University of Pittsburgh
Department of Communication Science and Disorders
School of Health and Rehabilitation Sciences

5012 Forbes Tower
Pittsburgh, PA, 15260
Tel (412).383.6540
Fax (412).383.6555

The Aspirometer: A Noninvasive Tool for Detecting Aspiration Aim 3

Cover Page

05/23/2022

NCT number: NCT06637774

The date on which the document was most recently updated and, if needed, approved by a human subjects protection review board, was 05/23/2022.

SPECIFIC AIMS

Hundreds of thousands of people annually suffer from compromised nutrition, hydration, and quality of life due to impaired swallowing (oropharyngeal dysphagia or OPD), and aspiration of swallowed food into the respiratory system. OPD leads to aspiration pneumonia (AP) which increases the risk of death during hospitalization threefold, and adds 53,000 annual hospitalization days and nearly $550 million to US health care costs annually. Through our research, we seek to pre-emptively prevent OPD diagnoses from evolving into aspiration pneumonia, and mitigate these economic and human costs. Gold-standard videofluoroscopy (VF), used to objectively diagnose OPD, is not an appropriate screening tool due to its invasiveness, size and prohibitive cost, and it cannot be deployed immediately upon suspicion of OPD. Standard institutional screening (SIS) protocols are therefore used to predict OPD. But since they rely solely on subjective, non-instrumented human judgment of OPD risk by simply watching the patient swallowing and observing for choking, a) their sensitivity is compromised because half of aspirators do not choke due to silent aspiration, b) their specificity is compromised because up to 60% of nonaspirators cough during SIS, and c) in settings in which subsequent VF is not available or feasible, SIS provide no diagnostic information to guide intervention because they cannot identify the swallowing impairments leading to aspiration.

In our current NIH-funded effort (**for which the PI received the Presidential Early Career Award for Scientists and Engineers in 2016**), we have developed an instrumental tool that can noninvasively identify patients with OPD with high agreement with gold standard VF, through innovative *high-resolution cervical auscultation* (HRCA) methods. Through collection of concurrent VF and HRCA data from 274 patients and using advanced data analytics methods, we showed that HRCA can accomplish two outcomes previously only possible with VF: a) differentiate between severe aspiration and unimpaired swallowing in patients with suspected OPD, and b) detect kinematic components of abnormal swallowing physiology that lead to aspiration. Our next major step is to translate these advances into *an objective, precise instrumental screening tool that significantly increases accuracy of SIS in a convenient and easily adoptable form factor.* There are three gaps we need to address to accomplish these goals. We need to finish characterizing the entire range of swallowing function from unimpaired through severe OPD using HRCA as our HRCA research has relied on data from patients with OPD. We then need to equate HRCA predictions to validated gold-standard derived cutoffs of OPD severity, and finally to combine these results into a deployable too that can be tested clinically. Therefore, we propose research leading to *novel clinical and engineering advances* that position our HRCA tool to accurately identify silent aspiration and OPD to enable patients to be immediately triaged for treatment to prevent AP and related adverse events, and prevent unnecessary treatment to unimpaired people.

AIM 1: Complete collection of the entire continuum of HRCA swallowing signals from unimpaired to severely impaired, by collecting HRCA swallow data from healthy people. *Hypothesis: HRCA signal signatures of swallowing in unimpaired people are distinguishable and significantly different discriminating from swallows from people with OPD.* The aim will dramatically improve screening accuracy by completing characterization of the entire HRCA OPD severity continuum from unimpaired to severely impaired.

AIM 2: Translate and equate HRCA swallow signal signatures to validated measures of swallowing impairment. *Hypothesis: HRCA cutoffs will be significantly associated with validated VF-derived OPD impairment cutoffs.* Accomplishment of this aim positions us to establish independent HRCA cutoffs for levels of OPD severity that differentiate clinically significant OPD and aspiration from benign swallowing impairments.

AIM 3: Prospectively assess the effectiveness of our HRCA system in predicting clinically significant OPD and aspiration in a randomized, controlled trial. *Hypothesis: HRCA, will detect significantly more OPD and significantly more non-OPD, compared to SIS alone.* For this *major step*, we will deploy combinations of HRCA and SIS with consenting patients, and compare all screening predictions (SIS, HRCA, SIS + HRCA) to VF data from all participants.

The *outcome* of this research will be a clinically accurate, inexpensive, and noninvasive HRCA screening tool that will *fundamentally advance efforts to reduce morbidity and mortality caused by OPD.* The *positive translational impact* of this work is the melding of engineering (HRCA) with the clinical (SIS) screening processes. This major technological leap will *elevate the current standard of patient care* by ensuring that patients with OPD are correctly identified before adverse events can occur, patients without OPD are not unnecessarily deprived of food more accurately than current methods, as well as lowering health care expenditures and lengths of stay and improving quality of lives.

SIGNIFICANCE

Aspiration pneumonia (AP), caused by inhalation of food or liquids (aspiration) in people with oropharyngeal dysphagia (OPD), has been increasingly recognized as a significant cause of morbidity and mortality [1], raising its contribution to known overall pneumonia incidence five-fold (Figure 1) [2]. If patients with cardiovascular disease and ischemic stroke develop OPD during their illness, the chance of death can be doubled [3]. In acute care and nursing homes, where OPD has up to 75% prevalence, and for the half of the 800,000 US citizens who suffer strokes each year and develop OPD, late detection of OPD leads to AP, increasing mortality risk up to three-fold, adding nearly $500 million to US health care costs, and causing dramatic deterioration in quality of life [4-10]. Screening for OPD in these settings, a process based on human observation of a patient swallowing without the use of instrumentation (videofluoroscopy – "VF"), fails to identify many patients with silent OPD who remain unidentified until adverse events like AP occur. Thus, a quick, accurate method of predicting the presence and absence of silent and overt OPD is needed to prevent the inadvertent aspiration of food, liquids and colonized oral secretions that lead to pneumonia. We are developing such an instrumental screening tool, the **Aspirometer**, which, when deployed at the time of admission or first suspicion of a disease that causes OPD, can identify OPD early, and prevent the consequences of silent OPD.

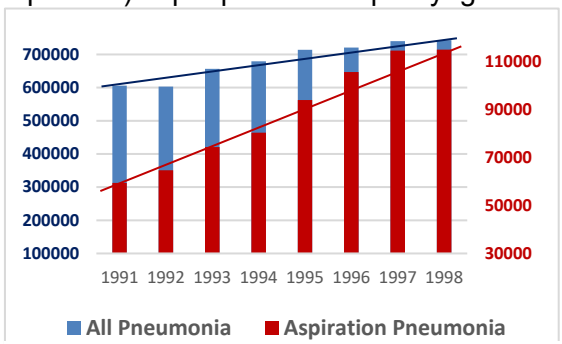

Figure 1 – Increased pneumonia (22.6%) vs aspiration pneumonia (93.5%) incidence 1991-1998.

Scientific Premise: OPD is caused by disease-related disruptions in swallowing kinematics (e.g., timely and complete movement of oropharyngeal structures) or swallow physiology (force and symmetry of muscular contractions, neuromuscular transmission, sensory function). These impairments lead to outcomes such as airway penetration and aspiration, and excessive amounts of post-swallow oral or pharyngeal residue that are aspirated. OPD patients are suspected of aspirating when they cough or choke while eating or drinking or fail a screening test. They are then referred for diagnostic testing with VF which is the gold standard for characterizing silent aspiration and OPD. VF is never used for screening because it requires trained personnel to perform and interpret [13] and would add costs of over $320 million annually to screen just people with stroke. Many people who aspirate do not have reflexive airway protective responses to aspiration and do not cough or choke rendering this "silent aspiration" undetectable at the bedside, hence many patients develop aspiration pneumonia [11, 12] before its risk is known.

A major gap exists between the convenience, low cost and imprecision of screening, and the sophistication, expense, precision and preventive benefits of VF. Inexpensive and convenient bedside standard institutional screening (SIS) protocols for OPD are present in many settings [14, 15]. Published, validated SIS's [21-23] are based on human observations of patients swallowing water, observing for signs of OPD using standard procedures (Figure 2). SIS performed by ordinary observers (nurses, nursing assistants) relies on whether the patient coughs or chokes during or after wallowing to predict aspiration (Figure 3). Patients who "fail" SIS all receive interventions to mitigate pneumonia risk including gold standard testing using VF, to guide these interventions, whether or not they have OPD. Patients who "pass" SIS (no coughing or choking) either do not aspirate, or they have undetected silent aspiration (which occurs in up to 40% of aspirators), and resume unsafe oral intake without intervention [16]. Popular, but weak, SIS signs of aspiration such as "wet voice quality" after swallowing, have not proven sufficiently reliable as valid predictors of aspiration [17]. A "wet voice" is absent in up to 80% of thin-liquid aspiration events, and in up to 50% of thicker liquid aspiration events among people with Parkinson's disease [18]. Moreover, judgments of wet voice are misleading and poor indicators of aspiration or dysphagia [17], exhibit poor sensitivity and inter-judge reliability [19], and even using acoustic analysis of voice production parameters to assess voice after swallows cannot reliably predict airway penetration [20]. Aside from their previously

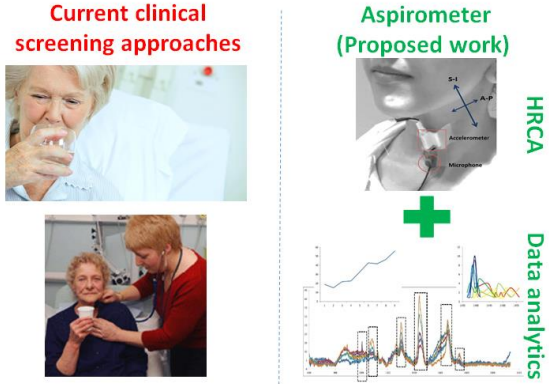

Figure 2 – Comparing the current practices with data analytics of HRCA. Forms and patient observations are currently used by clinicians to subjectively judge the presence of dysphagia. The Aspirometer can provide an objective dysphagia assessment approach.

described weaknesses, adherence to the screens' protocols varies [5, 24], reducing the validity and precision of SIS. **No currently available SIS can identify silent aspiration or OPD-related** risk of pneumonia, malnutrition, and dehydration [25, 26]. Thus, an inexpensive and accurate silent aspiration detection tool is needed and our research has produced strong lines of evidence toward that end. Our scientific premise is that the Aspirometer, an accurate, early-warning, easy to use, noninvasive tool to detect silent aspiration and OPD, can lead to pre-emptive identification of silent aspirators and significantly reduce morbidity, mortality, and health care expenditures.

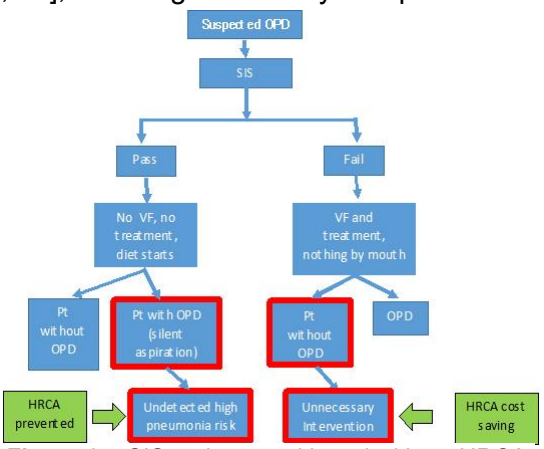

Figure 3 – SIS pathways with and without HRCA.

"Cervical auscultation" (CA) methods rely on use of a stethoscope (Figure 2) to listen to and subjectively interpret the sounds emanating from the throat during a swallow. Limited by the narrow detection capacity of the human auditory system and limited signal transmission by the stethoscope, research has repeatedly confirmed CA's poor accuracy and reproducibility, and poor inter-examiner agreement as to the kinematic impairments producing the sounds observed, leaving its ability to identify at-risk patients with silent aspiration poor [27, 28]. Our previous work has shown promising results toward improving the objectivity and accuracy of CA [29-31], with high resolution instrumentation that can record the entire digital spectrum of these swallowing sounds that analog methods with stethoscopes and the human auditory system cannot transmit, perceive and process. The **Aspirometer**, relies on high resolution cervical auscultation (HRCA) that records swallowing vibrations and sounds with miniaturized high-resolution triaxial accelerometers and microphones placed over the anterior throat (Figure 2). Signals are then analyzed objectively with advanced data analytics far exceeding the abilities of stethoscope-human judgment.

The central challenge to deployment of the Aspirometer is that our current methods have been developed only with 274 patients with suspected OPD. Our preliminary results (see A1.c and A2.c) have shown that our algorithms have become increasingly accurate at identifying HRCA signals that correspond to many swallow kinematic events contributing to OPD and airway protection during swallowing [32-36]. To define the entire dysphagia severity continuum and a cutoff for silent OPD presence, we need to complete the severity continuum by analyzing swallows from completely healthy control participants and compare them to impaired swallows in patients with dysphagia including those with silent aspiration. Our *overall hypothesis*, formed on our strong preliminary results (see **Approach**), is that the HRCA-based screening can independently and accurately predict silent aspiration and OPD before it can cause harm in patients with OPD. Based on our strong preliminary data, we expect that HRCA-based screening with the Aspirometer will identify pneumonia risk earlier in people with new diagnoses that cause OPD and silent aspiration by detecting significantly more patients with clinically significant OPD than SIS alone, and identify those who fail screens but do not have OPD (Figure 4). The proposed approach will lead to HRCA-based characterization of the entire continuum of healthy and disordered swallow function, equation of this HRCA continuum with established measures of OPD severity, and development of the Aspirometer as a reliable dysphagia screening tool that can be implemented immediately upon the first suspicion that a patient has suspected OPD, regardless of the setting. This will lead to pre-emptive prevention of healthcare associated, hospital and community acquired OPD-related pneumonias and other OPD-related adverse outcomes.

	OPD screening protocols	VF	Cervical auscultation	HRCA (proposed approach)
Excellent accuracy		✓		✓
Affordable	✓		✓	✓
Easily administered	✓		✓	✓
Silent aspiration		✓		✓

Figure 4 – The significance of the proposed work.

INNOVATION

Our approach represents a major leap forward in the inexpensive and noninvasive screening of OPD, through use of novel theoretical concepts and technologies and objective decision-making methods that will mitigate dysphagia-related adverse events in ordinary clinical scenarios, while at the same time directing resources to gold standard diagnostic testing only for those patients who need it [37]. Our goal is to develop a novel screening paradigm using the Aspirometer, as a universal OPD screening tool that can be deployed in ordinary and often chaotic clinical settings like hospital emergency rooms, nursing homes, and home care

situations [38, 39], where OPD is prevalent and imaging studies are unavailable or unacceptable to the patient. But that leap requires our further engineering and clinical developments to enable an HRCA system to predict which patients need protective interventions to mitigate their pneumonia risk.

In our currently R01 funded research, we have established moderate but significant relationships between swallow kinematic events observed via VF and the HRCA signals they generated (see section A2.c) as well as correlations between HRCA signals and airway protection, a key predictor of aspiration pneumonia. Our findings have advanced the science of OPD early detection beyond that of previous studies that have not culminated into integration of these findings to characterize actual risk of OPD-related adverse events like AP [40-58]. These earlier studies attempted to match VF images to CA signals to associate swallow events to sounds [59, 60], or infer the relation between kinematic events and key features of the swallowing signal [27, 61-64]. But unlike our research, none of these studies has directly linked distinct waveform features to underlying swallow physiology or silent aspiration, and they have established only the presence of weak correlations between swallow events and signals [60, 64] (Figure 5).

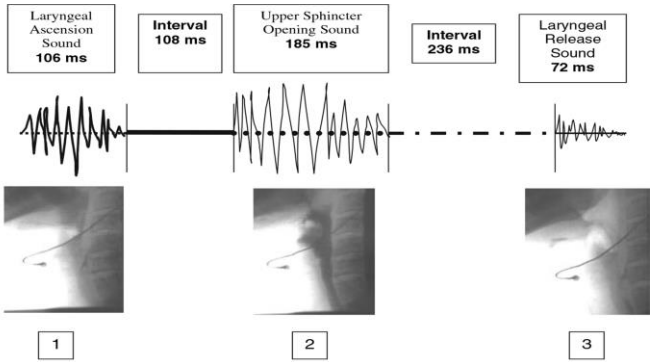

Figure 5 – Some established relationships between HRCA and swallowing kinematic events found in the literature [24].

Our approach breaks new ground by equating swallow physiologic data collected in ordinary settings to accepted metrics of swallow impairment, and defining HRCA outputs that can identify patients in need of intervention without the use of VF imaging. We seek to further innovate and develop HRCA as a feasible method that can produce generalizable clinical results (Table 1). First, we will collect and analyze swallows from healthy participants in order to establish cutoffs for "healthy swallows" (see A1.c.). Second, we will equate HRCA signals to OPD impairment levels derived from a validated and widely used profile of OPD impairment using robust big-data analysis approaches, not previously used in this line of research. Third, we will test our HRCA-based Aspirometer system in a blinded, randomized controlled trial comparing the outcomes of SIS with and without our HRCA-based tool.

Table 1 – The innovation of the proposed project. SIS denotes standardized institutional screening.

Open questions	Current state-of-the-art	Proposed research
Define the HRCA range of "normal swallowing signals" from healthy people	Our large data set from 4000 swallows of people referred for dysphagia testing has been analyzed; no "healthy data"; prior studies of "normal" used different signal processing and data collection methods	Collect and analyze swallows from healthy persons; repeat analyses performed on 4000 swallow data set from patients; completes the range of data collected from healthy → severely dysphagic
Equate the HRCA signal results to accepted standard of swallow impairment	Not understood; prior research has equated signals and signal features to specific events and not to accepted, clinically utilized and validated measures of swallow impairment	Rate all swallows in both data sets (4000 swallows from patients + swallows from healthy people) with the "Modified Barium Swallow Impairment Profile"
Can HRCA identify dysphagia more accurately than SIS?	Can differentiate grossly abnormal from normal. Demonstrated only for small sample sizes. Not clinically validated.	Deploy a HRCA system; blinded, randomized controlled trial comparing SIS to SIS + HRCA, using videofluoroscopy as the gold standard

APPROACH

PROGRESS REPORT FOR RENEWAL: The project (July 2013-June 2018) revolved around the following aims:

1) **In order to accumulate an adequately-powered reference data set for training signal processing classifiers, we will collect swallowing accelerometry signals from a larger sample of individuals undergoing concurrent videofluoroscopy.**
2) **In order to enhance the accuracy of signal processing classification algorithms to detect problems in swallowing safety and efficiency, we will add an additional physiological signal to the Aspirometer design (acoustic information, collected concurrently with a co-located microphone). We will explore the value of any non-overlapping information in this additional signal for improving the accuracy of the classifier.**

3) **In order to explore the potential of non-invasive swallowing signal processing classifiers to detect swallowing problems *beyond the context of thin liquid swallows*, we will expand our data collection protocol to include swallows of nectar-thick and honey-thick liquids.**

Aim 1 was successfully completed, as we collected HRCA data from 274 patients (24 more patients than initially proposed) undergoing a concurrent VF exam. As a result, we have a unique, large database of simultaneously acquired HRCA signals and VF images that is unparalleled in OPD research.

Per Aim 2, we clearly demonstrated that multiple sound and vibrations signal features acquired simultaneously during VF exams contain complimentary information, and they should not be substituted for each other. Figure 6(A) summarizes our main results from [67]. The shaded columns and rows indicate microphone and accelerometer axis combinations with the greatest number of dissimilarities indicating the complementary nature of acoustic and vibratory signal features, while the red dots indicate signal features in which the vibratory signal features had significantly higher values than the acoustic signals. Figure 6(B) summarizes our main results of [68]. Specifically, although the swallowing sounds and swallowing vibrations might have the same kinematic sources, swallowing signals recorded by the microphone (sounds) and the accelerometer (vibrations) differed from each other in the time and frequency domains. These findings shift the existing paradigm that swallowing sounds and vibration information are equivalent [78, 79], and support our two-sensor method as superior to a single acoustic detector [79, 80]. In fact, our findings confirm that swallowing signals from bothsensors provide useful information about swallowing function. Hence, our subsequent research of swallowing physiology with these sensors using concurrent VF images advanced our understanding of the sources of swallowing-related vibrations and sounds.

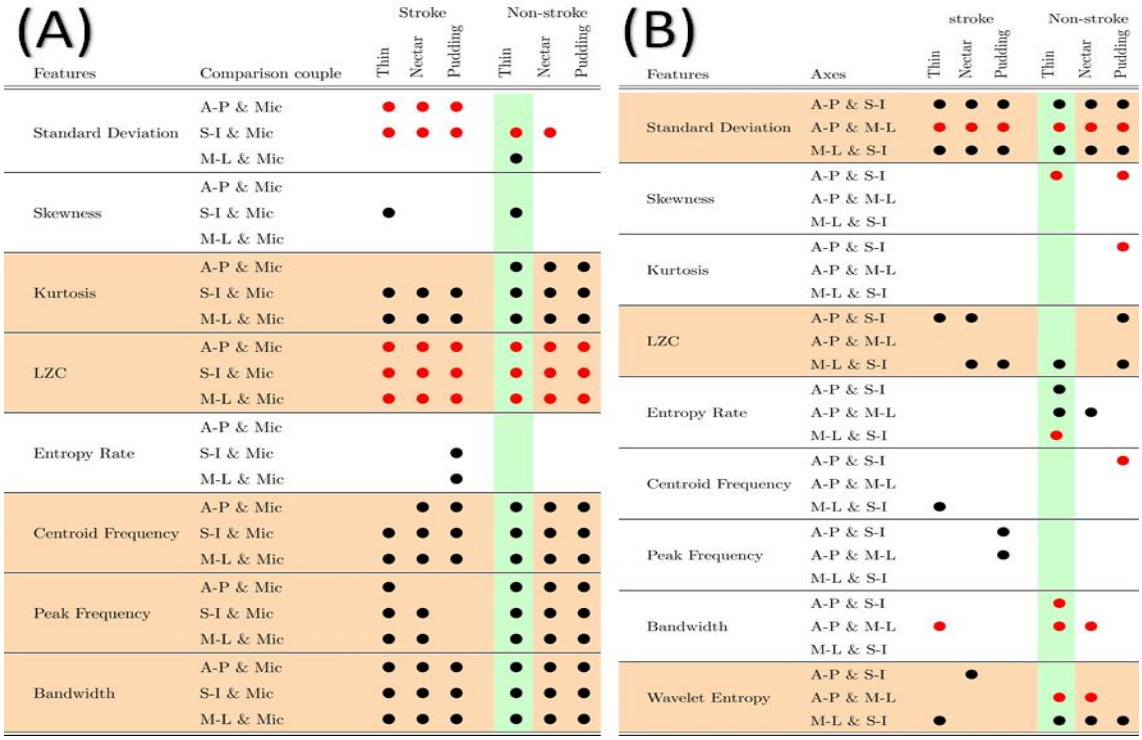

Figure 6 – Our results for Aim 2: (A) A summary of differences between swallowing sounds and vibrations among groups of study. Red/black circles indicate that the axis/mic in "Comparison couple" column has the higher value in a specific feature mentioned in "Features' column than the mic/axis. The column highlighted in light green and five rows highlighted in light orange indicate group/features with the largest number of dissimilarities. (B) A summary of directional differences. All dots (red and black) indicated the existence of directional dissimilarities. Axes column demonstrates which two axes are compared to each other. Red dots indicate that the first axis in the axes column has a higher value of the computed feature in features column than the second axis, while black dots indicate the second axis has a higher value than the first axis.

As per Aim 3, we clearly demonstrated that swallowed fluid viscosity strongly influences the swallowing assessment (Figure 7 summarizes the main results of [70]). We found that HRCA can detect several statistical differences between unsafe swallows of viscous fluid, in which clinically significant aspiration and laryngeal penetration occurred, and safe swallows that exhibited airway protection scores that fall within the normal range for healthy people [81]. This is of interest because aspiration of thicker liquids has been shown to produce higher rates of pneumonia and longer hospitalization durations than aspiration of thin liquids [82]. Past research has suggested that thickening agents used during videofluoroscopy exams exhibit non-Newtonian fluid properties, which lead to the reduced aspiration rate in dysphagic patients [83, 84].

Based on this research by our team, Dr. Sejdic received the **Presidential Early Career Award for Scientists and Engineers** in 2016. Overall, the project was very successful as all three aims were successfully

completed and over 10 publications have been disseminated in major research journals [65-77], in addition to numerous presentations by Dr. Sejdic and Dr. Coyle at domestic and international institutions/conferences. Our line of research has also begun investigating theoretical frameworks linking swallowing signals to other central and peripheral mechanisms of recent interest to researchers by investigating brain networks on a swallow-by-swallow basis using electrophysiologic monitoring [73-77]. One of our future mechanistic goals is to relate central neurological changes in disease states to features extractable from HRCA recordings to portray a complete picture of swallowing, from central neurological changes in the brain to peripheral kinematic events observed aerodigestive tract.

(A)

	Thin		Viscous	
	Safe	Unsafe	Safe	Unsafe
Skewness	0.867, 1.470	0.642, 1.963	0.491, 1.455	0.759, 1.621
Kurtosis	87.04, 25.48	27.56, 29.84	96.20, 30.07	39.69, 15.85
Entropy Rate	0.987, 0.007	0.987, 0.007	0.989, 0.006	0.986, 0.004
L-Z Complexity	0.059, 0.031	0.065, 0.030	0.056, 0.039	0.064, 0.029
Peak Freq (Hz)	16.56, 4.732	7.162, 5.161	56.29, 4.414	15.22, 5.613
Center Freq (Hz)	189.7, 138.3	109.2, 115.4	204.7, 113.4	141.0, 78.93
Bandwidth (Hz)	221.1, 222.6	198.1, 158.2	273.7, 174.7	264.2, 86.94
Wavelet Entropy	1.034, 1.348	1.003, 0.976	0.928, 1.139	1.066, 1.120

(B)

	Thin		Viscous	
	Safe	Unsafe	Safe	Unsafe
Skewness	−0.557, 1.082	−0.435, 2.305	−0.129, 1.207	−0.441, 0.754
Kurtosis	28.91, 14.79	101.6, 31.11	66.26, 11.13	22.68, 8.000
Entropy Rate	0.988, 0.005	0.989, 0.003	0.989, 0.006	0.988, 0.004
L-Z Complexity	0.068, 0.033	0.067, 0.032	0.062, 0.038	0.069, 0.032
Peak Freq (Hz)	11.33, 3.660	19.52, 7.336	10.79, 3.627	30.60, 3.812
Center Freq (Hz)	67.53, 47.45	143.4, 56.31	105.7, 44.94	85.52, 20.85
Bandwidth (Hz)	114.7, 99.64	238.4, 62.16	145.3, 107.5	180.4, 35.51
Wavelet Entropy	1.160, 1.178	0.978, 0.996	1.138, 1.001	1.004, 1.408

(C)

	Thin		Viscous	
	Safe	Unsafe	Safe	Unsafe
Skewness	−0.317, 3.334	−1.564, 3.531	−0.525, 3.894	−0.125, 3.873
Kurtosis	149.2, 117.0	187.2, 101.0	191.8, 132.4	157.3, 88.60
Entropy Rate	0.985, 0.009	0.986, 0.009	0.987, 0.007	0.987, 0.007
L-Z Complexity	0.055, 0.031	0.055, 0.048	0.050, 0.026	0.052, 0.038
Peak Freq (Hz)	94.10, 122.3	99.52, 77.71	99.46, 130.4	92.88, 100.2
Center Freq (Hz)	312.5, 315.9	348.5, 245.7	340.3, 305.1	382.2, 294.2
Bandwidth (Hz)	348.2, 281.8	393.6, 170.0	402.7, 284.0	399.0, 230.7
Wavelet Entropy	1.723, 1.151	1.641, 1.119	1.596, 0.946	1.697, 1.615

Figure 7 – Our results for Aim 3: (A) Feature values corresponding to anterior-posterior swallowing vibrations. (B) Feature values corresponding to swallowing sounds. (C) Feature values corresponding to swallowing sounds. These values represent the mean and interquartile range of each feature of our data set separated by bolus viscosity and whether it was a safe or unsafe swallow.

PROPOSED WORK: Our strong preliminary results show that we are positioned to apply machine learning algorithms to extract swallowing events from HRCA recordings and relate those events to a score on standardized swallow impairment scales. Upon completion, we will be able to identify false-negatives (patients who pass current SIS because they silently aspirate), as well as OPD and penetration-aspiration events that are either clinically insignificant or do not require costly intervention or VF studies. This will help to allocate VF and intervention resources to those most in need, while preventing unnecessary food restrictions to those who currently fail dysphagia screens but are not at risk (false positives).

AIM 1: Complete the entire continuum of HRCA swallowing signals from normal to severely impaired, by collecting HRCA swallow data from healthy people.

A1.a. Introduction: The goal of a useful HRCA swallowing screening tool is to accurately distinguish healthy/normal swallowing from OPD that can pose health threats to the patient. We have a large database of 4000 swallows from patients referred for VF evaluation of dysphagia and have equated their VF-identified OPD characteristics with HRCA signal features, but we do not have data to complete the “normal” end of the impairment severity continuum from healthy people. The ***objective of this aim*** is to collect and analyze swallow VF data from healthy persons without dysphagia, extending our previous R01 project. This will complete a large, master set of swallows of all impairment severity levels, and our analysis will determine define the cutoff for “normal” (or “healthy/nonpathological”) swallows from HRCA signals. The ***working hypotheses*** for this aim is that pharyngeal swallowing events in HRCA signals from healthy people exhibit significantly different HRCA signal signature features than those from patients with dysphagia and that there is sufficient separation to allow discrimination (see A1.c.). We will use an ***approach*** that relies on modern machine learning methods [85]. We will collect a set of unimpaired swallows from healthy age-matched adults to represent the “normal” end of the OPD impairment continuum. This aim’s ***rationale*** is that our current data set’s least severely impaired swallows were obtained from patients with suspected dysphagia due to disease, and therefore are not valid representations of normal swallows from healthy people. We ***expect*** that completion of the entire continuum of impairment severity with HRCA will enable us to preemptively differentiate patients requiring more aggressive or immediate diagnostic intervention than is currently possible with SIS while more accurately identifying patients who do not require intervention. By achieving this aim we will accomplish an essential goal in healthcare associated pneumonia prevention: accurate and early detection of clinically significant OPD impairment from HRCA signals and expedited patient management in clinical and other naturalistic settings.

A1.b. Justification and feasibility – Review of relevant literature: Following development of the penetration-aspiration scale (PAS), it was determined that PAS scores differentiated healthy swallows from those obtained

from people with two conditions that cause OPD: stroke and treatment for head and neck cancer [81]. 71 of 95 normal participants produced PAS scores of “1” (no airway penetration) on the first and second swallows, with 19 producing a score of “2” and a single participant producing a “3” with no scores observed above “3”. Meanwhile patients in both patient groups scored significantly “higher” (more severe) on the PAS than did the normals during both first and second swallows (Figure 8). Likewise, significant kinematic differences between healthy and disordered swallows have been the benchmark for defining OPD for more than 3 decades [32, 86-89]. Studies have shown significant differences between healthy swallows and those observed in patients with OPD swallows, in the swallow kinematic events that we are measuring in this project (e.g., the duration of stage transition, oral and pharyngeal transit durations, and duration of laryngeal closure among many others) [90-92]. Because of the disparity in PAS and other measures of swallow function between controls and people with suspected OPD whose swallowing is not clinically unsafe, completion of the HRCA continuum to include normal swallows is necessary to advance our innovative approach to noninvasive OPD classification.

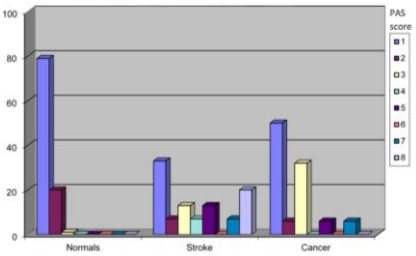

Figure 8 – PAS scores for healthy controls, stroke and cancer patients.

Past studies attempting to classify CA signals have had various limitations. First, many studies utilized less than optimal sample sizes and did not clearly differentiate independent judge training and testing groups, which limits the generalizability of the results [37, 58, 93-104]. Second, linear classifiers have possibly reduced the maximum potential accuracy of the classification method [37, 95, 96, 100-102, 105]. Finally, a number of studies incorporated measurements other than cervical auscultation (e.g., nasal airflow) [58, 93, 94, 100, 103], which introduced additional confounding variables. Our literature search found that techniques that utilize neural network-based classifiers have some of the highest reported accuracies for a given task [93, 94, 97-100, 105], but there are open problems still unresolved. These studies acknowledge that they are investigating a limited selection of mathematical signal features and that alternate choices may offer benefits to classification. From these previous attempts, the field would benefit from a technique that was both able to analyze higher-order signal features and could self-select features to analyze through use of unsupervised learning methods. One relatively new classification technique, deep learning, possess these desirable traits, thereby combining much of the past research on the topic into a single method.

Structure		Statistical Metrics		
Combination Network	Input Network	Specificity	Sensitivity	Accuracy
1-Layer	Small 1-Layer	90.7	83.7	87.2
	Small 2-Layer	93.3	81.6	87.5
	Small 3-Layer	90.9	82.2	86.5
	Large 1-Layer	93.0	81.7	87.4
	Large 2-Layer	**96.9**	**85.7**	**91.3**
	Large 3-Layer	98.5	75.3	86.9
2-Layer	Small 1-Layer	94.3	80.7	87.5
	Small 2-Layer	92.0	83.3	87.6
	Small 3-Layer	87.5	84.2	85.9
	Large 1-Layer	97.5	79.7	88.6
	Large 2-Layer	96.2	81.1	88.7
	Large 3-Layer	97.8	77.6	87.7
3-Layer	Small 1-Layer	91.1	83.7	87.4
	Small 2-Layer	92.0	82.9	87.5
	Small 3-Layer	83.3	77.4	80.3
	Large 1-Layer	97.5	78.3	87.9
	Large 2-Layer	95.4	78.0	86.7
	Large 3-Layer	98.5	75.9	87.2

Figure 9 – Preliminary results for Aim 1. Using different configurations of artificial neural networks, we can achieve very high accuracies. In this case, a 1-layer combination of two large 2-layer networks for each axis provided the best results (bolded above).

***A1.c. Justification and feasibility – Preliminary studies*:** In our preliminary research using an artificial intelligence method was used to differentiate swallows made by healthy subjects and the least impaired swallows produced by patients with OPD [70]. A total of 55 healthy participants (28 men, 27 women, mean age 39) with no history of swallowing disorders, head or neck trauma or major surgery, chronic smoking, or other conditions which impair swallowing performance, completed a total of 30 independent swallows of several liquid viscosities while their head was in a neutral position. The non-healthy participants consisted of a total of 53 patients (34 men, 19 women, mean age 63) with suspected dysphagia who were undergoing a VF evaluation at the discretion of the examining clinicians and based on patient needs, rather than an artificially controlled, standardized data collection procedure. Presentation order, head position, and other environmental factors were unique for each patient. The materials swallowed during the examination were of comparable consistencies (thin (<5 cps), `nectar' (300 cps),`honey' (2000 cps) consistency liquids) to those provided to healthy subjects based on available product information and qualitative guidelines. Using all of these swallows from both groups, we built an artificial intelligence method [70] based on deep belief networks [107], one of the newest forms of artificial neural networks [108], which combines multiple neural networks in different layers into a single decision process. Figure 9 summarizes our results. Our combined deep belief network configuration also demonstrated generally

greater sensitivity than our single-axis networks. But we do not have concurrent VF validation of the data obtained from the healthy people. Collection and analysis of these data will complete the range of swallow function and enable completion of our 2nd and 3rd aims, which seek to develop an HRCA impairment severity continuum.

A1.d. Experimental approach: STEP 1: We will collect concurrent VF and HRCA recordings from 70 healthy subjects (35 females and 35 males) with no previous history of swallowing difficulties who are **age matched** to our database of swallows from patients with OPD. Each subject will complete five swallows of 3mL thin liquid and five swallows of self-selected, comfortable volume of thin liquid from a cup, in a head-neutral position. STEP 2: We will first measure nine kinematic measures with VF (onset, offset, and time to peak hyolaryngeal excursion; laryngeal closure and reopening; UES closure and reopening; onset and offset of tongue base to posterior wall contact), penetration-aspiration scale scores [109], and pharyngeal retention/residue scores [89, 110, 111, 112]. STEP 3: Pre-process all HRCA recordings per steps taken in previous publications [29, 30, 71], to remove any disturbances and diminish noise in these recordings. STEP 4: VF results (STEP 2) will be equated with HRCA signal features and categorized by bolus volume of the swallowed material, these data will be combined with the data from over 4000 patient swallows from our previous R01 grant.

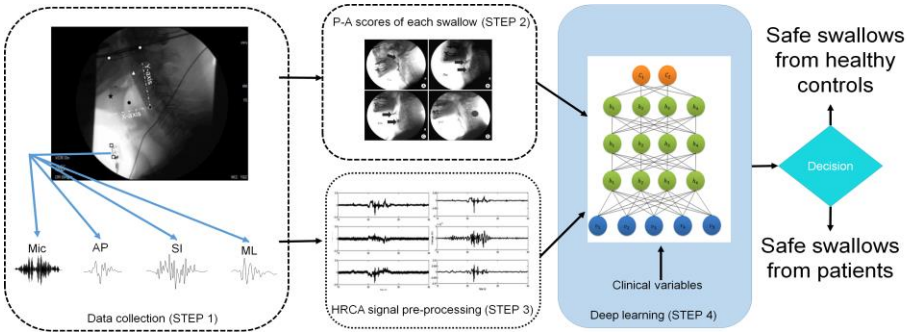

Figure 10 – Our proposed experimental and data analysis approach for Aim 1.

STEP 5: We will develop an algorithm based on the state-of-the-art machine learning concepts that will differentiate between healthy controls and people with suspected OPD whose swallows did not exhibit OPD (see Figure 10). Specifically, we will analyze a random 70% training subsample and use the deep belief machine learning approach as in our preliminary work [70]. Once modeling is complete, the remaining 30% validation subsample will be used to obtain accuracy estimates devoid of model overfitting.

A1.e. Data interpretation: In STEP 2, Dr. Coyle will train doctoral students to evaluate all VF dependent variables and establish their inter- and intra-rater reliability (intraclass correlation coefficient above 0.9 for continuous variables and kappa above 0.75 or percent exact agreement above 80% for categorical variables), in the measurement of kinematic event timing, and assignment of P-A and pharyngeal retention/residue scores. They will use ImageJ image processing software, to measure penetration-aspiration scores, and kinematic and pharyngeal retention/residue measures from all swallow recordings in this new set of healthy swallows, and complete the same measurements from the remaining 3900 swallows in our database that did not undergo the complete kinematic analysis that we performed to produce the preliminary data presented in section A2.c. To ensure their judgments do not drift over time, we will perform ongoing reliability measures using the same criteria, through a rolling re-analysis of a randomly selected 10% of analyzed swallow recordings. Then, to understand the accuracy of the developed HRCA analysis algorithm using only the training subsample in STEP 5, we will begin by calculating a confusion matrix [85]. The confusion matrix will be calculated by comparing the algorithm's output with scores from STEP 2. The confusion matrix will be then used to calculate false positives, false negatives, true positives and true negatives, and lastly sensitivity, specificity, predictive values and likelihood ratios for the algorithm. These values will be initially calculated using the leave-one-out approach, but we will then repeat the analysis with 10-fold cross-validation. Then in STEP 5, we will use the number of correctly and incorrectly HRCA-detected swallows to calculate the sensitivity and specificity values, again using the leave-one-out approach (the most exhaustive and computationally expensive cross-validation approach) and 10-fold cross-validation. We have proposed state-of-the-art machine learning methods based on deep learning as our primary analysis, but we will also consider other techniques such as classification tree methods [113], and generalized linear models due to their ability to produce simpler prediction rules for ease of use, cognizant of the potential loss of some accuracy compared to deep learning. Finally, we will use the validation subsample to obtain authoritative measures of accuracy devoid of risks of model overfitting.

A1.f. Expected outcomes: The benchmark for success of Aim 1 will be creation of a machine learning algorithm that completes the continuum of of HRCA signal characteristics from normal to the most severely impaired swallowing function that will then be available for future research. Specifically, we anticipate these algorithms

will correctly identify normal airway protection (PAS scores of 1-2) in healthy controls and patients with dysphagia with over 90% accuracy compared to the gold standard VF ratings for each swallow [70]. These outcomes will establish the evidence that the HRCA signals and advanced analytics form a robust and reliable swallowing screening system with comparable accuracy to VF, while also demonstrating the system's ability to identify additional swallowing diagnostic features that are currently only possible with VF, potentially advancing HRCA as not a screening tool with diagnostic capabilities far beyond SIS.

A1.g. Challenges and contingency plans: The preliminary results (see A1.c.) strongly support our hypothesis (see A1.a.). In the highly unlikely event that our VF judges' ratings drift unacceptably, we will increase surveillance on inter- and intra-rater reliability and pull judges from analysis and retrain them to criterion, retest their reliability before placing them back online.

***A1.h. Sample size justification*:** We currently have data on 4000 swallows from 274 dysphagic persons. We plan to add 700 swallows from 70 healthy persons to this data set. Allowing for some refusals, we anticipate obtaining 650 swallows from 65 healthy persons. Assuming the sensitivity and specificity will be approximately 90%, intra-class correlation of 0.7 from our prior data and a resulting design effect of 3.8 [114], and using published methods [115, 116] implemented in commercially available software (PASS 2012, Number Cruncher Statistical Systems, Kaysville, UT), conservatively we will be able to estimate sensitivity with a margin of error as small as ±2% and specificity with ±8% in the training sample, and ±3% and ±13% in the validation samples, at the 95% confidence level.

AIM 2: Develop tools for translating HRCA to equivalent validated measures of swallowing impairment.

A2.a. Introduction: We have successfully demonstrated HRCA's capabilities in grossly identifying pathological airway protection. However, HRCA's predictive capabilities lie in its ability to analyze the summation of all concurrent events occurring during swallowing. The *objective of this aim* is to equate, or elicit means of translating, HRCA signal analysis results to a validated clinical measure of swallowing impairment, namely, the Modified Barium Swallow Impairment Profile (MBSImP) [117]. To attain the objective of this aim, we will test the *working hypothesis* that HRCA can noninvasively quantify levels of dysphagia severity and airway protection comparably to accepted clinical OPD severity scales derived from gold standard VF data analysis. We will use an *approach* that relies on scoring each swallow in our large dataset according to the MBSImP component scales. Next, through advanced data analytics tools, we will establish relationships between HRCA signal features and the MBSImP scores for each swallow. The *rationale* for this aim is that HRCA signal analysis results must be equated with and translatable to an acceptable gold standard of swallowing impairment to validate its efficacy in identifying clinically significant dysphagia. We *expect* that achievement of this aim will substantially advance dysphagia screening and diagnostics by producing a readily deployable surrogate determination of swallowing disability in the absence or inaccessibility of gold standard VF testing.

A2.b. Justification and feasibility – Review of relevant literature: To accomplish our goal, it is necessary to equate HRCA signals to standardized and validated measures of swallow impairment and airway protection. As discussed in A1.b, the PAS differentiates normal vs. disordered airway protection [81]. More recently, the MBSImP has become widely accepted in both clinical and research domains as the gold standard for interpreting VF data to determine the degree of swallowing impairment in people with OPD [118]. MBSImP measures 17 components of swallowing impairment in oral, pharyngeal, and esophageal regions through analysis of VF data using ordinal severity scales of 17 components: six oral, ten pharyngeal, and one esophageal. Each component is rated based on specific criteria that were established and validated through expert consensus and repeated testing. Establishing HRCA signal features that predict MBSImP ratings can demonstrate the value of HRCA in the screening and diagnostic processes and potentially obviating the need for VF in some cases. Furthermore, combining MBSImP and PAS [81, 109, 119] leads to a complete multidimensional profile of swallow impairment and potential dysphagia-related risk to which HRCA can be equated. MBSImP has been used concurrently in several studies with PAS and both measures have shown their complementary value in the comprehensive quantification of swallow impairment and the airway protection outcomes that these impairments produce [118, 120-124].

***A2.c. Justification and feasibility – Preliminary studies*:** Our pilot study has identified strong differences in clusters of HRCA signal features that clearly separated less- and more-severely impaired swallows. We analyzed 100 swallows from our 274-patient data set, to determine if HRCA signal features can detect swallow kinematic events. All 100 swallows were simultaneously observed with VF and HRCA sensors, and 13 swallow

kinematic events (onset of barium entering pharynx, onset, offset and arrival at maximum displacement of the hyoid bone, onset and offset of laryngeal closure, onset of laryngeal reopening, onset and offset of UES opening, onset of UES reclosure, onset and offset of contact of the tongue base to the posterior pharyngeal wall, and first re-opening of tongue base to posterior pharyngeal wall contact) were measured by judges who were trained in VF image processing methods, blinded to patient diagnosis, and whose inter- and intra-rater reliability were acceptable. The results were compared to HRCA signals to determine the frequency of occurrence of 7 separate HRCA signal feature peaks (maxima) with each of the 13 swallow kinematic events, to a tolerance of within 0.1 seconds of the actual swallow kinematic events, the standard tolerance for temporal VF analysis [89], (Table 2). Fifty-two to 88% of the kinematic events were detected within this tolerance by HRCA sensors more than half of the time. Since the probability is <8% that any continuous vibratory or acoustic signal would exhibit a strongly systematic change that co-occurs with specific swallow kinematic events, these findings indicate that HRCA signal features are strongly associated with swallow kinematic events and may show promise in identifying abnormal vs. normal swallow function. We then stratified the data into two PAS score ranges: 1-2 (normal airway protection) and 3-8 (abnormal airway protection). Microphone and accelerometer signal feature peaks co-occurred with normal airway protection 40-49% of the time, but these peaks co-occurred only 11-14% of the time during abnormal airway protection swallows. Moreover, the ranges of these probabilities did not overlap for any of the four data collection channels, and the results were statistically significant as expected at p=0.018. These results indicate that HRCA can detect co-occurring swallow kinematic events while at the same time differentiating between normal and abnormal airway protection. Though these results indicate HRCA's ability to detect simultaneously occurring swallowing events and airway compromise in the presence of other noise, the necessary next step is to equate this capability to standard measures of overall swallow impairment.

Table 2 – Frequency of signal maxima co-occurring with swallow kinematic events; separated by PAS ranges PAS 1-2 vs. PAS 3-8. NUME denotes the number of signal maxima co-occurred with swallow kinematic events > 50% of the time. MIC denotes a microphone, while S-I, A-P, and M-L denote vibrations in superior-inferior, anterior-posterior, and medial-lateral directions captured by an accelerometer.

Sensor	NUME	PAS 1-2		PAS 3-8	
		overall %	range	overall %	range
MIC	80/91	49	37-65	13.6	10-18
S-I	64/91	45	29-62	11	7-16
A-P	55/91	43	26-62	11	6-17
M-L	48/91	40	25-61	10	3-16

A2.d. Experimental approach: STEP 1: All swallows from patients and healthy participants (Aim 1) will be rated using the MBSImP. Judges will undergo standardized training in visual inspection and MBSimP ratings of swallow kinematic functions and impairments, and establishment of inter- and intra-rater reliability before beginning scoring. STEP 2: In addition to MBSImP component 16 (pharyngeal residue), pharyngeal residue (valleculae, pyriform sinuses) will be measured using the Normalized Residue Rating Scale which standardizes areas of barium residue retained in pharyngeal recesses (valleculae, pyriform sinuses) using conversion factors based on individual patient height [112]. STEP 3: We will measure airway compromise using the PAS [109]. STEP 4: Pre-process HRCA recordings per steps taken in previous publications [29, 30, 71] to remove any disturbances and diminish noise in these recordings. STEP 5: We will develop an algorithm based on the state-of-the-art machine learning concepts whose output will be the differentiation between healthy controls and people with suspected dysphagia whose swallows did not exhibit dysphagia, healthy dysphagic (see Figure 11). Specifically, we will utilize a random 70% training subsample for the deep belief machine learning approach as in our preliminary works [70], and once modeling is complete, use the remaining 30% validation subsample to obtain accuracy estimates devoid of model overfitting.

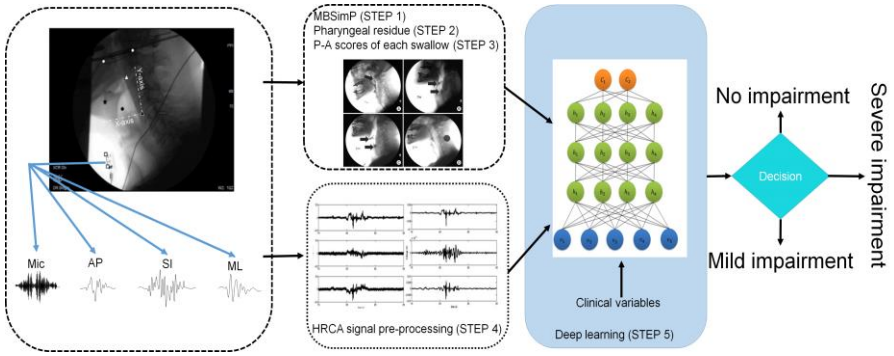

Figure 11 – Our proposed experimental and data analysis approach for Aim 2.

A2.e. Data interpretation: We will employ the same deep learning methods as in Aim 1 for our primary analysis, but instead will employ techniques suitable for categorical, ordinal dependent variables such as MBSImP and PAS. In addition, we will employ regression tree and linear mixed model methods in an effort to obtain simpler

means of converting HRCA signals. We will examine performance metrics such as root mean square error and multiple coefficient of determination (R^2) to evaluate our score equating models.

A2.f. Expected outcomes: The benchmark for success of Aim 2 will be creation of a set of HRCA signal signatures that can be translated to MBSImP, PAS, and pharyngeal retention measures. We anticipate a model can be built with sufficiently high predictive ability so that R^2 and/or root mean square error of score translation is no greater than 5% of the range of the swallowing impairment measure. The major outcome of this aim is that HRCA signal signatures will reflect swallow kinematic and airway protection function and equate to standard measures of swallow impairment which will help us develop the HRCA based Aspirometer as a tool that characterizes and predicts risk of adverse outcomes associated with dysphagia, without imaging.

A2.g. Challenges and contingency plans: As in Aim 1, in the highly unlikely event that our VF judges' ratings drift unacceptably, we will increase surveillance on inter- and intra-rater reliability and pull judges from analysis and retrain them to criterion, retest their reliability before placing them back online.

***A2.h. Sample size justification*:** The proposed approach is based on nonlinear modeling for which classical sample size calculation procedures are not suitable [125, 126]. As our augmented dataset is expected to contain more than 4000 (existing recordings)+700 (Aim 1) swallows, we strongly believe that it is a sufficient number of swallows as previous publications using similar nonlinear modeling techniques used data sets with a significantly lower number of samples [127-129]. Nonetheless, accounting for an intra-class correlation of 0.7 and a resulting design effect of 3.8 as in Aim 1, and assuming as many as 20 predictors will be needed in a linear model, we will be able to detect statistical significance of an R^2 as small as 0.03 in the training sample and 0.06 in the validation sample with 80% power at α=0.05.

AIM 3: Prospectively assess the accuracy of our HRCA system in predicting clinically significant dysphagia and aspiration in a randomized, controlled trial.

A3.a. Introduction: For Aspirometer-based swallowing screening to be useful in clinical settings, it needs to outperform SIS in identifying patients at risk of silent aspiration and clinically significant dysphagia before they are placed at risk of aspiration pneumonia, or its further development is not warranted. The *objective of this aim* is to establish the superiority of dysphagia screening with the Aspirometer to the existing non-instrumental SIS protocols. To attain the objective of this aim, we will test the *working hypothesis* that the Aspirometer combined with, and independent of, SIS will identify VF-confirmed clinically significant OPD more accurately than SIS alone. We will use an *approach* that screens consenting patients with ordinary SIS and HRCA, and compare four levels of screening predictions (SIS human judgment criterion only, HRCA criterion only, SIS and HRCA criteria, SIS or HRCA criteria) for identifying dysphagia as measured from gold standard VF testing of all participants performed within 24 hours of screening. The *rationale* for this aim is that a clinically useful and accurate HRCA-based instrumental screening method not only needs to be rigorously tested against current practices to establish its validity and accuracy, but also needs to be examined for possible incorporation into current clinical practices. The acquisition of such knowledge is critical to the improved mitigation of unnecessary and adverse health sequelae associated with OPD. Based on our preliminary data, we *expect* that HRCA-based screening will be able to identify (sensitivity=) 90% or more of patients with OPD needing intervention or follow-up with gold standard VF testing and (specificity=) 90% of those not needing VF testing using one of the 3 strategies incorporating HRCA. This would validate the development of HRCA-based swallow screening tools that pre-emptively identify patients with a high pneumonia risk due to OPD, expedite intervention or gold standard swallowing diagnostic tests when necessary, and to reject the need for VF testing when unnecessary.

Table 3 – Sensitivity and specificity of screening protocols for aspiration. SENS = Sensitivity; SPEC = Specificity; FPR = False Positive Rate; FNR = False Negative Rate.

Test	SENS	SPEC	FPR	FNR
Volume-Viscosity Screening Test	100%	29%	72%	0%
Daniels Swallow Screen	92%	66%	33%	8%
Gugging Swallow Screen	100%	50%	50%	0%
Yale Swallow Protocol	100%	44-64%	36-56%	0%

A3.b. Justification and feasibility – Review of relevant literature: SIS should rely on well-tested protocols that can detect true occurrences of OPD during screening, in comparison to subsequent gold-standard instrumental assessments [22, 130, 131, 132]. Though several SIS have been proposed and standardized in the literature (Table 3), previous SIS research contained confusing evidence [16, 21] by using different thresholds to define the presence of OPD. The most commonly reported screening metrics are sensitivity (the percentage of patients with an underlying problem, who are correctly

classified) and specificity (the percentage of patients without an underlying problem, who are correctly classified). When compared to blinded ratings of nonconcurrent instrumental exams, swallow screenings err on the side of over-identifying aspiration risk, i.e., good sensitivity but poor specificity (see Table 3). While it may be argued that this bias in favor of sensitivity constitutes a conservative "safety net" for finding swallowing difficulties, it also results in unnecessary interventions for patients without significant OPD (Figure 3) including withholding oral dietary intake and diet texture restrictions, placement of feeding tubes, and unnecessary referrals for costly assessments, all of which affect quality of life and place financial and other burdens. A screening protocol should be performed in ordinary settings by typical screening staff, and detect OPD accurately while incurring minimum risk for the patient. Our approach to this aim will produce results that can demonstrate superior identification of both people with and without OPD compared to prior OPD screening research which exhibits zero identification of silent aspiration and only about 60% identification of those without OPD.

Table 4 – HRCA-based screening can detect aspiration, validated against concurrent VF. SENS = Sensitivity; SPEC = Specificity; FPR = False Positive Rate; FNR = False Negative Rate; PB = Per bolus; PP = Per participant.

Parameter	Statistic	PB	PP
Impaired Swallowing Safety (13/40 patients; 55/154 swallows)	SENS	90%	100%
	SPEC	77%	54%
	FPR	23%	48%
	FNR	10%	0%

***A3.c. Justification and feasibility – Preliminary studies*:** In our initial study [31], we collected time-linked HRCA signals and VF, using a protocol of three sips of thin liquid barium (5 cc each). The classification algorithms were trained to discriminate swallows with PAS scores of 1 and 2 (safe) from those with scores ≥ 3 (penetration of material into the airway, above the level of the vocal cords, without clearance) and succeeded in this task at the level of the single bolus with 90% sensitivity and 77% specificity. When all the swallowing tasks performed by each patient were considered in aggregate, sensitivity for the detection of aspiration (i.e., anywhere in the protocol) improved to 100%, but specificity fell to 54%. These details are summarized in Table 4. Next, Dr. Sejdic has used HRCA signals collected from 30 older adults [101] to develop a support vector machine classifier to distinguish between grossly safe and unsafe swallowing with high sensitivity (97.1 ± 2%) and modest specificity (64 ± 8.8%). Also, we used HRCA signals from 29 pediatric participants along with a support vector machine classifier to achieve an adjusted accuracy of 89.6% ± 0.9 for the discrimination between swallows with and without airway entry [102]. Most recently, Dr. Sejdic has used a Bayes' machine learning approach to infer about the airway protection in 40 patients with dysphagia [105]. This was the first study that demonstrated that we can grossly differentiate healthy swallows (P-A scores ≤ 3) from penetration-aspiration swallows (P-A scores 4-8) with an accuracy greater than 90%. These preliminary results demonstrate that we can reliably differentiate safe and unsafe swallowing events.

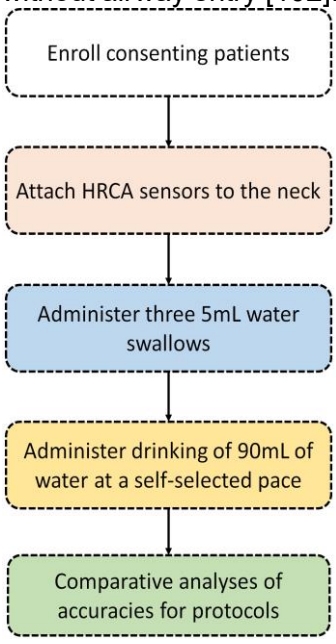

Figure 12 – Our proposed experimental and data analysis approach for Aim 3.

A3.d. Experimental approach: The main goal of this aim is to demonstrate that the proposed HRCA tool is objective and can improve upon the accuracy of SIS alone in identifying participants who have OPD and need to undergo a VF exam or need immediate intervention (Figure 11). To achieve this goal, we will carry out the following experimental steps: STEP 1: Enroll 50 consenting patients eligible for SIS in the experiment, and perform combined SIS screening and an HRCA screening. STEP 2: The HRCA system will be applied to all patients. The dysphagia SIS screen employed in the University of Pittsburgh Medical Center Presbyterian University Hospital will be performed, which consists of two or three 5mL water swallows and drinking 90mL of water at a self-selected pace. STEP 3: Nurses or other staff (non-SLPs or physicians) administering the screens and blinded to the HRCA output, will score the screens on the basis of the institutional SIS algorithm, denoting any signs of OPD or penetration/aspiration (e.g., wet voice, coughs) for each swallow that is observed. For the concurrent HRCA screening, we will record and denote the output of the algorithm for each observed swallow with findings from Aims 1 & 2. STEP 4: We will administer a VF exam for all patients using clinical protocols that include the same bolus conditions (5mL thin liquid, 30mL thin liquid) of swallowed material used in the SIS, within a 24-hour period to confirm the presence or absence of dysphagia/aspiration. STEP 5: The MBSImP, the PAS and the Normalized Residue Ratio Scale will be used to measure swallow impairment, airway protection and post-swallow pharyngeal residue. These measures will be made by our trained laboratory associates. STEP 6: HRCA, SIS, and VF results will be compared.

A3.e. Data interpretation: We will fit a series of logistic regression models with presence/absence of clinically significant OPD/aspiration as the dichotomous dependent variable, and HRCA signatures and SIS, both individually and in combination, as the independent variables. We will use areas under ROC curves (c-statistics) as measures of predictive accuracy, and compare them using DeLong's method [133]. We anticipate that the c-statistics for the 3 models involving HRCA will be significantly greater than that using SIS alone.

A3.f. Expected outcomes: The benchmark for success of Aim 3 will be a successful completion of proposed testing of the HRCA-based screening in a clinical setting yielding accurate identifications of patients at risk of silent aspiration. Specifically, we will: (1) test the HRCA-based screening in clinical settings and denote its accuracy; (2) understand if confounding clinical factors can affect the deployment of the HRCA-based screening (not expected from our preliminary work). Successful completion of this aim will demonstrate that the Aspirometer (HRCA and advanced data analytics) can conveniently, noninvasively, and inexpensively produce robust predictions of OPD presence and absence that are measurably superior to SIS, and produce some diagnostic results currently possible only with VF testing.

A3.g. Challenges and contingency plans: The preliminary results (see A3.c.) strongly support our hypothesis (see A3.a.). In the highly unlikely event that our judges' PA or MBSImP score ratings drift unacceptably, we will increase surveillance on inter- and intra-rater reliability and pull judges from analysis and retrain them to criterion, retest their reliability before placing them back online.

***A3.h. Sample size justification*:** We plan to recruit 50 patients, with an anticipated effective sample size of 46 after refusals. Assuming that approximately 50% of recruits will have clinically significant dysphagia/aspiration, a correlation of approximately 0.3 between SIS and HRCA, and an area under ROC curve of *c*=0.600 for SIS alone, with the proposed sample size, we will have 80% power to detect an increase in area under ROC curve as small as 0.240 at α=0.05 with one of the 3 strategies that involve HRCA [134, 135].

Project coordination and management: Dr. Sejdić will direct the study and will lead the analysis and algorithm testing components of the study. Dr. Coyle will lead the analysis of the VF images and clinical aspects of the study and be responsible for clinical dissemination of our results. Drs. Sejdić and Coyle have jointly or separately published over 25 publications describing how HRCA can be used as a reliable dysphagia tool. Dr. Subashan Perera, who has had a long successful collaboration with Dr. Sejdić, will support our proposal as a biostatistician. Hence, we have a unique set of skills and experiences to translate HRCA into a clinically useful tool for identifying patients in danger of imminent aspiration-related adverse events who require referral for comprehensive swallowing assessment (see Figure 13). Our results will be disseminated at international research meetings (e.g., Dysphagia Research Society) and manuscripts will be submitted to leading peer-reviewed journals (e.g., Dysphagia). We also plan to make relevant portions of the data (e.g., tables reporting key signal parameters by etiological group) available to the dysphagia clinical and research community via the internet and publications. Sample signals and/or sample code may also be appropriate for sharing via our website (www.imedlab.org).

Figure 13 – The timeline for the study.

Concluding remarks: Our engineering-clinical partnership will successfully demonstrate that the HRCA-based tools can be used for timely detection and monitoring of silent aspiration and swallowing impairment, and reduce the morbidity and mortality associated with silent aspiration. Our future studies will investigate the potential use of the device for a preliminary diagnosis of swallowing difficulties, and as a biofeedback instrument for the treatment of OPD and airway protection disorders. Our team has the necessary expertise and knowledge to tackle any obstacles regarding advanced signal analysis and/or clinical aspects of the study as demonstrated through numerous dysphagia-related publications (e.g., [65-77]). Effectively, we are likely the only group of researchers in the world that can deliver an accurate OPD screening device within the next 5 years.

PROGRESS REPORT PUBLICATION LIST

1. F. Movahedi, J. L. Coyle, E. Sejdić, "Deep belief networks for electroencephalography: A review of recent contributions and future outlooks" *IEEE Journal of Biomedical and Health Informatics,* accepted, 2017. PMC Number - In Process
2. F. Movahedi, A. Kurosu, J. L. Coyle, S. Perera, E. Sejdić “A comparison between swallowing sounds and vibrations in patients with dysphagia,” *Computer Methods and Programs in Biomedicine*, vol. 144, pp. 179–187, June 2017. PMCID: PMC5455149
3. F. Movahedi, A. Kurosu, J. L. Coyle, S. Perera, E. Sejdić “Anatomical directional dissimilarities in tri-axial swallowing accelerometry signals,” *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 25, no. 5, pp. 447-458, May 2017. PMID: 27295677, DOI: 10.1109/TNSRE.2016.2577882, PMC Number - In Process
4. I. Jestrović, J. L. Coyle, E. Sejdić, “Differences in brain networks during consecutive swallows detected using an optimized vertex-frequency algorithm,” *Neuroscience*, vol. 344, pp. 113-123, Mar. 2017. PMCID: PMC5303679
5. I. Jestrović, J. L. Coyle, E. Sejdić, “A fast algorithm for vertex-frequency representations of signals on graphs,” *Signal Processing*, vol. 131, pp. 438-491, Feb. 2017. PMCID**:** PMC5417719
6. I. Jestrović, J. L. Coyle, S. Perera, E. Sejdić, “Functional connectivity patterns of normal human swallowing: difference among various viscosity swallows in normal and chin-tuck head positions,” *Brain Research*, vol. 1652, pp. 158-169, Dec. 2016. PMCID: PMC5102805
7. J. M. Dudik, J. L. Coyle, A. El Jaroudi, M. Sun, E. Sejdić “A matched dual-tree wavelet denoising for tri-axial swallowing vibrations,” *Biomedical Signal Processing and Control*, vol. 27, pp. 112-121, May 2016. PMCID: PMC4853171
8. E. Sejdić, F. Movahedi, Z. Zhang, A. Kurosu, J. L. Coyle, “The effects of compressive sensing on extracted features from tri-axial swallowing accelerometry signals,” in *Proc. of SPIE – Compressive Sensing V: From Diverse Modalities to Big Data Analytics,* vol. 9857, Baltimore, MD, USA*,* Apr 20-21, 2016, pp. 985703-1- 985703-5. PMCID: PMC5042204
9. J. M. Dudik, A. Kurosu, J. L. Coyle, E. Sejdić, “A statistical analysis of cervical auscultation signals from adults with unsafe airway protection,” *Journal of NeuroEngineering and Rehabilitation*, vol. 13, pp. 7-1-10, 2016. PMCID: PMC4722771
10. I. Jestrović, J. L. Coyle, E. Sejdić, “Decoding human swallowing via electroencephalography: a state-of-the-art review,” *Journal of Neural Engineering*, vol. 12, no. 5, pp. 051001-1-15, October 2015. PMCID: PMC4596245
11. J. M. Dudik, J. L. Coyle, E. Sejdić, “Dysphagia screening: Contributions of cervical auscultation signals and modern signal processing techniques,” *IEEE Transactions on Human-Machine Systems,* vol. 45, no. 4, pp. 465-477, August 2015. PMCID: PMC4511276
12. I. Jestrović, J. L. Coyle, E. Sejdić, “Characterizing functional connectivity patterns during saliva swallows in different head positions,” *Journal of NeuroEngineering and Rehabilitation*, vol. 12, pp. 61-1-11, July 2015. PMCID: PMC4513710
13. J. M. Dudik, A. Kurosu, J. L. Coyle, E. Sejdić, “A comparative analysis of DBSCAN, k-means, and quadratic variation algorithms for automatic identification of swallowing from swallowing acceleromtry signals,” *Computers in Biology and Medicine*, vol. 59, pp. 10-18, Apr. 2015. PMCID: PMC4363248
14. I. Jestrović, J. L. Coyle and E. Sejdić, “The effects of increased fluid viscosity on stationary characteristics of EEG signal in healthy adults” *Brain Research,* vol. 1589, pp. 45-53, Nov. 2014. PMCID: PMC4253861
15. E. Sejdić, J. M. Dudik, A. Kurosu, I. Jestrović, J. L. Coyle, “Understanding differences between healthy swallows and penetration-aspiration swallows via compressive sensing of tri-axial swallowing accelerometry signals,” in *Proc. of SPIE – Compressive Sensing III,* vol. 9109, Baltimore, MD, USA*,* May 7-9, 2014, pp. 91090M-1-91090M-6. PMCID: PMC4201057