., 2008; Keochkerian et al., 2005). Interestingly, these values were associated with altered breathing patterns characterized by decreased inspiratory duty cycles (Keochkerian et al., 2005). These changes were theorized to help prevent inspiratory fatigue and maintain energy efficient breathing patterns (Hahn et al., 2008). Both airway obstruction and hyperinflation were suggested to influence the selected breathing strategies (Keochkerian et al., 2005). In this manner, IMS may also play a role in determining how inspiratory workloads are sustained. It is feasible that decreased IMS, whether a true weakness or a functional insufficiency relative to the inspiratory loads, can result in energy efficient breathing patterns that increase dead space ventilation. The potential for these changes related to IMS to compromise ventilatory efficiency and indirectly limit exercise tolerance should be investigated.

The present study is not without limitations. We used a sample of convenience from a single center to obtain our cohort and included adults with CF only. As such, inferences can be made from our results but may not truly apply to the entire CF population and should not be applied in pediatrics. A large
multi-center trial is needed to validate our findings. Though this study supports the influence of clinical measures on IMS, we were only able to account for 43% of the variance seen in MIP and 52% in %MIP. The small sample size limited the number of factors we could include in our model. Further research is warranted to identify additional factors that may be detrimental or protective to the inspiratory muscles.

Assessment of MIP is a volitional test that can be affected by patient technique and effort. All subjects were allowed adequate practice trials to ensure appropriate technique. Each trial was observed and the quality of the maneuver assessed by a single tester and appropriate guidelines were followed. In addition, visual biofeedback and strong encouragement was provided to each subject and adequate rest periods between trials were provided to minimize the effects of fatigue. We believe the values reported in this study are valid representation of MIP; however, the effect of subject effort cannot be completely ruled out.

Lung volumes were recorded from the most recent PFTs within 12 months of MIP resting. These values may not accurately reflect current lung volumes at the time of MIP testing. %FEV₁ on the recent PFTs was confirmed to be within 10% of current values and hyperinflation and airway obstruction are suggested to progress at similar rates (Kraemer et al., 2006). Post hoc analysis revealed that lung volumes were performed at a mean of 2 months within MIP testing. Given this time frame and comparable level of disease severity, we believe the
recorded values are acceptable representations of lung volumes at the time of testing.

The aim of this study was to develop predictive models for IMS using measures that would be readily available to the average clinician. As such, simple measures were selected to represent nutritional status and body composition. It is possible that more advanced techniques including dual-energy X-ray absorptiometry (DEXA) scans would provide a more accurate measure of LBM. However, the costs associated with DEXA scan would not justify their clinical use to screen for inspiratory muscle dysfunction over direct measurement of MIP and the assessments used in the present study are considered acceptable representations of nutritional status.
Conclusion

The present study demonstrates the negative influence of malnutrition, hyperinflation, and disease severity on the inspiratory muscles in adults with CF. The results of the present study suggests that while some individuals with CF can adapt with preserved or even above normal levels of IMS, disease-related effects may contribute to inspiratory weakness in others. The clinical significance of decreased in IMS in CF should be investigated as it may contribute to dyspnea and altered breathing patterns and indirectly limit exercise. The combined presence of severe pulmonary disease, malnutrition, and hyperinflation may identify candidates for interventions to enhance inspiratory muscle function to minimize the risk of inspiratory overload during exercise, pulmonary exacerbations, or even at rest in advanced disease. As the present model only accounted for approximately 50% of the variability in IMS, other detrimental factors along with possible protective factors should be identified. Such predictive models should include relevant measures to easily identify individuals in need of respiratory muscle testing and/or training in both clinical and research settings. Further research is needed to validate our findings.

Funding: This project was partially supported by the Ellen Ross Memorial Scholarship
References


Chapter V

Conclusion

The results of this study confirmed the initial hypotheses that IMS in adults with mild CF does not significantly differ when compared to healthy controls but is decreased in adults with CF with advanced pulmonary disease. Current literature favors the presence of preserved or above normal IMS in adults with CF without consideration of disease severity. The present data is consistent with this premise as the observed alterations in IMS were not apparent prior to grouping for disease severity. However, decreased IMS was confirmed after stratifying subjects based on pulmonary involvement. Though both MIP and %MIP trended lower prior to grouping by disease severity, these alterations failed to reach statistical significance (p= 0.172 and 0.130 respectively). A larger sample size may have identified differences in subjects with CF as compared to our healthy control group prior to grouping. However, these trends likely emerged secondary to the near equal representation of disease severities in our sample in contrast to other studies where advanced disease tends to be underrepresented. Collectively, our findings support the need to control for disease severity when evaluating inspiratory muscle function in adults with CF as interpretation may be biased in heterogeneous samples skewed towards mild severity.

In 2009, Troosters et al evaluated %MIP in 64 adults with CF as compared to healthy controls and reported no significant difference in IMS between groups.
(Troosters et al., 2009). Level of significance was not provided. Adequate detail pertaining to disease severity to describe their sample was not provided though mean \( \%\text{FEV}_1 \) was 65± 19\% suggesting less severe disease as compared to our subjects. In a sub-cohort of their sample, the authors further determined that IMS did not contribute to exercise capacity or physical activity in 20 adults with CF as compared to their 20 healthy subjects. The lack of controlling for pulmonary function may be considered a fault of this study as respiratory factors are not thought to influence exercise capacity in mild CF (Dodd, Barry, & Gallagher, 2006). Contributions of IMS to physical activity and/or exercise may become apparent in the presence of advanced disease where IMS is decreased and pulmonary factors are suggested to limit exercise tolerance (Moorcroft, Dodd, Morris, & Webb, 2005).

Variability in IMS was noted in our sample of adults with CF suggesting not all individuals with CF were subject to declining IMS. As can be seen in Table 5.1, heterogeneity is noted in the ranges for both MIP and \%MIP for all groups. This finding is consistent with literature on IMS in healthy subjects as well as adults with CF. However, the prevalence of decreased IMS as compared to healthy controls was greater in moderate and severe CF within our cohort though some select individuals maintained above normal levels. In contrast, individuals with mild CF appear to maintain normal or above normal strength. MIP was below the lower bound of the 95\% confidence interval of our healthy group in 11(55\%) of the subjects with moderate CF and 13(72\%) of the subjects with severe CF. \%MIP was below these levels in 16(80\%) of the subjects with
moderate CF and 16(89%) of the subjects with severe CF. In contrast, only 5 (25%) subjects with mild CF were below these levels for MIP and 2(10%) subjects were below these levels for %MIP. These findings suggest that decreased IMS may not be an issue in individuals with mild CF but may develop in the presence of advancing lung disease. Interventions such as IMT may be indicated in select individuals with moderate to severe CF who present with decreased IMS. The presence of mild lung disease in CF may exclude individuals in whom IMT is truly warranted.

Table 5.1

*Ranges and 95% confidence intervals for IMS by group and combined CF subjects*

<table>
<thead>
<tr>
<th>Group</th>
<th>MIP Range</th>
<th>MIP 95% CI</th>
<th>%MIP Range</th>
<th>%MIP 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>81 – 150</td>
<td>105.18 – 124.42</td>
<td>80 – 162</td>
<td>102.33 – 123.07</td>
</tr>
<tr>
<td>Mild CF</td>
<td>82 – 175</td>
<td>111.71 – 132.39</td>
<td>89 – 167</td>
<td>118.25 – 137.05</td>
</tr>
<tr>
<td>Moderate CF</td>
<td>48 – 130</td>
<td>89.11 – 110.69</td>
<td>63 – 151</td>
<td>82.70 – 104.00</td>
</tr>
<tr>
<td>Severe CF</td>
<td>55 – 166</td>
<td>80.24 – 107.87</td>
<td>63 – 134</td>
<td>74.95 – 92.71</td>
</tr>
<tr>
<td>Combined CF</td>
<td>48 - 175</td>
<td>98.68 – 112.77</td>
<td>63 – 167</td>
<td>94.96 – 109.49</td>
</tr>
</tbody>
</table>

*Note.* IMS=inspiratory muscle strength; MIP=maximal inspiratory pressure in cmH₂O; %MIP=maximal inspiratory pressure in percent of predicted; CF=cystic fibrosis.
As with many of the phenotypic presentations in adults with CF, IMS is no different and heterogeneity is obvious. The above normal values associated with mild CF and those in select individuals with advancing lung disease may not represent IMS in the majority of adults with CF in the presence of moderate and severe pulmonary disease. Full variability in IMS cannot be explained by our data though the effect of disease severity appears to play a role. In addition, our hypothesis that combination of disease severity, hyperinflation, and nutritional status will significantly contribute to the variance seem in IMS was confirmed. However, the pattern of wasting represented in the upper extremity muscle mass did not contribute to our model. This lack of contribution may be explained by the preservation of UEMM in our cohort as no value fell below 70% of predicted which is associated with decreased IMS in CF (Ionescu et al., 1998). Nonetheless, our best predictive models only accounted for 43% and 52% of variance seen in MIP and %MIP respectively. Future research is needed to improve the proposed models and should consider the potential protective role of physical activity. Still, adults with CF presenting with malnutrition, hyperinflation, moderate to severe pulmonary disease and complaints of dyspnea may present with decreased IMS warranting assessment of the inspiratory muscles and/or interventions aimed at enhancing inspiration.

The clinical presentation of IMS in adults with CF as a whole does not appear to be in direct agreement to COPD where inspiratory muscle weakness is more prevalent (Larson, Covey, & Corbridge, 2002). This knowledge is relevant as specific interventions such as IMT aimed at enhancing inspiratory muscle
function in COPD appears most efficacious in the presence of IMW and when designed to enhance IMS (Gosselink et al., 2011). Though pathologic similarities exist between COPD and CF, they follow divergent pathways in clinical management. With the advent of newborn screening, the diagnosis of CF is known soon after birth. The immediate emphasis on intervention including early identification and management of pulmonary exacerbations, nutritional maintenance, and aggressive airway clearance may delay or prevent a decline in IMS. Future research should investigate other interventions such as aerobic exercise and breathing exercises that may prove to be protective to the inspiratory muscles. Current theories pertaining to IMT in COPD may not directly transfer to individuals with CF in the same manner and should be applied with caution. Discretion is required when recommending additional interventions to individuals with CF given the already elevated burden associated with day to day care. Additional time may be better spent on other well established treatments such as traditional exercise which may also have a training effect on the IM among numerous other health benefits.

Nonetheless, our data has identified alterations in IMS relative to disease severity that warrant further investigation and consideration. The significance of our findings should be evaluated to determine the clinical implications of the observed alterations in IMS on exercise tolerance and other aspects of CF disease including dyspnea. In addition, research is warranted to determine the effect of CF on other aspects of inspiratory muscle function such as IME and inspiratory work capacity to help establish proper training protocols if indicated.
The results of this study support the need to control for disease severity, nutritional status, and hyperinflation when considering inspiratory muscle function in adults with CF for proper interpretation. Properly sequenced research may ultimately identify adults with CF with inspiratory muscle impairments, determine appropriate interventions and training protocols, and identify expected health-related outcomes to treatment.
References


**Appendix A:** Outcome summary of inspiratory muscle training in COPD

<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>Age of subjects</th>
<th>Severity of disease</th>
<th>Baseline MIP**</th>
<th>Mode</th>
<th>Intensity</th>
<th>Duration and frequency</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harver, 1989 n=10</td>
<td>61.1</td>
<td>%FEV$_1$42.7</td>
<td>47cmH$_2$O - FRC 83.5cmH$_2$O- RV</td>
<td>F-IMT</td>
<td>“at all 6 levels, range 5-35 cmH$_2$O”</td>
<td>15min, BID 7 days/week 8 weeks</td>
<td>↑ IMS ↓ Dyspnea</td>
</tr>
<tr>
<td>Sanches Riera, 2001 n=10</td>
<td>67</td>
<td>%FEV$_1$38.3</td>
<td>44.5 cmH$_2$O - FRC</td>
<td>F-IMT</td>
<td>60-70%SMIP</td>
<td>15min, BID 6 days/week 24 weeks</td>
<td>↑ IMS ↑ IME ↓ Dyspnea ↔ Max exercise ↑ Exercise (shuttle test)</td>
</tr>
<tr>
<td>Guyatt, 1992 n=43</td>
<td>66.5</td>
<td>FEV$_1$(L)=1.04</td>
<td>52.5 cmH$_2$O - FRC</td>
<td>F-IMT</td>
<td>Poorly described</td>
<td>10min, 5x/day 7 days/week 24 months</td>
<td>↔IMS ↔IME ↔Exercise (6MWT or max)</td>
</tr>
<tr>
<td>Falk, 1985 n=12</td>
<td>61</td>
<td>%FEV$_1$27.1</td>
<td>Not measured</td>
<td>F-IMT</td>
<td>Poorly described</td>
<td>10min, TID 7 days/week 12 weeks</td>
<td>↓Dyspnea ↑ Exercise(time at 2/3 max)</td>
</tr>
</tbody>
</table>
### Appendix A continued: Outcome summary of inspiratory muscle training in COPD

<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>Age of subjects</th>
<th>Severity of disease</th>
<th>Baseline MIP**</th>
<th>Mode</th>
<th>Intensity</th>
<th>Duration and frequency</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Larson, 1988 n=10</td>
<td>60</td>
<td>%FEV$_1$=36</td>
<td>61cmH$_2$O-RV</td>
<td>T-IMT</td>
<td>30%MIP</td>
<td>30min, QD 7 days/wk 8 weeks</td>
<td>↑IMS</td>
</tr>
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<td></td>
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<td></td>
<td>↑IME</td>
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<td></td>
<td></td>
<td>↑Exercise (12MWT)</td>
</tr>
<tr>
<td>Kim, 1993 n=41</td>
<td>66</td>
<td>%FEV$_1$=40</td>
<td>60cmH$_2$O-RV</td>
<td>T-IMT</td>
<td>30%MIP</td>
<td>30min, QD 7 days/wk 24 weeks</td>
<td>↑IMS</td>
</tr>
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<td>↓Dyspnea</td>
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<td></td>
<td></td>
<td>↑Exercise (12MWT)</td>
</tr>
<tr>
<td>Lisboa, 1994 n=10</td>
<td>67</td>
<td>%FEV$_1$=36</td>
<td>65cmH$_2$O-FRC</td>
<td>T-IMT</td>
<td>40%MIP</td>
<td>15 min, BID 6 days/wk 5 weeks</td>
<td>↑IMS</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>↑Exercise (6MWT)</td>
</tr>
<tr>
<td>Lisboa, 1997 n=10</td>
<td>61</td>
<td>%FEV$_1$=40</td>
<td>61cmH$_2$O-FRC</td>
<td>T-IMT</td>
<td>40%MIP</td>
<td>30 min, QD 6 days/wk 10 weeks</td>
<td>↑IMS</td>
</tr>
<tr>
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<td>↓Dyspnea</td>
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<td></td>
<td>↑Exercise (6MWT)</td>
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<td>↔ Max exercise</td>
</tr>
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</table>
### Appendix A continued: Outcome summary of inspiratory muscle training in COPD

<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>Age of subjects</th>
<th>Severity of disease</th>
<th>Baseline MIP**</th>
<th>Mode</th>
<th>Intensity</th>
<th>Duration and frequency</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seron, 2005 n=15</td>
<td>55.1</td>
<td>%FEV$_1$=55.4</td>
<td>56.5cmH$_2$O-FRC</td>
<td>T-IMT</td>
<td>40%MIP</td>
<td>30min, QD 7 days/wk 8 weeks</td>
<td>↑IMS ↓Dyspnea ↔Exercise(6MWT)</td>
</tr>
<tr>
<td>Ramirez, 2002 n=7</td>
<td>65</td>
<td>%FEV$_1$=33</td>
<td>77 cmH$_2$O</td>
<td>T-IMT</td>
<td>40-50%MIP</td>
<td>30 min, QD 5 days/wk 5 weeks</td>
<td>↑IMS ↑IME ↔Exercise (6MWT or Max) +Myogenic changes</td>
</tr>
<tr>
<td>Garcia, 2008 n=8</td>
<td>63.7</td>
<td>%FEV$_1$=43.9</td>
<td>83.3cmH$_2$O</td>
<td>T-IMT</td>
<td>40-50%MIP</td>
<td>30min, QD 5 days/wk 5 weeks</td>
<td>↑IMS ↓Dyspnea ↔Exercise (shuttle walk)</td>
</tr>
<tr>
<td>Beckerman, 2005 n=17</td>
<td>67.7</td>
<td>%FEV$_1$=42</td>
<td>71cmH$_2$O-RV</td>
<td>T-IMT</td>
<td>60%MIP</td>
<td>15 min, BID 6 days/wk 48 weeks</td>
<td>↑IMS ↓Dyspnea ↑Exercise (6MWT)</td>
</tr>
<tr>
<td>Covey, 2001 n=12</td>
<td>65</td>
<td>%FEV$_1$=35</td>
<td>64cmH$_2$O-RV</td>
<td>T-IMT</td>
<td>60%MIP</td>
<td>30 min, QD 5 days/wk 16 weeks</td>
<td>↑IMS ↑IME ↓Dyspnea</td>
</tr>
</tbody>
</table>
### Appendix A continued: Outcome summary of inspiratory muscle training in COPD

<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>Age of subjects</th>
<th>Severity of disease</th>
<th>Baseline MIP**</th>
<th>Mode</th>
<th>Intensity</th>
<th>Duration and frequency</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiner, 2004 n=19</td>
<td>66.3</td>
<td>%FEV$_1$=45</td>
<td>66cmH$_2$O-RV</td>
<td>T-IMT</td>
<td>60%MIP</td>
<td>30 min, QD 6 days/week 12 weeks</td>
<td>↑IMS ↑IME ↓Dyspnea ↑Exercise (6MWT)</td>
</tr>
<tr>
<td>Hill, 2006 n=16</td>
<td>69.4</td>
<td>%FEV$_1$=37.4</td>
<td>62.7 cmH$_2$O-FRC</td>
<td>T-IMT</td>
<td>“Max tolerable”</td>
<td>Seven 2 min intervals 3x/week 8 weeks</td>
<td>↑IMS ↑IME ↑Exercise (6MWT) ↔Max or sub-max exercise</td>
</tr>
<tr>
<td>Flynn, 1989 n=8</td>
<td>70</td>
<td>FEV$_1$(L)=0.9</td>
<td>59cmH$_2$O-RV 40cmH$_2$O-FRC</td>
<td>T-IMT</td>
<td>Max sustainable for 15 min</td>
<td>15 min, BID 7 days/week 6 weeks</td>
<td>↑IMS ↔IME ↔ Exercise (12MWT or Max)</td>
</tr>
<tr>
<td>Villafranca, 1998 n=10</td>
<td>61</td>
<td>FEV$_1$/FVC=0.40</td>
<td>70 cmH$_2$O-FRC</td>
<td>T-IMT</td>
<td>30%MIP</td>
<td>15min, BID 6 days/week 10 weeks</td>
<td>↑IMS Increase IM power as well Increase inspiratory flow No assessment of exercise etc.</td>
</tr>
</tbody>
</table>
## Appendix A continued: Outcome summary of inspiratory muscle training in COPD

<table>
<thead>
<tr>
<th>Author and sample size</th>
<th>Age of subjects</th>
<th>Severity of disease</th>
<th>Baseline MIP**</th>
<th>Mode</th>
<th>Intensity</th>
<th>Duration and frequency</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koppers, 2006 n=18</td>
<td>54.4</td>
<td>%FEV₁=50</td>
<td>69 cmH₂O –RV</td>
<td>VIH</td>
<td>60%MVV</td>
<td>15min, BID</td>
<td>↔ IMS</td>
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<td></td>
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<td>7 days/week 5 weeks</td>
<td>↑ IMS</td>
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<td>↑ Submax</td>
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<td>↑ 6MWT</td>
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<td></td>
<td></td>
<td></td>
<td>↑ Max exercise</td>
</tr>
<tr>
<td>Scherer, 2000 n=15</td>
<td>66.9</td>
<td>%FEV₁=50.2</td>
<td>66.5cmH₂O-RV</td>
<td>VIH</td>
<td>60%MVV</td>
<td>15min, BID</td>
<td>↔ IMS</td>
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<td>5 days/wk 8 weeks</td>
<td>↑ IMS</td>
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<td>↑ Peak exercise</td>
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<td>exercise</td>
</tr>
</tbody>
</table>

SMIP: sustainable maximal inspiratory pressure; IME: inspiratory muscle endurance; IMS: inspiratory muscle strength; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; MVV: maximal voluntary ventilation; %: value expressed as percent predicted; RV: measurement taken from residual volume; FRC: measurement taken from functional residual capacity; F-IMT: flow-based inspiratory muscle training; VIH: voluntary isocapnic hyperpnea; QD: once per day; BID: twice per day; TID: three times per day; 6MWT: 6 minute walk test.

*values reported are for the training group only
*subject characteristics are listed as mean values.
** potential criteria to identify inspiratory muscle weakness include MIP ≤ 80 cmH₂O, MIP ≤ 60 cmH₂O, or MIP ≤ 80% of predicted.
Appendix B: Data collection form for adult subjects with CF

Subject #: __________________

Demographics/Baseline Data

Age (yrs): ________  Sex:  M  F  Ethnicity: ________________________

Genotype: ________________________________________________________

ΔF508/ ΔF508  ΔF508/ Other  Other/Other

CFRD:  Y  N  Panc. Ins.:  Y  N  Smoker:  Y  N

Sputum colonization: ______________________________________________

Current Corticosteroid Usage:________________________________________

___________________________________________________________________

Other Medications: _________________________________________________

___________________________________________________________________

Current Airway Clearance:  Mode: _________________________________

Frequency/Duration: ____________________

MMRC Dyspnea Scale:

0  1  2  3  4
Subject #: ________________

**Nutritional Data**

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<thead>
<tr>
<th>Height (cm): ______</th>
<th>Weight (kg): ______</th>
<th>IBW (kg): ______</th>
<th>%IBW ______</th>
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<table>
<thead>
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<th><strong>BMI</strong></th>
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<td>M2</td>
<td>M3</td>
<td>Average</td>
</tr>
<tr>
<td>Triceps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Db&lt;sub&gt;sf&lt;/sub&gt;:</td>
<td>%BF&lt;sub&gt;sf&lt;/sub&gt;:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM&lt;sub&gt;sf&lt;/sub&gt;:</td>
<td>LBM&lt;sub&gt;sf&lt;/sub&gt;:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBM&lt;sub&gt;sf&lt;/sub&gt;/IBW&lt;sub&gt;sf&lt;/sub&gt;:</td>
<td></td>
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</table>

<table>
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<tr>
<th><strong>Body Impedance Analysis</strong></th>
<th></th>
<th></th>
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<tr>
<td>Conductance:</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Midarm Muscle Circumference** | | | |
| MAC(cm):                       | Triceps (cm) | MAMC(cm):      |
### Pulmonary Data

#### Maximal Inspiratory Pressure at Residual Volume

<table>
<thead>
<tr>
<th>Practice</th>
<th>Measured</th>
<th>Recorded</th>
<th>%Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>P2</td>
<td>M1</td>
<td>M2</td>
</tr>
<tr>
<td>MIP – RV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP-FRC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Technical Notes:**

#### Current Spirometry – from medical record

<table>
<thead>
<tr>
<th>Test Date:</th>
<th>Measured</th>
<th>Pred</th>
<th>%Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁(L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC(L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF₂₅-₇₅%(L/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIF max (L/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Lung Volumes – from medical record

<table>
<thead>
<tr>
<th>Test Date:</th>
<th>Measured</th>
<th>Pred</th>
<th>%Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

☐ %FEV₁ confirmed within 10% predicted of current spirometry.

| RV (L) |          |      |       |
| TLC (L) |          |      |       |
| RV/TLC (%) |          |      |       |
Appendix C: Data collection form for healthy control subjects

Subject #:___________________

Demographics/Baseline Data

1. Age: __________

2. Ethnicity: __________

3. Sex: M F

4. Pregnant: Y N

5. Diabetes: Y N

6. Current Smoker: Y N

7. Other pulmonary condition (i.e. asthma): Y N

8. Current respiratory infection: Y N

9. Allergy or flu-like symptoms: Y N

10. Other cardiac condition (i.e. heart failure): Y N

11. Neuromuscular condition: Y N

12. Skeletal condition: Y N

13. Other condition that may affect MIP: Y N

    If yes to item # 9, explain:

14. MMRC Dyspnea Scale:

    0 1 2 3 4
Subject #:__________________

**Nutritional Data**

<table>
<thead>
<tr>
<th>Height (cm): ______</th>
<th>Weight (kg): ______</th>
<th>IBW (kg): ______</th>
<th>%IBW: ______</th>
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<table>
<thead>
<tr>
<th>BMI</th>
<th>%BF&lt;sub&gt;BMI&lt;/sub&gt;:</th>
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<tbody>
<tr>
<td>FM&lt;sub&gt;BMI&lt;/sub&gt;:</td>
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<tr>
<td>LBM&lt;sub&gt;BMI&lt;/sub&gt; / IBW&lt;sub&gt;BMI&lt;/sub&gt;:</td>
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<table>
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<tr>
<th>Skinfolds</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>Average</th>
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<tr>
<td>Triceps</td>
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<td></td>
<td></td>
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<tr>
<td>Biceps</td>
<td>FM&lt;sub&gt;sf&lt;/sub&gt;:</td>
<td>LBM&lt;sub&gt;sf&lt;/sub&gt;:</td>
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<td></td>
</tr>
<tr>
<td>LBM&lt;sub&gt;sf&lt;/sub&gt; / IBW&lt;sub&gt;sf&lt;/sub&gt;:</td>
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<table>
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<th>Body Impedance Analysis</th>
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<td>LBM&lt;sub&gt;BIA&lt;/sub&gt;:</td>
</tr>
<tr>
<td>LBM&lt;sub&gt;BIA&lt;/sub&gt; / IBW&lt;sub&gt;BIA&lt;/sub&gt;:</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Midarm Muscle Circumference</th>
<th>MAC(cm):</th>
<th>Triceps (cm)</th>
<th>MAMC(cm):</th>
</tr>
</thead>
</table>
Pulmonary Data

<table>
<thead>
<tr>
<th>Maximal Inspiratory Pressure at Residual Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice</td>
</tr>
<tr>
<td>P1</td>
</tr>
<tr>
<td>MIP – RV</td>
</tr>
<tr>
<td>MIP- FRC</td>
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<tr>
<td>Technical Notes:</td>
</tr>
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</table>

<table>
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<tr>
<th>Current Spirometry</th>
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<tbody>
<tr>
<td>Date:</td>
</tr>
<tr>
<td>Measured</td>
</tr>
<tr>
<td>FEV₁(L)</td>
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</tbody>
</table>
Appendix D: IRB approval notice from Rutgers, The State University of New Jersey

** This is an auto-generated email. Please do not reply to this email message. The originating e-mail account is not monitored. If you have questions, please contact your local IRB office or log into eIRB.Rutgers.edu. **

DHHS Federal Wide Assurance Identifier: FWA00003913
IRB Chair Person: Robert Fechtner
IRB Director: Carlota Rodriguez
Effective Date: 8/23/2013

eIRB Notice of Approval

STUDY PROFILE

Study ID: Pro2012002110
Title: Alterations in Inspiratory Muscle Strength in Adults with Stable Cystic Fibrosis
Principal Investigator: Robert Dekkerlegand, Denis Hadjiliadis, Albert Heuer
Co-Investigator(s): Mary Jane Mysinski, James Parrott, Anne Swisher
Sponsor: Department Funded
Risk Determination: Minimal Risk
Review Type: Expedited
Subjects: 320

Approval Cycle: Twelve Months
Expedited Category: 4

CURRENT SUBMISSION STATUS

Submission Type: Continuation (CR00000700)
Report type: Continuing Report
Submission Status: Approved
Study Status: Active - Open to Enrollment,
Enrollment has begun

Review Type: Expedited
Approval Date: 8/19/2013
Expiration Date: 8/18/2014

Pregnancy Code: No Pregnant Women as Subjects
Pediatric Code: No Children As Subjects
Prisoner Code: No Prisoners As Subjects

Pro2012002110
Consent
Cystic Fibrosis_Protocol
UMDNJ Version 3.0 – dated 1/8/13

E - Pro2012002110 IM in Adult in CF_Consent Process Checklist.docx
D - Pro2012002110 IM in Adult in CF_Consent
C - Pro2012002110 IM in Adult in CF_Consent for Healthy.docx
B - Pro2012002110 IM in Adult in CF_Reruitment Flyer for Healthy Subjects.docx
A - Pro2012002110 IM in Adult in CF_Reruitment Flyer for CF Subjects.docx
J - Pro2012002110 IM in Adult in CF_MicroRPM_Brochure.pdf
I - Pro2012002110 IM in Adult in CF_Tania BC418 BIA_manual.pdf
H - Pro2012002110 IM in Adult in CF_Data Collection Form_Healthy Controls.docx
G - Pro2012002110 IM in Adult in CF_Data Collection Form_CF Subjects.docx
F - Pro2012002110 IM in Adult in CF_Scripted questions to verify consent.docx

* Study Performance Sites:
RBHS School of Health Related Professions, Stanley S. Bergen Building, Newark, NJ, 07107
RBHS School of Health Related Professions, University Educatonal Center, Suite 2105, 40 East Laurel Road, Stratford, NJ 08084
University of Pennsylvania Adult Cystic Fibrosis Clinic Perelman Center for Advanced Medicine, 3400 Civic Center Blvd, 1st Floor West, Philadelphia, PA 19104

ALL APPROVED INVESTIGATOR(S) MUST COMPLY WITH THE FOLLOWING:
1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.
2. Continuing Review: Approval is valid until the protocol expiration date shown above. To avoid lapses in approval, submit a continuation application at least eight weeks before the study expiration date.
3. Expiration of IRB Approval: If IRB approval expires, effective the date of expiration and until the continuing review approval is issued. All research activities must stop unless the IRB finds that it is in the best interest of individual subjects to continue. (This determination shall be based on a separate written request from the PI to the IRB.) No new subjects may be enrolled and no samples/charts/surveys may be collected, reviewed, and/or analyzed.
4. Amendments/Modifications/Revisions: If you wish to change any aspect of this study, including but not limited to, study procedures, consent form(s), investigators, advertisements, the protocol document, investigator drug brochure, or accrual goals, you are required to obtain IRB review and approval prior to implementation of these
changes unless necessary to eliminate apparent immediate hazards to subjects.

5. Unanticipated Problems: Unanticipated problems involving risk to subjects or others must be reported to the IRB Office (45 CFR 46, 21 CFR 312, 812) as required, in the appropriate time as specified in the attachment online at: http://rbhs.rutgers.edu/hsweb

6. Protocol Deviations and Violations: Deviations from/violations of the approved study protocol must be reported to the IRB Office (45 CFR 46, 21 CFR 312, 812) as required, in the appropriate time as specified in the attachment online at: http://rbhs.rutgers.edu/hsweb

7. Consent/Assent: The IRB has reviewed and approved the consent and/or assent process, waiver and/or alteration described in this protocol as required by 45 CFR 46 and 21 CFR 50, 56, (if FDA regulated research). Only the versions of the documents included in the approved process may be used to document informed consent and/or assent of study subjects; each subject must receive a copy of the approved form(s) and a copy of each signed form must be filed in a secure place in the subject’s medical/patient/research record.

8. Completion of Study: Notify the IRB when your study has been stopped for any reason. Neither study closure by the sponsor or the investigator removes the obligation for submission of timely continuing review application or final report.

9. The Investigator(s) did not participate in the review, discussion, or vote of this protocol.

CONFIDENTIALITY NOTICE: This email communication may contain private, confidential, or legally privileged information intended for the sole use of the designated and/or duly authorized recipients(s). If you are not the intended recipient or have received this email in error, please notify the sender immediately by email and permanently delete all copies of this email including all attachments without reading them. If you are the intended recipient, secure the contents in a manner that conforms to all applicable state and/or federal requirements related to privacy and confidentiality of such information.
Appendix E: IRB approval notice from the University of Pennsylvania

University of Pennsylvania
Office of Regulatory Affairs
3624 Market St., Suite 301 S
Philadelphia, PA 19104-6096
Ph: 215-573-2540/ Fax: 215-573-9438
INSTITUTIONAL REVIEW BOARD
(Federalwide Assurance # 00004028) 11-Sep-2013

Denis Hadjiiliadis
denis.hadjiiliadis@uphs.upenn.edu
Attn: Robert Dekkerlegand
Robert.Dekkerlegand@uphs.upenn.edu

PRINCIPAL INVESTIGATOR : Denis Hadjiiliadis
TITLE : Alterations in Inspiratory Muscle Strength in Adults with Stable Cystic Fibrosis
SPONSORING AGENCY : No Sponsor Number
PROTOCOL #: 81648
REVIEW BOARD : IRB #7

Dear Dr. Denis Hadjiiliadis:

The above referenced protocol was reviewed and re-approved by Dr. Emma Meagher, Executive Chair of the IRB (or her authorized designee), using the expedited procedure set forth in 45 CFR 46.110(b) (4.5), on 10-Sep-2013.

Approval by the IRB does not necessarily constitute authorization to initiate the conduct of a human subject research study. You are responsible for obtaining any relevant committee approvals.

This approval is for the period 10-Sep-2013 to 09-Sep-2014.

The following documents were included in this review:

- HS-ERA Continuing Review Submission (confirmation: bdccebbdd), submitted 9.4.13
- Revised Project Protocol, v4.0, dated 8.6.13
- Revised Recruitment Flyer (Healthy Adult Volunteers), v3.0, dated 8.6.13
- Revised Recruitment Flyer (Adults With Cystic Fibrosis), v3.0, dated 8.6.13
- Revised Informed Consent Form for Adults With Cystic Fibrosis, v4.0, dated 8.6.13
- Revised Informed Consent Form for Healthy Adults, v3.0, dated 8.6.13
- Email Correspondence, RE: Regarding your continuing review submission for Dr. Hadjiiliadis’ study, protocol #1648, dated 9.5.13 - 9.10.13

When enrolling subjects at a site covered by the University of Pennsylvania’s IRB, a copy of the IRB approved informed consent form with the IRB approved from/to stamp must be used unless a waiver of written documentation of consent has been granted.

If you have any questions about the information in this letter, please contact the IRB administrative staff. Contact information is available at our website: http://www.upenn.edu/regulatoryaffairs.

Thank you for your cooperation.

Sincerely,

David Heagerty
IRB Administrator
### Appendix F: List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD</td>
<td>Six-minute walk distance</td>
</tr>
<tr>
<td>ADD</td>
<td>Average daily dose of corticosteroids</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>%BF</td>
<td>Percent of body fat</td>
</tr>
<tr>
<td>%BF&lt;sub&gt;BIA&lt;/sub&gt;</td>
<td>Percent of body fat estimated from body impedance analysis</td>
</tr>
<tr>
<td>%BF&lt;sub&gt;BMI&lt;/sub&gt;</td>
<td>Percent of body fat estimated from body mass index</td>
</tr>
<tr>
<td>%BF&lt;sub&gt;SF&lt;/sub&gt;</td>
<td>Percent of body fat estimated from skin folds</td>
</tr>
<tr>
<td>BIA</td>
<td>Body impedance analysis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>CFF</td>
<td>Cystic Fibrosis Foundation</td>
</tr>
<tr>
<td>CFRD</td>
<td>Cystic fibrosis related diabetes</td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane regulator</td>
</tr>
<tr>
<td>Cl&lt;sup&gt;-&lt;/sup&gt;</td>
<td>Chloride</td>
</tr>
<tr>
<td>cmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>Centimeters of water pressure</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Db&lt;sub&gt;SF&lt;/sub&gt;</td>
<td>Body density estimated from skin fold measurements</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>F-IMT</td>
<td>Flow-based inspiratory muscle training</td>
</tr>
<tr>
<td>FEC</td>
<td>Functional exercise capacity</td>
</tr>
<tr>
<td>%FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in one-second as percent of predicted</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in one-second in liters</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>Ratio of FEV&lt;sub&gt;1&lt;/sub&gt; to FVC</td>
</tr>
</tbody>
</table>
%FIF\textsubscript{50}\%: Mid-inspiratory flow rate as percent of predicted
FIF\textsubscript{50}\%: Mid-inspiratory flow rate in liters per minute
FVC: Forced vital capacity
FM: Fat mass
FRC: Functional residual capacity
HUP: Hospital of the University of Pennsylvania
IBW: Ideal body weight
%IBW: Percent of ideal body weight
IC: Inspiratory capacity in liters
%IC: Inspiratory capacity as percent of predicted
IRB: Institutional review board
Ht: Height
IM: Inspiratory muscles
IME: Inspiratory muscle endurance
IMS: Inspiratory muscle strength
IMT: Inspiratory muscle training
IMW: Inspiratory muscle weakness
kg: Kilogram
LBM: Lean body mass
LBM/IBW: Ratio of lean body mass to ideal body weight
LBMI: Lean body mass index
LBM\textsubscript{BIA}: Lean body mass estimated from body impedance analysis
LBM\textsubscript{BMI}: Lean body mass estimated from body mass index
LBM\textsubscript{SF}: Lean body mass estimated from skin fold measurements
LE: Lower Extremities
logIL-8: Logarithmic representation of interleukin 8 inflammatory marker
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>Mid-arm circumference</td>
</tr>
<tr>
<td>MAMC</td>
<td>Mid arm muscle circumference</td>
</tr>
<tr>
<td>%MIP</td>
<td>Maximal inspiratory pressure at the mouth represented as percent of predicted</td>
</tr>
<tr>
<td>MIP</td>
<td>Maximal inspiratory pressure measured at the mouth and represented as cmH₂O</td>
</tr>
<tr>
<td>MIP-FRC</td>
<td>Maximal inspiratory muscle strength measured from functional residual capacity</td>
</tr>
<tr>
<td>MIP-RV</td>
<td>Maximal inspiratory pressure measured from residual volume</td>
</tr>
<tr>
<td>MVV</td>
<td>Maximal voluntary ventilation</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Pabd</td>
<td>Pressure within the abdominal cavity during inspiration</td>
</tr>
<tr>
<td>Pbr</td>
<td>Mean inspiratory pressure per breath</td>
</tr>
<tr>
<td>Pbr/MIP</td>
<td>Ratio of the mean pressure per breath to the maximal inspiratory pressure</td>
</tr>
<tr>
<td>Pes</td>
<td>Pressure within the esophagus during inspiration</td>
</tr>
<tr>
<td>Ppl</td>
<td>Pressure within the pleural cavity during inspiration</td>
</tr>
<tr>
<td>PFS</td>
<td>Pulmonary function score</td>
</tr>
<tr>
<td>PFT</td>
<td>Pulmonary function test</td>
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<tr>
<td>QOL</td>
<td>Quality of Life</td>
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<tr>
<td>RPM</td>
<td>Respiratory pressure meter</td>
</tr>
<tr>
<td>%RV</td>
<td>Residual volume as percent of predicted</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume in liters</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>Ratio of residual volume to total lung capacity</td>
</tr>
<tr>
<td>SF</td>
<td>Skin folds</td>
</tr>
<tr>
<td>SMIP</td>
<td>Sustained maximal inspiratory pressure</td>
</tr>
<tr>
<td>T-IMT</td>
<td>Threshold-based inspiratory muscle training</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$T_{di}$</td>
<td>Trans-diaphragmatic pressure</td>
</tr>
<tr>
<td>$T_{di\max}$</td>
<td>Maximal trans-diaphragmatic pressure</td>
</tr>
<tr>
<td>$T_{di}/T_{di\max}$</td>
<td>Ratio of trans-diaphragmatic pressure to Maximal trans-diaphragmatic pressure</td>
</tr>
<tr>
<td>$T_i$</td>
<td>Time spent during inspiration</td>
</tr>
<tr>
<td>$T_i/T_{tot}$</td>
<td>The fraction of time spent during inhalation relative to the total breathing time</td>
</tr>
<tr>
<td>$T_{lim}$</td>
<td>Time that the inspiratory muscles can sustain an imposed workload</td>
</tr>
<tr>
<td>$T_{tot}$</td>
<td>Total time spent breathing during both inhalation and exhalation</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>TTI</td>
<td>Tension-time index of the inspiratory muscles</td>
</tr>
<tr>
<td>TTI$_{di}$</td>
<td>Tension-time index of the diaphragm</td>
</tr>
<tr>
<td>TTI$_{mouth}$</td>
<td>Tension-time index measured at the mouth</td>
</tr>
<tr>
<td>UEMM</td>
<td>Upper extremity muscle mass</td>
</tr>
<tr>
<td>VIH</td>
<td>Voluntary induced hyperpnea</td>
</tr>
<tr>
<td>$VO_2$-breath</td>
<td>Rate of oxygen consumption associated with breathing</td>
</tr>
<tr>
<td>$VO_2$-legs</td>
<td>Lower extremity rate of oxygen consumption</td>
</tr>
<tr>
<td>$VO_2$-tot</td>
<td>Whole body rate of oxygen consumption</td>
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<tr>
<td>WOB</td>
<td>Work of breathing</td>
</tr>
<tr>
<td>Wt</td>
<td>Weight</td>
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