

## ABSTRACT

Title of Document: RESPIRATORY RESISTANCE AND THE EFFECT OF EXERCISE IN FEMALE TEEN ATHLETES WITH PARADOXICAL VOCAL FOLD MOTION

Sally J. K. Gallena, Doctor of Philosophy, 2012

Directed By: Assistant Professor, Wei Tian  
Department of Hearing and Speech Sciences

Paradoxical vocal fold motion (PVFM) disorder, often referred to as vocal cord dysfunction (VCD), interferes with breathing because the vocal folds adduct during inspiration making it difficult to inhale. When PVFM is triggered by exercise, it can impact competitive play. Athletes with PVFM are often misdiagnosed as having exercise-induced asthma, but do not respond to asthma treatment. Directly visualizing the larynx (laryngoscopy) when symptoms are present is the current “gold standard” for diagnosing PVFM. However, laryngoscopy is invasive and expensive. Standardized noninvasive alternative methodologies are needed for clinically feasible assessment of PVFM by the speech-language pathologist. Respiratory resistance ( $R_r$ ), measured with the Airflow Perturbation Device (APD), may be useful for assessing PVFM because vocal fold adduction can increase  $R_r$  markedly.

This research comprises three studies with an overarching goal to validate an objective, non-invasive measure of  $R_r$  for identifying abnormal constriction of the

laryngeal airway associated with PVFM disorder. Study 1 compared APD-measured  $R_r$  to glottal area (GA) assessed through laryngoscopy in a healthy subject feigning PVFM-type breathing. Study 2 assessed intra- and intersession test-retest reliability of APD-determined  $R_r$  for a control group of 12 healthy female teenage athletes during resting tidal breathing (RTB) and post-exercise breathing (PEB). Study 3 examined differences between the same 12 healthy athletes with 12 athletes diagnosed with PVFM matched for sex, age, and activity level, for  $R_r$ , exercise duration, and dyspnea ratings for RTB and PEB.

The results revealed: 1) a strong negative correlation ( $r = -0.824$ ) between  $R_r$  and GA suggesting that the APD can indirectly measure changes in the laryngeal airway; 2) strong test-retest reliability for APD-measured inspiratory ( $R_i$ ) and expiratory ( $R_e$ ) resistance during RTB (ICC > .95), and PEB (ICC > .85); and 3) in control athletes,  $R_i$  and  $R_e$  decreased during PEB as compared with RTB, whereas in athletes with PVFM, both  $R_i$  and  $R_e$  increased during PEB with statistical significance reached for  $R_i$  ( $p < .001$ ). During exercise, athletes with PVFM reported severe dyspnea and exercised for shorter durations. This research demonstrates that a diagnostic protocol for PVFM should include measures of  $R_r$ , exercise duration, and perceived dyspnea.

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EXERCISE IN FEMALE TEEN ATHLETES WITH PARADOXICAL VOCAL  
FOLD MOTION

By

Sally J. K. Gallena

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Advisory Committee:

Assistant Professor Wei Tian, Chair

Dr. Nancy P. Solomon

Professor Nan Bernstein Ratner

Professor Emeritus Arthur T. Johnson, Dean's Representative

Associate Professor Rochelle S. Newman

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As I have worked on this dissertation I have been consumed by words. Every writing session is a search to find the best words. My emotions surrounding this power of words have ranged from utter frustration to indescribable joy-- a remarkable realization for a speech-language pathologist. This dissertation is finished and once again I'm searching for the best words to tell special people how thankful I am for them and how they have helped me...and the words don't seem adequate. Sincere gratitude, after all, is a feeling that can't truly be put into words.

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## Chapter 1: Introduction

The human vocal tract needs to perform several very different functions; to create sound for communication, it needs to be partially closed, yet, to breathe deeply, it must be fully open. To meet these contradictory needs, the vocal folds have to be capable of a great range of mobility and to accurately coordinate with the whole body system. They can approximate within the vocal tract, allowing for phonation, but also fully dilate to allow as much air as possible to pass through. Occasionally, the vocal folds may not move appropriately. Paradoxical vocal fold motion disorder (PVFM), previously referred to as vocal cord dysfunction (VCD), is a condition where the vocal folds adduct (close) during inspiration when they should abduct (open), decreasing airway patency. Although sporadic case reports have described symptoms suggestive of PVFM in the early literature, the disorder has not gained broad recognition until the past 15 years. Various triggers can lead to difficulty breathing (known as dyspnea) lasting for minutes to hours and prompting patients to seek medical care (Andrianopoulos, Gallivan, & Gallivan, 2000; Hicks, Brugman, & Katial, 2008). Patients are commonly misdiagnosed as having asthma, yet they do not respond to aggressive asthma therapy. They can experience dyspnea for months to years without receiving an accurate diagnosis, causing physical, psychosocial, and financial consequences. Typically patients' descriptions of their symptoms and results from pulmonary function tests suggest a diagnosis of PVFM. However, the most accurate method for diagnosis is direct visualization of the larynx when symptoms are present. This becomes a conundrum because of unpredictability of PVFM symptoms and the limitations of laryngeal imaging, including availability and patient comfort.

After PVFM is diagnosed, speech-language pathologists (SLPs) can provide behavioral therapy to teach patients to modify and control their breathing. First, however, there is a need for equipment and standardized methodologies so that diagnostic accuracy of PVFM can be improved. Thus, the overall purpose of this dissertation is to expand the current knowledge of PVFM, targeting diagnosis for teenage female athletes who experience exercise-induced PVFM.

## **Overview**

Since first described by Jackson and Jackson in 1942 as “spasmodic closure of the glottis” (Gallivan, Hoffman, & Gallivan, 1996), there have been more than 70 names used to describe PVFM in the literature (Hicks et al., 2008). The earliest diagnostic label was Munchausen’s Stridor (Patterson, Schatz, & Horton, 1974), described as intermittent vocal fold adduction during breathing attributed to a psychogenic etiology. Because the symptoms were often confused with those of asthma, it has also been called factitious asthma (Downing, Braman, Fox, & Carrao, 1982). More commonly, the term vocal cord dysfunction (VCD) has been used, especially by medical practitioners in pulmonology (Christopher & Morris, 2010; Christopher et al., 1983; Newman, Mason, & Schmaling, 1995). The term “paradoxical” was first used by Rogers and Stell (1978) to describe the involuntary vocal fold adduction observed when vocal fold abduction should occur during the inspiratory phase of breathing (Powell et al., 2000). The label Paradoxical Vocal Fold Motion is preferred by SLPs and otolaryngologists (Divi et al., 2008; Hicks et al., 2008; Mathers-Schmidt, 2001).

Prevalence data for patients with PVFM are typically reported for two groups of individuals – those presenting to hospitals and clinics with dyspnea originally thought to be caused by asthma, and athletes experiencing breathing problems during exercise. Hicks et al. (2008) reported that 2.8% of 1,025 patients seen at a pulmonary center had PFVM. Rundell and Slee (2008) diagnosed PVFM in 2.4% of a group of 370 elite athletes.

PVFM has been reported across the life span in individuals as young as 2 months and up to 82 years of age (Hicks et al., 2008). In Hicks et al.'s review, 65% of the patients with PVFM were adults and 35% were children under the age of 19 (Hicks et al., 2008). Young female athletes seem to be a group with particularly high prevalence of PVFM. Among pediatric athletes, the average age at the time of diagnosis is 14 years (Powell et al., 2000; Sandage & Zelanzny, 2004).

With regard to gender, more females are reported to have PVFM, with reported female-to-male ratios ranging from 2:1 (Hicks et al., 2008), 4:1 (Powell et al., 2000), to 9:1 (Patel, Jorgensen, Kuhn, & Merati, 2004). Following a chart review of 95 adult patients with PVFM and combined PFVM and asthma, Newman et al. (1995) described the typical PVFM patient as young, white (40 of 42), and female (41 of 42) (p. 1383). A chart review of 265 consecutive patients diagnosed with PVFM (127 active duty and 138 non-active-duty retirees and dependents) seen at Walter Reed Army Medical Center, revealed in the non-active-duty patients a female-to-male ratio commensurate with what is commonly reported in the literature. For the active-duty patients in an overwhelmingly male profession – the female-to-male ratio was 1.2:1 (Gurevich-Uvena et al., 2010).

There are many symptoms associated with PVFM, the most common being dyspnea (Andrianopoulos, Gallivan, & Gallivan, 2000; Hicks, Brugman, & Katial, 2008). Because the area of constriction is at the larynx, stridor (a phonation-like sound that is produced by the approximated vocal folds) is generated, most often during inspiration (Andrianopoulos et al., 2000; Brugman & Simons, 1998). According to Koufman and Block (2008), the pattern and high-pitched sound of stridor differentiate upper airway obstruction (i.e., PVFM) from lower airway obstruction (i.e., asthma). Individuals with PVFM consistently identify the neck, throat and upper chest as areas of perceived constriction. It is reported as a choking sensation (Andrianopoulos et al., 2000; McFadden & Zawadski, 1996) and although it causes abrupt and transitory airway compromise, hypoxemia (oxygen deprivation) is rarely reported (Hicks et al., 2008). Increased upper torso muscle tension is manifested with suprasternal (upper chest) and neck muscle retraction (Brugman & Simons, 1998). Frequently, cough co-occurs, explained by some as part of the PVFM syndrome (Altman, Mirza, Ruiz, & Sataloff, 2002; Morrison, Rammage, & Emami, 1999; Vertigan, Theodoros, Gibson, & Winkworth, 2006, 2007). Others have suggested that cough is used as an attempt to briefly abduct (open) the vocal folds during breathing difficulty (Brugman & Simons, 1998). Vocal hoarseness (also known as dysphonia) frequently accompanies PVFM. Some have explained dysphonia as a result of vocal fold tension secondary to PVFM, creating muscle tension dysphonia (Morrison et al., 1999). Others explain dysphonia as a consequence of laryngeal constriction and vocal fold swelling occurring during an episode of PVFM (Andrianopoulos et al., 2000). Symptoms characteristic of hyperventilation –



rapid breathing, dizziness, numbness of the extremities- are frequently associated with PVFM (Hicks et al., 2008). In addition to physical symptoms, feelings of anxiety, fear and panic are commonly reported by those with PVFM because of the frightening nature and sudden onset of the symptoms (Brugman & Simons, 1998).

Because of the variability in symptoms and triggers of PVFM, some have proposed that it is a syndrome (Heinle, Linton, & Chidekel, 2003; Morrison et al., 1999). Maschka and colleagues (1997), described PVFM as “a group of disorders which share the common finding of mobile vocal cords that adduct inappropriately during inspiration” (p.1429). This statement appropriately summarizes the variability and consistency of PVFM.

### **Anatomical and Physiological Aspects of PVFM**

**Anatomy and physiology of the larynx.** Prior to understanding PVFM, a review of the anatomy and physiology of the larynx is necessary. The larynx is vital to airway protection, ventilation, and phonation, however, the latter (phonation) will not be discussed since the focus of this research is primarily on ventilation. During breathing, the larynx (generally), including the vocal folds, (specifically) has unique sensory and motor functions that allow unimpeded respiration, as well as airway protection. The upper airway can be functionally divided into thirds – the supraglottis (the laryngeal structures superior to the vocal folds), the glottis (the opening between the vocal folds) and the subglottis (the laryngeal area immediately below the vocal folds). The tenth cranial nerve (Vagus nerve) branches off in the neck to form the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN). The SLN has afferent fibers providing sensation to the supraglottis and vocal folds and efferent

fibers innervating the paired cricothyroid muscles. The RLN branch supplies sensation for the subglottis and movement for the remaining intrinsic laryngeal muscles, including the thyroarytenoid muscles that form the muscular portion of the vocal folds. Efferent fibers of the Vagus nerve start in the somatosensory gyrus and partially decussate before synapsing with the motor neurons in the nucleus ambiguus in the medulla. The nucleus ambiguus receives bilateral motor input from the cortex as well as sensory input from the nucleus solitarius. This network allows the vocal folds to function simultaneously (Balkissoon, 2007; Colton, Casper, & Leonard, 2006).

While most of the intrinsic laryngeal muscles function as vocal fold adductors, the paired posterior cricoarytenoid (PCA) muscles widen the glottis by abducting the vocal folds. The paired cricothyroid muscles function to change vocal pitch, but may have an abductory influence based upon the findings of Woodson (1990), who investigated respiratory activity of the cricothyroid muscle in six healthy participants. During a deep breath respiratory maneuver, cricothyroid activity was observed during both inspiration and expiration, suggesting that it may work with the posterior cricoarytenoid in certain tasks to maximally open the glottis. A serial relationship exists between the activation of the PCA muscles and the diaphragm for inspiration, such that contraction of the PCA opens and stiffens the airway before diaphragmatic contraction creates negative inspiratory pressure allowing airflow without obstruction (Eichenwald, Howell, Kosch, Ungarelli, & Stark 1992). Eichenwald et al. (1992) studied this relationship in full term and preterm infants and observed that for most breaths, the PCA led the diaphragm in activation. Yet there were instances in all of

the babies when diaphragm activation led PCA muscle activation. In their study, this occurred unpredictably for a mean of 33% (and range of 6 – 61%) of the analyzed breaths. They questioned if this finding was unique to infants. Ruddy et al. (2004) employed a stringent program of inspiratory muscle training to successfully treat an athlete with PVFM. The researchers hypothesized that based upon the diaphragm and PCA relationship, increased movement of the diaphragm during inspiration might cause increased contraction of the PCA muscle, allowing those with PVFM to volitionally widen the glottis.

In addition to its function during respiration, the larynx also provides protection to the lower airway through reflexive actions that close the glottis (Hicks et al., 2008) and/or elicit cough. Laryngeal sensory receptors respond to temperature changes (cold), chemical irritants (including water and aerosols), pressure, and motion (Hicks et al., 2008). Chemoreceptors in the laryngeal mucosa (located in the interarytenoid space) trigger glottal closure in response to fluid in the upper airway (Thach, 1997). The glottal closure reflex is a three-tier action beginning with constriction of the aryepiglottic folds, whereby the arytenoid cartilages fold over the posterior glottis as the epiglottis inverts to protect the anterior airway. The next two protective tiers are adduction of the ventricular (false) folds and adduction of the true vocal folds. This serves to protect the lower airway from irritants resulting from refluxed materials and cough (Koufman & Block, 2008). In some instances, PVFM may occur to close and protect the airway from irritants (Morrison, Rammage & Emami, 1999).

**Ventilation.** Breathing (involving gas exchange for oxygenation of the blood) is under the control of the autonomic nervous system although it can be overridden by

the cortex. While sleeping one has no awareness of **their** breathing, yet when awake, one can choose to take control of their breathing for short durations. Breathing is accomplished through active and passive muscle contraction and relaxation and is divided into two phases – inspiration and expiration – with different vocal fold positions occurring during each phase. The main respiratory muscle of inspiration is the large, dome-shaped diaphragm that sits below the lungs and separates the thorax from the abdomen.

During inspiration for rest (also referred to as tidal or eupneic) breathing, widening of the glottis is usually accomplished through contraction of the paired PCA muscles milliseconds before diaphragmatic activation occurs (Eichenwald et al., 1992). This allows for unimpeded airflow through the laryngeal airway to the lungs created by a negative thoracic pressure change caused by thoracic and abdominal expansion (Aronson, 1990; Hixon & Hoit, 2005). The glottis typically achieves its maximum width at mid-inspiration (Beaty, Wilson, & Smith, 1999) and although this occurs primarily through activation of the PCA muscle, partial muscle activation of the adductor muscles has been observed during electromyographic studies (Maschka et al., 1997; Woodson, 1990).

Slight medial movement of the vocal folds normally occurs during the expiratory phase for rest breathing. Less than 30% narrowing of the glottis from inspiration to expiration (Balkissoon, 2007) is typical, although there is variability across individuals. This medial movement serves the purpose of slowing the exhaled airflow in order to create a steady respiratory collapse (Cole, Savard, Miljeteig, &

Haight, 1993; Mathers-Schmidt, 2001), that in turn, maintains the alveolar patency of the lungs (Koufman & Block, 2008).

Breathing during physical activity differs from resting tidal breathing (RTB) with regard to change in glottal area. There is a need for maximum vocal fold abduction during exercise to accommodate increased airflow turbulence (Beaty et al., 1999; Silverman, Johnson, Scott, & Koh, 2005b). Beaty et al. (1999) observed laryngeal changes in eight healthy controls during exercise using flexible nasoendoscopy and noted that, as the exercise work load increased, five of the participants experienced increased laryngeal lumen size (the cross-sectional area between the abducted vocal folds at mid-inspiration), while the three remaining athletes experienced no change. They also observed two participants with PVFM, and noted that laryngeal lumen size decreased during exercise coincident with dyspnea and stridor. For the control athletes, other changes in the larynx were observed during exercise. The supraglottic larynx dilated and rotated anteriorly and the epiglottis flattened against the base of the tongue to improve the efficiency of airflow and minimize resistance in the airway. For the two participants symptomatic of PVFM, when the supraglottic larynx dilated and moved forward, the posterior larynx collapsed into the airway and the vocal folds moved medially from their previous fully abducted position, thus decreasing the laryngeal lumen consistent with exercise-induced laryngomalacia (Beaty et al., 1999). Silverman and colleagues (2005b) assessed respiratory resistance ( $R_r$ ), while controlling for flow rate, in 12 healthy adult athletes and observed that the effects of exercise on breathing began to return to

rest levels quickly after exercise ceased (within 55 seconds for  $R_r$  during inspiration and 35 seconds for  $R_r$  during expiration).

### **Classification Models and Hypotheses for PVFM**

Differing triggers and symptom patterns have led to proposals of classification models (or subtypes) of PVFM disorder. Most of these models hypothesize etiologies and underlying laryngeal neurophysiology based upon PVFM-triggering stimuli without strong scientific evidence. When discussing etiologies for PVFM, there are overlapping reports of triggering stimuli that initiate PVFM symptoms. First, a summary of the published classification models and proposed etiologies for PVFM will be presented, followed by a discussion of PVFM triggers.

The earliest models recognized a distinction between organic and nonorganic etiologies for PVFM. Maschka et al. (1997) included brainstem compression, upper motor neuron injury, lower motor neuron injury, movement disorder, and reflux as organic causes for PVFM. Nonorganic causes included psychological conditions and malingering. Altman et al. (2000) proposed a similar model, citing laryngeal dystonia (a neurological movement disorder) and psychogenic (conversion) etiology as causes for PVFM. Mathers-Schmidt (2001) made a further distinction, delineating three categories of PVFM: neurologic, psychogenic, and upper airway sensitivity. Divi et al. (2008) expanded the classification further by including a descriptor of laryngeal physiology (supraglottic collapse with vocal fold hypomobility) in addition to neurologic, psychiatric and laryngeal irritability. Christopher and Morris (2010) used the term “periodic occurrence of laryngeal obstruction” (POLO), as a general term for three different patterns of laryngeal obstruction all triggered by irritants, exertion, or

psychological disorders. According to Christopher and Morris (2010), VCD is complete although intermittent adduction of the vocal folds; PVFM is paradoxical yet symmetrical motion during inspiration; and intermittent arytenoid region prolapse is comparable to laryngomalacia. Koufman and Block's (2008) etiology-based model for PVFM seems most detailed and includes: 1) reflux; 2) asthma and hyper-immune disorders; 3) psychogenic stridor; 4) respiratory-type dystonia and brainstem abnormalities; and the relatively rare 5) drug-induced dystonia. Their model, however, did not recognize exercise-induced PVFM.

The pathophysiology of PVFM is unknown and may differ depending upon symptom presentation and triggering stimuli. Christopher and Morris (2010) recognized this when they posed the rhetorical question: "Is the endoscope used to visualize a limited number of end-organ laryngeal responses without fully understanding the spectrum of causes that are literally hidden from sight?" (p. 44).

One theory proposes that hypersensitivity and hyper-reactivity of the larynx and vocal folds from repeated exposure to a triggering stimulus results in a heightened glottal closure reflex (Newman et al., 1995; Morrison, et al., 1999; Hicks, et al., 2008). Morrison and colleagues (1999) expanded this by developing the "Irritable Larynx Syndrome," suggesting that PVFM is caused by altered central neuronal control of the larynx (neural plasticity). After repeated exposures to triggering stimuli, neural changes to the central brainstem nuclei occur such that the larynx stays in a "spasm ready" state, needing only the stimulus to trigger PVFM.

Cukier-Blaj, Bewley, Aviv and Murry (2008) tested laryngeal sensitivity in 75 patients with PVFM (who also had a high incidence of laryngopharyngeal reflux and

cough) and found them to have lower-than-normal laryngeal reflex thresholds. By delivering a calibrated puff of air to the left and right aryepiglottic folds to stimulate the laryngeal adductor reflex, their patients were found to have reduced laryngeal sensation (hyposensitivity) compared with pre-established norms. The researchers hypothesized that PVFM in patients who have reflux results from a laryngeal sensory deficit manifesting in a compensatory hyper-reactivity of the vocal fold closure reflex in order to protect the upper airway.

It could be argued that neither of the above hypotheses – hyposensitivity or hypersensitivity from repeated exposure – account for instances in which an individual has a single exposure (i.e., a work related chemical exposure) yet continues to experience PVFM when no longer in the presence of that original trigger. Hicks et al. (2008) explained this as a “priming effect,” where the original trigger is absent, yet previously benign irritants become new triggers. Mathers-Schmidt (2001) described a transfer of symptoms, whereby those that occurred in only one setting (i.e., exercise) begin to be seen in other situations (i.e., test taking).

Neurological explanations for PVFM are directly related to the site of lesion within the central or peripheral nervous systems and can often be validated by the pattern of symptoms, the presence of other comorbidities, and the response to treatments. Respiratory-type adductor laryngeal dystonia is one of the most common signs of several different neurological conditions (Blitzer & Brin, 1991; Koufman & Block, 2008). It is characterized by continual (versus episodic) symptoms that worsen when the individual breathes deeply, and are present during wakefulness but absent during sleep (Koufman & Block, 2008). It responds well to botulinum toxin



(Botox<sup>®</sup>) injections in the thyroarytenoid muscles (Blitzer & Brin, 1991; Koufman & Block, 2008). Other conditions such as brainstem abnormalities associated with trauma, disease, and stroke may cause consistent PVFM symptoms that are present during sleep as well as wakefulness (Koufman & Block, 2008; Maschka et al., 1997).

In some individuals, recent respiratory tract infections appear to precede the onset of PVFM ( Hicks et al., 2008; Koufman, 1994; Koufman & Block, 2008; Maschka et al., 1997; Morrison et al., 1999). In 17 of the 39 patients studied by Morrison and colleagues (1999), onset of PVFM followed a recent viral infection. It is well documented that asthma can be triggered by viral infections. Hicks and colleagues (2008) question if the same mechanism can cause upper airway hyper-responsiveness resulting in PVFM. A possible neurological explanation for PVFM following an initial inflammatory event such as a virus was discussed by Ayres and Gabbott (2002). They proposed that laryngeal hyper-responsiveness resulted from “an altered autonomic balance” (p.284). Increased activity within the areas of central brain regions that are linked with the larynx cause a change in the parasympathetic/sympathetic nervous system output that heightens the glottic closure reflex. This autonomic preset, according to the authors, can be temporary or long-lasting.

Structural laryngeal explanations have also been suggested. Posterior laryngeal collapse of the arytenoid and corniculate cartilages causing or synchronous with vocal fold adduction has been a common finding in athletes presenting with PVFM symptoms. Alteration in the anatomy of the larynx during pubescent growth was proposed by Richter, Rutter, deAlarcon, Orvidas, and Thompson (2008) to

account for PVFM in adolescents. Several changes associated with the maturing larynx occur between the ages of 10 – 14 years (and for some beyond the age of 14): the vocal folds lengthen, and the cartilages change in malleability, size, and shape. The narrowest part of the larynx moves from the subglottis in children to the glottis in adults (Sapienza, Ruddy, & Baker, 2004).

Psychological health and emotions are associated with changes in breathing patterns (Boiten, Frijda, & Wientjes, 1994). Psychological explanations for PVFM are mentioned briefly in the Irritable Larynx Syndrome model (Morrison et al., 1999) as well as the Altered Autonomic Balance model (Ayres & Gabbott, 2002). A study describing 42 hospitalized patients with PVFM (Newman et al., 1995) revealed that 22% had prior psychiatric hospitalizations, leading the authors to conclude that individuals with PVFM are a psychiatrically impaired group. It should be noted that their sample was taken from a hospitalized group, which could have impacted the results. Maschka et al. (1997) described two non-organic subtypes of PVFM – factitious/malingering, and somatization/conversion (p. 1430). Others have also regarded PVFM as a conversion disorder where physical manifestation (somatization) of anxiety or stress is motivated by secondary gain, providing benefit from their PVFM symptoms (Christopher et al., 1983). Gavin, Wamboldt, Brugman, Roesler, and Wamboldt (1998) evaluated personality and family characteristics of children with PVFM, and noted increased anxiety in the youth with PVFM, some of whom had separation anxiety which is thought to be a precursor to panic anxiety in adulthood. According to Gavin et al. (1998), the primary physiological abnormality in adults with panic disorder is hyper-responsiveness of the “brainstem respiratory

chemosensor system” (p. 416). The overlapping symptoms of panic anxiety and PVFM lead the authors to question whether the brainstem respiratory area might be implicated in those with psychogenic PVFM. In addition to anxiety and stress, depression was a significant influence in a study comparing personality characteristics in different categories of voice and laryngeal disorders (Dietrich, Verdolini-Abbott, Gartner-Schmidt, & Rosen, 2008).

### **Triggers for PVFM**

**Laryngopharyngeal reflux (LPR).** Perhaps the triggering stimulus reported most often for PVFM in children and adults is reflux (Andrianopoulos et al., 2000; Balkissoon, 2007; Gurevich-Uvena et al., 2010; Koufman & Block, 2008; Morrison et al., 1999; Powell et al., 2000). LPR is characterized by a backflow of gastric contents into the larynx and pharynx (Balkissoon, 2007). Typical symptoms of gastroesophageal reflux disease (GERD), such as heartburn, are not common to LPR; rather, LPR is associated with cough, throat clear, dysphonia, and PVFM. As few as three LPR episodes per week can lead to significant laryngeal damage (Balkissoon, 2007). In canine models, exposure of supraglottic receptors to a pH environment of 2.5 or lower from gastric fluid provoked laryngospasm (reflexive tight glottal closure) through reflexes mediated by the vagus nerve (Koufman & Block, 2008). LPR can cause swelling of the laryngeal structures that can further reduce laryngeal lumen size and increase resistance to airflow (Powell et al., 2000). Laryngeal changes caused by LPR, such as edema, thickened secretions, and space-occupying lesions, are reported in those with PVFM (Colton, Casper, & Leonard, 2006; Cukier-Blaj et al., 2008). Powell et al. (2000) reported that 95% of the 36 children with PVFM showed signs of

laryngeal tissue damage secondary to reflux. A study by Morrison and colleagues (1999) revealed that 85% of 39 patients with PVFM had evidence of LPR. Cukier-Blaj et al. (2008) reported that reflux was diagnosed in 70.4% of 75 patients diagnosed with PVFM. Strenuous exercise is hypothesized to induce reflux because of a reduction in gastric blood flow causing reduced gastric emptying and decreased motility and pressures of the esophagus (Jozkow, Wasko-Czopnik, Medras, & Paradowski, 2006; Richter et al., 2008). Body postures and strain associated with exercise also may cause refluxed material to enter the laryngeal inlet (Jozkow et al., 2006; Richter et al., 2008). The LPR-PVFM connection appears to be protective such that the glottic closure reflex is on high alert in response to LPR.

**Airway irritants.** Allergic rhinitis or sinusitis with post-nasal drip has been implicated in PVFM (Brugman & Simons, 1998; Morrison et al., 1999). Inhaled allergens are hypothesized to cause throat clearing, coughing, and post-nasal drip, which result in hypersensitivity of the airway. Brugman and Simons described this as a “twitchy airway” (p. 66), whereas Morrison et al. (1999) considered inhaled allergens as one of many triggers that over time keeps the airway in a “spasm-ready” state, adducting the vocal folds to protect the lower airway. Many patients with PVFM describe onset of their symptoms from exposure to inhaled airborne substances (Balkissoon, 2007; Morrison et al., 1999). Commonly identified triggers are strong fumes (paint or gasoline) or certain fragrances (perfumes and candles). Gartner-Schmidt, Rosen, Radhakrishnan, and Ferguson (2008) found that when odors were presented transnasally to a blindfolded person with odor-induced PVFM, her report of throat closure was verified through nasoendoscopy. However, when the

irritant challenge was repeated with her nose occluded, requiring her to breathe through her mouth, throat closure occurred for only one irritant, suggesting that different levels of sensitivity may be associated with olfaction. Asthma appears to be a trigger for PVFM when the two co-occur, yet many patients with PVFM are initially misdiagnosed as asthmatic. The same conditions and stimuli, such as allergens, chemicals, strong fragrances (Koufman et al., 2008), high humidity experienced by swimmers (Langdeau et al., 2000), and cold and dry air experienced by athletes of winter sports (Rundell & Spiering, 2003), can trigger both conditions.

**Psychological.** Extreme emotion, anxiety, and stress are associated with the onset of PVFM (Andrianopoulos et al., 2000; Gavin et al., 1998; Husein et al., 2008; Patterson et al., 1974; Ramirez, Leon, & Rivera, 1986; Wamboldt & Wamboldt, 2008). Anxiety has long been recognized as comorbid with respiratory symptoms as observed in panic anxiety (with hyperventilation) and post-traumatic stress disorder (Baker, 2003). Anxiety, competitiveness, intolerance of personal failure, and Type A personality characteristics have been reported frequently in athletes with PVFM (Brugman & Simons, 1998; Newsham, Klaben, Miller, & Saunders, 2002). They have been described as “choking” during sports participation because of their inability to perform to expectations at critical and emotionally laden times (McFadden & Zawadski, 1996, p.942). In a study by Powell et al. (2000), 55% of athletes with PVFM reported experiencing a high level of social stressors, especially associated with sports performance. Brugman and Simons (1998) caution that anxiety and stress may be antecedent to the psychological consequences of PVFM.

**Exercise.** PVFM triggered by exercise (i.e., exercise-induced PVFM or EIPVFM) is frequently reported in athletes and active duty military (Gurevich-Uvena et al., 2010). The typical profile of an athlete with PVFM is a female adolescent or teen, competitive high- performing athlete, who has been misdiagnosed with exercise-induced asthma (Beaty et al., 1999; Christopher et al., 1983; Heinle et al., 2003; Landwehr, Wood, Blager, & Milgrom, 1996; Langdeau et al., 2000; Mathers-Schmidt, 2001; Newsham et al., 2002; Rundell & Spiering, 2003). The athlete may be forced to discontinue her sport because of PVFM symptoms that negatively impact performance (Brugman & Simons, 1998; McFadden & Zawadski, 1996). A rapid onset of symptoms that resolve with cessation of exercise and a lack of responsiveness to asthma medications are further indicators of PVFM (Brugman & Simons; Hicks et al., 2008; Mathers-Schmidt, 2001; Newsham et al., 2002; Sandage & Zelanzny, 2004). Prevalence data lack reliability since so many athletes with PVFM are misdiagnosed as having asthma. However, Brugman and Simons estimated that 3% of the collegiate level athletes with a history of activity induced respiratory distress have PVFM. In a study of 370 athletes, Rundell and Spiering (2003) found that 5% had inspiratory stridor consistent with a diagnosis of PVFM.

### **Differential Diagnosis of PVFM**

PVFM must be differentiated from other organic and non-organic disorders of the larynx and vocal folds that can also impact breathing and produce stridor. When severe, adductor spasmodic dysphonia (ADSD), a focal dystonia causing adductor voice spasms, may be described as eliciting a “choking” feeling and may create respiratory irregularities as the individual attempts to talk against adductor spasms of

the vocal folds (Hicks et al., 2008). When not phonating, however, persons with ASD should experience unimpeded breathing (Balkissoon, 2007; Koufman & Block, 2008). Bilateral adductor vocal fold paralysis, interarytenoid web and cricoarytenoid joint fixation can also cause upper airway constriction (Maschka et al., 1997). These disorders can be diagnosed through laryngoscopy and distinguished from PVFM by the presentation of persistent breathing symptoms as opposed to the transient nature of most subtypes of PVFM. Acute onset of stridor and dyspnea caused by airway obstruction related to trauma, foreign body and infection should be accurately diagnosed through the case history, symptom pattern, and specific diagnostic tests (Balkissoon, 2007; Maschka et al., 1997) .

Exercise-induced hyperventilation resembles PVFM. Common symptoms of hyperventilation include chest tightness, difficulty breathing, rapid breathing, dizziness and numbness of the extremities resulting from a reduction of carbon dioxide in the blood (also known as hypocapnia) from breathing too rapidly or too deeply. A reduced level of end tidal carbon dioxide helps to confirm a diagnosis of hyperventilation (Hammo & Weinberger, 1999).

Most challenging is distinguishing PVFM from asthma, especially in athletes and individuals experiencing both conditions. Asthma involves bronchoconstriction (tightness) of lower airways as opposed to constriction of the upper airway for PVFM (Christopher et al., 1983). When asthma symptoms are provoked only by exercise or exertion, it is referred to as exercise-induced asthma (EIA) or exercise-induced bronchospasm (EIB). There are characteristics of PVFM that clearly distinguish it from asthma.

PVFM and asthma differ with regard to locus of constriction (throat versus chest), breath sounds (stridor rather than wheeze), and affected breathing phase (inspiration versus expiration) (Andrianopoulos et al., 2000; Brugman & Simons, 1998; Mathers-Schmidt, 2001). When the vocal folds of a symptomatic asthma sufferer are visualized through laryngoscopy, increased adduction of the vocal folds may be observed during expiration for stabilization of ventilation (Balkissoon, 2007; Hurbis & Schild, 1991; Mathers-Schmidt, 2001). This is in contrast to adduction that is observed primarily during inspiration for PVFM. A negative response to asthma medicines seems to be the hallmark diagnostic predictor of PVFM for those misdiagnosed as having asthma (Altman et al., 2000; Andrianopoulos et al., 2000; Balkissoon, 2007; Brugman & Simons, 1998; Christopher et al., 1983; Gallivan et al., 1996; Heinle et al., 2003; Hicks et al., 2008; Landwehr et al., 1996; Martin, Blager, Gay & Wood, 1987; Mathers-Schmidt, 2001; McFadden & Zawadski, 1996; Sandage & Zelanzny, 2004).

The patterns of symptoms differ between the two conditions. Asthma requires more time for resolution of symptoms than PVFM (Brugman & Simons, 1998). Pulmonary function tests performed several weeks following a severe asthma attack can still detect abnormalities (Mathers-Schmidt, 2001). Exercise-induced PVFM symptoms often resolve within minutes after ceasing exercise, yet will recur when strenuous exercise resumes (Brugman & Simons, 1998; Hicks et al., 2008; Powell et al., 2000). Onset of asthma is frequently during sleep (nocturnal), whereas there are few accounts of nocturnal onset of PVFM (Koufman & Block, 2008; Mathers-Schmidt, 2001). Reisner and Belson (1997) reported on four patients with nocturnal



PVFM (two of whom may have had comorbid asthma). In contrast, patients experiencing PVFM typically report that sleep re-establishes comfortable breathing.

Asthma is diagnosed by pulmonary function tests (PFTs) such as spirometric measures of forced expiratory volume in one second ( $FEV_1$ ), and the ratio of forced expiratory flow to forced inspiratory flow under different provocation challenges involving medication administration or conditions established to purposefully provoke symptoms (Mathers-Schmidt, 2001; Seiner, Staudenmayer, Koepke, Harvey, & Christopher, 1987). Another diagnostic spirometric measure is the ratio of forced expiratory flow at mid-expiration to forced inspiratory flow at mid-inspiration ( $FEF_{50}/FIF_{50}$ ). For this particular diagnostic test, a quotient less than 1.0 is suggestive of asthma, whereas a quotient greater than 1.0 suggests upper airway involvement (Hicks, et al., 2008). The percentage of oxygen concentration carried by arterial blood measured through pulse oxymetry or arterial blood gas sampling typically reveals decreased oxygenation during an asthma attack. Hicks and colleagues (2008) reviewed case studies where oxygen concentration levels were sampled during PVFM episodes. They concluded that over 75% of the patients had normal blood oxygen levels despite their apparent respiratory distress. None of the 17 female teenage athletes with PVFM investigated by Heinle et al. (2003) experienced decreased oxygen saturation during an exercise challenge.

However, asthma and PVFM may co-exist. Hicks et al. (2008) reviewed the literature and reported that 40% of children and 38% of adults with PVFM had co-existing asthma. Newman and colleagues (1995) reported that 56% of their patients had asthma and PVFM. In a study of elite athletes by Rundell and Spiering (2003),

52% of the athletes with “inspiratory stridor” (i.e., a sign consistent with PVFM) had exercise-induced bronchospasm (i.e., asthma). Confirming both conditions requires obtaining a positive result for a lower airway bronchial provocation challenge in conjunction with a positive finding of PVFM through laryngoscopic examination (Hicks et al., 2008). Patients having both conditions can often distinguish differences in their symptoms and describe each with accuracy (Sandage & Zelanzny, 2004). Complications such as unnecessary drug use, hospitalization, tracheotomy, and intubation arise when patients with PVFM are treated as asthmatic (Heinle et al., 2003; Newman et al., 1995). In a retrospective chart review of 95 patients with confirmed PVFM, Newman et al. (1995) reported that 81% had been treated with high doses of corticosteroids for severe asthma for an average of 4.8 years. The complications of unnecessary corticosteroid use can be severe, resulting in significant adrenal suppression (Heinle et al., 2003). Thus it is of extreme importance to accurately diagnose PVFM, while excluding other disorders with similar symptoms.

### **Diagnosing PVFM Disorder**

PVFM is most accurately diagnosed by integrating information from the case history, symptom description, clinical examinations and provocation challenges. A multidisciplinary team should include the specialties of speech-language pathology, pulmonology, otolaryngology, and psychology. The SLP contributes greatly to the team through his or her experience in behavioral treatment and knowledge of the larynx (Sandage & Zelanzny, 2004). Laryngeal examination is recognized by the American Speech-Language-Hearing Association as within the SLP’s scope of practice. SLPs who perform laryngoscopy, although they cannot diagnose medical

disorders of the vocal folds and larynx, can contribute to the team by describing the physiology of the larynx and vocal folds during asymptomatic and symptomatic periods of PVFM.

**Laryngeal assessment.** Observation of the larynx when the patient is symptomatic of PVFM provides the defining criterion for diagnosis (Brugman & Simons, 1998). Typically, the larynx is examined through flexible transnasal laryngoscopy or rigid transoral stroboscopy. Flexible laryngoscopy allows the clinician to visualize the nasopharynx, pharynx, and larynx providing information about allergic rhinitis, post-nasal drip, as well as signs of reflux (Balkissoon, 2007) . When the scope is passed through the nose, instead of the mouth, the patient can produce various speech tasks that help rule out conditions such as spasmodic dysphonia. Respiratory maneuvers such as panting and sniffing, are potentially easier to perform during endoscopy with a transnasally placed flexible scope, than during endoscopy with an orally placed rigid scope. (Maschka et al., 1997; Powell et al., 2000; Sandage & Zelanzny, 2004). Provocation challenges such as exercise have been conducted with the flexible scope transnasally passed throughout the challenge (Beaty et al., 1999; Gartner-Schmidt et al., 2008; Heinle et al., 2003; Tervonen, et al., 2009), allowing real-time monitoring of vocal fold motion and laryngeal changes.

Rigid transoral laryngoscopy has been used successfully for diagnosing PVFM in approximately 70% of the athletes seen at the Loyola Clinical Center. The primary reason for failure in the remaining patients is a strong gag reflex elicited by the rigid scope that prevents visualizing the larynx. Advantages of its use are the efficiency and speed with which the rigid scope can be placed to document PVFM.

Powell et al. (2000) criticized this method, noting that of eight participants examined with oral (rigid) endoscopy, six were erroneously described as having a posteriorly displaced epiglottis. The investigators cautioned that the use of oral endoscopy may introduce confounding factors.

There are problems associated with laryngoscopy for diagnosing PVFM. It is somewhat invasive and cannot be tolerated by everyone (Rundell & Slee, 2008; Rundell & Spiering, 2003). Furthermore, timing the placement of the scope with the occurrence of symptoms can be challenging. Inconsistency of the symptoms sometimes prevents documentation of PVFM despite clinically convincing signs and symptoms (Christopher & Morris, 2010). Availability, expense, and equipment limitations must be considered as well.

*Laryngeal findings for PVFM symptoms.* During PVFM episodes, various laryngeal findings have been observed. These include: 1) adduction of the anterior aspect or the full length of the vocal folds, and 2) prolapse of the posterior aspect of the larynx, most commonly referred to as laryngomalacia. Each of these will be described.

Adduction of the anterior two thirds of the vocal folds with abduction of the arytenoid cartilages results in the classic “diamond shape” glottic gap for PVFM (Christopher, et al., 1983). In a review of the PVFM literature, however, Hicks and colleagues (2008) reported that only 6% of cases reported this closure pattern. In 15 athletes presenting with significant laryngeal findings during exercise, only four demonstrated the classic PVFM pattern, whereas the other eleven had exercise-induced laryngomalacia with or without the classic vocal fold adduction (Heinle et

al., 2003). Complete adduction of the vocal folds is also frequently reported, with some degree of movement during breathing (Balkissoon, 2007; Brugman & Simon, 1998; Hicks et al., 2008). The adductory motion is present predominantly on inspiration, but it may continue into expiration beyond what is typical during expiration as well. Brugman and Simons (1998), observed this in 50% of patients with PVFM. They cautioned, however, that adductor motion on expiration alone should not be considered PVFM, as this can be an adaptive ventilatory response to lower airway constriction.

Laryngomalacia refers to abnormal laryngeal motion in the posterior (arytenoid) region with prolapse of the glottic structures into the airway during inspiration (Beaty et al., 1999; Christopher & Morris, 2010; Heinle et al., 2003; Richter et al., 2008). This diagnostic term was originally given to newborns during the first year of life if they presented with inspiratory stridor that was attributed to underdeveloped upper airway muscle tone and laryngeal cartilages (Richter et al., 2008). Divi et al. (2008) described laryngomalacia as airway obstruction caused by a weakened laryngeal framework or arytenoid tissue redundancy in conjunction with the Bernoulli effect that, because of the negative pressure within the glottis during inspiration, draws the glottic and supraglottic tissues toward the midline resulting in vocal fold adduction. Brugman and Simons (1998) described a similar phenomenon in which the periglottic structures prolapsed toward the abducted vocal folds at mid-inspiration, which they called a “functional form of laryngomalacia” (p. 68). Beaty et al. (1999) observed exercise-induced laryngomalacia through transnasal flexible laryngoscopy that resolved when exercise ended in two athletes with PVFM, as did

Heinle et al. (2003), in which seven athletes had laryngomalacia and four others had combined PVFM and laryngomalacia. Richter et al. (2008), described “late-onset laryngomalacia” in three teenage female athletes with arytenoid rotation and supraarytenoid prolapse into the glottis. They were asymptomatic when not exercising. They attributed this condition to tissue redundancy, supraglottic edema, and altered laryngeal muscle tone that was further intensified by the Bernoulli effect. Thus, exercise-induced laryngomalacia may be the catalyst for vocal fold adduction or be a separate laryngeal condition causing air hunger and mimicking PVFM.

There is evidence supporting subtle laryngeal abnormalities even when the person with PVFM is not experiencing dyspnea. Powell et al. (2000) retrospectively reviewed laryngoscopic evaluations for 22 asymptomatic patients under the age of 19 diagnosed with PVFM. Twelve had abnormal vocal fold adduction during “quiet respiration” (p. 31). (The authors did not specify in which breathing phase it was observed.) Treole, Trudeau, and Forrest (1999) observed the larynx in 50 patients diagnosed with PFVM when they were asymptomatic. They observed adduction of the vocal folds in all 50 patients during inspiration. The researchers concluded that PVFM is a type of laryngeal dystonia because movement abnormalities were consistently present in the larynx in varying degrees, yet exacerbated under certain conditions. Newman et al. (1995) also reported the presence of inspiratory closure and biphasic closure in 79% of 58 participants who claimed to be asymptomatic at the time of laryngoscopy. These reports present convincing evidence that there is subtle aberrant movement of the vocal folds even when there was no awareness of dyspnea.

**Respiratory assessment.** Respiratory tests are typically the first diagnostic procedures performed when individuals present with the complaint of breathing difficulty. Balkissoon (2007) suggested that spirometry is best used as a screening procedure for PVFM, with actual diagnosis made only following laryngoscopy. The test most often reported as being sensitive to PVFM is a flow-volume study that generates a graph depicting rate of airflow over respiratory volume while the subject performs a maximum inspiration and expiration (Brugman & Simons, 1998). A normal flow-volume graph reveals symmetrical curved loops that slope towards the  $x$  axis for inspiration and expiration, since they are comparable in airflow and volume. For individuals symptomatic of PVFM, the inspiratory and expiratory curves lack symmetry revealing a flattening (or truncation) of the inspiratory loop indicative of reduced airflow into the lungs caused by extra-thoracic obstruction (i.e. narrowing of the glottis) (Andrianopoulos et al., 2000; Balkissoon, 2007; Brugman & Simons, 1998; Heinle et al., 2003; Mathers-Schmidt, 2001; McFadden & Zawadski, 1996; Rundell & Slee, 2008; Sapienza & Hoffman-Ruddy, 2009).

In a study of 95 patients with PVFM, 25% had truncated flow-volume loops during inspiration even when they were asymptomatic at the time of the test (Newman et al., 1995). Koufman and Block (2008) stated that flattening of the inspiratory limb of the flow-volume loop “generally rules in PVFM and rules out asthma or other lower respiratory diseases” (p. 330). Blunting on the expiratory (in addition to inspiratory) curve of the flow-volume loop suggests concurrent asthma or biphasic PVFM (Brugman & Simons, 1998)

There are problems associated with using the aforementioned respiratory test for diagnosing PVFM. Most notable is that it is an indirect method of assessing laryngeal behavior. The timing of the assessment in relation to symptom onset can influence the results particularly if symptoms are present only under non-contrived conditions such as the work place or sports field (Rundell & Spiering, 2003). Interpretation of the qualitative findings that result from flow-volume loops introduces increased subjectivity into the diagnostic process (McFadden & Zawadski, 1996).

**Respiratory Resistance.** Resistance to airflow may be a useful measurement in the assessment of PVFM. Prior research has demonstrated that for most individuals without respiratory problems during resting breathing, inspiratory resistance is lower than expiratory resistance; this parallels greater vocal fold abduction for inspiration than expiration and slight contraction of the lower airways during expiration (Johnson et al., 2007). For PVFM, increased inspiratory resistance is expected because of the laryngeal constriction occurring most dramatically during inspiration. For individuals experiencing biphasic PVFM or PVFM and asthma, increased inspiratory and expiratory resistance might be experienced.

The Airflow Perturbation Device (APD) breathing instrument was developed by Johnson, Berlin and Purnell (1974) and further refined by Lausted and Johnson (1999) to provide accurate, near-real-time measures of inspiratory and expiratory respiratory resistance ( $R_r$ ). Respiratory resistance is defined as the sum of pulmonary (airway and lung tissue) and chest wall resistances (Silverman & Johnson, 2005; Silverman, Johnson, Scott, & Koh, 2005a). Johnson and Sahota (2004) used the



APD to measure resistance in excised sheep lungs at different levels within the airway and lungs to determine if the APD measured total airway resistance, pulmonary resistance (airway and alveolar resistance), or respiratory resistance (pulmonary and chest wall resistance). A single-subject study conducted by Lausted and Johnson (1999) revealed that the perturbations generated by the APD were detected by accelerometers adhered to the chest wall indicating its sensitivity to changes in chest wall motion. A study that was reported in the same publication (Lausted & Johnson, 1999) compared resistance values measured by the APD with those measured through whole-body plethysmography, and revealed that although the values from the APD were much higher than those obtained through plethysmography, the two measures were strongly correlated for all 20 participants.

The APD works in a manner similar to forced oscillation and flow-interrupter techniques (Lausted & Johnson, 1999). It consists of a pneumotachometer which comprises a fine mesh screen with differential pressure ports on either side and a cone on one end for attachment of the disposable mouth piece, and modified to include a rotating segmented wheel on the opposing end. Pressure transducers on either side of the screen determine differential pressure, which is used to determine airflow. The rotating wheel perturbs (or periodically slows) the downstream airflow, and is self-adjusting to be commensurate with changing resistances within the device and the respiratory system (Silverman, Johnson, Scott, & Koh, 2005b). Accurate assessment of airflow and air pressure generated by the participant in addition to the resistance provided by the device allows for the calculation of  $R_r$  (Silverman, et al.2005b). A typical trial requires approximately 100 perturbations (about one minute) before the

means for inspiratory and expiratory resistances are displayed. APD-measured respiratory resistance data were gathered for 900 people ranging in age from 2 to 88 years, revealing these findings: 1)  $R_T$  decreases when comparing the pediatric to the adolescent airway; 2) adult men have lower  $R_T$  than adult women; and 3) inspiratory resistance ( $R_i$ ) is typically less than expiratory resistance ( $R_e$ ) across the life span (Johnson et al., 2007). The first two findings are attributed to differences in airway size, and the last finding relates to decreased vocal fold abduction during expiration (as contrasted with that during inspiration) for purposes of slowing the exhaled airflow, or constricting lower distensible airways during expiration. The current model of the APD is compact, hand-held, and yields resistance values consistent with the measures obtained with the original desktop APD for calibration and human-subject measurement comparisons (Silverman et al., 2005a).

To date, only one published study has been conducted using the APD during exercise (Silverman et al., 2005b). Silverman et al. (2005b) measured respiratory resistance in 12 male and female non-asthmatic athlete volunteers aged 18 to 40 years. Their exercise protocol included a period of stretching, warm-up running to reach their target heart rate, and 6 minutes of running at 80 to 85% of their maximum heart rate.  $R_T$  was periodically measured, and when exercise ceased it was immediately and continuously measured for 6 minutes. The results indicated an “exercise effect” wherein  $R_i$  and  $R_e$  both decreased following exercise cessation. The duration of significant change was 55 seconds for  $R_i$  and 35 seconds for  $R_e$ . The authors attributed this to the body’s need for increased ventilation with decreased breathing effort (Silverman et al., 2005b).

**Provocation challenges.** The value of exposing patients to carefully controlled conditions that provoke onset of the symptoms has long been recognized (Rundell & Slee, 2008). This is especially true for intermittent complaints of dyspnea where methacholine challenges differentiate asthma from PVFM (Christopher & Morris, 2010; Mathers-Schmidt, 2001; McFadden & Zawadski, 1996; Rundell & Slee, 2008). Another essential component of diagnosing PVFM is performing flexible or rigid laryngoscopy during or immediately following the provocation challenge (exercise, irritant exposure, medication provocation) for purposes of observing and documenting changes in laryngeal cartilages and vocal fold motion (Beaty et al., 1999; Christopher & Morris, 2010; Gallivan et al., 1996; Gartner-Schmidt (2008); Guss & Mirza, 2006; Heinle et al., 2003; Rundell & Slee, 2008; Rundell & Spiering, 2003; Seiner et al., 1987; Tervonen et al., 2009).

Exercise challenges are used to assess many aspects of cardiac and pulmonary health as well as physical fitness (Thompson, Gordon, & Pescatello, 2010) across the life span. Procedures and protocols vary depending upon the purpose of the challenge (Paridon et al., 2006). The American Heart Association (AHA) has provided statements for exercise standards when testing and training pediatric and adult patients undergoing exercise challenges with recommendations for equipment, staff, procedures and exercise rigor (Fletcher et al., 2001; Paridon et al., 2006). Likewise, an 8<sup>th</sup> edition text published by the American College of Sports Medicine (Thompson et al., 2010) provides detailed and comprehensive guidelines for exercise challenges. In addition to duration of exercise and criteria for discontinuing exercise, the challenge must consider the mode of exercise (treadmill versus bicycle ergometer)

and type of protocol (multistage incremental, progressive incremental, constant work rate). The first two protocols differ by the duration that the exerciser remains at a given speed or work load prior to the next incremental increase, whereas for the latter, speed and work load remains constant throughout the challenge (Paridon et al. 2006; Thompson et al., 2010).

Most of the patients coming to the Loyola Clinical Centers with symptoms of PVFM have previously undergone an exercise challenge conducted by a pulmonologist to rule out asthma. Many have participated in a second exercise challenge conducted by a cardiologist to rule out cardiac disease. Typically, these assessments have followed standardized protocols. That is not the case for diagnosing exercise-induced PVFM. Previously published studies where exercise is used to trigger PVFM symptoms have lacked consensus in procedure and protocol (Beaty et al., 1999; Heinle et al., 2003; Mathers-Schmidt & Brilla, 2005; Tervonen et al., 2009). Additionally, there have been limited reports of within-patient repeated exercise challenge tests to measure PVFM status over time. Thus, there is a need to develop a standardized exercise challenge test that can induce symptoms of PVFM while meeting AHA's safety guidelines for exercising pediatric patients.

**Perceptual ratings of dyspnea.** Self-reported ratings of perceived dyspnea complement physical measures of exertion, both in everyday activities and during provocation challenges. The Borg Rating of Perceived Exertion Scale ® (Borg, 1998) seems to be used most frequently in cardiopulmonary and physical fitness testing. It was initially designed to rate perceived exertion (the feelings observed during physical activity) using a rating scale from 6 (no exertion) to 20 (maximal

exertion). More recently it was modified to include fewer numbers (0 indicating no dyspnea and 10 indicating the most severe dyspnea), and to assess more specific symptoms such as dyspnea. Prior studies in pulmonary medicine and exercise physiology have shown that the scale, when measuring dyspnea, strongly correlates with changes in workload (Belman, Brooks, Ross, & Mohsenifar, 1991; Mahler, Mefia-Alfaro, Ward, & Baird, 2001). Fletcher et al. (2001) reported consistency in patients' ratings of perceived exertion using the Borg Scale, suggesting that the scale can be used for test-retest purposes. Mahler et al. (2001) found advantages to having patients continuously rate their perceived dyspnea using the Borg scale throughout an exercise challenge, as opposed to providing a rating at specified intervals (i.e., each minute). Although the two methods (continuous and discrete) were strongly correlated, the continuous measurement method was particularly informative when patients could only exercise for a few minutes before needing to stop. Mahler et al. (2001) recognized the problem of "poor raters," or individuals whose ratings did not coincide with changes in work load. Mathers-Schmidt and Brilla (2005) and Hoffman-Ruddy et al. (2004) incorporated the Borg scale into their single subject treatments for PVFM. Whereas Mathers-Schmidt and Brilla (2005) used the Borg scale and a second scale for dyspnea ratings, Hoffman-Ruddy et al. (2004) modified the scale to ratings of 0 – 5. It seems that the modified Borg Dyspnea Scale (with ratings from 0 – 10) could have clinical and research implications in assessing patients with PVFM.

## **Proposed Research Experiments and Rationale**

A summation of the literature on PVFM contributed by researchers from various disciplines reveals emergent understanding of this disorder. Nevertheless, methods and equipment for improving diagnostic accuracy have not been well researched. Misdiagnoses lead to unnecessary medical and pharmacological intervention and resource utilization, as well as delayed treatment, impacting the physical and psychological health of the sufferer. Many clinicians lack access to the instrumentation and personnel needed for laryngoscopic examination. Even those who perform laryngoscopy may avoid repeated examinations to follow patients' progress because of the time and cost involved in performing the procedure. To date, less invasive objective diagnostic tools for assessing the presence and severity of PVFM have been unavailable.

Respiratory resistance ( $R_r$ ), especially when separated for inspiratory and expiratory phases of the breathing cycle, should be helpful in monitoring and quantifying changes within the airway that are caused by changes in the size of the laryngeal lumen. If this is the case, the APD may be a promising tool for differentiating PVFM from other pathologies involving lower airway obstruction such as asthma, and for assessing treatment outcomes. Because of its ease of use, noninvasiveness, and portability, it could be an excellent supplement to indirect laryngoscopy. Prior to adopting the APD in clinical practice, however, it is important to establish the validity and reliability of the APD for detecting changes in glottal area at rest and following exercise for athletes with PVFM (experimental group) and athletes with normal respiratory-related laryngeal function (control group).

Subsequently, the APD can be used to provide outcomes data by which to compare athletes with and without PVFM, and to assess changes in  $R_r$  presumably owing to changes in resistance across the larynx, during exercise.

This dissertation comprises three studies. The first two are aimed at validating the APD for the purpose of assessing airway changes related to PVFM, and are foundational for the third study. The third study investigates the effect of exercise on  $R_r$  in female teen athletes with PVFM and a matched control group of athletes without PVFM. A brief description of each study and its associated research question(s) follow.

The Validity Study, (Study 1) investigates the validity of the APD to document changes in  $R_r$  with concurrent changes in glottal area in order to answer the question: How strongly does  $R_r$ , as measured with the APD, correlate with glottal area?

The Reliability Study (Study 2) focused on test-retest reliability of  $R_r$  in athletes with PVFM and athletes without PVFM. The research questions for this study are: 1) What is the test-retest reliability for APD-determined measures of  $R_r$  during resting tidal breathing (RTB) in female teen athletes with PVFM? 2) What is the test-retest reliability for APD-determined measures of  $R_r$  during RTB in female teen athletes without PVFM? 3) What is the test-retest reliability for APD-determined measures of  $R_r$  during post-exercise breathing (PEB) across three sessions in athletes without PVFM? There are eight dependent variables (DVs) – two of which were provided directly by the APD, whereas the rest were calculated from them. Measures of  $R_r$  include the direct measure of inspiratory resistance ( $R_i$ ), and expiratory

resistance ( $R_e$ ), and the calculated mean of inspiratory and expiratory resistance ( $R$ ), ratio of inspiratory to expiratory resistance ( $R_i/R_e$ ), change in inspiratory resistance ( $\Delta R_i$ ), change in expiratory resistance ( $\Delta R_e$ ), change in mean respiratory resistance ( $\Delta R$ ), and change in the ratio of inspiratory to expiratory resistance ( $\Delta R_i/R_e$ ). Based upon the results from the intraclass correlation coefficient analyses, in Study 2, it should be apparent which of the DVs are reliable. Once identified, only those salient DVs will be investigated in the subsequent studies.

The Exercise Study (Study 3) investigates the effect of exercise on  $R_r$  in female teen athletes with and without PVFM. The research questions are: 1) To what extent do APD-determined measures of  $R_r$  change from RTB to PEB in female teen athletes with PVFM? 2) To what extent do APD-determined measures of  $R_r$  change from RTB to PEB in female teen athletes without PVFM? 3) To what extent do measures of  $R_r$  change after exercise over a 2-minute course of recovery in teen female athletes with PVFM? 4) To what extent do measures of  $R_r$  change after exercise over a 2-minute course of recovery in athletes without PVFM? Study 3 also investigates differences between the experimental and control groups for  $R_r$ , exercise duration, and dyspnea ratings from the modified Borg Dyspnea Scale. This research aimed to answer the following questions: 1) Do APD-determined measures of  $R_r$  during RTB differ between female teen athletes with and without PVFM? 2) Do APD-determined measures of  $R_r$  during PEB differ between female teen athletes with and without PVFM? 3) Do athletes without PVFM outperform athletes with PVFM in terms of running duration in the exercise challenge test? 4) Do severity ratings of dyspnea



reported at the end of an exercise challenge test differ between female teen athletes with PVFM and those without PVFM?

Each study and its associated background, research questions, results, and discussion are presented as a separate chapter in this dissertation. The APD was used in all three studies. The participants, equipment, and procedures used for Studies 2 and 3 are described in Study 2. A general discussion integrating the findings from all three studies concludes the dissertation.

## Chapter 2: Study 1 Validity of APD-Measured Respiratory Resistance for Detecting Glottal Change

This study sought to validate the hypothesis that changes in respiratory resistance ( $R_r$ ) measured with the Airflow Perturbation Device (APD), correspond with concurrent changes in glottal area (GA). When paradoxical vocal fold motion (PVFM) is experienced, the glottis constricts during inspiration because of the medial movement of the vocal folds or the prolapse of the arytenoid region into the laryngeal airway (Beaty et al., 1999; Christopher & Morris, 2010). Reduction in GA results in greater  $R_r$ , which may be further increased by greater airflow turbulence through the glottis (Beaty et al., 1999; Ferris, Mead, & Opie, 1963). Patients experiencing dyspnea caused by PVFM are often misdiagnosed as having exercise-induced asthma (Brugman & Simons, 1998; Christopher et al., 1983; Mathers-Schmidt, 2001; Newman et al., 1995). Unlike PVFM, asthma causes constriction in the bronchi and bronchioles; therefore, it affects the expiratory phase of the breathing cycle more than the inspiratory phase (Brugman & Simons, 1998; Collett, Brancatisano & Engel, 1983; Hurbis & Schild, 1991). Despite both PVFM and asthma being associated with increases in  $R_r$ , their effects on inspiratory and expiratory phases differ, which helps differentiate them in diagnosis.

$R_r$  measured by the APD is the sum of pulmonary (airways and lung tissue) (Johnson & Sahota, 2004) and chest wall resistances (Lausted & Johnson, 1999). It provides separate reports for inspiratory and expiratory resistances ( $R_i$  and  $R_e$ , respectively) based on concurrent recordings of airflow direction. Before using the

APD for research in patients with PVFM, it is essential to examine whether APD-measured  $R_r$  is sensitive enough to detect changes in the laryngeal airway when significant laryngeal constriction occurs. To validate the instrumentation needed for the series of studies to follow, the following question was posed: Does  $R_r$  measured by the APD strongly correlate with GA as measured from a two-dimensional aerial view of the larynx?

It was hypothesized that laryngeal constriction can be detected and quantified by  $R_r$  measured by the APD. To mimic PVFM, the laryngeal airway was volitionally constricted during inspiration. The specific hypothesis was that GA and  $R_r$  are inversely related.

## **Method**

### **Participant**

A healthy 55-year-old female (the investigator) with normal respiratory and laryngeal function participated in this study that took place at Greater Baltimore Medical Center (GBMC). A laryngologist at Loyola University Maryland (LUM) confirmed normal laryngeal structure and function in the participant through rigid laryngoscopy. Respiratory function was validated by an allergy and asthma physician through pulmonary function tests, which included forced vital capacity, forced inspiratory and expiratory volume in one second, and peak inspiratory and expiratory flow. Results from the pulmonary function tests were within normal limits for the participant's age and sex.

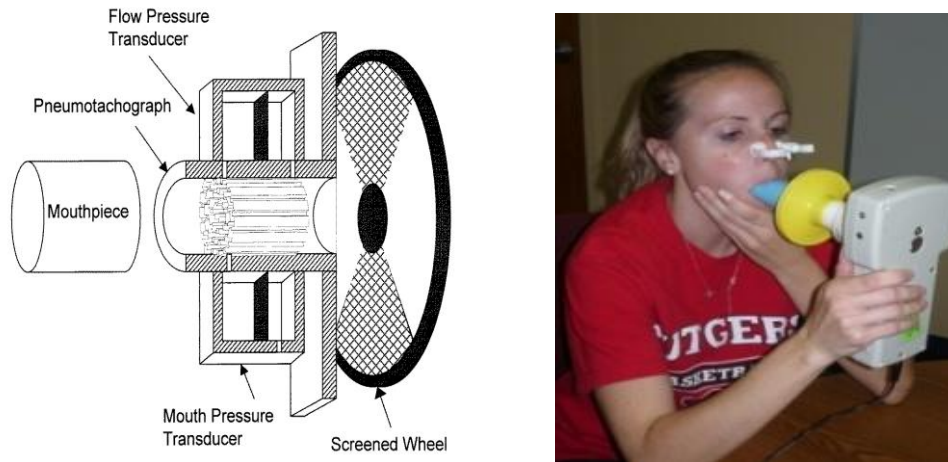
### **Instrumentation and Materials**

**Laryngoscope.** Laryngoscopy was conducted with a digital chip flexible nasolaryngoscope (70K Series, KayPentax, Montvale, NJ), connected to a Video

Stroboscopy System, (Model 9200C, KayPentax, Montvale, NJ), that digitally recorded and stored the laryngeal examination to a workstation for playback and analysis. During the examination, the laryngoscope operator (a speech-language pathologist) who was trained and experienced in performing the procedure, observed the laryngeal changes in real time on a LCD monitor.

**Airflow Perturbation Device.** The APD (Figure 1) is a hand-held unit with a rotating wheel that perturbs air flow and calculates  $R_r$  for each perturbation in near-real time based upon changes in airflow rate and air pressure. It operates on alternating electric current and transfers data to a laptop computer installed with custom software that constantly monitors and records  $R_r$  in  $\text{cmH}_2\text{O}/\text{L}/\text{s}$  during inspiration and expiration for each perturbation. Prior to use, the instrument self-calibrates when it is turned on and is recognized by the computer. During data collection, after the first 5 seconds of breathing,  $R_r$  is recorded in 1-minute trials into a Microsoft Excel spreadsheet. Specifically, for each trial (a continuous 1-minute recording of  $R_r$ ), the following data are recorded in separate columns: sequence of perturbations during inspiration and expiration, respectively; time of each perturbation (displayed to the nearest millisecond); air pressure (in  $\text{cmH}_2\text{O}$ ) for each perturbation; airflow (in  $\text{L}/\text{s}$ ) for each perturbation; and  $R_r$  (pressure/flow, in  $\text{cmH}_2\text{O}/\text{L}/\text{s}$ ).  $R_i$  and  $R_e$  displayed on the computer following each trial are the mean of all perturbations during inspiration ( $R_i$ ) and during expiration ( $R_e$ ), respectively. In Study 1,  $R_r$  for each perturbation was used in the analysis although the means of  $R_i$  and  $R_e$  of all trials are listed in Table 1 of the results, to show the contrasting  $R_r$  values

between rest and feigned PVFM breathing as well as between  $R_i$  and  $R_e$ . In subsequent studies, the means of  $R_i$  and  $R_e$  in the same trial were used.



*Figure 1.* Cut away diagram of the Airflow Perturbation Device (left) (reprinted with permission from Lausted & Johnson, 1999), and an athlete using the APD (right) (reprinted with permission by the athlete).

**Glottal area analysis.** Glottal area analysis was conducted with Kay's Image Processing System (KIPS), software produced by KayPENTAX (Montvale, NJ) that comes standard with the purchase of their High-Speed Video System (Model 9710).

### **Procedure**

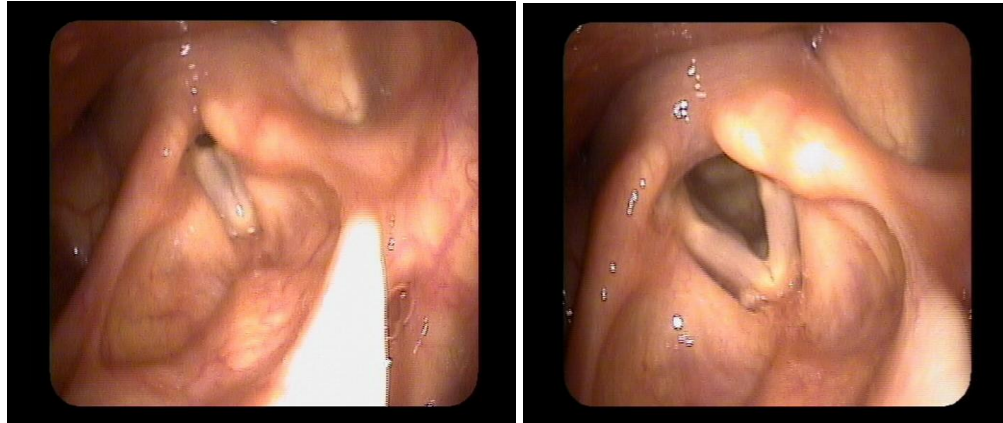
On the day of the study, the participant practiced simulating breathing that is characteristic of PVFM and visually monitored her vocal folds during inspiration and expiration using laryngoscopy at the Loyola Clinical Center in Columbia. The goal was to narrow the glottis during inspiration. Likewise, the participant practiced both comfortable resting breathing and simulated PVFM breathing with the APD in advance of data collection to ensure proper imitation. Data collection for the study began approximately 2 hours later at GBMC.

Prior to laryngoscopy, the participant performed two 1-minute trials of normal resting tidal breathing (RTB) with the APD to gather baseline  $R_r$  data. In preparation for the laryngoscopy procedure, the nasal mucosa was anesthetized with a cotton swab saturated with a 4% Xylocaine solution. Three minutes later, the SLP passed the flexible laryngoscope transnasally and simultaneously viewed the larynx on a monitor. Maintaining a consistent distance between the distal tip of the endoscope and the glottis was attempted. With the scope in position, the participant inserted the APD mouthpiece while maintaining a tight lip seal throughout the experiment (Lopresti et al., 2008). Throughout the experiment, the participant wore a nose clip that prevented transnasal breathing. The participant held the APD in one hand, firmly pressing her cheeks with her other hand. Another SLP viewed both the monitor and computer screen, while operating the computer and giving instructions. The participant then simulated laryngeal function characteristic of PVFM for a 1-minute trial. Following this, the scope, APD mouthpiece, and nose clip were removed. The laryngeal imaging digital file and the  $R_r$  data file were saved and electronically copied for future analysis.

### **Data Analysis**

**Laryngeal imaging.** Sixteen continuous breathing cycles were available for analysis. Narrowing of the glottis as a result of vocal fold adduction signaled inspiration, whereas glottal widening via vocal fold abduction signaled expiration. Identifying the beginning and ending of each cycle was also aided by the vertical descent of the larynx that occurred with each inspiration when feigning PVFM

breathing. Figure 2 illustrates extreme vocal fold approximation during inspiration and vocal fold separation during expiration of feigned PVFM in this study.

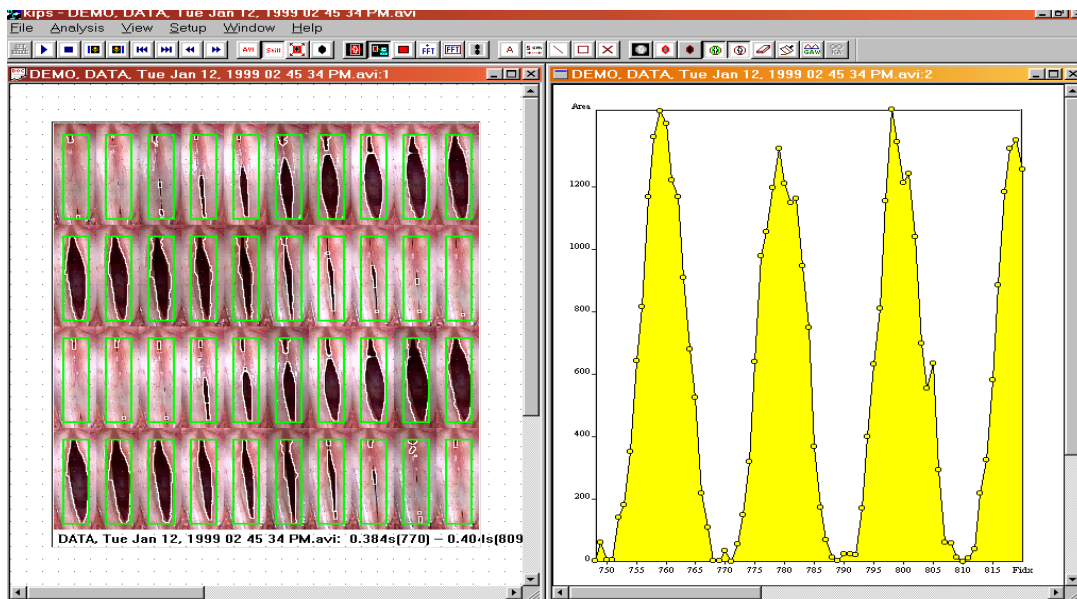


*Figure 2.* Maximal constriction of the laryngeal airway during inspiration (left) and minimal constriction during expiration (right) during feigned PVFM-type breathing.

Video frame numbers at the start of each inspiratory and expiratory phase were noted. From the 16 breathing cycles being video-recorded, seven were chosen for frame-by-frame GA analysis. These included breathing cycles 6-9 and cycles 14-16. The remaining data could not be analyzed for at least one of the following reasons: a) fogging of the endoscopic image, b) medial displacement of the arytenoid cartilages during inspiration that obscured the view of the glottis, and c) indeterminate moments of inspiratory and expiratory onset and offset (Cycle 11).

After converting the video file into AVI (Audio/Video Interleaved) format at a rate of 30 frames per second, KIPS software was used to segment and measure GA. This was accomplished by creating a montage of multiple frames, detecting glottal area, modifying the tracing of the glottis, and measuring the area between the vocal

folds. A GA waveform (extracted from the analysis of a sequence of glottal images) is generated with frame number on the abscissa and GA (measured in square pixels) on the ordinate (Figure 3). Results of the maximum GA for the corresponding video frame are saved in a numerical report. The onset of each inspiratory phase was identified as the first frame when adductory motion of the vocal folds occurred. Inspiration continues until the first frame when abductory motion began which signaled the beginning of expiration. The GA analysis included breathing cycles 6, 7, and 8, beginning on frame 1102 and ending on frame 1443, for a total of 341 frames.



*Figure 3.* Glottal area (GA) montage (left) illustrating vocal fold opening, closing and closed phases, and GA waveform (right) with video frame number on the  $x$  axis and glottal area measured in square pixels on the  $y$  axis from KayPENTAX's Image Processing Software (KIPS manual, p. 9, Montvale, NJ, reprinted with permission).



**Respiratory Resistance.** Using data from the second APD trial that corresponded to the laryngeal recording,  $R_i$  and  $R_e$  for each perturbation were identified for all 16 breathing cycles and graphed in a spreadsheet program (Microsoft Excel, 2007). Each data point identified a particular moment of perturbation and the corresponding resistance value. From this, the beginning and ending points of every inspiration and expiration were identified on the graph. As in the video recording described above, Cycle 11 was noted to be aberrant in duration and resistance values. For this reason, cycles 6, 7, and 8 were chosen for analysis. The first inspiratory perturbation of Cycle 6 began at 18.52 seconds and the last expiratory perturbation for Cycle 8 occurred at 29.77 seconds. By converting the perturbation time segments to frames (time multiplied by 30) and rounding to the nearest whole number, breathing cycles 6-8 encompassed 337 frames. A comparison of number of frames in the analysis revealed 4 more frames in the glottal analysis than in the respiratory resistance analysis, a difference of 0.133 seconds. This discrepancy can be explained by the error introduced by  $R_i$  that has a lower sampling rate (in this sample, a perturbation occurred approximately every 0.118 seconds on average) than GA (measured every 0.033 seconds). Thus, the error was equivalent to approximately one perturbation.

Video images were synchronized to the breathing cycles by first matching Cycle 3. This cycle was synchronized by the examiner's verbal prompt "Okay," a robust inspiration from the video recording, and an obvious increase in  $R_i$  in the APD signal. From that moment, the frames corresponding to the onset and offset of each breathing phase were identified. The video frame for the first inspiration for Cycle 6

(Frame 1102) was matched with the time segment for the first inspiratory perturbation (18.52 seconds) for the same cycle. The graph created from the  $R_r$  during all perturbations is pictured in Figure 4. The three cycles selected for analysis are indicated by arrows. Also labeled are Cycles 3 and 11 as previously described.

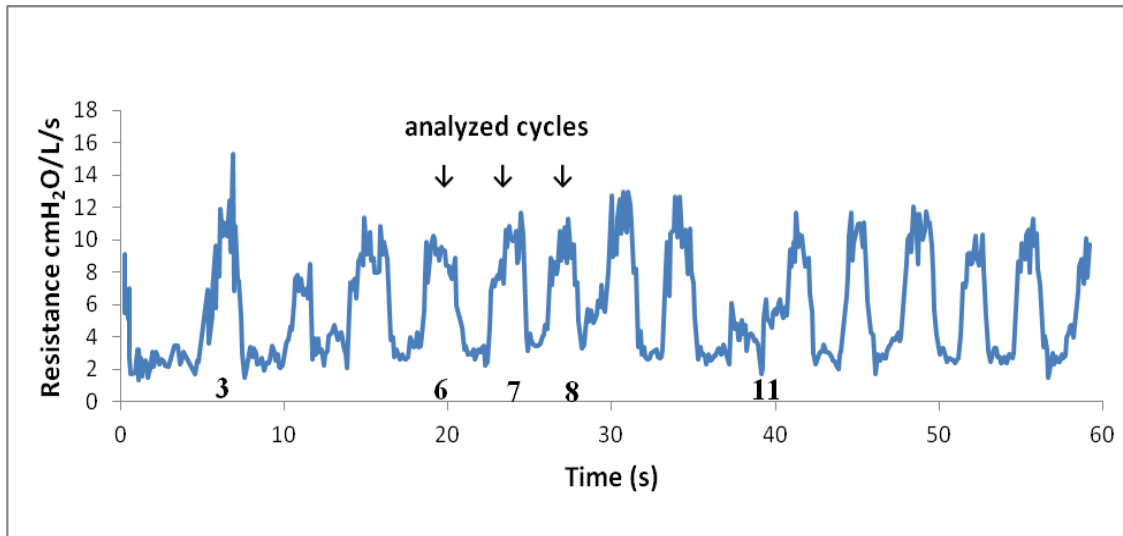


Figure 4. Breathing cycles generated from respiratory resistance ( $R_r$ ) values with three cycles selected for analysis.

$R_r$  and GA were compared directly by aligning the two waveforms for visual inspection. Associations between the two variables were evaluated with cross-correlation analysis performed in SPSS version 18, to compare the variables while accounting for time.

## Results

### Respiratory Resistance

To ensure that the participant's breathing when feigning PVFM differed from her normal breathing, two trials of normal resting tidal breathing (RTB) were performed using the APD. The mean  $R_i$  and  $R_e$  during RTB were compared to results during simulation of PVFM breathing. Table 1 summarizes the results of  $R_i$  and  $R_e$

during RTB and feigned PVFM breathing in all 16 breathing cycles, and in Cycles 6-8 (the cycles selected for correlation analysis between  $R_r$  and GA).

Table 1

*Inspiratory and Expiratory Resistance during Resting Tidal Breathing (RTB) and feigned Paradoxical Vocal Fold Motion (PVFM) Breathing*

Condition	Inspiratory Resistance (cmH <sub>2</sub> O/L/s)	Expiratory Resistance (cmH <sub>2</sub> O/L/s)
RTB	2.37	2.61
PVFM Breathing		
Cycles 1-16	8.01	3.30
Cycle 6	8.58	3.11
Cycle 7	8.80	3.85
Cycle 8	8.67	5.26

During RTB,  $R_i$  values were lower than those for  $R_e$ , with a ratio of 0.91, indicating perhaps, in part, greater vocal fold abduction during inspiration than during expiration. When feigning breathing like that of PVFM, it is clear that the greatest deviation from RTB occurred during inspiration.  $R_i$  in cycles 6-8 were quite comparable to each other yet slightly higher than the average  $R_i$  across all 16 cycles.  $R_e$  in cycles 6 and 7 were comparable to each other and to the overall PVFM average. Cycle 8, on the other hand, differed by 59% when compared to  $R_e$  averaged across all 16 cycles. A drastic difference was seen between  $R_i$  during RTB when compared to PVFM breathing (238% increase). The difference between  $R_i$  and  $R_e$  also increased (143% difference) during PVFM breathing as compared to RTB.

## Glottal Area and Respiratory Resistance

GA and  $R_r$  were synchronized and graphed for breathing cycles 6-8 (Figure 5). The initial scatterplot of  $R_r$  over GA suggests a semi-logarithmic correlation between the two variables; therefore,  $\log_{10}(GA)$  is used in subsequent graphs. When observing  $R_r$ , higher values (i.e., peaks) are associated with inspiration, and lower values (i.e., valleys) with expiration. GA, in contrast, is larger during expiration and smaller during inspiration. In addition to their changes in the opposite directions during breathing, the data in Figure 5 show that  $R_r$  and GA exhibit similar periodicity — both parameters undergo three complete cycles during the 11.25 seconds of recording.

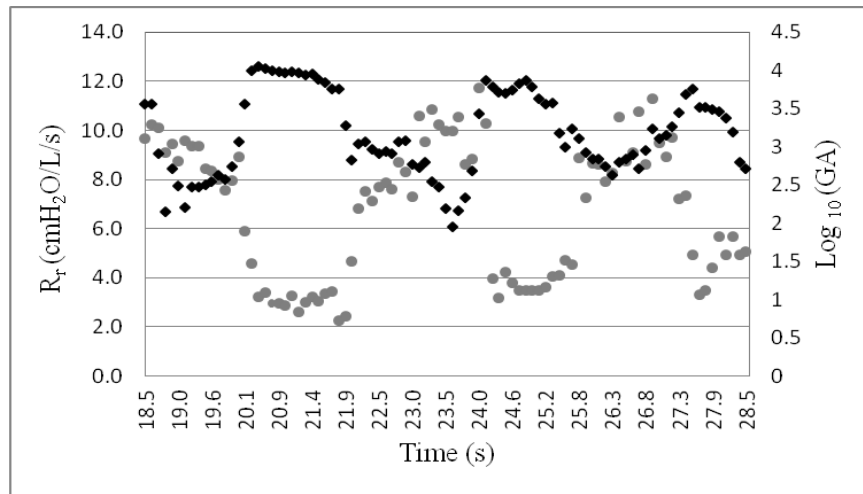
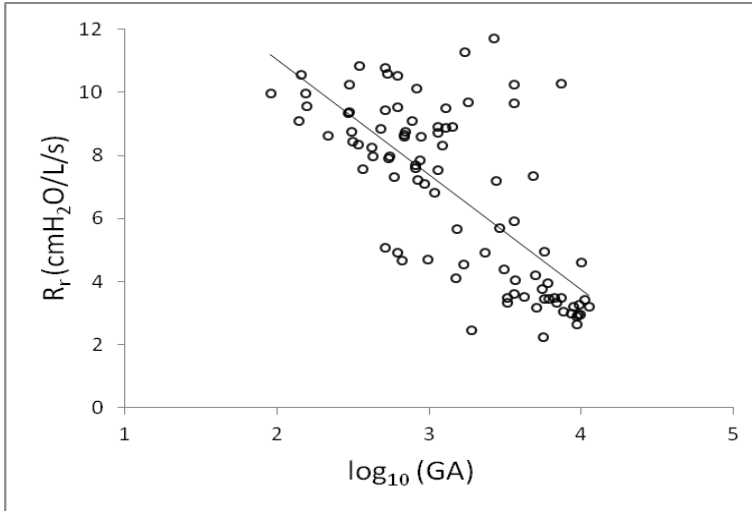


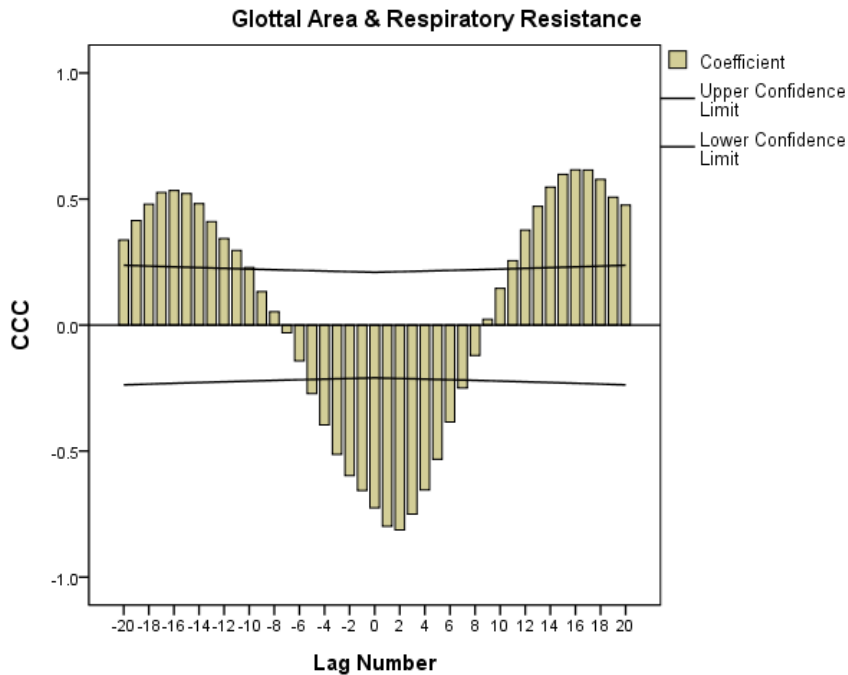
Figure 5.  $R_r$  (grey) and  $\log_{10}(GA)$  (black) waveforms for PVFM breathing cycles 6-8

The scatter plot in Figure 6 shows the relationship between  $R_r$  and log transform of GA obtained from cycles 6-8. The log transform of GA reduced the large spread in GA pixel values ranging from 81 to 11,448 square pixels during three complete breathing cycles.



*Figure 6.* Respiratory resistance ( $R_r$ ) and log-transformed glottal area [ $\log_{10}(GA)$ ] for three complete breathing cycles (6-8) shown in Figure 5. The linear trend line shows that  $R_r$  gradually increases as GA decreases.

To explore the time-locked relationship between  $R_r$  and GA, cross-correlation analysis was conducted to determine a potential time delay between  $R_r$  and GA, as well as the magnitude of the correlation. The cross-correlation coefficient (CCC) was computed between 20 future and 20 previous values of  $R_r$  for each GA data point. This window of preceding and subsequent data points (i.e., lags) can accommodate delays between the two signals of more than one breathing cycle since each complete cycle comprises roughly 30 consecutive data points. The result of this analysis is a vector of non-differenced cross correlation function values computed between  $R_r$  and GA for each positive and negative lag position. The graph of the correlation (Figure 7) illustrates the same periodicity that was observed in the  $R_r$  and GA graphed signals from Figure 5.



*Figure 7.* Cross correlation coefficients (CCC) for  $R_r$  and GA plotted against lag position. Confidence limits mark 2 standard errors at each lag position.

The computed CCCs for each of the 20 forward and backward lag positions show that the largest CCC occurs at a lag position of +2. A CCC of -0.824 shows that there is a strong and negative linear relationship between changes in GA and changes in  $R_r$  (i.e., an increase in GA leads to a reduction in  $R_r$ ). The lag position of +2 indicates that the cyclic changes in GA occur approximately two data points (0.2 s) ahead of the measured  $R_r$  and confirm that both parameters are nearly synchronized. The time delay is calculated based upon a perturbation data point occurring on average every 0.118 s such that 2 lags would approximate 0.2 seconds.

## Discussion

The hypothesized inverse relationship between GA and  $R_r$  during feigned PVFM breathing is supported by the results reported herein. The cross-correlation analysis revealed a strong negative correlation between GA and  $R_r$  with a lag of approximately 0.2s between GA and  $R_r$ . This reveals that  $R_r$  decreases when GA increases, and that changes in GA precede changes in  $R_r$ . Although it is logical that the change in GA occurs first, the lag time was somewhat greater than expected.

There are two possible explanations for the slight asynchrony between GA and  $R_r$ . First, the onsets of inspiration and expiration were marked by the first observed video frame signaling vocal fold adduction and abduction, respectively. Thus, human error may have contributed to a misidentification of each breathing phase within a few video frames. Also, synchrony of GA and  $R_r$  may have been impacted by a time delay between the beginning of vocal fold movement and the measurement of air pressure and flow change by the APD (A. T. Johnson, personal communication, October 11, 2011). A change in airflow sensed at the mouth opening is not recorded by the device until the next perturbation. This delay can be as great as 100 ms, which is equivalent to the average period between adjacent perturbations. Overall, however, the lag between the data signals was small and was accounted for in the calculation of the cross correlation coefficient.

This is the first known attempt to correlate  $R_r$ , measured with the APD, with GA, and as such presented challenges. The authenticity of this study would be improved if it was performed during exercise with a participant diagnosed with PVFM. However, simultaneous placement of the nasal endoscope and the APD does

not easily accommodate performing exercise, which would have been required to induce PVFM signs. Likewise, the intermittent nature of PVFM cannot guarantee the desired response. To ensure observable data that would illustrate the issue at hand, a normal and well-informed adult feigned breathing typical of PVFM while seated. The participant purposely over-exaggerated glottal constriction during inspiration so that the two phases of the respiratory cycle were distinctly different. This amount of glottal constriction sometimes interfered with clear visualization of the laryngeal airway that was required for GA analysis, thus limiting the number of cycles available for analysis.

Additional challenges for this study and proposed solutions include the following: (1) Synchronizing the laryngeal recording with the start of the APD trial. This could have been remedied with an external beep tone. (2) Identifying the beginning and ending of each breathing phase from the laryngeal images. This could have been solved by using respiratory inductance plethysmography simultaneously with laryngoscopy and the APD to clearly define breathing phases. (3) Controlling for the distance between the tip of the scope to the vocal folds. This could have been facilitated by marking the place on the scope where it entered the nose in order to keep a constant distance. However, the natural descent of the larynx during inspiration would vary this distance. (4) Finally, analyzing more breathing cycles than what was done for this study would inevitably provide a better understanding of the relationship between  $R_r$  and GA.



## **Conclusions**

This preliminary study supports the hypothesis that  $R_r$  assessed with the APD is negatively correlated with changes that occur at the vocal folds in a single participant volitionally producing glottal constriction during the inspiratory phase of breathing. Study 2 will investigate test-retest reliability of the  $R_r$  measurements in athletes who have been diagnosed with PVFM as well as in healthy control athletes.

## Chapter 3: Study 2 Test-Retest Reliability of Respiratory

### Resistance Measured with the APD

Findings from Study 1 revealed that there was a strong negative correlation between respiratory resistance ( $R_r$ ) as measured with the Airflow Perturbation Device (APD) and glottal area (GA). This suggests that  $R_r$  measures may be a non-invasive alternative to laryngoscopy in diagnosis and outcome assessment for PVFM. To further investigate whether  $R_r$  can be adopted for clinical and research use in individuals with PVFM and healthy controls, its reliability has to be established. Likewise, generating reliable results with the measurement protocol including an exercise challenge to elicit changes in  $R_r$  should be proven.

The purpose of this study is to determine if  $R_r$  measures are reproducible across trials within the same session (short-term reliability) and across sessions (long-term reliability) during resting tidal breathing (RTB) and post-exercise breathing (PEB). RTB is tested during three consecutive 1-minute breathing trials conducted before exercise begins, whereas PEB is assessed from three consecutive 1-minute breathing trials conducted immediately after exercise ends.

Strong within-subject test-retest reliability is desired during RTB, for both short- (intrasession) and long-term (intersession) comparisons. Likewise,  $R_r$  during PEB should show strong within-subject test-retest reliability when trials of the same order are compared across sessions (i.e.,  $R_r$  in PEB trial 1 during session 1 should be consistent with that in PEB trial 1 during session 2).

Lausted and Johnson (1999) tested reliability of  $R_r$  measured by the APD during RTB. The researchers used the grand mean ( $R_r$ ) of inspiratory ( $R_i$ ) and expiratory ( $R_e$ ) resistance as their dependent variable rather than parceling  $R_i$  and  $R_e$ .  $R_r$  was measured in four participants for five trials occurring across 15 minutes on the same day, in six participants for one trial per day over three consecutive days, and in seven participants for one trial per week over three consecutive weeks. Their results showed that reliability was strongest when one measure was taken per day for three days yielding a coefficient of variation (CV) of 1.8%, followed closely by multiple measures during the same day, with a coefficient of variation  $< 4\%$  (an exact CV was not provided). The greatest variation was observed when resistance was measured once per week for three weeks, yielding a CV of 7.2%. They concluded that test-retest reliability overall was strong. This study, however, used small sample sizes and lacked clarity regarding whether the same participants were used for each test session since numbers of participants varied from four (study 1) to seven (study 3). In addition,  $R_r$  was measured during RTB only, and there was no exercise component included in the study.

In another experiment, Silverman et al. (2005) investigated changes in  $R_i$  and  $R_e$  following exercise in 12 adult athletes using the APD, to determine if an exercise effect could be detected and if so, to quantify the duration of the exercise effect. Their exercise protocol followed this sequence: a 5-minute treadmill warm-up at 50-60% maximum heart rate ( $HR_{max}$ ); 5-minute stretching; a moderate-exercise period where treadmill speed and incline were increased in 3-minute increments until achieving 80-85%  $HR_{max}$ ; and a 6-minute period of running while maintaining 80-85%  $HR_{max}$ .  $R_r$

was first recorded during RTB prior to exercise. It was recorded again following the stretching portion and finally for six consecutive minutes immediately after the moderate exercise portion. A comparison of pre- to post-exercise results demonstrated a significant decrease of  $R_i$  following exercise that lasted for 55 seconds, while a concomitant decrease in  $R_e$  occurred within the first 35 seconds following exercise. After these intervals, both resistance measures progressively returned to pre-exercise baseline levels. This is the first exercise study in which the APD was used, and as such provided insight regarding the methodology for the present study. Measuring  $R_r$  prior to and following the warm-up and stretch portions of the exercise protocol (Silverman et al., 2005) did not appear to provide useful data, and may have negatively impacted the athletes' performance for the moderate-exercise portion (for which the researchers were most interested). The researchers used an exercise program where speed and incline were adjusted at 3-minute intervals that may have created uneven changes in physiological response to exercise and overestimated exercise capacity (Thompson et al., 2010, p. 112). The researchers reported that it required 5 seconds for the athlete to transfer from the treadmill to the APD, and typically 30 seconds for APD measurement to begin, suggesting that they lost at least 35 seconds of post-exercise breathing assessment. Finally, statistical significance was based upon multiple related-samples *t*-tests with no reported control for Type I error. Nevertheless, this study demonstrated that the APD could handle high airflow rates associated with exercise and could capture an exercise effect that differed between  $R_i$  and  $R_e$ . These two studies (Lausted & Johnson, 1999; Silverman et al., 2005) established high test-retest reliability of  $R_r$  during RTB, and

demonstrated that significant changes of  $R_r$  following exercise could be detected by the APD.

The present investigation was designed to measure  $R_r$  within and across sessions in healthy female athletes for three sessions during RTB and PEB following a customized exercise protocol. There were three consecutive trials in each session. The study also tested cross-trial reliability of  $R_r$  in athletes with PVFM during RTB, taken at the beginning of an initial evaluation session only. The decision for them to participate in only one exercise challenge test before receiving any treatment was deliberate. Prior to the athletes with PVFM coming to Loyola Clinical Centers (LCC) for an evaluation by the SLP, they had undergone at least one diagnostic exercise challenge by the pulmonologist, and often more diagnostic exercise challenges by an otolaryngologist and/or a cardiologist because the differential diagnosis for PVFM is often challenging and interdisciplinary. By the time the athletes came to LCC, they were usually very anxious to get a definitive diagnosis and begin treatment. While baseline data from repeated exercise challenge tests for these athletes can help to determine test-retest reliability, it seemed unethical to delay treatment so that another exercise challenge can be conducted. Also, potential psychological consequences of repeated testing prior to treatment may have a negative impact on the success of treatment.

For the purposes of this dissertation research, the reliability of  $R_r$  measured by the APD needed to be evaluated with repeated measures on the same group of athletes following a consistent exercise protocol that was appropriate to elicit PVFM symptoms. The research questions for this study are: 1) What is the test-retest

reliability for  $R_r$  measured by the APD during resting tidal breathing for female teen athletes without PVFM? 2) What is the test-retest reliability for  $R_r$  measured by the APD during post-exercise breathing across three sessions for female teen athletes without PVFM? 3) What is the test-retest reliability for  $R_r$  measured by the APD during resting tidal breathing for female teen athletes with PVFM?

There are eight dependent variables for this study. Two are reported directly by the APD: inspiratory resistance ( $R_i$ ) and expiratory resistance ( $R_e$ ). Six others are calculated from  $R_i$  and  $R_e$ : the mean of  $R_i$  and  $R_e$  ( $R_r$ ), ratio of inspiratory to expiratory resistance ( $R_i/R_e$ ), change in inspiratory resistance ( $\Delta R_i$ ), change in expiratory resistance ( $\Delta R_e$ ), change in mean  $R_r$  ( $\Delta R_r$ ), and change in the ratio of inspiratory to expiratory resistance ( $\Delta R_i/R_e$ ) (the latter four measured in percent). This study aimed to assess reliability of all eight variables, described in detail in the following paragraphs. Only the variables with high reliability would be selected for the subsequent studies in this project. It was hypothesized that  $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$  during RTB in both athlete groups would show strong reliability within the same session based upon the findings of Lausted and Johnson (1999). Between sessions, reliability can be influenced by internal validity threats, particularly maturation (physical health and athletic condition of the individual at the time of testing), test-retest difference (reduced or increased anxiety with each subsequent session), and procedures (instructions given, use of the APD). Based upon the findings of Lausted and Johnson (1999), greater variability was expected across sessions compared with that across trials within the same session. For this reason, it was deemed important to investigate the dependent variable  $R_i/R_e$  when comparing separate rest measures and

exercise measures since it may be a more consistent variable for intersession comparisons (Johnson et al., 2007).

Decreased intersession reliability was anticipated during PEB as compared with that during RTB because exercise can invoke threats to internal and external validity. Performance during each exercise challenge can vary because of fluctuations within the respiratory system in general. Similarly, variations in exercise duration for each session and across athletes can be expected. Increased familiarity with the exercise protocol may change performance as well. Nevertheless, the direction of change in  $R_r$  measures should be consistent as the respiratory system responds to the demands of increased ventilation. Results from the same trial sequence (1<sup>st</sup>, 2<sup>nd</sup>, or 3<sup>rd</sup> trial) are hypothesized to be reliable across three sessions in the control athlete group. The intra-session cross-trial test-retest reliability during PEB was not of interest in this particular study because the previous study by Silverman et al. (2005) showed that the exercise effect on  $R_r$  was transitory. Consequently,  $R_r$  varied significantly as the respiratory system recovered to its baseline level following exercise. Thus, while reliability is expected for intra-session measures during RTB, changes across trials for PEB are expected because of the possible effect of exercise on the respiratory system. The final study in this project will investigate how exercise influences  $R_r$  measures in athletes with and without PVFM.

## **Methods**

### **Participants**

Twelve female teen athletes with PVFM composed the experimental group and 12 female teen athletes without PVFM composed the control group in this study.

Inclusion criteria for all participants (summarized in Table 2) included: female, ages 12-19 yr, participation in at least two seasons per year of aerobic sports, and willingness to run on a treadmill. Only females were selected for this study because there is a much higher incidence of PVFM in females (Hicks et al., 2008; Patel et al., 2004; Powell et al., 2000). Exclusion criteria included: a concurrent diagnosis of asthma, or a history of cardiac problems, joint or back pain, or shin splints. All races and ethnicities were eligible to participate. All but two participants in each group self-reported to be Caucasian. Two of the athletes in the experimental group self-reported to be Hispanic-Caucasian and two (sisters) in the control group claimed to be part Native Asian Islanders. Table 3 describes age, height and weight for both athlete groups.

Each athlete in the experimental group received the diagnosis of PVFM by their referring otolaryngologist or pulmonologist prior to or at the time of their first appointment at LCC by the consulting otolaryngologist. If diagnosis was not confirmed with a laryngoscopic examination, this was conducted during the first appointment at the LCC. Candidates qualified to be in the experimental group if they demonstrated glottal constriction during inspiration after an exercise challenge, as described below under recruitment procedures. Participants in the control group were excluded if they answered positively to the list of symptoms suggestive of PVFM or asthma (See Appendix A for the Control Athlete Questionnaire).

All participants or their parents provided informed consent or assent in accordance with the rules and regulations of the Institutional Review Board at Loyola University. Control participants received \$20.00 compensation for every session in



which they participated. Experimental participants did not receive financial compensation, but they were provided a complete diagnostic evaluation of PVFM and treatment recommendations by the investigator, a speech-language pathologist (SLP) who specializes in this disorder.

Table 2

*Inclusion and Exclusion Criteria for Experimental and Control Athletes*

PVFM Athletes		Control Athletes	
Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
Age 12 – 19 years	Asthma	Age 12 – 19 years	Asthma
Female	Cardiac condition	Female	Cardiac condition
≥ 2 sport seasons/yr	Back or joint pain	≥ 2 sport seasons/yr	Back or joint pain
Diagnosis of PVFM from referring physician or Laryngoscopic evidence of PVFM	Shin splints		Shin splints  Symptoms suggestive of PVFM or asthma

Table 3

*Descriptive Statistics for Age, Height, and Weight for the Experimental and Control Athletes*

Demographics	PVFM Athletes			Control Athletes		
	M (SD)	Range		M (SD)	Range	
Age (yr)	14.8 (1.6)	12 - 19		14.5 (1.4)	12 – 17	
Height (cm)	160.5 (6.4)	149.9 – 170.2		162.8 (6.7)	149.9 – 175.3	
Weight (kg)	52.0 (8.6)	46.4 – 78.2		54.5 (4.7)	46.8 – 62.7	

## **Equipment**

**Treadmill.** The exercise task was carried out on a commercial grade treadmill (Nautilus NTR700) that allows changes in speed and incline. The displayed items of interest include speed, incline, and time. There are two controls that stop the treadmill, one being a red lever that immediately stops the treadmill and that is easily accessible to the runner as well as the research personnel monitoring the exercise challenge, and the other being the power button. Prior to each exercise challenge, the treadmill was calibrated with its automatic calibration feature. When this feature is activated, the treadmill cycles through all of its speed and incline settings, and displays on the treadmill monitor that calibration has been successful. In all instances of treadmill calibration throughout this research, the calibration standards were met. Between uses, the treadmill hand-railings and control panel were carefully cleaned with a hospital-grade antibacterial wipe.

**Heart rate monitor.** Heart rate was monitored continuously prior to, during, and following the exercise challenge using a Polar FS2C heart rate monitor (Polar Electro Inc., Lake Success, NY). The heart rate monitor comprises a transmitter with two surface electrodes that detect the heart beat and transmit it to a wrist watch unit. The transmitter is held in place by its connection to an elastic strap that goes around the chest below the breasts. The wrist unit displays heart rate and exercise time. Once the heart rate monitor is activated, it requires 15 seconds to begin displaying heart rate. The wrist unit picks up the transmitted signal within 3 feet of the transmitter, thus allowing the investigator to hold the unit or attach it to the treadmill while the participant exercises. For the purpose of universal precautions to prevent transmission

of diseases, every participant had her own elastic strap that was labeled, laundered between appointments (for the control athletes), and stored in a zip-lock bag according to her participant number. The transmitter was wiped with a hospital-grade antibacterial wipe between uses, per the instruction of a representative of the Polar Company (email communication, February 18, 2010).

**Airflow Perturbation Device (APD).** The APD was used to assess respiratory resistance in this study. Details regarding this device are provided in Chapter 2.

### **Facilities and Personnel**

**Test and observation rooms.** All evaluation sessions were conducted at LCC Columbia campus. The test room had an adjoining private room where parents could observe the diagnostic sessions. When parents observed, a Loyola University SLP graduate student was present to answer questions and relay pertinent information to the investigator. The participant was always informed that her parent would be observing from the adjoining room.

The equipment in the test room included a table and several chairs, a treadmill, and an APD connected to a laptop computer. Additionally, an otolaryngology examination chair and laryngoscopy equipment were housed in this room. The room was also equipped with a telephone, portable oxygen supply, and ammonia inhalants. Fortunately, there were no accidents or other adverse events during implementation of this research project.

**Graduate SLP student assistants.** The investigator (also a clinical supervisor) is assigned a cohort of graduate students for the duration of each

academic semester. The investigator provided extensive training to the graduate students regarding their involvement of this research which was repeated each semester until the completion of the study. The graduate students practiced interviewing and assisting with exercise challenges prior to any interaction with the experimental or control participants. The investigator was present in the test room for every exercise challenge.

All graduate students as well as the investigator were certified in adult and child cardiopulmonary resuscitation (CPR) and use of the automated external defibrillator (AED).

## **Procedure**

**Recruitment of athletes with PVFM.** The participants with PVFM were referred to LCC by local pulmonologists, immunologists (asthma and allergy physicians), otolaryngologists, cardiologists, and pediatricians. In all cases, the diagnosis of PVFM was suspected, but few patients had undergone laryngoscopy to confirm the diagnosis of PVFM. Thus, most patients coming to LCC needed a definitive diagnosis of PVFM. The diagnosis was made by reviewing previous medical findings, listening to their symptom description, and then examining their larynx and vocal folds prior to and immediately following an exercise challenge test. Laryngeal examination was conducted by the investigator, who holds the ASHA Certificate of Clinical Competence, in accordance with the guidelines determined by the American Speech-Language-Hearing Association (American Speech-Language Hearing Association, 1998, 2004a, 2004b) and the Maryland Board of Examiners for Audiology, Hearing Aid Dispensers and Speech-Language Pathologists. It was also

performed by a consulting otolaryngologist to LCC. ASHA mandates that all laryngeal imaging studies be reviewed by a qualified medical doctor who makes the diagnosis.

**Recruitment of control athletes.** Female athletes were recruited from middle and high schools in the local area by contacting school personnel. They were informed that the control athletes would receive compensation of \$20.00 for their participation in each session.

**Screening of athletes with PVFM.** The PVFM diagnostic questionnaire (Appendix B) that is used routinely at LCC for all diagnostic evaluations served as one method for determining candidacy for the study. Of particular interest were answers to these questions: personal information (age); sports information (type of sport, level of play, seasons per year for athletic involvement); medical diagnoses (conditions and medications taken); psychological diagnoses (conditions and medications); PVFM ratings (symptom severity, frequency and sense of control). The participants also rated their general overall health on the day that the questionnaire was completed to alert the interviewer of possible illness. Race and ethnicity, although voluntary information, was provided by all participants. Information from the diagnostic questionnaire supplemented the case history form completed by the parent as part of the clinical record at LCC.

Athletes were invited to participate in the study if their answers to the screening questions met the study criteria, and if evidence of PVFM (medial movement of the true vocal folds and/or prolapse of the corniculate and arytenoid cartilage during inspiration) was confirmed through indirect laryngoscopy. They (and

their parent) received education about the purposes of the study and the time commitment. Written informed consent and assent for parents and participants (respectively) were granted. One 19-year-old athlete self-consented. All participants were assigned a seven-digit medical record number that served as their research identification number.

**Screening of control athletes.** For athletes without diagnosed asthma or PVFM who expressed an interest in participating, the investigator communicated with their parent(s) explaining the study, answering questions, and seeking written informed consent and assent. The control group questionnaire asks similar sport and health-related questions as the one for athletes with PVFM, yet also queries possible symptoms associated with undiagnosed PVFM or asthma. These symptoms include: dyspnea (breathing difficulty), feelings of throat tightness or closure, stridor, hyperventilation, chest tightness, and wheezing.

Over the course of the research, five athletes came to the clinic and answered positively to symptoms suggestive of PVFM or asthma, or disclosed that they had used an inhaler within three months prior to coming to LCC. Although none of the five had a confirmed diagnosis of PVFM or asthma, they were excluded from the study. The data for another control athlete (attending all three sessions) were excluded because her PVFM counterpart, after attending the session, retrospectively withdrew from the study.

## **Experimental Procedures**

**Pre-exercise interview of athletes with PVFM.** A graduate student clinician and the investigator greeted the athlete with PVFM in the clinic waiting room and

escorted her to the test room where an explanation of the components of the session was given in the order that that each would occur. Laminated pictures of a female teen athlete using the APD, running on the treadmill, and receiving a stroboscopic examination of her larynx were shown to the participant. Then through interview format, the participant answered questions about her symptom severity, frequency, feelings of control, medical and psychosocial history. The athletes' answers were validated by her parent, who was in the observation room, or from the case history completed by the parent prior to the appointment.

**Pre-exercise interview of control athletes.** The control athletes followed the same procedures as those with PVFM for the pre-exercise portion. The screening questionnaire that was administered during the first session was reviewed with the control athletes prior to each of the subsequent two sessions to document changes that may have occurred. Attempts were made to schedule each of the three sessions biweekly. Because the athletes were involved in school, sports, and other activities and had to travel to LCC, they attended each session as their schedule allowed. The interval between sessions averaged 40 days, but ranged from same day to 343 days.

**Exercise challenge test for all athletes.** The exercise challenge began following the interview using a treadmill, a heart-rate monitor, and an APD. Severity of breathlessness was continuously rated using the modified Borg Dyspnea Scale. The protocol for the exercise challenge integrated aspects from previously published protocols (Fletcher et al., 2001; Paridon et al., 2006; Thompson et al., 2010), and published recommendations for pediatric exercise testing (Fletcher et al., 2001).

***Instruction for using the heart-rate monitor.*** The investigator explained the purpose of the heart-rate monitor and instructed correct placement of the sensor band and strap. The athlete was shown to the restroom where she put on the band unassisted. When the athlete returned to the room from putting on the band, the researcher activated the heart-rate monitor, and ensured that it was functioning correctly. Maximum heart rate for females within the 12 – 19 year old range was calculated using the formula:  $HR_{max} = 207 - (0.07 \times \text{age})$  (Gellish et al. 2007), posted on a white board and noted on the participant's exercise challenge data sheet. Heart rate was monitored and recorded prior to and following exercise, and at 1-minute intervals throughout exercise.

***Instruction for using the Modified Borg Dyspnea Scale.*** Instruction was provided about the modified Borg Dyspnea Scale (Borg, 1998) used to query severity of breathlessness prior to, during and following exercise. The investigator described the term dyspnea as “difficulty breathing” or “a feeling of breathlessness.” The scale begins at 0 (“*nothing at all*”), progresses to 0.5 (“*very, very slight*”), and continues with whole number ratings through 10 (“*maximal severity*”), having a total of 11 increments. This scale was chosen because it has been validated and confirmed reliable by published studies, and is popular in pulmonary medicine and sports medicine (Elliott et al., 1991; Mahler et al., 2001).

***Instruction for using the Airflow Perturbation Device.*** Use of the APD was described in the following steps: 1) seating the participant, 2) placing the disposable nose clip to prevent transnasal breathing, 3) placing the mouthpiece securely in the mouth, ensuring a good seal between the mouthpiece and the mouth, 4) resting the



elbows on the table to stabilize the upper torso, 5) gently but firmly holding the cheeks so that air does not pocket in the buccal spaces, and 6) breathing naturally through the mouthpiece until the end of each breathing trial. Before collecting data, the investigator described these procedures to the participant, and placed a picture illustrating an athlete correctly using the APD on the table in full view as a reminder. The athlete was told that she would be performing three 1-minute trials with the APD before exercise and then three 1-minute trials immediately after exercise. The time interval between the end of one trial and the start of the next was approximately 5 seconds. Each athlete practiced putting the mouthpiece in her mouth in order to ensure correct placement and lip seal which was confirmed by the investigator.

***Instruction for using the treadmill.*** The athlete was shown the emergency stop feature of the treadmill. She was told that either she or the investigator would stop the treadmill upon her request or the investigator's observations. After the treadmill stopped, she would be assisted as needed to sit in the chair that was positioned within two feet of the treadmill to begin the APD trials. She was given the option to stretch prior to exercise or to walk on the treadmill prior to beginning the challenge in order to acclimate to the motion.

**Instruction for the exercise challenge and safety monitoring.** Information about the exercise challenge format and conditions that would result in discontinuing the exercise challenge was provided and explained to the participants. The exercise challenge followed a progressive incremental protocol (Fletcher et al., 2001; Paridon et al., 2006) whereby the speed and incline of the treadmill were gradually and progressively increased at fixed intervals. The protocol incorporated a warm-up phase

(2 minutes of easy jogging at 4 miles/hour, with a 0% incline in the first minute and a 1% incline in the second minute). This was followed by a continuous exercise phase with either a 0.5 or 1.0 mph increase every 2 minutes and 1% increase in incline at alternate 2 minute increments so that a change in either speed or incline was occurring each minute with the exception of the ninth and eleventh minutes of exercise. The ending speed and incline of the exercise challenge is 7.0 mph and 4%. (Appendix C illustrates the exercise challenge.) The duration of the exercise challenge did not exceed 12 minutes, a ceiling used by the American Heart Association for Pediatric Exercise Challenges (Fletcher et al., 2001; Paridon et al., 2006). The exercise challenge was discontinued prior to 12 minutes if the athlete's heart rate exceeded the pre-determined maximum rate, if the participant reached a subjective symptom rating of 8 on the 10-point modified Borg Dyspnea Scale; or if the participant requested discontinuation of the exercise challenge. Upon cessation of exercise, the duration of exercise to the nearest second was recorded for later analysis.

### **Data Analysis**

**Control athletes.** To address test-retest reliability for the control group, intraclass correlation coefficient (ICC) analysis determined the strength of the relationship between dependent variables (DVs). The ICC is superior to Pearson product moment correlation analysis because it takes into account the correlation in individual data pairs along with the correlation between groups of related data (Yaffee, 1998). Thus, it describes the strength and agreement of the relationship between units of the same group (i.e.,  $R_i$  during RTB for trials 1, 2, and 3 for sessions

1, 2, and 3) rather than individual paired data. For Question 1, pertaining to test-retest reliability of APD-determined measures of  $R_r$  during RTB, DVs were  $R_i$ ,  $R_e$ ,  $R_r$ ,  $R_i/R_e$ . For Question 2 pertaining to test-retest reliability of APD-determined measures of  $R_r$  during PEB, DVs were  $R_i$ ,  $R_e$ ,  $R_r$ ,  $R_i/R_e$ , as well as change from rest to exercise for  $R_i$ ,  $R_e$ ,  $R_r$  and  $R_i/R_e$ . Independent variables were session (3) and trial (3) for each of two conditions (RTB and PEB). The same DVs were tested for group effects with repeated-measures multivariate analysis of variance (RM-MANOVA), with trial (3), session (3), and condition (2) as within-subject variables.

**Athletes with PVFM.** To address test-retest reliability for the experimental group, intraclass correlation coefficient (ICC) analysis determined the strength of the relationship between DVs. For Question 3, pertaining to test-retest reliability of APD-determined measures of  $R_r$  during RTB, DVs were  $R_i$ ,  $R_e$ ,  $R_r$ ,  $R_i/R_e$ . The same DVs were tested for group effects with repeated-measures multivariate analysis of variance (RM-MANOVA), with trial (3) as the within-subject variable. All statistical analyses were performed using SPSS version 18 (IBM Corporation, Armonk, NY).

## **Results**

### **Athletes without PVFM**

**Resting tidal breathing.** Descriptive statistics for RTB for three sessions and three APD trials per session are provided for the control participants in Table 4 for DVs  $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$ . Results for the ICC analyses for RTB for all three trials during three sessions are presented in Table 5 for the same DVs. Strong reliability ( $ICC > .95$ ) was demonstrated for all four DVs— $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$ . The RM-MANOVA for RTB for the four DVs met the assumptions of sample size, normality

(Mahalanobis distances maximum value of 12.78 did not exceed the critical value of 18.47 for four dependent variables), and linearity. There were no statistically significant differences for trial, Wilks' Lambda = .505,  $F(7, 5) = .700$ ,  $p = .678$ , or for session, Wilks' Lambda = .285,  $F(7, 5) = 1.793$ ,  $p = .269$ . From the results of ICC analysis and RM-MANOVA, test-retest reliability was ascertained between trials and sessions for each of the four dependent variables for the control group of athletes without PVFM during RTB. Results for the RM-MANOVA for control athletes for all conditions (RTB, PEB, and change from RTB to PEB) are reported in Table 6.

Table 4

*Descriptive Statistics for Resting Tidal Breathing (RTB) for Sessions (3) and Trials (3) for Athletes Without PVFM.*

Variables	First Trial <i>M (SD)</i>	Second Trial <i>M (SD)</i>	Third Trial <i>M (SD)</i>
RTB Session 1			
R <sub>i</sub> (cmH <sub>2</sub> O/L/s)	3.87 (0.56)	3.89 (0.63)	3.96 (0.60)
R <sub>e</sub> (cmH <sub>2</sub> O/L/s)	4.41 (1.14)	4.38 (1.21)	4.39 (1.06)
R <sub>r</sub> (cmH <sub>2</sub> O/L/s)	4.14 (0.81)	4.13 (0.88)	4.17 (0.78)
R <sub>i</sub> /R <sub>e</sub>	.904 (.142)	.918 (.15)	.927 (0.16)
RTB Session 2			
R <sub>i</sub> (cmH <sub>2</sub> O/L/s)	3.74 (0.50)	3.74 (0.54)	3.72 (0.59)
R <sub>e</sub> (cmH <sub>2</sub> O/L/s)	4.17 (1.05)	4.05 (1.08)	4.05 (0.93)
R <sub>r</sub> (cmH <sub>2</sub> O/L/s)	3.95 (0.74)	3.89 (0.77)	3.88 (0.72)
R <sub>i</sub> /R <sub>e</sub>	.920 (0.11)	.957 (0.16)	.934 (0.11)

Variables	First Trial <i>M (SD)</i>	Second Trial <i>M (SD)</i>	Third Trial <i>M (SD)</i>
RTB Session 3			
R <sub>i</sub> (cmH <sub>2</sub> O/L/s)	3.62 (0.48)	3.54 (0.47)	3.46 (0.56)
R <sub>e</sub> (cmH <sub>2</sub> O/L/s)	4.07 (0.77)	4.01 (0.65)	3.96 (0.61)
R <sub>r</sub> (cmH <sub>2</sub> O/L/s)	3.85 (0.60)	3.78 (0.50)	3.71 (0.54)
R <sub>i</sub> /R <sub>e</sub>	.902 (0.12)	.893 (0.12)	.876 (0.11)

Table 5

*Intraclass Correlation Coefficients for Athletes Without PVFM across all Trials (3) in all Sessions (3) During Resting Tidal Breathing (RTB).*

Dependent Variable	ICC <sup>a</sup> Average Measure	95% CI	<i>p</i>
R <sub>i</sub>	.952	[.896, .984]	<.001***
R <sub>e</sub>	.968	[.933, .989]	<.001***
R <sub>r</sub>	.962	[.919, .987]	<.001***
R <sub>i</sub> /R <sub>e</sub>	.966	[.927, .988]	<.001***

<sup>a</sup>Two-way random effects model with absolute agreement definition

\**p* < .05. \*\**p* < .01. \*\*\**p* < .001.

Table 6

*RM-MANOVA Results for Athletes Without PVFM for Resting Tidal Breathing (RTB), Post-Exercise Breathing (PEB), and Change( $\Delta$ ) from RTB to PEB using Wilks' Lambda statistic.*

Factor	Condition	<i>df</i>	<i>F</i>	$\eta$	<i>p</i>
Trial	RTB	7, 5	0.70	.495	.678
	PEB	6, 6	15.37	.939	.002**
	$\Delta$ RTB to PEB	8, 4	42.63	.988	.001**
Session	RTB	7, 5	1.79	.715	.269
	PEB	6, 6	2.09	.676	.196
	$\Delta$ RTB to PEB	8, 4	1.10	.687	.498
Trial*Session	RTB	16, 126	1.02	.089	.438
	PEB	12, 111	0.54	.049	.883
	$\Delta$ RTB to PEB	4, 44	0.47	.044	.955

\**p* < .05. \*\**p* < .01.

**Post-Exercise Breathing.** Descriptive statistics for PEB for three sessions of three breathing trials per session for the control participants are provided in Table 7 for DVs  $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$ . The results of the ICC analysis during PEB for same breathing trial cross-session are presented in Table 8.  $R_i$ ,  $R_e$ , and  $R_r$  demonstrated strong test-retest reliability ( $ICC > .88$ ). ICC results varied across the three trials for  $R_i/R_e$ . There is a strong relationship ( $ICC = .893$ ) for  $R_i/R_e$  in the first trial across sessions, whereas correlations were weaker ( $ICC = .762$  and  $.576$  respectively) in the second and third trials. A two-way RM-MANOVA for PEB was conducted to compare the results for the four DVs of  $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$  for the same trial across sessions; the difference was not statistically significant (Wilks' Lambda = .324,  $F(6,$

6) = 2.087,  $p = .196$ ). The main effect for trial was significant (as expected) according to the multivariate model (Wilks' Lambda = .061,  $F(6, 6) = 15.371$ ,  $p = .002$ ) because exercise impacts APD measures across trials within the same session. There was no interaction effect between trial and session (Wilks' Lambda = .861,  $F(12, 111) = .542$ ,  $p = .883$ ).

Table 7

*Descriptive Statistics for Post-Exercise Breathing (PEB) for Sessions (3) and Trials (3) for Athletes Without PVFM.*

Variables	First Trial <i>M (SD)</i>	Second Trial <i>M (SD)</i>	Third Trial <i>M (SD)</i>
PEB Session 1			
R <sub>i</sub> (cmH <sub>2</sub> O/L/s)	3.70 (0.52)	3.45 (0.35)	3.44 (0.40)
R <sub>e</sub> (cmH <sub>2</sub> O/L/s)	3.35 (0.37)	3.44 (0.47)	3.55 (0.62)
R <sub>r</sub> (cmH <sub>2</sub> O/L/s)	3.53 (0.37)	3.44 (0.38)	3.50 (0.48)
R <sub>i</sub> /R <sub>e</sub>	1.11 (0.16)	1.01 (0.10)	0.98 (0.11)
PEB Session 2			
R <sub>i</sub> (cmH <sub>2</sub> O/L/s)	3.75 (0.52)	3.45 (0.60)	3.55 (0.58)
R <sub>e</sub> (cmH <sub>2</sub> O/L/s)	3.47 (0.48)	3.52 (0.61)	3.58 (0.69)
R <sub>r</sub> (cmH <sub>2</sub> O/L/s)	3.61 (0.42)	3.48 (0.58)	3.57 (0.61)
R <sub>i</sub> /R <sub>e</sub>	1.09 (0.17)	.983 (0.10)	1.00 (0.01)
PEB Session 3			
R <sub>i</sub> (cmH <sub>2</sub> O/L/s)	3.70 (0.70)	3.51 (0.77)	3.48 (0.69)
R <sub>e</sub> (cmH <sub>2</sub> O/L/s)	3.37(0.43)	3.40 (0.57)	3.45 (0.58)
R <sub>r</sub> (cmH <sub>2</sub> O/L/s)	3.54 (0.46)	3.45 (0.65)	3.47 (0.60)
R <sub>i</sub> /R <sub>e</sub>	1.11 (0.23)	1.03 (0.10)	1.01 (0.11)

Table 8  
*Cross-Session Intraclass Correlation Coefficients for Athletes Without PVFM for 3 Sessions During Post-Exercise Breathing (PEB).*

Dependent Variable	ICC Average Measure	95% CI	<i>p</i>
$R_i$			
Trial 1	.903	[0.740, 0.970]	<.001***
Trial 2	.886	[0.695, 0.964]	<.001***
Trial 3	.885	[0.696, 0.964]	<.001***
$R_e$			
Trial 1	.927	[0.811, 0.977]	<.001***
Trial 2	.948	[0.867, 0.984]	<.001***
Trial 3	.940	[0.843, 0.981]	<.001***
$R_r$	.926	[0.808, 0.977]	<.001***
Trial 1			
Trial 2	.931	[0.816, 0.978]	<.001***
Trial 3	.940	[0.844, 0.981]	<.001***
$R_i/R_e$			
Trial 1	.893	[0.714, 0.967]	<.001***
Trial 2	.762	[0.389, 0.925]	.002**
Trial 3	.576	[0.159, 0.869]	.048*

<sup>a</sup>Two-way random effects model with absolute agreement definition

\*  $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .

**Change in  $R_r$  from RTB to PEB.** The variables measuring change from rest to exercise in percent for  $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$  were analyzed for test-retest reliability and statistical significance using ICC and RM-MANOVA. Descriptive statistics for the control group are presented in Table 9. The ICC analysis results are presented in Table 10, and demonstrate a different finding for  $\Delta R_i$  and  $\Delta R_r$  as compared with  $R_i$



and R during RTB and PEB. The correlation is very weak for  $\Delta R_i$ , especially trials 2 and 3, with the confidence interval covering a wide range. Similarly, the second and third trials for  $\Delta R$  reveal weak correlations. A two-way RM-MANOVA was conducted to analyze the results for change from RTB to PEB for the four DVs ( $R_i$ ,  $R_e$ , R, and  $R_i/R_e$ ) for the same trial across sessions. There was no statistically significant effect for session, Wilks' Lambda = .313,  $F(8, 4) = 1.097$ ,  $p = .687$ . There was statistical significance for trial, Wilks' Lambda = .012,  $F(8, 4) = 42.628$ ,  $p = .001$ . There was no interaction effect between trial and session, Wilks' Lambda = .836,  $F(16, 126) = .474$ ,  $p = .955$ .

Table 9

*Descriptive Statistics for Post-Exercise Change in Percent in Athletes Without PVFM**(N=12)*

Variables	First Trial <i>M (SD)</i>	Second Trial <i>M (SD)</i>	Third Trial <i>M (SD)</i>
Post-exercise Change Session 1			
$\Delta R_i$	-4.10% (13.26)	-10.75% (9.10)	-11.22% (6.42)
$\Delta R_e$	-20.24% (17.93)	-19.15% (13.93)	-16.73% (14.49)
$\Delta R_r$	-13.01% (13.65)	-15.53% (10.31)	-14.37% (11.07)
$\Delta R_i/R_e$	24.54% (25.36)	12.71% (17.37)	8.62% (14.19)
Post-exercise Change Session 2			
$\Delta R_i$	0.81% (9.72)	-7.91% (7.27)	-5.00% (7.57)
$\Delta R_e$	-13.20% (15.41)	-12.33% (11.24)	-11.23% (10.85)
$\Delta R_r$	-6.45% (10.50)	-10.48% (7.38)	-8.46% (7.45)
$\Delta R_i/R_e$	18.98% (25.84)	6.57% (15.53)	8.35% (13.86)
Post-exercise Change Session 3			
$\Delta R_i$	4.60% (13.23)	-1.19% (14.83)	-1.87% (12.21)
$\Delta R_e$	-14.69% (13.31)	-15.06% (8.65)	-13.65% (9.65)
$\Delta R_r$	-5.95% (9.50)	-8.90% (8.89)	-8.38% (8.71)
$\Delta R_i/R_e$	26.17% (29.97)	17.06% (18.25)	14.56% (16.56)

Table 10

*Cross-Session Intraclass Correlation Coefficient Analysis for Post-Exercise Changes in Athletes without PVFM*

Dependent Variable	ICC <sup>a</sup> Average Measure	95% CI	<i>p</i>
$\Delta R_i$			
Trial 1	.350	[-0.583, 0.789]	.176
Trial 2	-.139	[-1.533, 0.613]	.586
Trial 3	-.037	[-1.172, 0.635]	.509
$\Delta R_e$			
Trial 1	.839	[0.589, 0.949]	< .001***
Trial 2	.697	[0.242, 0.903]	.006**
Trial 3	.691	[0.206, 0.903]	.009**
$\Delta R_r$			
Trial 1	.659	[0.162, 0.890]	.010**
Trial 2	-.094	[-1.636, 0.643]	.548
Trial 3	.442	[-0.339, 0.818]	.102
$\Delta R_i/R_e$			
Trial 1	.861	[0.638, 0.956]	<.001***
Trial 2	.790	[0.468, 0.933]	<.001***
Trial 3	.696	[0.219, 0.904]	.008**

<sup>a</sup>Two-way random effects model with absolute agreement definition

\*  $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .

**Athletes with PVFM**

**Resting Tidal Breathing.** The same statistical tests that were used for the control group were also conducted for the variables in the experimental group which was assessed for three trials of RTB during only one session. Table 11 shows descriptive statistics and Table 12 shows the results of the ICC analysis for four DVs during three trials of RTB. Across the three rest breathing trials, strong correlations

were observed for all variables ( $ICC \geq .968$  for  $R_i$ ,  $R_e$ , and  $R_r$ ; and  $ICC = .788$  for  $R_i/R_e$ ). The lower ICC for  $R_i/R_e$  is attributed to  $R_i$  and  $R_e$  varying in different directions despite their overall consistency. A one-way RM-MANOVA was conducted for breathing trial and the dependent variables  $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$ ; it failed to demonstrate significant differences (Wilks' Lambda = .520,  $F(6, 6) = .925$ ,  $p = .537$ ).

Table 11

*Descriptive Statistics for Resting Tidal Breathing (RTB) in Athletes with PVFM for 3 Consecutive Trials.*

Variables	First Trial <i>M (SD)</i>	Second Trial <i>Mean (SD)</i>	Third Trial <i>Mean (SD)</i>
RTB			
$R_i$ (cmH <sub>2</sub> O/L/s)	3.03 (.66)	2.88 (.67)	2.90 (.61)
$R_e$ (cmH <sub>2</sub> O/L/s)	3.23 (.80)	3.13 (.80)	3.04 (.73)
$R_r$ (cmH <sub>2</sub> O/L/s)	3.13 (.72)	3.01 (.70)	2.97 (.65)
$R_i/R_e$	0.949 (.08)	0.927 (.09)	0.965 (.11)

Table 12

*Cross-Trial Intraclass Correlation Coefficients for Athletes with PVFM during Resting Tidal Breathing (RTB).*

( $N = 12$ )

Dependent Variable	ICC <sup>a</sup> Average Measure	95% CI	<i>p</i>
$R_i$	.968	[0.916, 0.990]	<.001***
$R_e$	.974	[0.929, 0.992]	<.001***
$R_r$	.976	[0.936, 0.993]	<.001***
$R_i/R_e$	.790	[0.457, 0.934]	.001**

<sup>a</sup>One-way random effects model with absolute agreement definition

\*  $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .

## Discussion

Results of this study show that  $R_i$ ,  $R_e$ ,  $R_r$ , and  $R_i/R_e$  measures obtained with the APD during RTB have strong test-retest reliability. For the control athletes, this was demonstrated across three consecutive trials within the same session, and across three separate sessions during RTB using ICC and RM-MANOVA analyses. For the athletes with PVFM, the same measures also demonstrated strong test-retest reliability across 3 trials within one session during RTB.

Immediately following exercise, these measures remained highly reliable in the trials of the same order across three sessions, suggesting that the respiratory system responds to exercise in a consistent manner in athletically trained young females who do not have asthma or PVFM. Although measures of post-exercise change were strongly correlated across sessions for  $\Delta R_e$  and  $\Delta R_i/R_e$ , this was not observed for  $\Delta R_i$  and  $\Delta R_r$  (the latter influenced by the former).

Using both ICC and RM-MANOVA was important to investigate relatedness and potential differences in the data and revealed several important implications.

(1) The results provided by both analyses confirmed the consistency of  $R_r$  measures obtained with the APD during very different conditions – breathing during rest and breathing immediately following exercise. Significant changes in respiratory resistance may indicate varying respiratory physiology. (2) Based upon the strong test-retest reliability for  $R_i$  and  $R_e$  during RTB for both athlete groups, their means across three trials within one session are accurate representations of baseline conditions. *Post hoc* analyses for statistically significant findings from the RM-MANOVA will use the means of the 3 trials for RTB for Study 3 that focuses on

within and between-group differences. (3) Because the respiratory system changes differently in inspiratory and expiratory phases when there is a PVFM episode, using both  $R_i$  and  $R_e$  rather than their mean ( $R_r$ ) will provide information more specific to PVFM and more likely will reveal changes in respiratory resistances that otherwise can be masked by averaging  $R_i$  and  $R_e$  into  $R_r$ . Eliminating the dependent variable  $R_r$  (mean of  $R_i$  and  $R_e$ ) from further analyses in Study 3 as explained in (1), will also reduce the number of DVs, thus strengthening future analyses. (4) Contrary to expectation,  $\Delta R_i$  and  $\Delta R_r$  were not reliable.  $\Delta R_e$  and  $\Delta R_i/R_e$ , although statistically reliable, showed weaker ICCs compared to  $R_i$ ,  $R_e$ ,  $R$ , and  $R_i/R_e$ . These percent change variables, therefore, were not included in the subsequent study.

### **Caveats**

The study hypotheses were supported, although the present study had several limitations. Cross-session reliability would have been assessed in athletes with PVFM during RTB and PEB if they had participated in at least two baseline sessions prior to receiving therapy. The decision not to do this was made purposefully, as previously explained in the Methods Section. Many athletes return to LCC after the initial diagnostic/treatment session for additional therapy sessions, that allows re-assessment of  $R_r$  during RTB. However, it is unknown whether the previous intervention provided by the SLP might have changed  $R_r$  baselines. This study was designed to exclude any potential influence of previous treatment; therefore, no athlete who had been treated previously was enrolled into this study.

The second limitation involved scheduling sessions for the athletes in the control group. Many of the athletes did not come for repeated sessions over a

regularly scheduled time interval as was initially designed (i.e., once per week for three consecutive weeks). Although the statistical mode was 7 days between sessions, two challenge sessions were conducted on the same day at minimally one hour intervals for four athletes, and almost one year elapsed between one athlete's second and third sessions. Interestingly, all four athletes who participated in two sessions during the same day completed the full 12 minutes of exercise for both exercise challenges suggesting that two sessions within the same day did not negatively influence exercise duration. Overall, their busy schedules, the commute to the clinic, and for some, their hesitancy to return after the first session, interfered with regular attendance. Despite these factors, test-retest reliability remained strong.

### **Conclusions**

The results from the previous study (Study 1) demonstrated that changes in glottal area measured from a two-dimensional aerial view of the larynx correlated well with changes in  $R_r$  as measured by the APD. The results from the present study (Study 2) confirm strong test-retest reliability of  $R_r$  measured by the APD during RTB in healthy control athletes and athletes with PVFM. The same strong reliability is also observed across sessions during PEB in control participants. The subsequent study will examine the effect of exercise on  $R_i$  and  $R_e$  within and between athlete groups.

## Chapter 4: Study 3 Effect of Exercise on Athletes With and Without PVFM

Aerobic exercise requires changes in the respiratory, circulatory, and metabolic systems, to meet the increased demand of oxygen and carbon dioxide exchange. The goal of the respiratory system during exercise is to maintain high airflow with low respiratory resistance ( $R_r$ ) and with a minimum amount of energy expenditure (England & Bartlett, 1982). This is accomplished, in part, through increased respiratory rate and greater air volume exchange. The mathematic product of tidal volume during inspiration and expiration and respiratory rate during one minute of breathing is called minute ventilation (Rundell & Slee, 2008). It varies greatly when transitioning from resting tidal breathing (RTB) to exercise breathing (EB). For example, respiratory rate during RTB is approximately 15 breaths per minute, as contrasted with peak exercise where respiratory rate can increase to 40 breaths per minute (Jones, 1984; Templer, VonDoersten, Quigley, Scott, & Davis, 1991). Minute ventilation during RTB averages 5-10 L/min, whereas during EB it may increase to 40-60 L/min coinciding with a higher velocity of airflow.

Airflow within the airways can be either laminar or turbulent. Laminar flow is found in the lower, smaller airways, and turbulent flow results from the mixing of gases in the larger airways of the trachea, larynx, and oral and nasal cavities (Dekker, 1961; Ferris, 1963, Templer et al., 1991). When airflow velocity increases (e.g., during aerobic exercise), it either transitions from laminar to turbulent or becomes



increasingly more turbulent (Dekker, 1961). This causes increased  $R_r$  (Templer et al., 1991; Titze, 1994), such that during exercise the upper airway has a disproportionate increase in resistance compared to the lower airways (Hurbis & Schild, 1991).

During RTB, Ferris et al. (1963) observed that when breathing through the mouth, the upper airway contributed 28% to total respiratory resistance and that the larynx alone contributed 16%. The remaining resistance derives from the lower airways, lungs, and chest wall. During RTB, the vocal folds abduct for inspiration and adduct slightly for expiration (Balkissoon, Beaty, et al., 1999; England & Bartlett, 1982; Templer et al., 1991).  $R_e$  during RTB was reported to be greater than  $R_i$  in adult and pediatric participants (Dekker, 1961, Ferris et al., 1963; Johnson et al., 2007; Silverman et al., 2005), suggesting the inverse relationship of GA and  $R_r$  (England & Bartlett, 1982). The glottal narrowing that occurs during expiration functions as a braking mechanism to control the rate of airflow as the lungs return to resting volume (Balkissoon, 2007; Collett, Brancatisano & Engel, 1983; England & Bartlett; Templer et al., 1982).

Increases in airflow velocity are accompanied by increases in the laryngeal contribution to respiratory resistance (Ferris et al., 1963). The larynx, considered to be the lower boundary of the upper airway, accommodates higher airflow levels primarily through widening of the glottis. Beaty et al. (1999) observed that at higher airflow levels associated with exercise, the vocal folds maintained a relatively fixed abducted posture during both inspiration and expiration in healthy athletes. In other words, the normal braking mechanism provided by the vocal folds during expiration is suspended during exercise breathing (England & Bartlett, 1982). Additionally, the

supraglottic larynx dilates and rotates anteriorly, and the epiglottis flattens (Beaty et al., 1999; Hurbis & Schild, 1991). By doing so, glottal area increases, thereby reducing turbulence and resistance in the upper airway. If, however, GA does not change proportionately with increased airflow, then  $R_r$  will increase during inspiration and/or expiration, making it difficult to breathe (Beaty et al., 1999; England & Bartlett, 1982; Hurbis & Schild, 1991). This can result in the sensation of dyspnea, defined as “consciousness of the necessity for increased respiratory effort” (Jones, 1984, p.14).

Several studies have investigated changes in GA with continuous laryngeal imaging before and during exercise among healthy athletes, athletes with exercise-induced asthma (EIA), and athletes with paradoxical vocal fold motion (PVFM). Because athletes with PVFM are commonly misdiagnosed as having asthma, it is important to understand differences in glottal area during inspiration and expiration observed during laryngoscopy for all three groups. When transitioning from RTB to EB and continuing throughout EB, inspiratory GA ( $GA_i$ ) tends to increase or remain unchanged for healthy athletes and those with EIA (Beaty et al., 1999; Hurbis & Schild, 1991). Athletes with PVFM respond very differently. Two athletes with PVFM in the study by Beaty et al. (1999) demonstrated a decrease in  $GA_i$  that corresponded with their complaints of dyspnea. Similarly, Heinle et al. (2003) performed laryngoscopy during bicycle ergometry on 15 adolescents suspected of having PVFM. They observed vocal fold adduction and/or exercise-induced laryngomalacia only during inspiration, which could be heard as inspiratory stridor.

Vocal fold movement during expiration when transitioning from RTB to EB differs from that during inspiration. For healthy athletes, glottal area during expiration ( $GA_e$ ) is consistently reported to be greater during EB than during RTB, although it is still relatively smaller during expiration than inspiration during EB (England & Barlett, 1982; Hurbis & Schild, 1991). This difference between RTB and EB in the relative GA during inspiration and expiration has been demonstrated in healthy athletes (Beaty et al., 1999; Hurbis & Schild, 1991; Tervonen et al., 2009). Whereas PVFM negatively impacts  $GA_i$ , asthma affects  $GA_e$ . Athletes with moderate asthma did not demonstrate an increase in  $GA_e$  during EB; rather  $GA_e$  remained consistent with that of RTB. Athletes with severe asthma experienced a decrease in  $GA_e$  during and following exercise compared with that during RTB, despite high airflow rates (Hurbis & Schild, 1991). For people with asthma, laryngeal airway constriction during expiration may offer continuous positive airway pressure that is needed to maintain lower airway patency and reduce asthma severity (Collett et al., 1983; England & Bartlett, 1982; Hurbis & Schild, 1991). The findings for healthy athletes suggest that the larynx normally offers less resistance to airflow during exercise than at rest, most likely associated with increased minute ventilation and in response to increased airflow turbulence (England & Barlett, 1982; Hurbis & Schild, 1991), whereas the larynx continues to provide a braking action during expiration in athletes with asthma.

The aforementioned research investigated changes in GA prior to and during exercise through continuous laryngoscopy. Often pulmonary function flow-volume measures were recorded prior to and following exercise for purposes of identifying

lower versus upper airway obstruction (the former is characteristic of asthma, the latter of PVFM). Respiratory resistance was not assessed during exercise, most likely because of the difficulty of simultaneously viewing the larynx and assessing pulmonary function during exercise. There has been only one published study where  $R_r$  was measured using the Airflow Perturbation Device (APD) in athletes (Silverman et al., 2005). Twelve non-asthmatic adult volunteers exercised on a treadmill achieving 85% of  $HR_{max}$ .  $R_r$  was measured prior to exercise, after a brief warm-up exercise period, and then immediately and continuously for 6 minutes after exercise ceased. Their results indicated an “exercise effect” such that a statistically significant decrease of  $R_r$  after exercise was detected for 55 seconds during inspiration and 35 seconds during expiration.

To date, there are no known studies that have investigated changes in  $R_r$  in athletes diagnosed with PVFM. Information of how  $R_i$  and  $R_e$  change during exercise in athletes with PVFM and how resistance differs between athletes with PVFM and a control group of athletes without PVFM, can elucidate potential abnormalities in respiratory function that occur with exercise-induced PVFM. Depending upon the findings for the two athlete groups, measures of  $R_i$  and  $R_e$  can potentially provide quantitative data to screen athletes with complaints suggestive of PVFM as well as to provide treatment outcome measures for athletes diagnosed with PVFM.

This study builds upon the two previous ones in this dissertation that addressed the validity and reliability of  $R_r$  measured by the APD developed by Lausted and Johnson (1999). The first study assessed the relationship between  $R_r$  and GA. The results indicated, as predicted, that changes in GA were negatively

correlated and well timed with changes in  $R_r$ . The second study suggested strong test-retest reliability of  $R_r$  during RTB in both athlete groups and during PEB in control athletes. Measures with weak reliability ( $\Delta R_i$ ,  $\Delta R_r$ ) were not selected for this study because differences revealed by these variables might not indicate an actual change in the respiratory system. Although  $\Delta R_e$  and  $\Delta R_i/R_e$  had strong reliability, they too were eliminated from further analyses since  $\Delta R_i$  and  $\Delta R_r$  were eliminated. Further, although strong test-retest reliability was demonstrated in Study 2 for the dependent variable  $R_r$  (the mean of  $R_i$  and  $R_e$ ), it was eliminated from the present study because it failed to demonstrate the discrepancy between  $R_i$  and  $R_e$  that is characteristic of PVFM.

The purpose of this study was to investigate changes in respiratory resistance, exercise duration, and dyspnea ratings following exercise in female teenage athletes with PVFM (experimental group) and athletes without PVFM (control group). The present study adopted the dependent variables with strong reliability ( $R_i$ ,  $R_e$ ,  $R_i/R_e$ ) and aimed to answer the following within-group research questions: 1) To what extent do APD-determined measures of  $R_r$  change from RTB to PEB in athletes without PVFM and athletes with PVFM? 2) To what extent do measures of  $R_r$  change over a 2-minute post-exercise period in athletes without PVFM and athletes with PVFM? It also aimed to answer the following between-group research questions: 1) Do APD-determined measures of  $R_r$  for RTB and PEB differ between athletes with and without PVFM? 2) Do athletes without PVFM outperform athletes with PVFM in terms of running duration as measured during the exercise challenge test? 3) Do severity ratings of dyspnea reported at the end of an exercise challenge test differ between athletes with and without PVFM?

Based on previous literature and clinical experience, the following hypotheses are offered. For athletes without PVFM, who have no known respiratory or laryngeal problems, 1)  $R_i$  will decrease during PEB as compared with RTB; 2)  $R_e$  will decrease during PEB as compared with RTB; and 3)  $R_i$  and  $R_e$  will decrease the most during the first minute after exercise with the subsequent trial showing a progressive recovery toward  $R_i$  and  $R_e$  during RTB. For athletes with PVFM, characterized by dyspnea and laryngeal constriction during an exercise-induced episode, 1)  $R_i$  during PEB will be greater than that during RTB; 2)  $R_e$  may increase after exercise, but to a lesser extent than  $R_i$ ; and 3) the most substantial change in  $R_i$  and  $R_e$  will occur during the first minute after exercise ( $PEB_1$ ); thereafter,  $R_i$  and  $R_e$  will demonstrate a progressive return toward baseline levels.

For the between-group comparison, the two groups are expected to have comparable  $R_i$  and  $R_e$  during RTB. This hypothesis is based on the common observation that PVFM is asymptomatic during RTB, and because both groups are comparable in gender, age, size, and exercise conditioning. Following exercise, athletes with PVFM are expected to have greater  $R_i$  values and possibly greater  $R_e$  values compared to athletes without PVFM because of reduced GA. It is also anticipated that athletes with PVFM will exercise for shorter durations and have higher dyspnea ratings than athletes without PVFM.

## **Method**

### **Participants**

The same experimental and control participants described in Study 2 participated in this study.

## **Procedure**

The equipment, facility, personnel, participant selection and consent, and experimental procedures for the present study are the same as those described in Study 2. Although athletes without PVFM participated in three separate sessions performing three RTB and three PEB trials per session, data from only the first session are used in this study so that the novelty of the exercise challenge is matched for both groups. The athletes with PVFM participated in only one session when they performed three trials of RTB and either two or three trials of PEB. Seven of the twelve athletes with PVFM did not perform the third PEB trial because they were visibly distressed by dyspnea while breathing into the APD following exercise for the first two trials (PEB<sub>1</sub> and PEB<sub>2</sub>). The investigator reminded them that they could stop their participation at any time, and these athletes chose to stop after PEB<sub>2</sub>.

## **Data Analysis**

All analyses were conducted using SPSS version 18 (IBM Corporation, Armonk, NY). To address the effects of exercise on  $R_i$  and  $R_e$ , a repeated-measures multivariate analysis of variance (RM-MANOVA) was conducted with group (with and without PVFM) as the between-subjects factor, and trial (1 and 2) and condition (RTB and PEB) as within-subjects factors. The ratio of  $R_i$  to  $R_e$  was analyzed in a separate repeated-measures analysis of variance (RM-ANOVA) using the same model. Results for Wilks' Lambda test are reported. The assumption of sphericity for the analyses of variance was met according to Mauchley's test. The RM-MANOVA revealed dependent main effects and interaction effects that were further tested through univariate tests of hypotheses for within-subjects effects. *Post hoc* testing for

significant dependent variables was accomplished with related samples *t* tests with Bonferroni corrections (with alpha level established by dividing .05 by the number of *t* tests). Significant between-group differences were further investigated through univariate ANOVA.

Differences between groups for exercise duration were investigated using an independent samples *t* test. Between-group difference in dyspnea ratings from the modified Borg Dyspnea Scale (Borg, 1998) was investigated using the Mann-Whitney *U* test because this scale produces ordinal data. The  $\alpha$  level for significance was determined *a priori* to be .05 for each analysis.

## **Results**

### **Changes in $R_r$ from RTB to PEB – Overview for both Athlete Groups**

The results for athletes with PVFM and the control participants are described separately, followed by the results of between-group comparisons. Descriptive statistics for  $R_i$ ,  $R_e$ , and  $R_i/R_e$  in both groups during two pre- and two post-exercise trials are presented in Table 13. The results of the RM-MANOVA for respiratory resistance during the two separate phases of breathing ( $R_i$  and  $R_e$ ) are listed in Table 14, and univariate RM-ANOVAs for  $R_i$ ,  $R_e$ , and the derived variable  $R_i/R_e$  are listed in Table 15.



Table 13

*Descriptive Statistics for Respiratory Resistance for Two 1-Minute Breathing Trials during Resting Tidal Breathing (RTB) and Post-Exercise Breathing (PEB) in 12 Athletes without PVFM (Control) and 12 Athletes with PVFM.*

Group	Control		PVFM	
	1	2	1	2
Trial	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
<b>RTB</b>				
$R_i$ (cmH <sub>2</sub> O/L/s)	3.87 (0.56)	3.89 (0.63)	3.03 (0.66)	2.88 (0.67)
$R_e$ (cmH <sub>2</sub> O/L/s)	4.41 (1.1)	4.38 (1.2)	3.23 (0.80)	3.13 (0.80)
$R_i/R_e$	0.904 (0.14)	0.917 (0.15)	0.949 (0.08)	0.927 (0.09)
<b>PEB</b>				
$R_i$ (cmH <sub>2</sub> O/L/s)	3.70 (0.52)	3.45 (0.35)	4.36 (0.72)	3.59 (0.51)
$R_e$ (cmH <sub>2</sub> O/L/s)	3.35 (0.37)	3.44 (0.47)	3.61 (0.68)	3.45 (0.41)
$R_i/R_e$	1.11 (0.16)	1.01 (0.10)	1.21 (0.15)	1.04 (0.12)

When  $R_i$  and  $R_e$  were collapsed in the RM-MANOVA, main effects for breathing condition and trial number were statistically significant, as were the interactions of condition by group, trial by group, and condition by trial. The group main effect and the 3-way interaction did not meet statistical significance. When analyzed separately, the main effects of condition and trial were statistically significant for  $R_i$ , but neither differed significantly for  $R_e$ . The main effect of group did not meet criterion for statistical significance for  $R_i$  or  $R_e$ , but the interaction of condition by group was significant for both  $R_i$  and  $R_e$ . The interactions of trial by

group and condition by trial also met statistical significance for  $R_i$  (only). The 3-way interaction of condition, trial, and group was not significant for either  $R_i$  or  $R_e$ .

Table 14

*Results from RM-MANOVA for Inspiratory Resistance ( $R_i$ ) and Expiratory Resistance ( $R_e$ ) for Two Groups of Athletes (With and Without PVFM) for Resting and Exercise Breathing (Condition) across Two Trials.*

Variable	<i>df</i>	<i>F</i>	$\eta^2$	<i>p</i>		power
Group	2, 21	2.15	.170	.141		.391
Condition	2, 21	21.37	.671	<.001	***	1.000
Trial	2, 21	28.20	.729	<.001	***	1.000
Condition*Group	2, 21	28.95	.734	<.001	***	1.000
Trial*Group	2, 21	8.55	.449	.002	**	.940
Condition*Trial	2, 21	14.55	.581	<.001	***	.996
Condition *Trial*Group	2, 21	1.45	.121	.257		.275

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .

Table 15

*Results from Univariate RM-ANOVAs for Inspiratory Resistance ( $R_i$ ) and Expiratory Resistance ( $R_e$ ) and Inspiratory-to-Expiratory Resistance Ratio ( $R_i/R_e$ ) for Athletes without PVFM and Athletes with PVFM.*

Wilks' Lambda	<i>df</i>	<i>F</i>	$\eta^2$	<i>p</i>		power
<b>Group</b>						
$R_i$	1, 22	1.44	.062	.242		.210
$R_e$	1, 22	3.89	.151	.061		.471
$R_i/R_e$	1, 22	1.80	.076	.193		.250
<b>Condition</b>						
$R_i$	1, 22	17.91	.449	<.001	***	.981
$R_e$	1, 22	4.24	.162	.051		.504
$R_i/R_e$	1, 22	30.32	.580	<.001	***	1.000
<b>Trial</b>						
$R_i$	1, 22	50.92	.698	<.001	***	1.000
$R_e$	1, 22	1.16	.050	.292		.178
$R_i/R_e$	1, 22	25.76	.539	<.001	***	.998
<b>Condition*Group</b>						
$R_i$	1, 22	60.65	.734	<.001	***	1.000
$R_e$	1, 22	18.42	.456	<.001	***	.984
$R_i/R_e$	1, 22	0.39	.018	.536		.092
<b>Trial*Group</b>						
$R_i$	1, 22	17.63	.445	<.001	***	.980
$R_e$	1, 22	2.63	.107	.199		.342
$R_i/R_e$	1, 22	3.57	.140	.072		.439

Wilks' Lambda	<i>df</i>	<i>F</i>	$\eta^2$	<i>p</i>		power
Condition*Trial						
R <sub>i</sub>	1, 22	20.43	.482	<.001	***	.991
R <sub>e</sub>	1, 22	0.065	.003	.801		.057
R <sub>i</sub> /R <sub>e</sub>	1, 22	17.75	.447	<.001	***	.980
Condition *Trial*Group						
R <sub>i</sub>	1, 22	3.03	.121	.096		.384
R <sub>e</sub>	1, 22	0.740	.033	.399		.131
R <sub>i</sub> /R <sub>e</sub>	1, 22	0.29	.013	.594		.081

\**p* < .05. \*\**p* < .01. \*\*\**p* < .001.

Inspiratory-to-expiratory resistance ratio (R<sub>i</sub>/R<sub>e</sub>), when analyzed in a separate RM-ANOVA, differed significantly across condition and trial. A significant interaction between condition and trial revealed that R<sub>i</sub>/R<sub>e</sub> increased from RTB to PEB, and decreased from Trial 1 to Trial 2 when collapsed across groups. *Post-hoc* analysis (Table 16) revealed that when the two trials of R<sub>i</sub>/R<sub>e</sub> during RTB were averaged, the mean of R<sub>i</sub>/R<sub>e</sub> during RTB significantly differed from PEB<sub>1</sub> and PEB<sub>2</sub>. Likewise, there was a statistically significant difference between PEB<sub>1</sub> and PEB<sub>2</sub>. No statistically significant effect or interaction was found for the group factor or for the three-way interaction.

Table 16.

*Post-hoc Analyses for Statistically Significant Findings from Omnibus Univariate test for Inspiratory-to-expiratory ratio ( $R_i/R_e$ ) during Resting Tidal Breathing (RTB) and Post-Exercise Breathing (PEB)*

Variable $R_i/R_e$	<i>df</i>	<i>t</i>	<i>p</i>
Contrasts			
Average of RTB <sub>1-2</sub> and PEB <sub>1</sub>	23	-6.11	<.001**
Average of RTB <sub>1-2</sub> and PEB <sub>2</sub>	23	-3.86	.001**
PEB <sub>1</sub> and PEB <sub>2</sub>	23	4.98	<.001**

\**p* < .017. \*\**p* < .003.

**Within-Group Results: Athletes without PVFM (Control Group)**

**Inspiratory resistance.** The descriptive statistics for the athletes without PVFM revealed that  $R_i$  was less than  $R_e$  for both trials of RTB (Table 13). During both trials of PEB,  $R_i$  was lower than it was during RTB, although  $R_i$  for PEB<sub>1</sub> decreased less than for PEB<sub>2</sub> (Figure 8). The change from RTB to PEB<sub>2</sub> was statistically significant, as was the decrease of  $R_i$  from PEB<sub>1</sub> to PEB<sub>2</sub>. *Post-hoc* related-samples *t*-test results for all significant variables from the MANOVA and ANOVAs for the control group of athletes without PVFM are reported in Table 17. The average of RTB<sub>1-2</sub> was used (based upon strong test-retest results from Study 2), to reduce the number of *post hoc* paired comparisons.

Table 17.

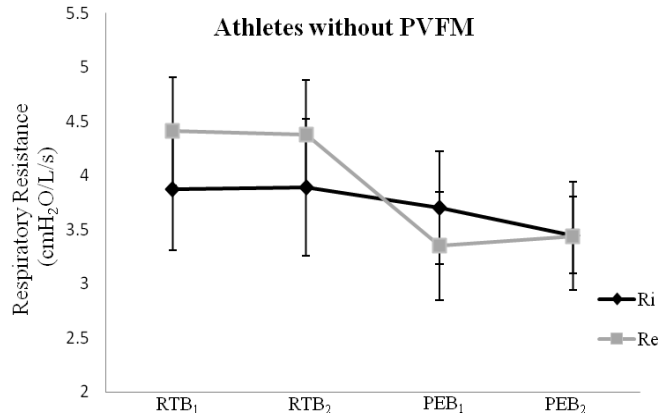
*Post-hoc Related-Samples t tests for Significant ANOVA Omnibus Results for Inspiratory Resistance ( $R_i$ ), Expiratory Resistance ( $R_e$ ) and Inspiratory-to-Expiratory Resistance Ratio ( $R_i/R_e$ ) for Athletes Without PVFM.*

Contrasts	<i>df</i>	<i>t</i>	<i>p</i>
$R_i$			
Average of RTB <sub>1-2</sub> and PEB <sub>1</sub>	11	1.09	.297
Average of RTB <sub>1-2</sub> and PEB <sub>2</sub>	11	3.69	.004*
PEB <sub>1</sub> and PEB <sub>2</sub>	11	3.01	.012*
$R_e$			
Average of RTB <sub>1-2</sub> and PEB <sub>1</sub>	11	3.29	.007*
Average of RTB <sub>1-2</sub> and PEB <sub>2</sub>	11	3.62	.004*
PEB <sub>1</sub> and PEB <sub>2</sub>	11	-0.92	.379
$R_i/R_e$			
Average of RTB <sub>1-2</sub> and PEB <sub>1</sub>	11	-3.29	.007*
Average of RTB <sub>1-2</sub> and PEB <sub>2</sub>	11	-2.37	.037
PEB <sub>1</sub> and PEB <sub>2</sub>	11	3.22	.008*

\* $p < .017$ . \*\* $p < .003$ .

**Expiratory resistance.**  $R_e$  was considerably lower for both trials of PEB as compared to RTB for the control group (Figure 8). The greater change occurred during PEB<sub>1</sub>. By PEB<sub>2</sub>, the summary statistics suggested a recovery towards its level during RTB, although it still differed significantly from RTB. Greater variability

(standard deviation) was observed for  $R_e$  (as compared with  $R_i$ ) across both trials of RTB (Table 13).  $R_e$  during  $PEB_1$  and  $PEB_2$  did not differ significantly.



*Figure 8.* Mean inspiratory (black) and expiratory (grey) resistances for athletes without PVFM for two trials of two breathing conditions (resting-tidal and post-exercise breathing). Error bars = +/- 1 SD.

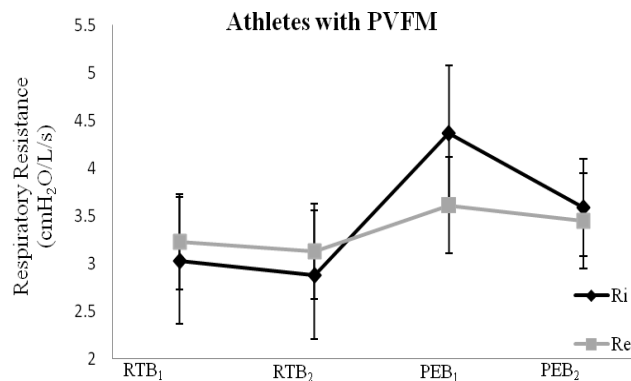
**Ratio of inspiratory to expiratory resistance.**  $R_i/R_e$  changed from a ratio < 1.0 during both trials of RTB to a ratio > 1.0 during both trials of PEB, reaching statistical significance for  $PEB_1$  in the athletes without PVFM. This is related to the proportionally greater decrease in  $R_e$  as compared with  $R_i$  during PEB.  $R_i/R_e$  also differed significantly between the two trials of PEB.

### **Within-Group Results: Athletes with PVFM (Experimental Group)**

**Inspiratory resistance.** During RTB,  $R_i$  was relatively consistent across trials for the athletes with PVFM (Table 13). Immediately following exercise, a dramatic change was observed whereby  $R_i$  was highest for  $PEB_1$ , which was then followed by a partial recovery during  $PEB_2$  toward the level of  $R_i$  during RTB (Figure 9). *Post hoc* related-samples *t*-test results (Table 18) indicated significant changes of

$R_i$  from RTB to PEB for trial 1 and trial 2, and between trials PEB<sub>1</sub> and PEB<sub>2</sub>. The average of RTB<sub>1-2</sub> was used to reduce the number of *post-hoc* paired comparisons for athletes with PVFM (based upon strong test-retest results from Study 2).

**Expiratory resistance.** The values for  $R_e$  were greater during both trials of PEB as compared with both trials of RTB. *Post-hoc* related-samples *t* tests for comparing RTB<sub>2</sub> to PEB<sub>1</sub> and PEB<sub>2</sub>, were not statistically significant after Bonferroni adjustment. The difference between PEB trials was not statistically significant.



*Figure 9.* Mean inspiratory (black) and expiratory (grey) resistances for athletes with PVFM for two trials of two breathing conditions (resting-tidal and post-exercise breathing). Error bars = +/- 1 SD.

**Ratio of inspiratory to expiratory resistance for athletes with PVFM.**

Respiratory resistance values during RTB were smaller for  $R_i$  than for  $R_e$  yielding a ratio < 1.0. The change from RTB to PEB was statistically significant for PEB<sub>1</sub> and PEB<sub>2</sub>. The two trials of PEB differed significantly as well.



Table 18.

*Post-hoc Related Samples t tests for Significant ANOVA Omnibus Results for Inspiratory Resistance ( $R_i$ ), Expiratory Resistance ( $R_e$ ) and Inspiratory-to Expiratory-Resistance Ratio ( $R_i/R_e$ ) for Athletes With PVFM.*

Contrasts	<i>df</i>	<i>t</i>	<i>p</i>
$R_i$			
Average of RTB <sub>1-2</sub> and PEB <sub>1</sub>	11	-11.64	<.001**
Average of RTB <sub>1-2</sub> and PEB <sub>2</sub>	11	-4.90	<.001**
PEB <sub>1</sub> and PEB <sub>2</sub>	11	5.85	<.001**
$R_e$			
Average of RTB <sub>1-2</sub> and PEB <sub>1</sub>	11	-2.70	.021
Average of RTB <sub>1-2</sub> and PEB <sub>2</sub>	11	-1.97	.075
PEB <sub>1</sub> and PEB <sub>2</sub>	11	1.06	.312
$R_i/R_e$			
Average of RTB <sub>1-2</sub> and PEB <sub>1</sub>	11	-5.66	<.001**
Average of RTB <sub>1-2</sub> and PEB <sub>2</sub>	11	-3.07	.011*
PEB <sub>1</sub> and PEB <sub>2</sub>	11	3.23	.002**

\* $p < .017$ . \*\* $p < .003$ .

### Between-Group Comparison Results

**Respiratory resistance during resting tidal breathing.** During both trials of RTB, athletes with PVFM had lower  $R_i$  values than the athletes without PVFM (Table 13) as illustrated in Figure 10. *Post-hoc* one-way ANOVA results for all significant group variables from the R-M ANOVAs for athletes with and without PVFM are reported in Table 19. These results revealed that during RTB, athletes with

PVFM had statistically significant lower  $R_i$  values for both trials --  $RTB_1$  and  $RTB_2$ . Likewise, athletes with PVFM had statistically significantly lower  $R_e$  values than the athletes without PVFM for both trials –  $RTB_1$  and  $RTB_2$ . The two groups did not differ significantly for  $R_i/R_e$  during  $RTB$ .

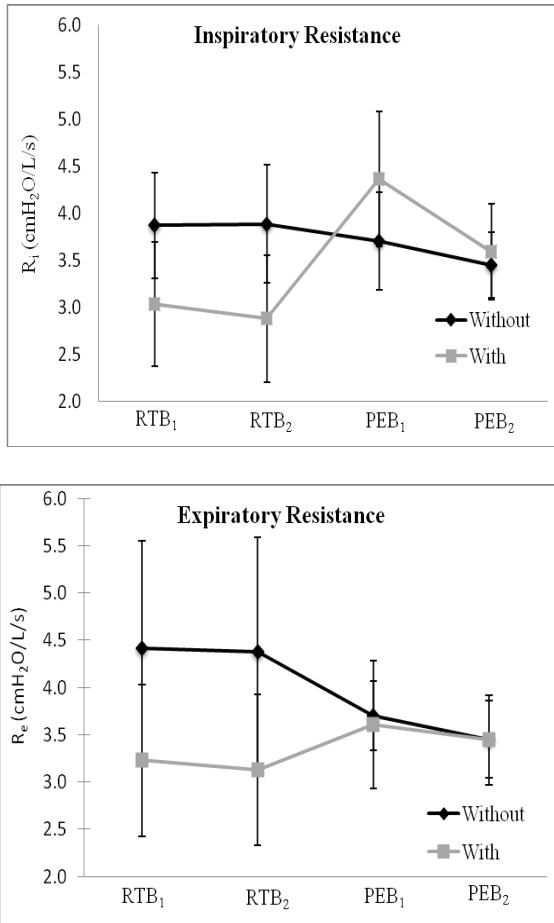


Figure 10. Mean inspiratory (top) and expiratory (bottom) resistances for two groups of athletes (with PVFM = grey; without PVFM = black) for two trials of two breathing conditions (resting-tidal and post-exercise breathing). Error bars = +/- 1 SD.

**Respiratory resistance during post-exercise breathing.** During the first trial of PEB, athletes with PVFM had substantially higher  $R_i$  values than the athletes without PVFM (who experienced a modest decrease) (Table 13) as illustrated in

Figure 10. One-way ANOVA post hoc test results (Table 19) revealed statistically significant differences for trial 1. However, by PEB<sub>2</sub>, the two groups did not differ significantly for R<sub>i</sub>. The two groups did not differ significantly for R<sub>e</sub> for either trial of PEB, although athletes with PVFM demonstrated an increase during PEB<sub>1</sub> from their R<sub>e</sub> during RTB, and athletes without PVFM demonstrated a decrease in R<sub>e</sub>. By PEB<sub>2</sub>, both groups had similar values for R<sub>e</sub>. The groups did not differ significantly for R<sub>i</sub>/R<sub>e</sub> for PEB<sub>1</sub> or PEB<sub>2</sub> (Figure 11).

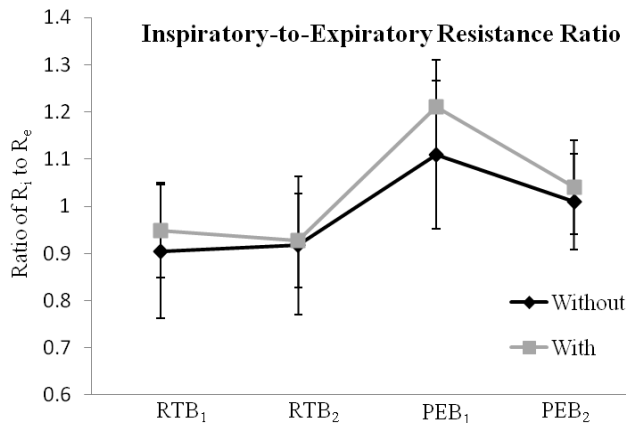


Figure 11. Mean inspiratory-to-expiratory resistance ratio for two groups of athletes (with PVFM = grey; without PVFM = black) for two trials of two breathing conditions (resting-tidal and post-exercise breathing). Error bars = +/- 1 SD.

Table 19. .

*Post-hoc Between-Group ANOVA results for Significant Univariate Omnibus Tests for Inspiratory Resistance ( $R_i$ ), Expiratory Resistance ( $R_e$ ) and Inspiratory-to-Expiratory Resistance Ratio ( $R_i/R_e$ ).*

Condition	<i>df</i>	<i>F</i>	<i>p</i>
RTB			
$R_{i1}$	1,22	11.11	.003**
$R_{i2}$	1,22	14.26	.001**
$R_{e1}$	1,22	8.66	.008**
$R_{e2}$	1,22	9.30	.007**
$R_i/R_{e1}$	1,22	0.92	.349
$R_i/R_{e2}$	1,22	0.04	.838
PEB			
$R_{i1}$	1,22	6.65	.017*
$R_{i2}$	1,22	0.65	.427
$R_{e1}$	1,22	1.41	.248
$R_{e2}$	1,22	0.00	.948
$R_i/R_{e1}$	1,22	2.67	.116
$R_i/R_{e2}$	1,22	0.51	.482

\* $p < .05$ . \*\* $p < .01$ .

**Exercise duration and Borg dyspnea ratings.** Descriptive statistics for exercise duration and dyspnea ratings from the modified Borg Dyspnea Scale are reported in Table 20. For exercise duration, an independent samples  $t$  test (one-tailed) revealed statistically significant between-group differences,  $t(22)= 3.502, p=.001$ . Athletes with PVFM discontinued the exercise challenge test sooner than the athletes without PVFM (Figure 12).

Borg dyspnea ratings differed significantly between groups, Mann-Whitney  $U= 5.00, z = -3.93, p <.001$ . On average, athletes without PVFM rated dyspnea 3.6 whereas athletes with PVFM rated dyspnea 7.4 (Figure 12).

Table 20

*Mean (and SD) Exercise Duration and Borg Dyspnea Rating in 12 Athletes without PVFM (Control) and 12 Athletes with PVFM*

Group	Control		PVFM	
	Mean (SD)	Min-Max	Mean (SD)	Min-Max
Exercise Duration (min)	10.91 (1.04)	9.08-12.00	9.04 (1.53)	5.0-10.5
Borg Rating (0-10)	3.6 (1.7)	0.5-6.0	7.4 (1.2)	5.0-9.0

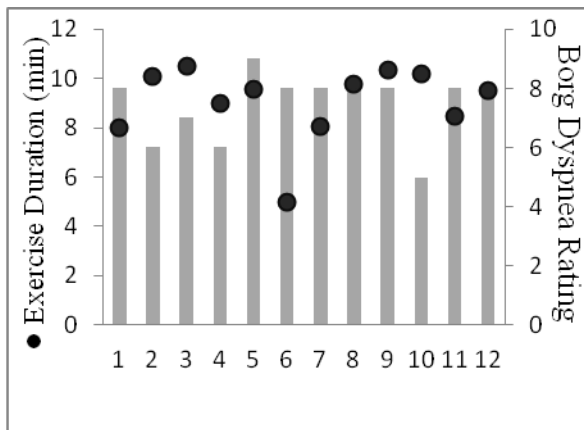
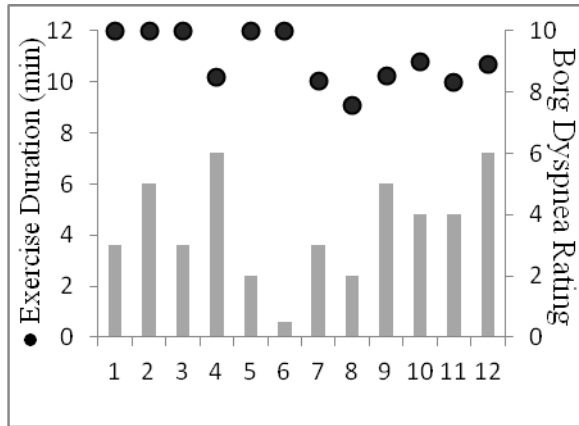


Figure 12. Exercise Duration (black circle) and Borg Dyspnea Ratings (grey bar) for the Athletes without PVFM (top) and the Athletes with PVFM (bottom).

### Discussion

This study examined respiratory resistance for athletes with and without PVFM over repeated trials before and after a customized exercise-challenge test. The primary findings before exercise were that: (1)  $R_i$  and  $R_e$  were generally consistent across trials; (2)  $R_i$  was lower than  $R_e$  for both groups; (3)  $R_i$  and  $R_e$  were lower for athletes with PVFM than for those without PVFM. After exercise, athletes without PVFM demonstrated a decrease in both  $R_i$  and  $R_e$ , whereas athletes with PVFM demonstrated an increase in  $R_i$  and  $R_e$ , with a much greater change occurring for  $R_i$ . Athletes with PVFM did not run as long as athletes without PVFM, and they rated

their dyspnea as substantially more severe than athletes without PVFM. These results are discussed in detail as follows and in relation to previous literature.

### **Athletes without PVFM**

Results for this group demonstrated remarkably consistent values of  $R_i$ ,  $R_e$ , and  $R_i/R_e$  during two 1-minute trials of RTB. Normative data for  $R_i$  obtained with the APD have been published for 534 individuals with unknown respiratory health conditions, of which 102 were between the ages of 12 and 18 years (Johnson et al., 2007). Unfortunately, the data were reported by age groups, but not separated by sex. The average  $R_i$  and  $R_e$  values in Johnson et al.'s (2007) study were 3.73 cmH<sub>2</sub>O/L/s and 4.26 cmH<sub>2</sub>O/L/s respectively, which are quite similar to the results during RTB ( $R_i = 3.92$  cmH<sub>2</sub>O/L/s and  $R_e = 4.40$  cmH<sub>2</sub>O/L/s) for the female teen athletes without PVFM in the present study.

Following exercise,  $R_i$  decreased slightly but significantly in athletes without PVFM. This exercise effect was small in the first minute after exercise, a decrease of 3.39% from RTB (when the two trials were averaged) to PEB<sub>1</sub>, yet continued to become more evident by the end of the second minute following exercise decreasing by 10.1% from RTB to PEB<sub>2</sub>. Since these control athletes had participated in three separate exercise-challenge sessions, mean values for  $R_i$  from the second and third sessions were analyzed and revealed the same pattern (Session 2 PEB<sub>1</sub>: 3.75 cmH<sub>2</sub>O/L/s, PEB<sub>2</sub>: 3.45 cmH<sub>2</sub>O/L/s; Session 3 PEB<sub>1</sub>: 3.7 cmH<sub>2</sub>O/L/s, PEB<sub>2</sub>: 3.51 cmH<sub>2</sub>O/L/s).

$R_i$  reduction that continued into the second minute after exercise in this group of healthy athletes may be explained by procedural and/or physical factors.

Immediately prior to exercise cessation, the athletes provided their final dyspnea rating. They began their first post-exercise trial within 10 seconds. They wore nose clips, secured their lips around the mouthpiece while they or the investigator held their cheeks to prevent air pocketing and air leakage around the mouthpiece. Despite their mild-to-moderate dyspnea ratings at the end of the exercise task, dyspnea may have increased markedly with the APD in place. This sense of discomfort likely lessened during the subsequent trial when breathing became less laborious. Several athletes commented on a claustrophobic feeling when using the APD immediately following exercise, while others were observed to show their discomfort by rapidly tapping their feet or drumming their fingers on the table while breathing into the APD. In response to feelings of dyspnea during  $PEB_1$ , the athletes may have increased musculoskeletal tension of the upper torso and chest wall that could feasibly increase  $R_r$ . After a minute of recovery ( $PEB_2$ ), some of the athletes appeared more comfortable and later commented on a reduced sense of dyspnea.

Silverman et al. (2005) measured respiratory resistance in 12, 18-40 year-old male and female non-asthmatic athletes before exercise and continuously for 6 minutes immediately after exercise. The results of their study indicated an “exercise effect” where  $R_i$  and  $R_e$  both decreased following exercise cessation. Although athletes in both Silverman et al.’s (2005) study and the present study experienced a decrease in  $R_i$ , the pattern of change was not the same. Within the first minute following exercise cessation,  $R_i$  decreased the most in Silverman et al.’s study (2005), with a gradual return to resting breathing during the subsequent 5 minutes that  $R_i$  was



measured. Control athletes without PVFM in the present study experienced a greater decrease in  $R_i$  during  $PEB_2$  than  $PEB_1$ .

Differences in results between these two studies may derive from differences in participants and exercise protocols. The athletes in the present study were all girls at an average age of 14 years. Both sex and age affect the anatomy and physiology of the airways and the larynx. Johnson and colleagues (2007) found that APD-measured respiratory resistance followed a decreasing trend throughout childhood, stabilizing during early adulthood, and that  $R_r$  for adult males is approximately 80% that of adult females. According to Sapienza and Huffman-Ruddy (2009), aspects of the larynx may not reach full maturity until the later teen years. Thus, it is possible that a teenage girl's upper airway may not yet have the anatomical and physiological capability to make an immediate adjustment to the increased turbulence associated with strenuous aerobic exercise.

There was also a difference in the exercise protocol between the present study and that of Silverman et al. (2005). Their treadmill exercise challenge aimed at achieving a "moderate exercise level" (p. 31) by first having the athletes participate in 5 minutes of warm-up running (at 50-60% of their age-predicted maximum heart rate) followed by a period where the treadmill speed and incline were increased at 3-minute intervals to reach 80–85% of the athlete's age-predicted  $HR_{max}$ . Once achieved, athletes ran continuously for 6 minutes. Thus, the exercise challenge designed by Silverman et al (2005), required a longer time to complete and used heart rate as the criterion for determining exercise level. The teen athletes in the present

study consistently used the same graded treadmill exercise challenge that was time limited, with the level of exercise becoming more difficult each minute.

The predicted decrease in  $R_e$  from RTB to PEB<sub>1</sub>, trending towards complete recovery to pre-exercise levels by PEB<sub>2</sub>, was observed in the athletes without PVFM. These findings are in agreement with Silverman et al. (2005). Although the vocal folds were not observed during PEB in these studies, the decrease in  $R_e$  is consistent with increased vocal fold abduction during expiration, as observed by Beaty et al. (1999), England and Bartlett (1982), and Hurbis and Schild (1991).

The predicted decrease in the ratio of inspiratory to expiratory resistance immediately following exercise was not observed for the athletes without PVFM. Because the extent and course of change in  $R_i$  from RTB to PEB was not the same as that of  $R_e$ , following exercise,  $R_i/R_e$  increased for both trials of PEB. The change from RTB to PEB for  $R_i/R_e$  was 25.1% for trial 1 and 13.22% for trial 2. Following exercise,  $R_i/R_e$  was greater than 1.0 during the first trial and approximated 1.0 during the second trial. Thus,  $R_i/R_e$  is sensitive to an exercise effect; however, it was not the negative change that was hypothesized.

Regarding the research questions for the athletes without PVFM, the results of this study demonstrated that: (1)  $R_i$  and  $R_e$  decreased following exercise with the effect being more pronounced for  $R_e$ ; and (2) the exercise effect for  $R_i$  was smaller immediately following exercise (PEB<sub>1</sub>) and became more obvious one minute later (PEB<sub>2</sub>), whereas the exercise effect for  $R_e$  was greater during PEB<sub>1</sub> than PEB<sub>2</sub>.

## **Athletes with PVFM**

During the two trials of RTB when the athletes were not experiencing symptoms of PVFM, all three dependent variables were consistent.  $R_i$  was lower than  $R_e$  suggesting that the vocal folds were abducted more during inspiration than during expiration. This observation is expected with normal laryngeal function. Following exercise, however,  $R_i$  and  $R_e$  both increased significantly.  $R_i$  increased 50% from RTB to PEB<sub>1</sub>, and 24% from RTB to PEB<sub>2</sub>, demonstrating a decrease of 26% in  $R_i$  by the end of the second post exercise trial. This is congruent with reports from direct observation of changes in glottal area during exercise among athletes with PVFM (Beaty et al., 1999; Heinle et al., 2003; Tervonen et al., 2009). Templer and colleagues (1991) altered the glottic aperture of cadaver larynges and measured airflow rates. The resistance to airflow increased as the cross-sectional area of the glottis decreased. The significant increase in  $R_r$  (especially  $R_i$ ) in athletes with PVFM in the present study supports this inverse relationship between  $R_r$  and GA demonstrated in the first study of this dissertation project. Furthermore, it is consistent with the reduction of GA that is expected during the inspiratory phase of symptomatic PVFM.

Incomplete laryngeal maturation may be another contributing factor in constriction of the laryngeal airway, and therefore, increased respiratory resistance. Young athletes with PVFM may experience supraglottic collapse of the posterior laryngeal structures into the airway, often referred to laryngomalacia. The laryngeal cartilages of the pediatric larynx are more pliable and the arytenoid cartilages are proportionately larger than the other laryngeal cartilages, allowing them to collapse

into the airway during inspiration because of negative pressure induced by the Bernoulli principle (Sapienza & Huffman-Ruddy, 2009).

$R_e$  also increased following exercise (18% and 13% from RTB to PEB<sub>1-2</sub>, respectively) in the athletes with PVFM. However, the increase was substantially smaller than the change in  $R_i$ . This coincides with reports that PVFM impacts inspiration much more than expiration (Christopher & Morris, 2010; Divi et al., 2008; Hicks et al., 2008). Like  $R_i$ , the exercise effect on  $R_e$  was most remarkable during PEB<sub>1</sub>. Post-exercise  $R_i/R_e$  revealed statistically significant changes. Because of the greater magnitude of the change in  $R_i$  from RTB to PEB,  $R_i/R_e$  becomes greater than 1.0 in the athletes with PVFM.

Results from the experimental group indicate that: (1)  $R_T$  increased following exercise presumably due to changes in GA, with a greater increase observed for  $R_i$  than for  $R_e$ ; and (2) the exercise effect for  $R_i$  and  $R_e$  was larger immediately following exercise, and started to decrease by PEB<sub>2</sub>.

### **Experimental and Control Group Comparison**

At rest, the athletes with PVFM had lower respiratory resistances than the athletes without PVFM in the present study. This difference was surprising and cannot be explained by differences in sex, age, body size, and athletic experience between the two groups because they were well-matched in these characteristics. A hypothesis for this is discussed in Chapter 5. Additional research is needed to explore this issue further. Following exercise, the groups differed significantly in  $R_i$  during PEB<sub>1</sub> only, but not in  $R_e$ . These data validated the complaints of athletes with PVFM that it is harder for them to “get air in” when they are symptomatic. Athletes without

PVFM ran for longer durations, which also indicates that they tolerated faster speeds and steeper inclines since these two factors increased progressively over time.

Borg dyspnea ratings at the end of the exercise challenge test also differed significantly between the two athlete groups, although as stated previously, athletes with PVFM were requested to exercise until they rated their breathing difficulty as 8 (7 is *very severe* and 9 is *very, very severe*). This could have artificially inflated their ratings because they knew they could stop exercising if they reported a dyspnea rating of 8, whereas the athletes without PVFM never reached a dyspnea rating of 8 within the allotted time limit. Some of the athletes in both groups stopped running, even though they gave low ratings on the Borg dyspnea scale. For example, three athletes with PVFM requested discontinuing exercise prior to reaching the requested Borg rating of 8. From the investigator's questioning of athletes from both groups, it appeared that athletes with and without PVFM had difficulty rating breathlessness exclusive from other competing sensations such as muscle fatigue. This may have been caused by the scale itself, or the instruction about the scale that was provided them. Athletes in the experimental group seemed to use the scale to rate their PVFM symptoms; whereas to the athletes without PVFM, the scale represented breathlessness and/or exertion. A future approach, if using the Borg scale for experimental and control athletes is to have athletes from both groups exercise until they reach the same dyspnea rating (e.g., 7 *severe dyspnea*), and assess group differences in exercise duration.

The modified Borg scale is commonly used to rate dyspnea in older children and adolescents with asthma or cystic fibrosis during clinical visits for diagnosis and

medication trials, as well as during exercise testing (McGrath, Pianosi, Unruh & Buckley, 2005; Wilson & Jones, 1989). Gros Lambert and Mahon (2006) found that children between the ages of 8 to 12 years can perceive 2-4 intensities of dyspnea and can separate dyspnea from other competing sensations during exertion. This suggests that using the Borg scale despite having written descriptors of the magnitude of dyspnea, may be too difficult of a task for adolescents who have not been pre-trained to use it during exercise.

A different type of scale, the Dalhousie Dyspnea Scale (DDS), may have future application for dyspnea ratings for individuals with PVFM. It is pictorial and comprises three different and separate scales – chest tightness, throat tightness, and exertion, with 7 increments per scale (McGrath, Pianosi, Unruh, & Buckley, 2005). Ratings of throat tightness and exertion based upon the DDS, may further clarify the sensations experienced during exercise of athletes with and without PVFM.

Regarding the research questions comparing the two athlete groups, it can be concluded that athletes with PVFM: 1) had significantly lower  $R_i$  and  $R_e$  during both trials of RTB, but significantly higher  $R_i$  during  $PEB_1$  as compared with the athletes without PVFM; 2) were outperformed by the control group during the exercise challenge in terms of exercise duration; and 3) reported more severe dyspnea during exercise than athletes without PVFM.

### **Caveats**

There are several limitations to this study. Ideally,  $R_r$  should be assessed during exercise rather than following exercise to truly capture the real-time exercise effect. However, the current version of the APD is not equipped to withstand the

motion associated with running on a treadmill. Therefore, it is limited to use when the participant is not exercising or is engaged in more stationary exercise such as a stationary bicycle. It is not known what effect, if any, the brief delay between stopping exercise and starting the APD has on  $R_r$ . Also, if  $R_r$  is significantly influenced by the requisite use of a mouthpiece and nose-clip, wearing an airtight mask that covers the mouth and nose might be more comfortable for the participants. This alteration comes with a critical disadvantage. The addition of the nasal airways would confound  $R_r$  measures because of the relatively small passageways and variability of the nasal airways. Finally, not all 12 athletes with PVFM were able to complete three PEB trials, resulting in the need to omit PEB<sub>3</sub> from the statistical analyses. The Clinical Center at Loyola University Maryland does not always have a physician on site to immediately manage emergency situations. The investigator decided that the risk of traumatizing and perhaps endangering the participants in this study by requiring them to complete the third PEB trial when they indicated substantial discomfort outweighed the benefits.

### **Conclusions**

This study demonstrated that APD-measured inspiratory and expiratory resistance differs across breathing conditions (rest versus exercise) and breathing trials in two groups of female teen athletes who either do or do not have PVFM. The groups differed most during resting breathing for both  $R_i$  and  $R_e$ , and immediately following exercise for  $R_i$ . Furthermore, the athletes with PVFM sensed more severe dyspnea and were unable to run as long as the athletes without PVFM.

The protocol for the exercise challenge in the present study was appropriately challenging for both groups, yet successfully differentiated the two groups. The inspiratory- to expiratory- resistance ratio did not differentiate athlete groups as anticipated during RTB or PEB, and consequently can be omitted as a dependent variable from future studies on this topic. Finally, the APD appears to be an effective and noninvasive tool for investigating PVFM because it separately measures inspiratory and expiratory resistances which can indicate glottal area changes. When attempting to identify individuals with PVFM, this has advantages over averaging resistance across the breathing cycle as do most other respiratory-resistance instruments.



## Chapter 5: General Discussion

### **Review of the Research and Results**

The overarching goal of this research is to validate an objective, non-invasive measure of respiratory resistance for identifying abnormal constriction of the laryngeal airway associated with paradoxical vocal fold motion disorder. To this end, three research questions were addressed: 1) Can the Airflow Perturbation Device provide valid and reliable measures of respiratory resistance in teenage female athletes with and without PVFM? 2) If so, does respiratory resistance for female athletes with PVFM disorder differ significantly from that of female athletes without PVFM disorder during resting breathing and following strenuous exercise? 3) Do the variables of exercise duration and dyspnea ratings, collected during an exercise challenge test, also separate the two groups of athletes?

It is widely accepted that PVFM causes complaints of dyspnea because of glottal constriction that, in turn, impacts athletic performance. The pathophysiology for PVFM is unknown. What is known is that rigorous exercise can be a triggering stimulus for the condition in athletes. Prior to this dissertation research, other investigators have observed changes in glottal area during exercise by performing continuous laryngoscopy before and throughout exercise (Beaty et al., 1999; Heinle et al., 2003; Hurbis & Schild, 1991). From video-recorded laryngeal images, they measured changes in glottal area occurring during exercise for athletes with and without breathing disorders. There are drawbacks to this method. The procedure of laryngoscopy during exercise is uncomfortable for participants, carries increased medical risk, and requires a high-level medical environment. Measuring glottal area

frame-by-frame is very time consuming, limiting the number of participants studied. Thus the challenge for the present research was finding a less invasive and more efficient way to discern changes in glottal area. Respiratory resistance seemed plausible provided that inspiratory and expiratory resistances could be separately measured since athletes with PVFM typically report that dyspnea is worse during inspiration.

The Airflow Perturbation Device, developed by Dr. Arthur Johnson and colleagues at University of Maryland, College Park, seemed a likely means for investigating respiratory resistance in athletes with PVFM. The APD had undergone several studies investigating its validity and limitations (Johnson & Sahota, 2004, Lausted & Johnson, 1999; Lopresti, et al., 2008); its capacity to separately measure inspiratory and expiratory resistance (Lausted & Johnson, 1999); and its application in healthy athletes following exercise (Silverman et al., 2005). In order to use the APD for a new application – to detect changes occurring at the glottis in female teen athletes and make comparisons with a control group – it was necessary to preliminarily investigate the validity and test-retest reliability of the APD.

The purpose of Study 1 was to determine that  $R_r$  measured by the APD was strongly correlated with glottal area. A healthy participant feigned breathing that is characteristic of severe PVFM while breathing into the APD and simultaneously undergoing transnasal flexible laryngoscopy. Three breathing cycles were analyzed by synchronizing and measuring glottal area images with respiratory resistance measures during inspiration and expiration. The results revealed a strong negative correlation ( $r = -0.824$ ) between glottal area and respiratory resistance such that

decreased glottal area was associated with increased respiratory resistance. This indicated that respiratory resistance, measured by the APD, could indirectly measure changes in glottal area caused by PVFM in athletes who do not have other competing respiratory diagnoses such as asthma.

The purpose of Study 2 was to confirm test-retest reliability of the APD to consistently assess respiratory resistance during breathing before exercise and immediately after exercise. In order to assess post-exercise breathing, an exercise challenge protocol was developed that met three criteria: a) aerobically challenge female teen athletes with and without PVFM; b) trigger PVFM symptoms in athletes having the disorder; and c) meet safety guidelines for adolescent exercise tests (Fletcher et al., 2001; Paridon et al., 2006). No existing exercise challenge “prescription” existed from the literature review, only descriptions of types of exercise challenges and their associated applications (Thompson et al., 2010). These varied by protocol (duration at each speed and workload setting), exercise mode (treadmill versus cycle ergometer), and level of difficulty (range of exercise settings, or the desired end-heart rate).

To achieve near-maximum heart rate by 12 minutes (the recommended extreme duration for pediatric exercise tests), a protocol was developed where speed or incline changed each minute. The treadmill was the preferred mode because both athlete groups participated in sports requiring running, and athletes with PVFM confirmed that their symptoms occur while running. Pilot testing determined that the range for speed, 4.0 mph – 7.0 mph, and incline, 0% - 4%, achieved the desired goals for both groups of athletes.

During the exercise challenge, the Modified Borg Dyspnea scale (Borg, 1998) was selected to monitor and quantify athletes' perceptions of dyspnea. Athletes with and without PVFM were asked to rate their sense of breathlessness on the modified Borg Dyspnea Severity Scale before starting the exercise challenge, and then at 1-minute intervals. When they sensed a change in severity, they were asked to say or use their fingers to designate a new rating (Mahler et al., 2001).

After the exercise challenge and modified Borg Scale were deemed appropriate for female teen athletes with and without PVFM, Study 2 was conducted to determine the test-retest reliability of the APD for measuring respiratory resistance. Twelve healthy, teenage, female athletes with no signs or symptoms of PVFM participated in three separate exercise sessions. Three trials of respiratory resistance were measured before exercise and immediately after exercise during each session. Twelve female teen athletes with confirmed diagnoses of PVFM participated in one session during which three trials of respiratory resistance were measured during RTB. Results revealed strong test-retest reliability ( $p < .01$ ) for inspiratory and expiratory resistance during resting tidal breathing for both groups of athletes. Immediately following exercise for athletes without PVFM, inspiratory and expiratory resistance measures remained highly reliable ( $p < .01$ ) in trials of the same order across the three sessions. This suggests that respiratory resistance is consistent for each of these breathing conditions (resting tidal breathing and post-exercise breathing), and that the respiratory system responds to exercise in a consistent manner in healthy female athletes who do not have PVFM. In addition to inspiratory and expiratory resistance, other dependent variables were also investigated in Study 2 – mean of inspiratory and

expiratory resistance ( $R_r$ ), ratio of inspiratory to expiratory resistance ( $R_i/R_e$ ), and the change from RTB to PEB for inspiratory resistance ( $\Delta R_i$ ), expiratory resistance ( $\Delta R_e$ ), mean of inspiratory and expiratory resistance ( $\Delta R_r$ ), and ratio of inspiratory to expiratory resistance ( $\Delta R_i/R_e$ ). Variables that were the most reliable and meaningful were retained for Study 3. These were  $R_i$ ,  $R_e$ , and  $R_i/R_e$ .

After establishing the reliability of APD-measured values of inspiratory and expiratory resistance and the ratio of inspiratory to expiratory resistance, Study 3 investigated the effect of exercise within and between groups of athletes with and without PVFM. Two 1-minute trials of respiratory resistance were measured before and after an exercise challenge for the purpose of observing how resistance differed from rest and changed over a 2-minute post-exercise recovery course for each group. This study also investigated exercise duration and dyspnea ratings during the exercise challenge for each group of athletes.

For athletes without PVFM (control group), both inspiratory and expiratory resistance decreased on average after the first post-exercise trial as compared with RTB, although statistical significance was only reached for expiratory resistance. By the end of the second 1-minute post-exercise trial, inspiratory resistance reached a statistically significant decrease when compared with RTB. In contrast, expiratory resistance began to increase, approaching that of RTB. The ratio of inspiratory-to-expiratory resistance was  $< 1.0$  during resting breathing, owing to a wider glottis during inspiration and laryngeal braking during expiration. Following exercise, this ratio increased significantly caused by a disproportionate decrease in expiratory as compared with inspiratory resistance. During the treadmill challenge, the control

group exercised for an average duration of 11 minutes, with five athletes completing the 12-minute challenge, and reported an average dyspnea rating of 3.6, which is between *moderate* and *somewhat severe*.

Athletes with PVFM significantly increased inspiratory resistance during both trials of post-exercise breathing as compared to RTB. By the end of the second trial of PEB, inspiratory resistance had decreased such that the change from RTB to PEB was 50% for the first trial and 24% for the second trial. Expiratory resistance also increased significantly during PEB<sub>1</sub> for the experimental group, although this increase (18%) was small when compared with that for inspiratory resistance. Most athletes with PVFM claim that once they stop exercising, their breathing becomes more comfortable. This claim was validated by the change in inspiratory resistance that occurred during the second minute following exercise cessation. The inspiratory- to- expiratory resistance ratio of <1.0 during resting breathing for athletes with PVFM suggested normal vocal fold motion for inspiration and expiration when they did not experience symptoms of dyspnea. Following exercise, the sharp increase in inspiratory resistance as compared with expiratory resistance resulted in a ratio that was >1.0. During the treadmill challenge, the athletes with PVFM exercised for an average of 9 minutes and none completed the exercise challenge. Their average dyspnea rating was 7 (*severe*).

Study 3 revealed three overall differences between athletes with and without PVFM. First, athletes with PVFM had lower inspiratory and expiratory resistance values during resting breathing than athletes without PVFM. This difference appears to be meaningful since the athletes without PVFM had  $R_r$  values during RTB that

were commensurate with those obtained for same-aged participants by Johnson and colleagues (2007). In the present study, a retrospective review of the laryngoscopic examinations performed on the athletes with PVFM by the investigator revealed that 4 of 12 of them experienced exercise-induced laryngomalacia only, while six others experienced exercise-induced laryngomalacia followed by vocal fold adductory motion. The two remaining athletes experienced vocal fold adduction without laryngomalacia. For those athletes with laryngomalacia, during exercise, it appears that high airflow rates in conjunction with the Bernoulli effect causes prolapse of the laryngeal structures impeding the glottal airway. Presumably the malleable laryngeal structures might also act to enlarge the laryngeal airway during resting tidal breathing, thus contributing to the lower respiratory resistance values for the athletes with PVFM in this study. Further study of this phenomenon is indicated by increasing the control and experimental group sample sizes while maintaining careful health screening procedures.

Second, following exercise, inspiratory but not expiratory resistance differed significantly between groups of athletes. These results validated the complaints from athletes with PVFM that they experience the most breathing difficulty during inspiration. Third, PVFM clearly impacted the experimental group's performance during the exercise challenge causing them, on average, to stop two minutes sooner than the control group because of the greater severity of dyspnea.

An additional finding initially appeared to indicate a difference between the groups, but in fact appears to reveal a similarity. Post-exercise inspiratory resistance values differed significantly between the two groups. However, the direction of

change from the first to the second post-exercise measure was the same for both groups. By the second post-exercise breathing measure, athletes with PVFM decreased both inspiratory and expiratory resistance as compared to the first post-exercise trial. This suggested that athletes with PVFM were recovering from glottal constriction and transitioning towards RTB, best illustrated by their inspiratory-to-expiratory resistance ratio that changed from 1.22 to 1.04 for PEB trials 1 and 2, respectively. Athletes without PVFM, by PEB<sub>2</sub> experienced a further decrease in inspiratory resistance while experiencing a modest increase in expiratory resistance. They too appeared to be recovering towards RTB levels, as evidenced by their inspiratory-to-expiratory resistance ratio that changed on average from 1.11 to 1.01 for PEB trials 1 and 2, respectively. Thus, although PEB inspiratory resistance values differed significantly between the two groups, they showed a similar recovery pattern as the effects of exercise resolved.

### **Method of Investigation: Limitations**

Specific limitations for each study were previously discussed as a part of that particular study, thus this section will address overall threats to validity.

**Participants.** Athletes without PVFM (control group) were self-selected and screened at the initial interview for diagnoses and/or symptoms suggestive of PVFM, asthma or other respiratory conditions. Three athletes answered positively to several of these questions and they were excluded from the study. Laryngeal examinations to confirm normal laryngeal anatomy and physiology were not required for athletes to qualify for the control group. However, including this examination would have enhanced the validity of the results. For example, one of the athletes who passed the



control group screening interview participated in two separate exercise challenges. The APD-measured respiratory resistance values following exercise for both sessions revealed a sharp increase in inspiratory resistance as compared with resting breathing that matched the profiles of athletes with PVFM. This athlete exercised for 10 minutes during the first session and 11.5 minutes during the second session, with Borg dyspnea ratings of 4 and 5 respectively. When she returned for the third session she agreed to undergo a laryngeal examination immediately after exercise. The examination revealed exercise-induced laryngomalacia (a type of PVFM), even though she denied all symptoms suggestive of glottal constriction. Based upon the results of laryngoscopy she was excluded from the study. The finding that a completely asymptomatic athlete showed evidence of PVFM upon laryngoscopy supports conducting laryngeal examinations for control subjects. On the other hand, it provided serendipitous evidence that the APD may be useful for detecting subclinical PVFM.

The second limitation for control participants is the remarkably different intervals between experimental sessions. The statistical mode between sessions was 7 days; however, many of the athletes from the control group did not come at the scheduled intervals. This potentially impacted the study's internal validity. When intervals between sessions exceeded two weeks, physical conditioning levels were subject to change if the athletes were between sports seasons or had started a different sport. Reasons for irregular attendance over three sessions included after-school sports practices, busy academic and extracurricular schedules, transportation limitations, and reduced motivation to return for the second and third sessions even

though they received payment for each session that they attended. Nevertheless, high test-retest reliability was maintained in Study 2.

The third limitation for the control participants dealt with the repetition effects of exercise challenges. Some of the participants were highly competitive and announced that their goal at each session was to complete the exercise challenge. Others who had not completed it during the first session returned to the second and third sessions desiring to beat their previous time. On the contrary, a third group recognized how difficult the exercise challenge was during their first session, and seemed to want to discontinue exercise sooner with each subsequent session. This may have impacted post-exercise group results. For ethical and safety reasons, an athlete's request to stop was one of the criteria for discontinuing exercise. Thus, this was honored for athletes without and with PVFM. Additional limitations of the study involving athletes with PVFM are associated with the exercise challenge procedures and the timing of APD use which will be discussed in the following section.

**Procedure.** The Modified Borg Dyspnea Scale was used initially for athletes with PVFM for safety purposes and to establish a ceiling for discontinuing exercise. The Loyola Clinical Center is not equipped to perform continuous laryngoscopy during exercise, making a symptom severity rating scale the primary means for the athlete to communicate the intensity of dyspnea associated with the occurrence of a PVFM episode. The Borg scale was chosen based upon a review of exercise studies (Borg, 1998; Elliott et al., 1991; Hajiro et al., 1998) and the extensive investigation leading to its development. The original scale comprises 20 ordinal ratings, but the modified scale was selected because it has fewer ratings and seemed less confusing

for teenagers. “Dyspnea” and “breathlessness”, however, are terms that are difficult to describe accurately. The instruction given to both groups by the investigator was “Please rate how out of breath you feel.” Prior to beginning exercise, athletes with PVFM were instructed to continue exercising until they reached a Borg rating of 8 (where a rating of 7 is *severe*, and 9 is *very, very severe*). The scale seemed to confuse some of the athletes with PVFM because they perceived feeling “out of breath” separately from feeling symptoms of PVFM. The investigator recognized the importance of giving better instructions for using the rating scale as the study progressed, but continued to use the same verbal instructions throughout the remainder of the study to maintain consistency. Overall, the Borg scale was not convincingly the best method for describing and rating breathlessness associated with PVFM. Teens’ accuracy of rating dyspnea may improve with a scale having fewer increments or a continuous scale, and by training teens to discriminate breathlessness from other competing stimuli that impact exercise performance. The Dalhousie Dyspnea Scale (DDS) (McGrath, Pianosi, Unruh & Buckley, 2005) may be an alternative to the Borg scale for children and adolescents with PVFM. It comprises a series of seven line drawings of the airway that illustrate incremental narrowing of the upper airway to indicate throat tightness (McGrath, Pianosi, Unruh & Buckley, 2005). The DDS will be piloted during future diagnostic exercise challenges with athletes referred with symptoms suggestive of PVFM.

The second procedural limitation also focuses on the attempt to elicit PVFM symptoms through a customized exercise protocol. The treadmill exercise test was rigorous, such that it challenged athletes with and without PVFM. This test however,

cannot replicate the physical, cognitive, or emotional demands of competitive play, nor the physical environment where the sport is played. In the future, a portable, battery-powered model of the APD may be available that would allow *in-situ* research in the environments and conditions where the athletes practice and compete, in order to better understand the contributing factors for PVFM.

An additional consideration for future studies is whether the exercise challenge protocol can reliably trigger PVFM symptoms in male athletes. Although males were not included in this study, during the time of data collection, the investigator worked clinically with three teenage male athletes (two participated in cross country, and one in football) whose PVFM symptoms could not be triggered using the same exercise protocol as in this study. Rather, they needed to sprint at high rates of speed before becoming symptomatic of PVFM which implies that a different protocol may be needed for high-level male athletes suspected of having PVFM.

Finally, the current model of the APD has inherent limitations. In Studies 2 and 3, exercise breathing was assessed after exercise stopped rather than during exercise. The APD cannot be used while running on a treadmill because it operates on alternating electric current, cannot be secured properly during movement that is associated with exercise, and requires breathing through a mouthpiece that alters natural breathing. With some modifications, the APD will become cordless and operate on DC rather than AC power. To reduce the amount of motion associated with exercising on a treadmill, a bicycle ergometer can be used instead with the APD affixed to it. Johnson is currently investigating APD-measured respiratory resistance at the end of an exercise task while participants are still active and comparing the

results with resistance values obtained immediately following exercise (A. T. Johnson, personal communication, December 27, 2011). Findings from this research will help to determine the critical timing for accurately measuring exercise-related respiratory resistance.

### **Theoretical Implications**

This dissertation research was designed to capitalize upon previous reports that found that the average age of PVFM diagnosis is 14 years (Hicks et al., 2008; Powell et al., 2000; Sandage & Zelanzny, 2004), and that it often occurs during sports where the athlete is maximally engaged in play (Heinle et al., 2003; McFadden & Zawadski, 1996). The results support previous reports that PVFM impacts inspiration more than expiration (Christopher & Morris, 2010; Divi, et al., 2008; Hicks et al., 2008), the PVFM symptoms quickly abate when exercise ceases (Beaty et al., 1999; Brugman & Simons, 1998; Rundell & Spiering, 2002), the symptoms correspond with the perception of dyspnea (Andrianopoulos et al., 2000; Hicks et al., 2008; Mathers-Schmidt & Brilla, 2005), impacting exercise performance (Brugman & Simons, 1998; McFadden & Zawadski, 1996).

For athletes who experience PVFM, exercise-induced laryngomalacia has often been described as the cause of dyspnea (Christopher & Morris, 2010; Heinle et al., 2003, Richter et al., 2008). The hypothesized etiologies of laryngomalacia include abnormal laryngeal and supraglottic neuromuscular tone (Beaty et al., 1999), tissue redundancy of the arytenoid cartilages (Richter et al., 2008), or poorly developed airway structures that tend to collapse during exercise because of increased airflow turbulence and negative pressure from the Bernoulli effect (Beaty et al., 1999;

Christopher & Morris, 2010). Interviews with athletes with PVFM often reveal that they experienced occasional episodes suggestive of PVFM in elementary or middle school when on the playground or in physical education class. However, it is not until their early teens when they show the typical PVFM symptom pattern. This coincides with participating in sports more frequently, at higher levels of competition, and playing with faster (and often older) athletes. Presumably a structural or functional laryngeal abnormality goes undetected until the respiratory system and laryngeal airway are taxed by strenuous exercise. These topics require additional investigation to support or refute clinical impressions and anecdotal reports.

Exercise-induced PVFM represents one of several recognized **types** of PVFM (Christopher & Morris, 2010). Although exercise is a direct trigger for the symptoms, the mechanism that causes glottal constriction may vary from one athlete to another. Among participants with PVFM in the current study, two athletes experienced intermittent vocal fold adduction, while the others experienced laryngomalacia either followed by vocal fold adduction, or laryngomalacia without vocal fold adduction. Although the period of laryngeal visualization following exercise is brief, and dyspnea severity level cannot be equalized across athletes, it appears that there is more than one phenomenon occurring that compromises the laryngeal airway. Currently the same label, paradoxical vocal fold motion, is used to describe involuntary adduction of the vocal folds, prolapse of the supraglottic structures into the airway (laryngomalacia), and any combination therein, for which the shared symptom is intermittent dyspnea. Thus, an initial step is to clearly define the disorder by observing and describing the type of laryngeal dysfunction so that the roles of

various triggering stimuli and the associated pathophysiology can be better understood. A better understanding of PVFM will positively impact treatment decisions and techniques.

Since PVFM disorder has traditionally been associated with partial or complete adduction of the vocal folds, treatment techniques have aimed to teach clients to volitionally abduct their vocal folds. The preferred treatment for PVFM is cognitive-behavioral therapy provided by speech-language pathologists (Brugman & Simons, 1998; Heinle et al., 2003; Sandage & Zelanzy, 2004). Brugman and Simons (1998) described the goals of therapy as teaching patients “to retrain their bodies to breathe under stress and to de-program the maladaptive pattern of PVFM” (p. 72). A brief summary of typical treatment techniques for PVFM and current understanding of their rationale follows.

Treatment begins by providing education and awareness about normal laryngeal and respiratory anatomy and physiology during comfortable breathing and when experiencing symptoms of PVFM (Brugman & Simons, 1998; Mathers-Schmidt, 2001; Pinho, Tsuji, Sennes, & Menezes, 1997). Education often attenuates fear that is associated with breathing difficulty (Sandage & Zelanzy, 2004). Behavioral techniques are aimed at retraining one’s breathing to be used preventatively or in response to the onset of PVFM symptoms. Using diaphragmatic breathing during inspiration reduces upper torso tension and is a direct contrast to upper-chest breathing that occurs during PVFM episodes (Pinho et al., 1997). It is hypothesized that increased motor drive to the diaphragm increases the abductor activity of the posterior cricoarytenoid muscle, such that purposeful diaphragmatic

breathing increases the glottal aperture (Sapienza, 2008). Inhaling through the nose, rather than through the mouth, may facilitate breathing since transnasal breathing during inspiration is a brainstem reflex linked with maximal vocal fold abduction (Andrianopoulos et al., 2000; Koufman & Block, 2008). Exhaling through pursed lips has been recommended in order to create positive pressure at the lips thus reducing laryngeal constriction at the glottis (Hicks et al., 2008). Alternately, exhaling while making a sustained hissing sound serves to provide auditory feedback of airway patency, while distracting the individual from their PVFM symptoms (Brugman & Simons, 1998; Christopher et al., 1983; Martin et al., 1987). Panting has been recommended for acute symptom management (Andrianopoulos et al., 2000; Brugman & Simons, 1998). Additional cognitive and behavioral techniques involve awareness and release of upper torso and laryngeal muscle tension through progressive relaxation (Mathers-Schmidt, 2001; Sandage & Zelanzny, 2004) and laryngeal massage (Aronson, 1990; Roy & Leeper, 1993).

Ever since Martin and colleagues (1987) pioneered the development of a treatment protocol for patients with PVFM, SLPs have continued to employ techniques from this protocol to PVFM treatment, despite unclear rationales for using the techniques and a lack of evidence for treatment efficacy. However, it is unknown if the same techniques designed to volitionally abduct the vocal folds are effective for exercise-induced laryngomalacia. Yet until the disorder is further clarified, there is no clear theoretical basis for the mechanism behind SLP-delivered therapy for PVFM. At best, qualitative and quantitative data from patient interviews and exercise challenges can provide outcome measures for treatment effectiveness. This basic research



involving the APD supports the potential for APD-assisted quantitative assessment of PVFM.

### **Clinical Implications**

Several diagnostic implications from this study have direct clinical application. The exercise challenge protocol appears to be a safe and effective way to trigger exercise-related PVFM symptoms in female teen athletes. Purposely triggering athletes' symptoms through using the exercise challenge provided a safe opportunity for the athlete to "show" the investigator her symptoms. A potential disadvantage is that administering the exercise challenge requires minimally two staff members – one to stand beside the treadmill to adjust the speed and incline while also recording data, and the other to stand behind the treadmill to ensure safety and prepare for post-exercise APD use.

Also, the results revealed two important questions that should be asked by the diagnostician during the patient interview for differentially diagnosing PVFM, especially when laryngoscopy and/or respiratory resistance instrumentation is unavailable. One is whether it is harder to inhale or exhale when experiencing dyspnea. This may require that the patient demonstrate her breathing when experiencing dyspnea since she may be confused by respiratory terminology. Although the athletes in this study experienced an increase in both inspiratory and expiratory resistance following exercise, clearly the greater difference occurred during inspiration. Thus, athletes stating that both breathing phases are equally hard, or that it is harder to exhale than inhale, most likely do not have PVFM unless it is accompanied by an additional condition. The patient should also be asked how soon

after exercise breathing become easier. For the athletes with PVFM in this study, by the end of the second post-exercise breathing trial, inspiratory resistance had decreased which coincided with the investigator's observations that they were breathing more comfortably.

Finally, the APD may be useful for both diagnostic and treatment applications. It offers the potential to screen athletes (and non-athletes) complaining of dyspnea so that preliminary medical referrals can be made. It also may contribute to the collection of treatment-outcomes data by measuring changes in respiratory resistance over time for athletes with PVFM. The APD gives near-real-time measures of inspiratory and expiratory resistance with only a 5-second delay, making it potentially useful as a biofeedback device as well. Patients with PVFM can practice breathing techniques while simultaneously monitoring inspiratory and expiratory resistance using the APD. To have maximum utility, the APD needs to provide immediate data display, become cordless by running on rechargeable batteries, and store data without connecting to a computer so that it can be used as a stand-alone unit.

### **Implications for Future Research**

This dissertation research has preliminarily shown that respiratory resistance can be quantified reliably and interpreted meaningfully in young athletes with PVFM. Currently, the results from Studies 2 and 3 may be generalized to teenage females who participate in a variety of sports and whose PVFM symptoms are triggered by exercise. Proposed studies that target diagnostic aspects of PVFM will be discussed first followed by a discussion of treatment studies.

Study 1 used a healthy participant feigning PVFM breathing to assess the validity of the APD to detect glottal area change during simultaneous laryngoscopy. This study should be repeated in patients with PVFM who demonstrate either laryngomalacia or glottal constriction or a combination of the two conditions to establish the validity and sensitivity of the APD in diagnosing PVFM. This type of study will require transnasal flexible laryngoscopy with simultaneous APD-measured respiratory resistance during exercise. The changes in laryngeal airway and respiratory resistance during exercise would allow observation of airway physiology and respiratory response before, during, and after onset of PVFM. Because of the risks associated with transnasal laryngoscopy, this experiment needs to be conducted at a medical facility with emergency medical personnel present.

With regard to furthering an understanding of differences between athletes with and without PVFM, Studies 2 and 3 should be replicated and expanded to include a larger sample of females. Study 2 revealed that during resting breathing, female athletes with PVFM had lower inspiratory and expiratory resistance than their matched controls without PVFM. This may imply an underlying difference in laryngeal anatomy and physiology. Studying a larger sample of teenage female athletes will verify this finding. A similar study of male athletes is also needed. Significantly more female athletes are referred for diagnosis and treatment of PVFM than males. Reported female-to-male ratios range from 2:1 (Hicks et al., 2008), to 4:1 (Powell et al., 2000), to 9:1 (Patel et al., 2004). It is important to know the reasons for between-sex differences and whether treatment options would vary depending upon the sex of patients affected by PVFM.

Athletes with exercise-induced PVFM are frequently misdiagnosed as having exercise-induced asthma (Andrianopoulos et al., 2000; Brugman & Simons, 1998; Mathers-Schmidt, 2001). To provide appropriate treatment and prevent unnecessary utilization of medical resources, a study should be conducted to assess APD-measured respiratory resistance during resting tidal breathing and post-exercise breathing in female and male teenage athletes diagnosed with exercise-induced asthma. This will provide insightful information regarding the differential diagnostic capability of the APD.

For athletes with PVFM, especially those with laryngomalacia, longitudinal research will provide insight into whether the condition is related to immaturity of laryngeal structures and as such can be “outgrown.” This should be done by studying girls diagnosed with PVFM disorder beginning by age 14 and following them through high school, assessing laryngeal function and respiratory resistance during exercise in conjunction with height and weight measurements at 6-month intervals.

PVFM has been reported in adult women who have reached maturity (Altman et al., 2000; Christopher et al., 1983; Gallivan et al., 1994; Gurevich-Uvena et al., 2010; Newman et al., 1995). To determine if adult women with PVFM are more likely to have problems related to vocal fold movement, a study that compares them with teenage girls for the type of laryngeal obstruction may answer these questions and guide the treatment decision-making process.

Diagnostic findings can influence the development of treatment techniques. Treatment outcomes for PVFM need to be researched. Quantitative and qualitative outcome measures can be used to evaluate treatment outcomes in randomized,

controlled clinical trials. The investigator conducted a pilot treatment study that provided a glimpse at the challenges associated with adopting various types of measures. Four teenage female athletes engaged in a standard behavioral treatment program focused on breathing techniques, while also providing qualitative (e.g., dyspnea ratings) and quantitative (APD) data. The qualitative data (self-reported ratings of practice, frequency and severity of symptoms, and sense of breathing control) from these four athletes suggested that practicing the breathing techniques learned during therapy was associated with the athletes' sense of breathing control, and inversely related with self-reported frequency of PVFM symptoms. However, exercise duration and post-exercise respiratory resistance measures did not support the athletes' self-reported improvement. The athletes were required to perform the exercise challenge test during each of the four or five sessions attended. The test was difficult for them and may have caused mounting performance anxiety with each subsequent test that negatively impacted exercise duration and respiratory resistance measures. Prior research has shown an association between anxiety and respiration patterns (i.e. increased respiratory rate, reduced respiratory depth, and decreased end-tidal CO<sub>2</sub>) (Boiten et al., 1994). Likewise, anxiety is associated with increased musculoskeletal tension to which the larynx is vulnerable (Aronson, 1990). Repeated trials of the exercise test may be comparable to the "white coat syndrome" where people experience hypertension caused by the anxiety of having their blood pressure taken at a medical doctor's office (Glen, Elliott, Curzio, Lees, & Reid, 1996).

With the capacity of APD to measure changes in the laryngeal airway indirectly, a treatment study should include use of APD measures. What is learned

from the present study suggests incorporating several changes for a better design: (1) selecting athlete participants who are active in their sport for minimally two consecutive seasons so that their level of athleticism remains consistent for a longer time frame; (2) requesting that they attend four sessions (including the initial diagnostic/treatment session) scheduled at 2 week intervals and providing an incentive for them to maintain regular attendance; (3) having a collaborator conduct the athlete interviews during the three treatment sessions (sessions 2-4) so that the researcher is blinded to the athletes' ratings of PVFM status and the athlete does not have to tell her ratings directly to the researcher; (4) administering the exercise challenge test at the first and last sessions only, to reduce possible effects of anxiety on the results; and (5) establishing an incentive-based method for athletes to document their daily therapy practice through an online survey or handwritten chart so that the amount and conditions of practice can be quantified for statistical analyses. Thus, a future treatment study will implement the proposed changes while retaining and refining the effective aspects of the pilot study.

## **Conclusion**

In conclusion, through a series of three studies, this research validated an objective and non-invasive measure of respiratory resistance that may detect abnormal constriction of the laryngeal airway associated with paradoxical vocal fold motion disorder. This research demonstrated that (1) respiratory resistance measured by the Airflow Perturbation Device negatively correlates with glottal area (GA) assessed through laryngoscopy; (2) there is strong intra- and intersession test-retest

reliability of APD-determined  $R_r$  for a control group of healthy female teenage athletes during resting tidal breathing (RTB) and post-exercise breathing (PEB); and (3) immediately following exercise, inspiratory resistance, exercise duration, and dyspnea ratings differ between healthy athletes without PVFM and athletes with PVFM matched for sex, age, and sport activity level.

These findings set the foundations of a new method to study exercise-induced PVFM. Inspiratory and expiratory resistance can be reliably and validly measured with the APD. Furthermore, symptoms of PVFM can be induced using a customized exercise protocol and monitored with a self-reported dyspnea rating scale. This, then, sets the basic methodology for future studies of exercise-induced PVFM and its treatment outcome, which can be expanded to other types of PVFM in various patient populations.

**Appendix A**  
Interview for Control Athletes who do not have PVFM

Sport	Level of Play participation				Number of seasons			
1.	JV	V	Club	Elite	1	2	3	year round
2.	JV	V	Club	Elite	1	2	3	year round
3.	JV	V	Club	Elite	1	2	3	year round

Sport(s) currently participating in \_\_\_\_\_

When exercising do you regularly experience any of the following? (Please assign severity (S) and frequency (F) ratings for each symptom from the table below)

Feeling	Rating	Feeling	Rating
Difficulty getting your breath	S F	Hyperventilating (fast breathing with dizziness)	S F
Feeling like your throat is closing	S F	Feeling like your chest is tight	S F
Making a noise in your throat	S F	Hearing a wheezing noise in your chest	S F

**Severity Rating:**

- 0 No problem
- 1 Had breathing difficulty, but continued activities at the same pace and intensity
- 2 Had to slow down temporarily because of breathing difficulty; but remained in play
- 3 Had to come out of play; breathing difficulty lasted shorter than 5 minutes
- 4 Had to come out of play, felt scared and lacking control of symptoms; breathing difficulty lasted 5-10 minutes
- 5 Had to come out of play, felt panic and no control of symptoms; breathing difficulty lasted longer than 10 minutes

**Frequency Rating**

- 0 never    1 seldom    2 occasionally    3 often    4 very often    5 always



Medical/Psychological History - conditions that have been diagnosed by a medical doctor or a psychologist/psychiatrist. (Please circle)

- |                            |  |
|----------------------------|--|
| Asthma                     | Allergies                                  |
| Chronic post nasal drip    | Reflux                                     |
| Chronic cough              | Chronic hoarseness                         |
| Attention deficit disorder | Attention deficit disorder & hyperactivity |
| Anxiety                    | Depression                                 |
| Other Medical              | Other Psychological                        |

What medications are currently being taken for the above conditions? Indicate when you last took each of these medications.

- |    | Medication | Last Taken |
|----|------------|------------|
| 1. |            |            |
| 2. |            |            |
| 3. |            |            |

Rate your health today (please circle)

Fine                      OK                      Not feeling well                      Sick

If you are willing to share your race and ethnicity, please circle the appropriate category(ies).

Native American	Asian	Black/African American
Hispanic	White	Native Pacific Islander
Other		

## Appendix B

### Interview for Athletes Referred for Paradoxical Vocal Fold Motion Disorder

1. History of the problem:
2. Under what conditions does PVFM occur?
  - Exercise yes / no
  - Sports played:                      Level:                      Seasons/yr:
  - Sports where PVFM is experienced:
  - Conditions where PVFM occurs: practice                      competition
  - Non-exercise yes / no    what conditions?
3. Identify symptoms:
  - Harder to breathe in / out / both                      Dizziness    yes / no
  - Stridor    yes / no    Numbness/tingling    yes / no
  - Throat tightness    yes / no                              Cough    yes / no
  - Voice Change/Loss during episode    yes / no
4. Rate the usual severity of your episode:
  - Mild: aware of breathing difficulty but can continue at my current activity level
  - Mild-Moderate: breathing difficulty interferes with activity requiring me to slow or stop; I stay on the field or in the pool
  - Moderate: symptoms interfere, requiring me to stop my activity and request time out;  $\leq 5$  min. recovery time needed before comfortable breathing returns
  - Moderate-Severe: symptoms require stopping activity, I feel scared and have a reduced sense of control of my breathing;  $> 5$  but  $\leq 10$  minutes needed before comfortable breathing returns
  - Severe: symptoms require stopping activity, I feel a sense of panic and a lack of control of my breathing no sense of control of breathing;  $> 10$  minutes needed before comfortable breathing returns.
5. Rate the frequency of your episodes:
  1. Seldom: rarely happens when I exercise at a hard level
  - 2 – Occasional: happens occasionally when I exercise at a hard level
  3. Sometimes: happens about half of the time I exercise at a hard level
  - 4 – Frequent: happens almost every time I exercise at a hard level
  - 5 - Very frequent: happens every time I exercise at a hard level (games & practices)
6. Rate your sense of control that you feel during a usual episode?

4 (full control)	3 (almost	2 (moderate control)	1 (some control)	0 (no control)
100%	full control)	50%	25%	0 – 10%
	75%			
7. Can you predict an episode? If so, what are the first symptoms?

8. Do the symptoms begin suddenly or gradually? (Estimate time from warning signs until episode)

9. Describe a usual episode. Describe your most severe episode. Have you required emergency intervention?

10. Do you experience repeat episodes within the same practice or game?

11. Are you currently using asthma medications? Do they seem to help?

12. What do you do to stop an episode? How long does it take for symptoms to subside?

### MEDICAL HISTORY

1. Indicate the specialists that have been consulted for this problem:

Asthma/Allergist  
Ear/Nose/Throat  
Speech-Language  
Pathologist

Pulmonologist  
Cardiologist  
Other:

Gastroenterologist  
Psychologist/Counselor

2. Indicate concurrent medical conditions:

Asthma  
Allergies  
Reflux  
Hoarseness  
Other:

Post-nasal drip  
Heart problem  
Back problem  
Depression

Shin splints  
Joint problems  
Chronic cough  
Anxiety

3. List all medications that are currently taken and date and time of last dose:

## Appendix C

### Exercise Challenge Data Recording Form

Participant Number: \_\_\_\_\_

Date: \_\_\_\_\_

Session # \_\_\_\_\_

Group: PVFM\_\_\_\_\_ Control: \_\_\_\_\_

Age: \_\_\_\_\_ Height: \_\_\_\_\_ Weight: \_\_\_\_\_ HR<sub>max</sub>  
\_\_\_\_\_

Consent signed: yes/no    Assent signed: yes/ no    Questionnaire completed:  
yes/ no

Name of Grad SLP assistant: \_\_\_\_\_

	Time (min)	Speed (mph)	Incline %	Symptom Borg 0–10	Heart rate (bpm)
<i>Pre-exercise</i>					
Exercise	0-1 min.	4.0	0%		
	1-2 min.	4.0	1%		
	2-3 min.	5.0	1%		
	3-4	5.0	2%		
	4-5	5.5	2%		
	5-6	5.5	3%		
	6-7	6.0	3%		
	7-8	6.0	4%		
	8-9	6.5	4%		
	9-10	6.5	4%		
	10-11	7.0	4%		
11-12	7.0	4%			
<i>Post-exercise</i>	<i>3 min.</i>				

Duration of exercise challenge: \_\_\_\_\_ minutes \_\_\_\_\_ seconds

Comments:

## List of Abbreviations

$\Delta R_r\%$	Change in respiratory resistance measured in percent
APD	Airflow Perturbation Device
CCC	Cross correlation coefficient
E-IA	Exercise-induced asthma
GA	Glottal area
GERD	Gastro-esophageal reflux disease
ICC	Intraclass correlation coefficient
LCC	Loyola University Clinical Centers
LPR	Laryngo-pharyngeal reflux
PEB	Post-exercise breathing
PFTs	Pulmonary function tests
PVFM	Paradoxical vocal fold motion
R	Mean of inspiratory and expiratory resistance
$R_e$	Expiratory resistance
$R_i$	Inspiratory resistance
$R_i/R_e$	Ratio of inspiratory to expiratory resistance
$R_r$	Respiratory resistance
RTB	Resting tidal breathing

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