# COMPARISON OF SWALLOWING OUTCOMES IN SINGLE VS. DOUBLE LUNG TRANSPLANT RECIPIENTS

by

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Swallowing is a physiologically complex, kinematic process that requires highly coordinated activity of numerous nerves and muscles to execute efficient transport of a bolus from the oral cavity to the stomach. Dysphagia, or a difficulty with swallowing, is a concern following lung transplantation due to the high risk of recurrent laryngeal nerve damage, required levels of life-long immunosuppression, and upper airway trauma secondary to prolonged endotracheal intubation (Pomfret, 2016). Post-operatively, repetitive aspiration events can lead to the development of Bronchiolitis Obliterans Syndrome (BOS), a major contributing factor in acute allograft rejection and long-term failure of lung allograft function. The goal of this descriptive, retrospective study is to describe the characteristics of double lung transplant (DLT) swallows through analysis of kinematic swallow durations, airway protection, and physiologic swallow impairments. These results are compared to single lung transplant (SLT) swallow characteristics and two previously published, historical normal cohorts. By explicitly describing the swallow physiology of DLT and SLT recipients, clinically significant risk factors have been identified to assist clinicians and researchers in the development and implementation of better treatment options and safer swallowing strategies post-operatively. These efforts can improve the functional lifespan of the newly transplanted organ and increase patient quality of life.

## TABLE OF CONTENTS

## LIST OF TABLES

**LIST OF FIGURES**

## PREFACE

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# 1.0 INTRODUCTION

Lung transplantation is an established standard of care to manage end-stage pulmonary diseases such as obstructive lung disease, septic lung disease, fibrotic lung disease, and vascular lung disease (Atkins et al., 2010; Yeung & Keshavjee, 2014). Given the relationship between the digestive and respiratory functions of the aerodigestive tract, postoperative disruption of swallowing function has been shown to be a relatively common, clinically significant adverse outcome in the lung transplant population (Baumann et al., 2017).

## 1.1 SWALLOWING & DYSPHAGIA

Swallowing is a physiologically complex, kinematic process. It requires highly coordinated activity of more than thirty nerves and muscles to execute efficient transport of a bolus from the oral cavity to the stomach. This is typically a synchronized sequence, however, damage to sensorimotor processing centers, sensory or motor signals via the cranial nerves, other peripheral nerves, or anatomical abnormalities can result in a disruption of swallowing or “dysphagia” (Coyle, 2008).

Swallowing is artificially separated into four stages to describe physiologic events occurring within a one-to-two second timeframe. Each stage is defined by the location of the bolus in the swallowing mechanism. The kinematic movements of oral, pharyngeal, and esophageal structures can be observed radiographically during the swallow (Matsuo & Palmer, 2009). The swallow begins with the *oral preparatory stage*; the material enters the oral cavity via spoon, straw, or cup and is masticated and prepared for efficient oral transit. At the onset of the *oral transit stage*, the bolus is propelled posteriorly by the tongue to allow the bolus to enter the posterior oral cavity. The bolus then passes the boundary of the faucial pillars and enters the *pharyngeal stage*. The pharyngeal stage consists of a rapid sequence of kinematic events to propel the bolus toward the next segment of the digestive system and to protect the airway (Kim, McCullough, & Asp, 2005). After the bolus tail passes through the opening of the upper esophageal segment (UES), the *esophageal stage* begins a series of peristaltic contractions to propel the bolus toward the stomach.

A swallow is disordered if there is abnormal obstruction of bolus flow or if incoordination occurs (Coyle, 2012). *Oropharyngeal* is one classification of dysphagia. It is often characterized by complaints of difficulty initiating a swallow, transitioning the bolus into the esophagus, meal-induced coughing/choking, or the sensation of "food getting stuck" immediately after swallowing (Ferguson & DeVault, 2004; Kotloff & Thabut, 2011; Pomfret, 2016). The transportation of the bolus through the four stages of swallowing is typically a coordinated sequence. The swallowing process may be partially or totally disrupted by damage to central sensorimotor processing centers, sensory or motor signals via the cranial nerves, other peripheral nerves, or anatomical abnormalities (Coyle, 2008). This disables efficient transfer of the bolus into the esophagus and digestive system; it may also lead to abnormal transfer of swallowed material into the airway and lungs (Kim et al., 2005). This misdirection of material may lead to penetration or aspiration; aspiration can lead to airway obstruction and pulmonary consequences (Matsuo & Palmer, 2009).

## 1.2 EVALUATION OF SWALLOWING FUNCTION & IMPAIRMENT

The videofluoroscopic swallowing examination (VFSS) is a valuable and reliable tool for assessment of the oropharyngeal swallowing (Eisenhuber et al., 2002). It has been accepted as the gold standard for evaluating disordered swallowing. VFSS provides real-time x-ray imaging of the oral and pharyngeal stages that can be recorded and analyzed through digital image processing software programs (Pomfret, 2016). The frame-by-frame, second-by-second precision allows clinicians and researchers to pinpoint specific physiologic events that fleetingly occur during the swallow and judge direction of bolus flow.

### 1.2.1 Modified Barium Swallow Study

The evaluation of the oropharyngeal swallow using videofluoroscopy is called a modified barium swallow study (MBSS) (Lof & Robbins, 1990). Patients consume specific amounts of radiopaque substances or barium for clinicians to visualize and diagnose impaired swallow physiology. Different volumes and consistencies are used to characterize swallowing kinematics and reflect materials that may be swallowed during a regular meal (Kim et al., 2005). The MBSS is inconsistently part of the post-operative evaluation for patients who have undergone a lung transplant (Atkins et al., 2010).

#### 1.2.1.1 Swallow Kinematic Assessment

Analysis of the MBSS recorded swallows involves measurement of various kinematic swallowing durations. Durations are comprised of swallow events and are measured by the timing of kinematic events in relation to one another. Duration events are measured by logging the time when the barium or bolus reaches a specific anatomical landmark or when oropharyngeal structures initiated, reached, or terminated maximal movements during the swallow (Table 1) (Lof & Robbins, 1990). Several temporal descriptions of oropharyngeal swallowing are used in clinical research to characterize typical swallowing patterns (Lof & Robbins, 1990). Events that require measurement of bony structures (Table 1: 1-4) are more reliable than soft tissue landmark-dependent durations (Table 1: 5-8) due to videofluoroscopy quality and clarity. Departures from these normal swallow characteristics give insights into assessment of pathological changes in swallowing function from disease states, idiopathic, or iatrogenic origin. The durations used in the present study were defined by Lof, Robbins, and colleagues (Table 2).

Duration of stage transition (DST) is the measure of the coupling of the voluntary oral stage to the involuntary pharyngeal stage and is a common index of the duration of delay in the onset of the pharyngeal stage (Lof & Robbins, 1990; Pomfret, 2016). It measures the time the propelled bolus is in the pharynx before the swallow begins (Coyle, 2008). The duration is calculated by subtracting the time at which the hyoid begins its maximal pharyngeal-stage related excursion from the time the first bolus head enters the pharynx as indicated by crossing the radiographic shadow of the mandibular ramus (Lof & Robbins, 1990).

Pharyngeal response duration (PRD) is a measure of pharyngeal physiological activity. It is measured by calculating hyoid movement from the time the hyoid begins its maximal pharyngeal excursion to the time the hyoid returns to rest at the end of the pharyngeal response (Lof & Robbins, 1990).

Pharyngeal transit duration (PTD) is the duration in which the swallowed material travels through the pharynx and is measured by subtracting the time at which the bolus tail passes through the upper esophageal sphincter from the time at which the first bolus head crosses the mandibular ramus (Lof & Robbins, 1990; Pomfret, 2016). PTD is reported as the most reliable or least variable duration by Lof & Robbins because of the structures used to calculate the duration.

Duration of upper-esophageal sphincter opening (DUESO) is the duration of the onset of UES opening to onset of UES closure. This is found by calculating the time between UES opening and closure (Lof & Robbins, 1990; Mendell & Logemann, 2007).

**Table 1. Discrete measures of biomechanical events used to compute durations**

| Swallow Event | |
|---|---|
| *Oral Events* | |
| 1 | First Barium Cross Ramus |
| 2 | First Bolus Cross Ramus |
| *Pharyngeal Events* | |
| 3 | First Hyoid Max |
| 4 | Hyoid to Rest |
| *UES Events* | |
| 5 | UES First Prox Open |
| 6 | Head into UES |
| 7 | Tail through UES |
| 8 | UES Closed |

**Table 2. Formulae for computing durations**

| Durations | |
|---|---|
| (3-2) | Duration of Stage Transition (DST) |
| (4-3) | Pharyngeal Response Duration (PRD) |
| (7-2) | Pharyngeal Transit Duration (PTD) |
| (8-5) | Duration of UES Opening (DUESO) |

#### 1.2.1.2 Penetration-Aspiration Scale

The Penetration-Aspiration Scale (PAS) a standard method of describing and measuring the severity of airway invasion during swallowing (Robbins, Coyle, Rosenbek, Roecker, & Wood, 1999; Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996; Steele & Grace-Martin, 2017). This measure provides an estimate of potential exposure of the respiratory tissues to swallowed material that has entered the airway. Rosenbek and colleagues developed the penetration-aspiration scale (PAS) to characterize the severity of airway compromise during swallowing by observing the course of swallowed material (Table 3) (Rosenbek et al., 1996). This information is based on whether material remains at the end of the swallow or has been ejected to safer (anatomically higher) locations (Steele & Grace-Martin, 2017).

Penetration-aspiration scale scores are determined by analyzing videofluoroscopic images. This measure helps to characterize a patient's airway protection competence using an eight-point scale (McCullough, 1998). The PAS identifies depth to which swallowed material enters and courses into the airway, specifies presence of airway residue after the swallow ends, and identifies whether there is an overt reflexive response to material entering the airway (Pomfret, 2016). Clinically, PAS scores are a relevant indicator of pulmonary aspiration and provide a component to the prognosis of aspiration pneumonia risk. Aspiration severity and impaired swallowing physiology seem to be closely linked. Identification of the severity of the aspiration and the biomechanical causes of impaired airway protection help to pinpoint the nature of dysphagia and lead to more accurate prognostic statements as well as intervention options to mitigate airway compromise during swallowing.

**Table 3. Penetration-aspiration scale as defined by Rosenbek et al., 1996**

| PAS Definitions | |
|---|---|
| *Score* | *Definition* |
| 1 | Material does not enter the airway |
| 2 | Material enters the airway, remains above the vocal folds, and is ejected from the airway |
| 3 | Material enters the airway, remains above the vocal folds, and is not ejected from the airway |
| 4 | Material enters the airway, contacts the vocal folds, and is ejected from the airway |
| 5 | Material enters the airway, contacts the vocal folds, and is not ejected from the airway |
| 6 | Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway |
| 7 | Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort |
| 8 | Material enters the airway, passes below the vocal folds, and no effort is made to eject |

### 1.2.1.3 The Modified Barium Swallow Impairment Profile (MBSImP)

The Modified Barium Swallow Impairment Profile (MBSImP) is an evidence-based, standardization of the performance and interpretation of the MBS study in adults (Martin-Harris et al., 2008). The MBSImP assesses 17 critical components of swallowing and provides an objective profile of the physiologic impairment affecting adult swallow function. MBSImP provides a means for clinicians to communicate MBSS results in a standardized manner that is consistent, specific, and accurate. MBSImP is a standardized approach to instruction, assessment, and reporting of physiologic swallowing impairment.

9 of the 17 components of MBSImP can be used to describe potential swallowing impairments for the stages of oropharyngeal swallowing, from the initiation of the pharyngeal stage through the pharyngeal stage (Table 4). The following definitions are from the MBSImP program training materials. Initiation of pharyngeal swallow (IPS) is defined by the first, brisk, hyolaryngeal excursion trajectory or first hyoid movement in relation to the location of the bolus

head in the pharynx. Soft palate elevation (SPE) is scored by observing the height of soft palate movement, the point of maximal upward and retracted movement to specifically score maximal soft palate displacement. Laryngeal elevation (LE) is scored by following the movement of thyroid cartilage by assessing upward movement of the larynx. Anterior hyoid excursion (HM) is measured as the completeness of anterior movement and alignment of hyoid to the thyroid cartilage. Epiglottic movement (EM) is scored as the completeness of inversion. Laryngeal vestibule closure (LC) requires the clinician to look for material or airspace in the laryngeal vestibule between the arytenoid cartilage and epiglottic base at the height of the swallow (moment of maximal, anterior hyoid displacement). Pharyngoesophageal segment opening (PESO) is observed at maximal opening by following the symmetric flow of the bolus as well as the degree and duration of PE segment opening. Tongue base excursion (TBR) in combination with the pharyngeal stripping wave as the soft palate is maximally displaced. The composite pressure is important for bolus propulsion. Tongue base (TB) retraction scores the completion of tongue base to posterior pharyngeal wall contact. Pharyngeal residue (PR) is the score made after the initial swallow (baseline impairment). This is quantified by the amount of contrast/ barium that remains in the pharynx after the initial swallow.

**Table 4. Components, scores, and score definitions of MBSImP**

| The Modified Barium Swallow Impairment Profile: MBSImP | |
|---|---|
| *Oral Impairment* | |
| Initiation of Pharyngeal Swallow (IPS) | 0 = Bolus head at posterior angle of ramus (first hyoid excursion)<br>1 = Bolus head in valleculae<br>2 = Bolus head at posterior laryngeal surface of epiglottis<br>3 = Bolus head in pyriform<br>4 = No visible initiation at any location |
| *Pharyngeal Impairment* | |
| Soft Palate Elevation (SPE) | 0 = No bolus between soft palate (SP)/ pharyngeal wall (PW)<br>1 = Trace column of contrast or air between SP and PW<br>2 = Escape to nasopharynx<br>3 = Escape to nasal cavity<br>4 = Escape to nostril with/without emission |
| Laryngeal Elevation (LE) | 0 = Complete superior movement of thyroid cartilage with complete approximation of arytenoids to epiglottic petiole<br>1 = Partial superior movement of thyroid cartilage/ partial approximation of arytenoids to epiglottic petiole<br>2 = Minimal superior movement of thyroid cartilage with minimal approximation of arytenoids to epiglottic petiole<br>3 = No superior movement of thyroid cartilage |
| Anterior Hyoid Excursion (HM) | 0 = Complete anterior movement<br>1 = Partial anterior movement<br>2 = No anterior movement |
| Epiglottic Movement (EM) | 0 = Complete inversion<br>1 = Partial inversion<br>2 = No inversion |
| Laryngeal Vestibular Closure – Height of Swallow (LC) | 0 = Complete; no air/ contrast in laryngeal vestibule<br>1 = Incomplete; narrow column air/contrast in laryngeal vestibule<br>2 = None; wide column air/ contrast in laryngeal vestibule |
| Pharyngoesophageal Segment Opening (PESO) | 0 = Complete distension and complete duration; no obstruction of flow<br>1 = Partial distension/ partial duration; partial obstruction of flow<br>2 = Minimal distension/ minimal duration; marked obstruction of flow<br>3 = No distension with total obstruction of flow |
| Tongue Base Retraction (TBR) | 0 = No contrast between TB and posterior pharyngeal wall (PPW)<br>1 = Trace column of contrast or air between TB and PW<br>2 = Narrow column of contrast or air between TB and PW<br>3 = Wide column of contrast or air between TB and PW<br>4 = No visible posterior motion of TB |
| Pharyngeal Residue (PR) | 0 = Complete pharyngeal clearance<br>1 = Trace residue within or on pharyngeal structures<br>2 = Collection of residue within or on pharyngeal structures<br>3 = Majority of contrast within or on pharyngeal structures<br>4 = Minimal to no pharyngeal clearance |

## 1.3 DYSPHAGIA MANAGEMENT

Dysphagia treatments include compensatory strategies, dietary modifications, and restorative interventions. Postural changes and compensatory maneuvers focus volitional augmentation of swallowing and exploit sensorimotor strengths while mitigating sensorimotor impairments. Dietary modifications change bolus volume or viscosity to change the temporal aspects of the oropharyngeal swallow. Increased bolus volume increases laryngeal closure, hyoid/laryngeal elevation, and UES opening diameter and duration. Increased viscosity can lead to slower bolus transit times. Restorative interventions are designed to restore and rehabilitate impaired function.

## 1.4 LUNG TRANSPLANTATION

Lung transplantation is an established treatment of end-stage lung diseases including obstructive lung disease, septic lung disease, fibrotic lung disease, and vascular lung disease (Yeung & Keshavjee, 2014). Of these broad categories, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and interstitial pulmonary fibrosis (IPF), and primary pulmonary arterial hypertension are the most common indicators for transplantation (Atkins et al., 2010; Floreth & Bhorade, 2010; Yeung & Keshavjee, 2014).

The International Society for Heart and Lung Transplantation (ISHLT) along with the American Thoracic Society (ATS) developed selection criteria to determine lung transplant candidacy. Criteria include appropriate age, disease severity, activities of daily living, limited life expectancy, current cardiac function, presence of coronary disease, ambulatory with rehabilitation potential, emotional support, and psychosocial profile (Yeung & Keshavjee, 2014).

The decision to transplant one or two lungs depends on the indication for transplantation, recipient factors, and donor availability. Several pre-operative factors help to make this determination including pre-transplant diagnosis and patient age (Hadjiliadis & Angel, 2006). In 2005, the lung allocation score system (LAS) was developed by the United Network for Organ Sharing (UNOS) to reduce wait-list mortality, decrease geographic distribution disparity, and assign organs based on severity of illness (Black, Trivedi, Schumer, Bousamra, & van Berkel, 2014). The current system uses a scoring algorithm that incorporates clinical data including the patient's diagnosis, pulmonary function, functional status, and hemodynamic status to make a single vs. double lung transplant determination. An urgency measure is subtracted from a benefit measure and then normalized to give a LAS. Higher scores are allocated lungs sooner (Yeung & Keshavjee, 2014).

Traditionally, a single-lung transplant (SLT) has been the treatment of choice for patients with nonsuppurative lung diseases (typically COPD or IPF) due to the restrictive pulmonary physiology that leads to selective ventilation and perfusion of the graft lung ((Hadjiliadis & Angel, 2006). During the single-lung transplant, either a left or a right lung is transplanted into a recipient and the contralateral native lung is left in place. Generally, SLTs are less operatively traumatic, leading to shorter procedure time and avoidance of longer ischemic time for the native lung (Neurohr et al., 2010).

Advances in surgical techniques and frequency of conditions that impact both lungs have led to increased popularity of double lung transplants (DLT). A DLT or a bilateral lung transplant involves a longer, more complex operation to successfully transplant two new lungs. Septic lung diseases, such as cystic fibrosis, tend to be treated with double-lung transplant as the standard operative approach (Neurohr et al., 2010). Due to the nature of the conditions requiring double-lung transplantation, DLT recipients tend to be younger; 49.3 years to 54.9 years. The DLT procedure reduced impaired postoperative pulmonary function in cases of early complications like reperfusion injury or tissue damage caused by reintroduced blood supply and acute graft rejections (Neurohr et al., 2010). As such, DLTs may lead to better baseline functional parameters, post-operatively.

Historically, double-lung transplantation survival rates are higher than those of single-lung transplantation, but in critically ill patients, a single-lung transplant with less associated operative morbidity could afford a better outcome (Hadjiliadis & Angel, 2006). Long-term survival, calculated by means of Kaplan-Meier survival statistics, reveal significantly lower survival rates in SLT recipients compared to DLT. The overall survival rates for SLT and DLT recipients were 82.6% vs. 93.3% at 3 months and 41.7% vs. 66.8% at 5 years. Additionally, in patients with a high (poor) preoperative LAS, individuals who received a single-lung transplant showed markedly reduced survival as compared to high LAS, double-lung transplant recipients. This indicated that patients with higher LAS (typically more critical cases) did substantially better in terms of survival when they received a DLT rather than a SLT (Black et al., 2014). Furthermore, Hadjiliadis & Angel (2006) report that SLT provides equivalent short-term and medium-term results when compared to double-lung transplantation, but long-term survival appears to be slightly better in DLT recipients. No studies have reported a consistent transplantation survival advantage for DLT recipients when analyzed as a whole.

Postoperative care focuses on ventilator and hemodynamic support and weaning. Ventilator weaning usually occurs within the first 6-12 hours. Transplant recipients are also placed on a three-drug regimen of immunosuppression agents target the immune system to maximize graft tolerance. Advances in both the immunosuppression regimens and surgical techniques are aimed at improving the quality of life for transplant recipients and well as increase the length of life post-transplant. Survival rates during the first-year of transplantation have improved; however, survival rates have not demonstrated improvement after the first year, post-transplantation (Floreth & Bhorade, 2010). It is suggested that this may be due to heightened levels of immunosuppression due to the increased risk of infections within the first year, as well as an increased risk for development of bronchiolitis obliterans syndrome (BOS) (Sithamparanathan et al., 2016). BOS is characterized by irreversible airflow obstruction with insidious onset of symptoms and progressive reduction in forced expiratory volume (FEV1) and mid-expiratory flow. It is hypothesized that the development of BOS is related to infections from microaspiration as well as the innate immunity deficits following transplantation (Floreth & Bhorade, 2010). BOS is considered a component of acute rejection syndromes and is associated with a significantly reduced survival (Neurohr et al., 2010). Despite the advances made in the modern immunosuppression regimen, acute and chronic rejections occur in the majority of lung transplants.

In 2016, Sithmparanthan et al., investigated lung transplant recipients who had long-term survival rates (20+ years). They also proposed that immunosuppression and overall management post-transplantation continues to improve, allowing more lung-transplant recipients to live longer. However, they cite that the development of BOS remains a significant factor in limiting these long-term survival rates; 50% of recipients develop BOS by five years status post-transplant. BOS not only affects long-term survival, but also causes loss of health-related quality of life long-term.

In 2010, Neurohr and colleagues found that a DLT cohort demonstrated superior functional capacities in comparison with SLT recipients, consistent with longer BOS-free survival and decreased rate of BOS-related deaths. As such, SLT recipients are at an increased risk for BOS-related viral, bacterial, and fungal infections that can negatively impact the native lung. DLTs may lead to improved mechanical function bilaterally and thusly postpone the development of respiratory failure secondary to BOS (Gerbase, Spiliopoulos, Rochat, Archinard, & Nicod, 2005; Sithamparanathan et al., 2016). The International Society for Heart and Lung Transplantation (ISHLT) further suggest an early survival advantage for SLT recipients but significantly reduced long-term survival rates (Neurohr et al., 2010). The development of BOS may be caused by or influenced by the presence of dysphagia post-operatively (Floreth & Bhorade, 2010). Further research into this correlation is warranted.

### 1.4.1 Dysphagia Following Transplantation

Oropharyngeal dysphagia frequently occurs following thoracic surgery due to the high risk of recurrent laryngeal nerve damage and disruption of the linkage of the chest wall to the lungs themselves (Harrington et al., 1998). Recurrent laryngeal nerve damage is likely caused by dissection of the recipient hilar structures (Atkins et al., 2007). Additionally, the anatomical position of the lungs exposes several peripheral sensory and motor nerves and receptors innervating pharyngeal, laryngeal, and respiratory muscles to damage during transplantation. Such damage negatively impacts the muscles needed to control/execute a swallow sequence and organize swallow-respiratory coordination.

The recurrent laryngeal nerve innervates all intrinsic laryngeal muscles (except cricothyroid) that are responsible for vocal fold adduction and subsequent airway protection. RLN also innervates the inferior constrictor, which is responsible for the final propulsion of the bolus into the digestive system and the function of its uppermost portion, the upper esophageal sphincter. This helps to prevent retrograde flow of swallowed material from the esophagus back into the pharynx and upper airway (Zemlin, 1998).

An injury to the phrenic nerve can lead to diaphragmatic paralysis, which leads to lower tidal volumes per respiratory cycle, which produces increased respiratory rate to compensate for the decrease in inspired air and maintain constant respiratory minute volume (volume of inspired gas per minute). This increase in respiratory rate leads to incoordination of ventilation and swallowing (Martin-Harris et al., 2008).

Previous research has identified new-onset, post-operative oropharyngeal dysphagia as a typical concern in lung transplant recipients (Atkins et al., 2010; Atkins et al., 2007; Baumann et al., 2017). Repetitive microaspiration events are a contributing factor in lung allograft dysfunction, manifested as bronchiolitis obliterans syndrome (BOS), which is considered a form of acute rejection. Oropharyngeal dysphagia is associated with respiratory complications, such as pneumonia. Pneumonia has been associated with increased postoperative mortality. Atkins and colleagues identified laryngeal penetration and tracheal aspiration (positive swallow evaluation) in 70.5% of their lung transplant cohort. Gross aspiration was identified in 63.8% of those with an initial positive swallow evaluation; 77.6% of those gross aspirations were silent aspirations. A silent aspiration is defined as no protective mechanism response, such as a reflexive cough.

Baumann and colleagues investigated bedside swallow evaluations and instrumental swallow evaluations of patients following lung transplantation. They found that 54% of patients had clinical signs of aspiration at the bedside. 67% of patients had deep laryngeal penetration or aspiration during instrumental testing. Additionally, 27% of patients had normal clinical swallow evaluations at bedside but were found to have either deep laryngeal penetration or aspiration upon instrumental examination. These findings support that the majority of patients aspirate after lung transplantation (Baumann et al., 2017).

In 2007, Atkins and colleagues found that nearly 25% of lung-transplant patients demonstrated vocal fold paresis, a potential consequence of recurrent laryngeal nerve damage (Atkins et al., 2007). Such damage may lead reduced airway protection and associated swallowing abnormalities. Previous studies have reported that aspiration occurs in 1 of 3 patients with vocal fold paralysis (Tabaee, Murry, Zschommler, & Desloge, 2005). Recurrent laryngeal nerve damage may also alter laryngopharyngeal and esophageal sensation. Atkins reported that laryngopharyngeal sensation was altered in 83% of aspirators; this highlights the importance of sensory function to successful swallowing.

Prolonged endotracheal intubation is associated with oropharyngeal dysphagia (Atkins et al., 2007; Nguyen et al., 2016). Endotracheal intubation is defined as placement of an artificial airway tube into the trachea to secure a patent airway (Coyle, 2016). Postoperative extubation typically occurs immediately following surgery. This causes minimal intrinsic airway injury. Prolonged intubation may cause laryngeal trauma, a risk factor for post-extubation dysphagia. Prolonged endotracheal intubation may also contribute to sensation loss in individuals following lung transplantation.

The duration of post-operative endotracheal intubation is a strong predictor of subsequent dysphagia that both prolongs the return to normal oral feeding and delays subsequent hospital discharge (Barker, Martino, Reichardt, Hickey, & Ralph-Edwards, 2009). In patients following cardiothoracic surgery, dysphagia frequency is highest following intubation exceeding 48 hours and the presence of dysphagia is negligible in patients intubated for less than 12 hours (Skortez, 2014). Oral feeding is an important component of patient recovery after high-risk surgery

(Barker et al., 2009). Delayed returns to normal oral feeding is often due to longer post-operative endotracheal intubation and the presence of dysphagia. Additionally, increased aspiration risk leads to increased vigilance in aspiration precaution enforcement, which may lead to increased hospitalization length (Atkins et al., 2007). Early recognition of swallowing disorders leads to earlier and more effective treatment by means of diet modifications, head maneuvers, and implementation of aspiration precautions. Utilization of these techniques can positively impact survival and quality of life in lung transplant recipients. The high incidence of dysphagia following thoracic surgery indicates a need for clinicians to actively monitor the presence of impairment.

### 1.4.2 Single Lung Transplant Swallowing Outcomes

In 2016, Pomfret described the swallow characteristics of an SLT cohort through analysis of kinematic durations and airway protection. Her results revealed that SLT recipients have reduced coupling of oral and pharyngeal stages as evidenced by long stage transition durations (DST). SLT recipients also had prolonged UES opening durations (DUESO) and reduced pharyngeal response durations (PRD) as compared to healthy age-matched peers. These patients also exhibited an increased risk for airway penetration and a reduced ability to eject the residual contrast material. These results indicate that patients with SLTs are at risk for dysphagia that may contribute to chronic rejection and compromised allograft function. These are potentially detrimental factors for long-term survival (Pomfret, 2016).

While the findings of the SLT cohort are interesting alone, a comparison to the DLT cohort will allow for better understanding of the nature of swallowing impairment following lung transplantation. Inherent variance in SLT and DLT procedure creates different risk profiles that may both be affected by swallowing disorders and impairments. It is of great interest to complete the early line of research by measuring swallow kinematic function, airway protection, and impairment levels to form preliminary profiles of these two samples.

# 2.0 PROJECT GOALS AND DESIGN

## 2.1 SPECIFIC AIMS

This descriptive, retrospective study seeks to define the swallow characteristics of patients who have undergone a double lung transplant and to compare these outcomes to previously defined swallow characteristics of single lung transplant recipients (Pomfret, 2016). While an association between lung transplantation and dysphagia is known, the results of this study will be the first published data comparing the specific characteristics of the single and double lung transplant samples. Through this study, I seek to determine whether statistically or clinically significant changes in swallow function at the kinematic and impairment levels may provide clinically relevant indicators of the need to proactively monitor swallowing function in order to reduce dysphagia-related, post-operative complications. The goals of this study are to (1) define the characteristics of double lung transplant swallows, (2) to compare these observations to published norms to determine if overt differences exist, and (3) to compare the kinematic and impairment-level characteristics of DLT swallows and SLT swallows to differentially describe swallow physiology of these two cohorts. Through these efforts, we can further reduce the risk of acute rejection and post-operative pneumonia by predicting a greater risk of oropharyngeal dysphagia sooner. These results can help clinicians to focus on specific physiologic impairments to identify and analyze when conducting a modified barium swallow study (MBSS). By targeting dysphagia effectively, LT patients may have a shorter time to oral feeding and a shorter hospital stay. This method of data analysis is an innovative way to use kinematic analysis, penetration-aspiration scale scores, and MBSImP congruently to characterize swallow impairment in this population. The results of this study provide an initial descriptive database to identify directions for future research.

## 2.2 HYPOTHESES

Several hypotheses were developed to investigate differences between DLT data, SLT data, and historical data. H1: DLT data will have longer duration of stage transition (DST), longer pharyngeal transit duration (PTD), shorter pharyngeal response duration (PRD), and longer duration of upper esophageal sphincter opening (DUESO) than SLT data, for both bolus volumes. H2: DLT data will have worse penetration-aspiration scale (PAS) scores than SLT data. H3: DLT data will present with worse MBSImP scores as compared to the SLT data for large and small bolus volumes. H4: DLT_SL and SLT_SL data will have longer duration of stage transition (DST), longer pharyngeal transit duration (PTD), shorter pharyngeal response duration (PRD), and longer duration of upper esophageal sphincter opening (DUESO) than the Lof & Robbins (1990) historical data. DLT swallow durations will present in the same pattern of difference compared to published norms, albeit more significant, and greater in magnitude than single-lung recipients. H5: DLT_SL and SLT_SL data will have worse penetration-aspiration scale (PAS) scores than the Robbins et al. (1999) historical data.

## 2.3 METHODS

### 2.3.1 Participants

Previously recorded data from 13 patients who had recently undergone a single-lung transplant and 13 patients who had recently undergone a double-lung transplant at the University of Pittsburgh Medical Center (UPMC) were analyzed. Patients with SLT were between the ages of 49-68 (mean age: 62) and patients with DLT were between the ages of 44-67 (mean age: 57). Participants consented to and participated in an NIH funded investigation (3R01HD074819-03S1) comparing videofluoroscopic images of swallow function with signals concurrently recorded during swallowing using high resolution cervical auscultation, accelerometers, and high resolution microphones (Dudik, Coyle, & Sejdic, 2015; Dudik, Kurosu, Coyle, & Sejdic, 2016).

#### 2.3.1.1 Double and Single Lung Transplant Recipients

Duration measures of swallow kinematics and airway protection (PAS) obtained from the DLT and SLT cohorts were analyzed and compared to each other. Portions of MBSImP were then used to analyze both groups of data and these impairment results were compared between cohorts.

#### 2.3.1.2 Lof and Robbins (1990) Historical Norms

Data from Lof & Robbins (1990) were used to compare data from the DLT and SLT cohorts' small liquid data (SL) to normative data of four durational measures (DST, PRD, PTD, DUESO). Sixteen subjects divided evenly into two age groups; middle aged (mean age: 45) and old aged (mean age: 66) consented to and participated in their study. The participants in the historical study received 2ml of barium via spoon during a MBSS. The DLT and SLT cohorts' small liquid data (3ml) were compared to the old aged group since the mean ages are comparable (DLT mean age: 57, SLT mean age: 62; old aged mean: 66). It is reported that bolus size between 2ml and 3ml do not have a significant effect on the likelihood of aspiration in adults (Butler, Stuart, Markley, Feng, & Kritchevsky, 2018).

#### 2.3.1.3 Robbins et al. (1999) Historical Norms

Data from Robbins et al. (1999) were used to compare the DLT and SLT cohort small liquid data to the normative PAS scores. 98 healthy subjects were divided into three age groups: 21-32 (mean age: 23), 43-47 (mean age: 40), and 63-84 (mean age: 68). The DLT and SLT cohorts' SL data were compared to the 63-84 age group since the mean ages are comparable (DLT mean age: 57; SLT mean age 62; old aged mean: 68).

### 2.3.2 Design

This descriptive, retrospective cohort study is centered on analyzing and documenting the swallowing characteristics of individuals with SLTs and DLTs in order to compare swallowing outcomes, status-post lung transplantation.

#### 2.3.2.1 Data Collection

Certified speech-language pathologists systematically collected all swallows at UPMC Presbyterian Hospital in the course of ordinary patient care. All radiographic data were de-identified at the time of recording using a bypass recording system that captured images prior to entering the hospital's recording and patient identification system. Data were then assigned a new identification number by study staff prior to the principal investigator having access to them.

#### 2.3.2.2 Data Analysis

91 swallows within the target conditions of first swallow, small thin liquid (spoon administered 3mL) and first swallow, large thin liquid (cup, self-administered, unmeasured volumes) in the neutral position were produced by the SLT and DLT cohorts (Table 5). The swallows were analyzed retrospectively using the software program ImageJ to determine durations, penetration-aspiration scores, and swallow impairment scores (Rashband, 1997-2015).

**Table 5. Swallows stratified by condition**

| | Small Liquid | Large Liquid | Total |
|---|---|---|---|
| SLT | 12 | 30 | 42 |
| DLT | 22 | 27 | 49 |

## 2.4 RELIABILITY

### 2.4.1 Inter-Rater

Inter-rater reliability was established in the same manner as the pilot study (Pomfret, 2016). Inter-rater reliability training was conducted a-priori in the swallowing research lab. Previously recorded, de-identified videofluoroscopic images were used as practice data. The principal investigator (SAP) scored 100 swallows on six swallow events and PAS scores. Scores were compared to a random 10% of the 100 swallows scored by the principal investigator's research mentor and expert judge (JLC). Inter-rater agreement was assessed by means of intra-class correlation coefficient (ICC) and percent exact agreements on IBM SPSS Statistics 23. Tolerance for agreement of kinematic measures was 0.1 second (Lof & Robbins, 1990). All six swallow events and PAS scores had 80% or higher exact agreement for frame selection. The intra-class correlation coefficient, using an absolute agreement definition, found that the 100 cases were highly reliable with an intra-class correlation coefficient of 1.000 ($p<0.001$).

Reliability was established for MBSImP through the online training program, MBSImP Standardized Training and Reliability Testing. Following the learning and training zones, 170 components were scored in the reliability zone. Judge (SAP) scores were 80% accurate using an exact agreement definition.

### 2.4.2 Intra-Rater

Intra-rater was established in the same manner as the pilot study (Pomfret, 2016). Intra-rater reliability training was conducted on data from previously recorded and de-identified videofluoroscopic images. Two weeks after inter-rater reliability was established, SAP scored a random 10% of the 100 practice swallows. Intra-rater agreement was assessed by means of intra-class correlation coefficient and percent exact agreement on SPSS statistical software. SAP was allowed a three-frame tolerance (or 0.10 second) between scores. All six swallow events had a greater than or equal to 80% exact agreement. An intra-class correlation coefficient, using an absolute agreement definition, found that the 10 cases were highly reliable at 1.000 ($p<0.001$).

SAP also retested a random 10% of the test data and ran an ICC using the same absolute agreement definition. The results of the 10 cases showed that the data were highly reliable at 1.000 ($p<0.001$).

# 3.0 RESULTS

## 3.1 SLT VS. DLT DATA

Appropriate descriptive statistics were used to summarize all variables by transplant group and bolus size. Independent observations are required for most statistical analyses. Multiple ratings (i.e. multiple swallows per participant) violate this assumption. To compensate for this, the maximum rating was used for all swallows from the same participant in the analyses.

### 3.1.1 Durations

DLT vs. SLT comparisons of max ratings were compared for each bolus size using a Wilcoxon rank sum test. The commonly used t-tests are not applicable because these ordinal values are not evenly distributed. Duration measures are continuous variables. Linear mixed models with a participant random effect were used to make DLT vs. SLT comparisons for each bolus size. This model can handle multiple observations per person.

The following table (Table 6) displays the group data for DLT and SLT groups for each bolus size, small liquid (SL) and large liquid (LL). The analyses found statistical significant results and clinical effect sizes (bold values). The Estimate indicates whether the DLT or SLT is a clinically “worse” duration. For DST, a negative number indicates that DLT is a *shorter* duration as compared to SLT. SLT DST is more impaired (prolonged) as compared to DLT DST.

For PTD, PRD, and DUESO, a positive estimate indicates that DLT is larger than SLT. The estimates show that PTD, PRD, and DUESO are *longer* for the DLT group than the SLT group.

The > |t| (absolute value) is equivalent to a p-value. The alpha is set to 0.05. For a comparison test where the N is less than 25, |t| (absolute value) is used to show significance. Although just shy of statistical significance, DLT_SL DST is shorter as compared to the SLT_SL group (p=0.0554). For PRD, DLT_LL is statistically significantly longer than SLT_LL (p=0.0029).

Cohen's d is an effect size that is used to indicate the standardized difference between two means. For smaller sample sizes, a Cohen's d has the potential to overinflate results, so the following statistics should be interpreted with some caution. Large effect sizes were found for DST, PRD, and DUESO (>0.8) for both bolus sizes. This suggests that although the results are not statistically significant, they may have some clinical significance.

**Table 6. Group data for SLT vs. DLT, SL and LL boluses**

| Dependent | Label | Estimate | > \|t\| | Cohen's d |
|---|---|---|---|---|
| DST | DLT_SL vs. SLT_SL | -0.1067 | 0.0554 | **-0.830** |
| | DLT_LL vs. SLT_LL | -0.09090 | 0.0726 | **-0.909** |
| PTD | DLT_SL vs. SLT_SL | 0.01011 | 0.9003 | 0.3181 |
| | DLT_LL vs. SLT_LL | 0.01172 | 0.8711 | 0.0262 |
| PRD | DLT_SL vs. SLT_SL | 0.1187 | 0.1532 | **1.2680** |
| | DLT_LL vs. SLT_LL | 0.2177 | **0.0029** | **1.11269** |
| DUESO | DLT_SL vs. SLT_SL | 0.05510 | 0.1824 | **0.7849** |
| | DLT_LL vs. SLT_LL | 0.06314 | 0.0901 | **0.7639** |

### 3.1.2 PAS

The penetration-aspiration scale possesses many qualities of an interval scale, but the true difference between scores is not equal. Steele & Grace-Martin argue that the scale has more categorical properties due to some questionable ordinal and interval qualities (Steele & Grace-Martin, 2017). Statistically, the PAS score should be analyzed as a non-parametric measure. Penetration-aspiration scale scores are most appropriately analyzed using frequency measures to represent the typical or most common patterns of airway protection seen in each group of patients. The max rating for PAS was used to find the clinically significant outcomes of adverse swallowing following lung transplantation. It is common practice in clinical research for the worst score to be used to represent a patient's impairment level; however, this limits the scope of scores that may be seen within one participant. Therefore, the most informative way to represent nonparametric scores, such as PAS, is to report both the mode and the max or worst score across a set of swallows.

A Wilcoxon rank sum test was used to find impairment differences between the two groups for both bolus sizes. This test did not reveal statistically significant results (Table 7). A Cohen's d would not be appropriate for this analysis because the data are non-parametric and not evenly distributed.

**Table 7. Descriptive Statistics for PAS, SLT vs. DLT, SL and LL boluses**

| GROUP | P-VALUE | MIN | MAX | MODE |
|---|---|---|---|---|
| SLT_SL | 0.92525 | 1 | 6 | 2 |
| DLT_SL | | 1 | 6 | 1 |
| SLT_LL | 0.90307 | 1 | 4 | 2 |
| DLT_LL | | 1 | 8 | 2 |

### 3.1.3 MBSImP

The Frequency Procedure and the Wilcoxon rank sum test were used to analyze MBSImP data (Table 8). Like PAS, the data are nonparametric and is not evenly distributed. The max was also used for these impairment scores in line with the principles of MBSImP. When analyzing a patient, the rater is to take the worst or max score to describe the particular impairment. This helps to characterize the worse events of the whole swallowing sequence to determine clinically significant adverse events.

A two-sided Wilcoxon rank sum test was used to compare DLT_SL and SLT_SL as well as DLT_LL and SLT_LL. There were no statistically significant findings between the groups for the SL condition. A statistically significant difference was found between DLT_LL and SLT_LL on the pharyngoesophageal segment opening (PESO) measure. DLT_LL had a significantly worse PESO (more impairment) than the SLT_LL group. There were no other significant MBSImP differences between the DLT_LL and SLT_LL groups.

**Table 8. Descriptive Statistics for MBSImP, SLT vs. DLT, SL and LL boluses**

| MEASURE | GROUP | P-VALUE | MIN | MAX | MODE | RANGE |
|---|---|---|---|---|---|---|
| IPS | SLT_SL | 0.23538 | 0 | 3 | 3 | 0-3 |
| | DLT_SL | | 0 | 3 | 2 | |
| | SLT_LL | 0.44678 | 0 | 3 | 2 | |
| | DLT_LL | | 0 | 3 | 1 | |
| SPE | SLT_SL | 0.28023 | 0 | 1 | 0 | 0-2 |
| | DLT_SL | | 0 | 1 | 0 | |
| | SLT_LL | 0.92489 | 0 | 1 | 0 | |
| | DLT_LL | | 0 | 2 | 0 | |
| LE | SLT_SL | 0.94436 | 0 | 2 | 0 | 0-2 |
| | DLT_SL | | 0 | 2 | 0 | |
| | SLT_LL | 0.25743 | 0 | 0 | 0/1 | |
| | DLT_LL | | 0 | 2 | 0 | |
| HM | SLT_SL | 0.54974 | 0 | 2 | 1 | 0-2 |
| | DLT_SL | | 0 | 2 | 1 | |
| | SLT_LL | 0.61924 | 0 | 2 | 1 | |
| | DLT_LL | | 0 | 1 | 1 | |
| EM | SLT_SL | 1.0000 | 0 | 2 | 2 | 0-2 |
| | DLT_SL | | 0 | 2 | 2 | |
| | SLT_LL | 0.71981 | 0 | 2 | 0 | |
| | DLT_LL | | 0 | 2 | 0 | |
| LC | SLT_SL | 0.24204 | 0 | 2 | 0 | 0-2 |
| | DLT_SL | | 0 | 2 | 1 | |
| | SLT_LL | 0.30056 | 0 | 1 | 1 | |
| | DLT_LL | | 0 | 1 | 1 | |
| PESO | SLT_SL | 1.00000 | 0 | 2 | 1 | 0-2 |
| | DLT_SL | | 0 | 2 | 1 | |
| | SLT_LL | **0.02985** | 0 | 1 | 0 | |
| | DLT_LL | | 0 | 1 | 1 | |
| TBR | SLT_SL | 0.84753 | 1 | 3 | 1 | 0-3 |
| | DLT_SL | | 0 | 3 | 1 | |
| | SLT_LL | 0.86333 | 1 | 2 | 1/2 | |
| | DLT_LL | | 1 | 3 | 1 | |
| PR | SLT_SL | 0.54131 | 0 | 3 | 1 | 0-3 |
| | DLT_SL | | 0 | 3 | 2 | |
| | SLT_LL | 1.00000 | 1 | 2 | 2 | |
| | DLT_LL | | 1 | 2 | 2 | |

## 3.2 SLT & DLT DATA VS. HISTORICAL NORMS

### 3.2.1 Durations

To compare duration variables to the values in Lof & Robbins (1990) for small bolus sizes, the published values were used as fixed values. One-sample t-tests were then used to compare duration measures. The analysis revealed several statistically significant results that are bolded in the table below (Table 9).

**Table 9. Group data for DLT_SL & SLT_SL vs. Lof & Robbins (1990)**

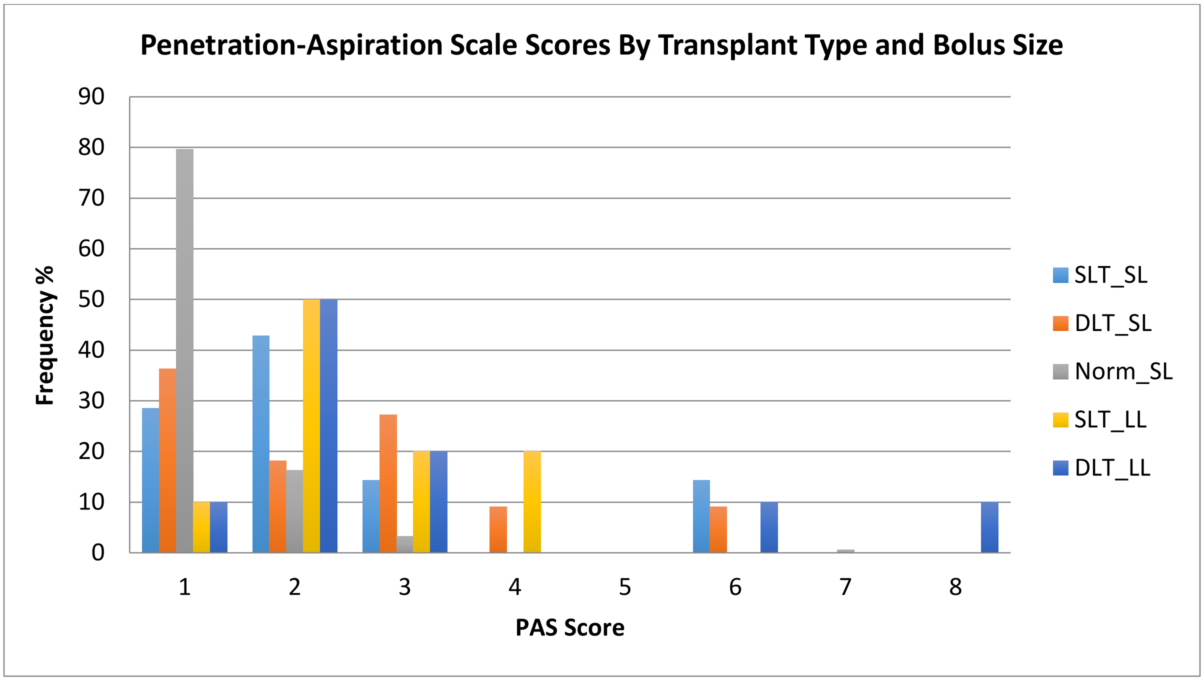
| Group | Duration | SL_Mean | Norm_Mean | SL_StdDev | Norm_StdDev | Pr > \|t\| | Cohen's d |
|---|---|---|---|---|---|---|---|
| SLT_SL | DST | -0.021 | -0.22 | 0.043 | 0.25 | **<0.0001** | **1.1094** |
| | PTD | 0.561 | 0.51 | 0.151 | 0.09 | **0.0062** | 0.410 |
| | PRD | 0.887 | 1.14 | 0.229 | 0.24 | **<0.0001** | **-1.0785** |
| | DUESO | 0.382 | 0.45 | 0.115 | 0.12 | 0.5732 | -0.5785 |
| DLT_SL | DST | -0.129 | -0.22 | 0.167 | 0.25 | **0.0001** | 0.428 |
| | PTD | 0.595 | 0.51 | 0.167 | 0.09 | **0.0012** | 0.633 |
| | PRD | 0.999 | 1.14 | 0.162 | 0.24 | **0.0028** | -0.6886 |
| | DUESO | 0.466 | 0.45 | 0.104 | 0.12 | 0.0591 | 0.142 |

### 3.2.2 PAS

To compare PAS scores to the values in Robbins (1999) for small bolus sizes, the published values were used as fixed values. Wilcoxon rank sum tests were used for the data because it is not evenly distributed.

A statistically significant difference was found between the Robbins (1999) norms and the DLT_SL ($p<0.00001$) and SLT_SL ($p<0.00001$) on the penetration-aspiration scale scores. The results of this analysis found that the DLT and SLT cohorts had significantly worse PAS Scores as compared to the normal cohort. These results are displayed graphically on the bar graph below (Figure 1).

**Figure 1. Penetration-Aspiration Scale Scores by Transplant Type & Bolus Size**



### 3.2.3 Summary of Results

Several statistically and clinically significant results were found from the above analyses. The table below is a summary of these results (Table 10). They are divided by dependent variables: durations, penetration-aspiration scale scores, and MBSImP. The results are then classified as statistically significant (S), clinically significant (C), or both statistically and clinically significant (S/C).

**Table 10. Summary of Statistically and/or Clinically Significant Results**

| Dependent Variable | Measure | Groups | Significance |
|---|---|---|---|
| Durations | DST | DLT_SL vs. SLT_SL | C |
| | | DLT_LL vs. SLT_LL | C |
| | | SLT_SL vs. Norm_SL | S/C |
| | | DLT_SL vs. Norm_SL | S |
| | PTD | SLT_SL vs. Norm_SL | S |
| | | DLT_SL vs. Norm_SL | S |
| | PRD | DLT_SL vs. SLT_SL | C |
| | | DLT_LL vs. SLT_LL | S/C |
| | | SLT_SL vs. Norm_SL | S/C |
| | | DLT_SL vs. Norm_SL | S |
| | DUESO | DLT_SL vs. SLT_SL | C |
| | | DLT_LL vs. SLT_LL | C |
| PAS | NORM | DLT_SL vs. Norm_SL | S |
| | | SLT_SL vs. Norm_SL | S |
| MBSImP | PESO | SLT_LL vs. DLT_LL | S |

## 4.0 DISCUSSION

The statistical analyses found significant differences between kinematic durations, penetration-aspiration scale scores, and impairment scores for the DLT and SLT samples. The analyses also found statistically significant differences between the lung transplant samples and the historical data for both durations and penetration-aspiration scale scores. Collecting and analyzing data to measure four durations, penetration-aspiration scale scores, and nine impairment components accomplished the three specific aims of this study.

### 4.1 DURATIONS

Durations were analyzed to describe specific kinematic swallowing characteristics of the double lung transplant cohort. These characteristics were then compared to the previously analyzed kinematic swallowing durations of the single lung transplant cohort and the Lof & Robbins (1990) historical, normal cohort.

Duration of stage transition (DST) is the time the propelled bolus is in the pharynx before the swallow begins (Coyle, 2008). DLT_SL data presented with shorter (more timely) DST than SLT_SL data ($t>0.0554$). Although just shy of statistical significance, there may be clinical relevance in these findings. The Cohen’s d analysis found that both bolus sizes have large effect sizes, indicating clinical significance in the difference between DLT and SLT duration of stage transition. A prolonged duration of stage transition indicates that the airway is left unprotected to potential penetration and aspiration. DST characterizes the transition from the oral stage to the pharyngeal stage. A prolonged transition between the end of the oral stage to the beginning of the pharyngeal stage has been linked to aspiration (Kim et al., 2005). These results suggest that a longer DST may contribute to aspiration related pneumonia in individuals following single lung transplantation.

Both DLT_SL and SLT_SL DST were significantly longer than the historical normal data ($|t|>0.0001$; $|t|<0.0001$). The clinical effect size for SLT_SL is larger than DLT_SL. The normal comparison group produced an average DST of about -0.22s. This means that, normally, the pharyngeal swallow begins approximately 0.22 seconds before the bolus enters the pharynx. The DLT and SLT subjects had an average DST of about 0.072s and -0.021s, respectively. This indicates that the bolus enters the pharynx *before* the start of hyoid elevation. DLT and SLT swallows both exhibit longer duration of pharyngeal airway exposure of swallowed material than the healthy normal group. This physiology is akin to swallowing characteristics of an older, healthy population (Lof & Robbins, 1990). These results suggest that as LT recipients age, their baseline deficits will be further compounded by advanced age-related changes. These results also indicate that disruption of the timing and sequencing of swallow events is a defining characteristic of swallowing changes, post-transplantation. The differences between the DLT & SLT cohorts and the historical norms support the hypothesis: the DLT & SLT cohorts will present with prolonged DST as compared to the healthy, normal cohort.

Pharyngeal transit duration (PTD) is the duration of bolus transit measured from the time the bolus enters the pharynx to the time it exits the pharynx. There were no statistically or clinically significant differences between SLT and DLT cohorts for either bolus volume condition. Both DLT_SL and SLT_SL PTD were significantly longer than the historical normal data (|t|>0.0012; |t|>0.0062). The clinical effect size for DLT_SL is larger than SLT_SL. This may be related to impaired PESO (diameter). The bolus may take longer to pass through the pharynx if clearance through the UES is impaired/ delayed due to a smaller UES opening diameter. This will be discussed further in the MBSImP section (4.3). The healthy population had a PTD of 0.51s, the DLT cohort had an average PTD of 0.707s, and the SLT cohort had a PTD of 0.561s. The healthy population and the SLT cohort presented with a similar albeit longer duration, while the DLT cohort presented with a *significantly* longer duration. These results indicate that the longer duration of bolus clearance is a defining characteristic of swallowing changes post-transplantation. Slower clearance may indicate issues with pharyngeal contraction muscles, innervated by the recurrent laryngeal nerve. Delayed triggering of the pharyngeal swallow (prolonged DST) may impact pharyngeal transit time as well (Bisch, Logemann, Rademaker, Kahrilas, & Lazarus, 1994). As hypothesized, DLT & SLT both exhibited prolonged PTD as compared to the healthy, normal cohort indicating a longer duration is necessary to clear swallowed material.

Pharyngeal response duration (PRD) is the duration of pharyngeal motor activity as indicated by hyoid onset of maximal motion to hyoid returns to rest. There were no statistically significant differences between SLT and DLT samples for the small liquid condition. Both DLT_SL and SLT_SL PRD were significantly shorter than the historical normal data (t>0.0028; t<0.0001). A shorter PRD may lead to impaired airway protection. A swallow that begins late and ends prematurely may expose the airway to penetration both before and after the swallow (Kim et al., 2005). The open airway is exposed to the bolus for a longer duration. The differences between the DLT & SLT cohorts and the historical norms support the hypothesis: the DLT & SLT cohorts will present with shorter PRD as compared to the healthy, normal cohort.

PRD was longer for DLT_LL swallows than SLT_LL swallows (t>0.0029). The Cohen's d calculated a clinically significant difference (large effect size) between these two groups. The difference between the DLT_LL and SLT_LL may be explained by SLT cohorts' incomplete anterior hyoid excursion. This component will be further reviewed in the MBSImP section (4.3). Patients' swallows with reduced anterior hyoid excursion often coincide with shorter pharyngeal response durations (Bisch et al., 1994). While the DLT_SL and SLT_SL durations were not statistically significant, there is high (large effect size) clinical relevance in the differences. DLT_SL PRD is longer than SLT_SL. The difference between the SLT_SL and DLT_SL groups as compared to the normal cohort is both clinically and statistically significant. SLT_SL and DLT_SL have shorter PRD than the normal population; shorter PRD is correlated to reduced/impaired airway protection.

Duration of UES opening (DUESO) is the duration between onsets of UES opening to onset of UES closure. There were no statistically significant differences between SLT and DLT cohorts for both bolus volume conditions. There is a medium effect size for the difference between these two groups. DLT_SL DUESO was longer (although not statistically or clinically significant) than the historical normal data (t>0.0591). There was no statistically or clinically significant difference between SLT_SL DUESO and the historical normal data (t>0.5732).

## 4.2 PAS

The penetration-aspiration scale was used to characterize DLT airway protection. These scores were then compared to SLT PAS scores and to the historical norms from Robbins et al., 1999. Robbins found that in a healthy, normal population between the ages of 63-84, 96% of all swallows received a score of 1 or 2. Only 55% and 71% of the first DLT and SLT swallows were scored in this range, respectively. Approximately 16.3% of the normal swallows received scores that reflect laryngeal penetration with clearance (score of 2 or 4), while DLT and SLT recipients penetrated on 27% and 43% of the small liquid swallows and 50% and 70% of the large liquid swallows, respectively. Large liquid swallows resulted in more frequent laryngeal penetration for the DLT and SLT cohorts. Only 3.3% of the normal swallows were scored a 3, indicating laryngeal penetration with no clearance. The DLT and SLT recipients penetrated without clearance on 14% and 27% of small liquid swallows and 20% of large liquid swallows, respectively.

Robbins et al., found that healthy individuals rarely exhibit more than transient, shallow laryngeal penetration. Their population did not deeply penetrate on any of their swallows. Deep laryngeal penetration (scores of 4 or 5) was scored in 9% of DLT_SL swallows and 20% of SLT_LL swallows. The normal population aspirated with a cough response only 0.6% of the time (score of 7) while the DLT_LL swallows were aspirated (scores of 6, 7, or 8) 20% of the time, DLT_SL swallows were aspirated 9% of the time, and SLT_SL swallows were aspirated 14% of the time. Ten percent of DLT_LL swallows were silently aspirated. Deep laryngeal penetration and aspiration were observed as the bolus volume increased in both cohorts. The DLT cohort was more at risk for aspiration, with and without an attempt to clear the residual contrast from the airway. These results support the hypothesis: DLT recipients will present with worse (higher) PAS scores than SLT recipients.

Compared to the normal cohort, SLT and DLT have an increased risk of airway penetration and a reduced ability to eject the residual contrast material. Generally, PAS was significantly worse for DLT_SL and SLT_SL as compared to Norm_SL ($p<0.00003$). Unsafe swallows receive penetration-aspiration scale scores of 4-8 (Robbins et al., 1999). Of the cohorts studied, 10% of the DLT_LL, 18% of the DLT_SL, 20% of the SLT_LL, and 14% of the SLT_SL first swallows were classified as unsafe. Comparatively, swallows with scores in this range occur in only 0.6% of swallows in healthy adults in this age range. This indicates that the DLT and SLT cohorts are at significant risk of aspiration. These findings support the present study's hypothesis: the SLT and DLT cohorts present with significantly higher (worse) PAS scores than the normal, healthy population.

## 4.3 IMPAIRMENT SCORES

The modified barium swallow study impairment profile (MBSImP) was used to characterize specific physiologic impairments of the double and single lung transplant swallows. These characteristics were compared to each other to determine if overt differences exist. Several of these impairments further inform the results found in the analysis of durations and penetration-aspiration scale scores.

Initiation of the pharyngeal swallow (IPS) measures the first hyoid movement in relation to the location of the bolus head. This measure is related to the duration of stage transition. Ninety percent of the DLT_LL, DLT_SL, and SLT_LL swallows were initiated *after* the bolus entered the valleculae or lower in the pharynx. Ten percent of the DLT_LL swallows, 27% of the DLT_SL swallows, and 20% of the SLT_LL swallows were not initiated until the bolus had entered the pyriform sinus. Approximately 86% of the SLT_SL swallows were initiated after the bolus entered the valleculae or lower in the pharynx. Over 57% of these swallows were initiated when the bolus entered the level of the pyriforms. Kinematic findings support these impairment findings as well; prolonged DST of the DLT and SLT cohorts is related to impaired initiation of the pharyngeal swallow (longer DST).

Soft palate elevation (SPE) measures the degree of soft palate movement. The results of this study suggest that this measure is correlated with increased bolus volume in the LT samples. Incomplete SPE, or a trace column of air, was observed during 30% of SLT and DLT large volume swallows. 70% of the DLT_LL and SLT_LL swallows were scored a 0, indicating complete contact between the soft palate and the pharyngeal wall. Over 80% of small liquid swallows had complete soft palate movement and contact with the posterior pharyngeal wall. This is not a significant component of the post-lung transplant swallow.

Laryngeal elevation (LE) measures movement of the thyroid cartilage by assessing upward movement of the larynx. The results of this study suggest that laryngeal elevation is correlated with increased bolus volume in the LT samples. DLT_SL and SLT_SL had complete LE in over 80% of swallows. Forty percent of DLT_LL and SLT_LL swallows demonstrate incomplete laryngeal elevation, defined as partial superior movement of the thyroid cartilage compounded by incomplete approximation of the arytenoids to the epiglottic petiole. Twenty percent of SLT_LL swallows demonstrated minimal superior movement. Incomplete laryngeal elevation may expose the airway to swallowed material. High PAS scores for DLT_LL and SLT_LL swallow may also be related to high or “worse” LE scores.

Anterior hyoid excursion (HM) measures the completeness of anterior hyoid movement. It is a component of superior airway closure. Both groups and volume conditions had mostly partial hyoid movement to no anterior movement. Eighty percent of DLT_LL, ~64% of DLT_SL, 50% of SLT_LL, and ~71% of SLT_SL swallows were scored a 1 (partial hyoid movement). Approximately 27% of DLT_SL, 10% of SLT_LL, and ~14% of SLT_SL swallows were scored a 2 (no anterior hyoid movement). Incomplete anterior hyoid movement often coincides with shorter pharyngeal response duration (Bisch et al., 1994). It follows that SLT recipients have both shorter PRD and incomplete HM as compared to DLT recipients.

Epiglottic movement (EM) is scored as the completeness of epiglottic inversion. EM is improved with LL bolus; incomplete inversion was observed with SL in both SLT and DLT. Sixty percent of DLT_LL swallows and 70% of SLT_LL were scored 0, indicating complete epiglottic inversion. Over 45% of DLT_SL swallows and over 57% of SLT_SL swallows were score a 2, indicating no epiglottic inversion. Decreased epiglottic movement for SL boluses may contribute to high pharyngeal residue scores that will be further described later in this section. The epiglottis inverts to protect the airway. Incomplete epiglottic inversion leaves the airway unprotected and at risk for penetration or aspiration of contrast material.

Laryngeal vestibule closure (LC) measures the amount of material or airspace in the laryngeal vestibule between the arytenoid cartilage and epiglottic base at the height of the swallow. Approximately 70% of DLT_LL and DLT_SL swallows were scored as incomplete laryngeal vestibule closure. Ninety percent of SLT_LL swallows were scored as incomplete laryngeal vestibule closure. Nine percent and 14% of DLT_SL and SLT_SL swallows scored a 2, defined as a wide column of air/ contrast in the laryngeal vestibule. High LC scores may be related to high LE scores. LE and LC are both incomplete, contributing to decreased airway protection in both DLT and SLT. High pharyngeal retention scores may also be related to incomplete LC (Eisenhuber et al., 2002).

Pharyngoesophageal segment opening (PESO) measures the degree and duration of upper esophageal sphincter opening and degree of obstruction of flow. Seventy percent of DLT_LL and SLT_SL swallows and 64% of DLT_SL swallows scored a 1, or partial distension and partial obstruction of flow. Eighteen percent of DLT_SL swallows and 14% of SLT_SL swallows scored a 2, or minimal distention and marked obstruction of flow. PESO was the only measure that had a statistically significant difference between DLT_LL and SLT_LL swallows. PESO was *significantly worse* for DLT_LL than SLT_LL. Incomplete PESO may be related to incomplete HM. Complete anterior hyoid movement helps to open the upper esophageal segment fully. Incomplete UES opening or shorter duration of UES opening (DUESO) would contribute to this obstruction as well. The UES may also be less compliant if it is not inhibited due to damage to the recurrent laryngeal nerve. DUESO was within normal limits/ slightly prolonged as compared to the normal cohort; however, the diameter of opening could be reduced while the duration of opening is typical. Increased DUESO may be a compensatory measure for the limited degree of opening and degree of obstruction of flow. Such obstruction increases pyriform residue; increased pyriform residue is a risk for aspiration. Reduced UES opening may also be due to decreased intrabolus pressure. If generating forces for intrabolus pressure are impaired, the UES may not be forced open to its fullest extent. These results support the hypothesis: DLT data will present with worse MBSImP scores than SLT data.

Tongue base retraction (TBR) measures the extent to which the tongue base makes contact with the posterior pharyngeal wall (PPW). The composite pressure generated by this movement aids in bolus propulsion through the pharynx. All conditions had swallows with trace to narrow columns of contrast between the tongue base (TB) and the posterior pharyngeal wall (PPW). Three conditions had swallows with a wide column of air or contrast between the TB and PPW. Sixty percent of DLT_LL swallows, 36.36% of DLT_SL swallows, 50% of SLT_LL swallows, and ~57% of SLT_SL swallows were scored as trace column of contrast or air present between the TB and PPW. Thirty percent of DLT_LL swallows, 27% of DLT_SL swallows, 50% of SLT_LL swallows, and ~29% of SLT_SL swallows were scored as narrow column of contrast/air between TB and PPW. Ten percent of DLT_LL swallows, ~18% of DLT_SL swallows, and ~14% of SLT_LL swallows were scored as wide column of contrast/ air between TB and PPW. These high scores indicate that the tongue is not completely in contact with the posterior pharyngeal wall in the majority of swallows of both conditions in the DLT and SLT groups. This may result in increased residue in the valleculae.

Pharyngeal residue (PR) is the score made after the initial swallow (baseline impairment). This is quantified by the amount of contrast/ barium that remains in the pharynx after the initial swallow. PR is high for both DLT and SLT (SL and LL). Sixty percent of DLT_LL and SLT_LL swallows were score a 2, indicating collection of residue within or on pharyngeal structures. SL swallows also had high PR scores. Approximately 36% of DLT_SL and ~29% of SLT_SL swallows were scored a 2. About 27% of DLT_SL swallows and ~14% of SLT_SL swallows were scored a 3, or majority of contrast within or on pharyngeal structures. Incomplete TBR may also contribute to PR in both DLT and SLT. High pharyngeal retention scores are related to increased risk for aspiration (Eisenhuber et al., 2002). As discussed previously, several components contribute to increased residue. Incomplete TBR, limited PESO, incomplete LC, incomplete EM, and decreased LE may all cause a collection of residue in the valleculae and pyriforms. It is important to note that while only the first swallows were analyzed, many boluses required second or sequential swallows to clear the bolus. This may serve as a compensatory strategy, but also indicated inadequate pharyngeal clearance at post operatively.

### 4.4 LIMITATIONS OF THE CURRENT STUDY

There are several limitations of the current study. This study is retrospective, which naturally exposes the study weak internal validity. Using these preliminary results, a prospective cohort study would be a natural next step to continue this line of research. A prospective study would allow the researchers to create more homogenous, controlled groups of subjects. The prospective would also help to clarify the group variability that was apparent from the results of the present study.

The PI did not have access to patient medical records. Comorbidities, surgical complications/details, and other specifics would help to capture a more complete clinical picture of individuals following a lung-transplant. Future research projects should also consider the differences between right and left lung transplantations. The recurrent laryngeal nerve (RLN) is potentially at higher risk of injury during a left lung transplant than a right lung transplant. The left RLN has a much longer course through the body, which makes it more prone to paralysis as compare to the right RLN. Some variability in the SLT results may be explained by the specific lung transplanted.

The retrospective design limited control over the MBS study itself. Bolus volume, mode of administration, and specific consistencies could not be controlled and standardized by the researchers. The modified barium swallow studies analyzed retrospectively were not standardized; each patient swallowed a different number of times and received different consistencies and volumes. A prospective study would also allow the researchers to control these specifics of the study's design.

Despite these limitations, these factors closely represent how patients with a lung transplant typically swallow. The goals of this study were to describe swallowing characteristics of double and single lung transplant recipients, and as such, the lack of internal consistency may increase the study's external validity.

## 4.5 DIRECTIONS FOR FUTURE RESEARCH

This study is a catalyst for future research into specific interventions that may be appropriate for many of the kinematic and physiologic impairments analyzed in the present study. Although not a specific aim of this particular research study, the results suggest that several compensatory strategies and restorative treatments would be appropriate for the lung transplant population. To compensate for prolonged stage transition duration (DST), a chin down position may aid in posterior bolus containment. For SLT and DLT recipients' limited UES opening diameter, a head rotation may aid in increasing the UES diameter to prevent obstruction of bolus flow and subsequent pyriform pooling. Effortful swallows and secondary/sequential swallows may help to increase intrabolus pressure and decrease vallecular residue. Respiratory-swallow coordination training may be appropriate to decrease risk of airway penetration, improve delayed pharyngeal response, and compensate for possible reduced sensation. A prospective study should be conducted to investigate the effectiveness of these strategies and training.

This study is the second installment in a long line of research waiting to be completed on the lung transplant population. Further investigation into this complex population is necessary to improve patient care and long term outcomes. Lung transplant patients' bedside clinical presentation is often drastically different from what is seen under fluoroscopy. The results of this study prove that lung transplant patients possess a high risk of oropharyngeal dysphagia. Specific kinematic, airway protection, and physiologic impairments provide compelling evidence for proactive screening and assessment before resuming full oral intake.

A logical step in this line of research would be to develop a protocol for pre- and post-operative management of swallowing following lung transplantation. A standardized, well-researched program would lead to development of optimal treatment and intervention strategies to prolong the functional lifespan of the transplant organ, decrease patient mortality, and increase overall patient quality of life.

## 4.6 CONCLUSION

This study described swallow kinematic durations and airway protection of patients with a double-lung transplantation. These results were then compared to the previously analyzed single-lung transplant data and two historical, normal cohorts. SLT and DLT data were then analyzed using MBSImP to investigate specific physiologic impairments.

*Durations*: The results of this study showed that DLT recipients have shorter (more typical) stage transition durations (DST) as compared to the SLT cohort. DLT recipients have longer pharyngeal transit durations (PTD) than SLT recipients. SLT recipients have shorter (worse) pharyngeal response durations (PRD) as compared to the DLT cohort. DLT recipients have longer (better) durations of UES opening (DUESO) as compared to SLT recipients. Both

DLT and SLT recipients have prolonged (worse) DST and PTD and shorter (worse) PRD as compared to the historical, normal cohort.

*PAS*: DLT recipients have worse PAS scores as compared to SLT recipients. Both SLT and DLT recipients have significantly worse PAS scores than the historical, normal cohort.

*MBSImP*: SLT and DLT recipients have several physiologic impairments. Notably, DLT recipients have significantly impaired (smaller opening/ diameter) PESO as compared to the SLT cohort.

These results demonstrate that both patient samples are at significant risk for dysphagia. SLT kinematic durations (DST, PRD, and DUESO) are worse than DLT durations. DLT recipients have longer PTD, are at greater risk of impaired UES opening (diameter), and silent aspiration (PAS: 8). These results indicate that SLT recipients have more difficulty *initiating* the pharyngeal swallow, while DLT recipients have more impairment *during* the pharyngeal stage. Generally, DLT and SLT swallows are significantly worse than the healthy, normal swallows. These deficits may be contributing factors in the long-term functioning of lung allografts and subsequent patient health outcomes.

The results of this study will help to inform clinical decision making for post-operative dysphagia management in lung transplant populations. These findings can help to further reduce the risk of acute lung allograft dysfunction and organ rejection by addressing post-operative aspiration pneumonia earlier. The specific physiologic and kinematic findings focus clinicians' attention to specific impairments when conducting and analyzing a modified barium swallow study. Effective management may allow patients to return to oral feeding sooner and reduce the length of hospital stay by targeting oropharyngeal dysphagia more effectively in lung transplant recipients.

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