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ORIGINAL ARTICLE

Swallow Safety in Infant Pigs With and Without Recurrent Laryngeal Nerve Lesion

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Abstract

Aerodigestive coordination is critical for safe feeding in mammals, and failure to do so can result in aspiration. Using an infant pig model, we analyzed the impact of recurrent laryngeal nerve (RLN) lesion on aerodigestive coordination and swallow safety at two time points prior to weaning. We used high-speed videofluoroscopy to record 23 infant pigs longitudinally at two ages (7 days, 17 days) feeding on barium milk. We measured respiration with a plethysmograph and used the Infant Mammalian Penetration–Aspiration Scale (IMPAS) to identify unsafe swallows. We tested for changes in swallow safety longitudinally in control and lesion pigs, and whether there was any interaction between the four different groups. On postnatal day 7, lesioned pigs exhibited differences in the frequency distribution of IMPAS scores relative to control pigs on day 7, and 17 day old lesion and control pigs. There were longitudinal changes in performance following RLN lesion through time, suggesting that the impact of RLN lesion decreases with time, as older lesioned pigs performed similarly to older control pigs. We found minimal differences in the impact of aerodigestive coordination on swallow safety, with shorter delays of inspiration onset reflecting higher rates of penetration in young lesioned pigs. Healthy pigs aspirated at a similar rate to those with an RLN lesion indicating that the occasional occurrence of dysphagia in infants may be a normal behavior.

Keywords Dysphagia · Aerodigestive · Respiration · Animal model · Neonate

Introduction

All mammals, including humans, must be able to coordinate breathing and swallowing. The pathways for food and air cross in the pharynx, with the potential to cause issues such as aspiration, which can lead to pneumonia. Aspiration is especially common in populations such as the elderly [1] and the very young [2, 3], which are at a higher risk of being neurologically compromised. The mechanisms driving aspiration are not fully understood, although one explanation is that swallow dysfunction arises due to poor coordination between swallowing and breathing [4]. The timing of a swallow relative to the respiratory cycle has been described for various species of mammals [5], including humans [4, 6]. However, few studies have correlated aerodigestive coordination with the occurrence of penetration and aspiration [7], and fewer still have followed infants through nursing to see how aspiration rates change as a function of development [8, 9]. Furthermore, it is often difficult to know what the baseline aspiration rate is in clinical populations. The gold standard for documenting dysphagia, videofluoroscopy, exposes patients to radiation, and is rarely used in infants without a diagnostic purpose [10].

Damage to the recurrent laryngeal nerve (RLN) changes aerodigestive coordination [5]. In premature infants, damage to the RLN frequently occurs as a complication of patent ductus arteriosus corrective surgery [11, 12]. The RLN activates the muscles that move the vocal folds, and provides sensation in the airway below the vocal folds [13–16]. Damage to this nerve causes varying degrees of dysphagia, and impacts severity and recovery [17]. For example, RLN lesion has been shown to increase rates of dysphagia in very young infant pigs (~7 days) [17], but also impacts how infant pigs control their tongue and form a bolus [18]. Previous work on the infant pig model also indicates that age, lesion, and the interaction between age and lesion status impacts aerodigestive

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coordination. Infant pigs with RLN lesion exhibited greater changes in aerodigestive coordination through nursing (7 vs 17 days) than those without a lesion [5]. However, those data did not examine the relationship between swallow safety and aerodigestive coordination longitudinally to determine if these changes were correlated with improved swallow safety.

One way to measure swallow safety is to document how much liquid/food passes into the airway by using video fluoroscopy. In adults, this is often assessed by the 8-point penetration–aspiration scale (PAS) [19]. Similarly, swallow safety in infant mammals is often assessed by using the Infant Mammalian Penetration–Aspiration Scale (IMPAS) [2]. In both scales, safe swallows involve those where all material in the oropharynx moves into the esophagus, penetration happens when material goes into the airway, but remains at or above the vocal folds, and aspiration occurs when material goes below the vocal folds.

Here, we used the infant pig model to study the longitudinal impact of RLN lesion on aerodigestive coordination and swallow safety until weaning age [20, 21]. Animal models offer an ability to design and arrange a more controlled study that includes normal, non-pathological animals, with high-speed videofluorography. Specifically, infant pigs are a validated animal model for studying infant dysphagia [17, 22]. In doing so, we are able to acquire data at a high temporal resolution (100 fps), test for how coordination matures longitudinally, and induce reproducible RLN lesions to measure its impact on performance, all of which is not feasible to perform on human infants [22]. In this study, we test the relationships between aerodigestive coordination, RLN lesion, postnatal maturation, and swallow safety with the following hypotheses:

H1 Aspiration frequency (higher IMPAS scores) will be lower in pigs at day 17 than at day 7.

H2 RLN lesion pigs will have increased rates of aspiration and penetration (higher IMPAS scores) relative to control pigs.

H3 There will be an interaction between age and lesion with respect to swallow safety.

H4 A greater delay of inspiration relative to the swallow will result in safer swallows.

Materials and Methods

Animal Collection and Housing

All animal work for this prospective study was done in accordance with NEOMED IACUC approval, protocol #17-04-071. Two Yorkshire/Landrace cross sows were used for this study (Shoup Farms, Wooster, Ohio) at two different dates, January 2017 ($N = 14$ piglets) and June 2017 ($N = 9$ piglets). A Caesarian section following standard aseptic technique was performed at NEOMED's Comparative Medicine Unit (CMU) to deliver the infant piglets at 114 days of gestation (full term). The procedures for delivering the infants by C-section are described in Ballester et al. [5]. Piglets were fed colostrum (CL Sow Replacer Cuprem Inc., Kenesaw, NE) within 2 h after being born and then were fed a piglet formula (Solustart Pig Milk Replacement, Land o' Lakes, Arden Mills, MN). The pigs were housed in the NEOMED's CMU throughout the duration of the experiments.

Surgical Procedure

Pigs were divided randomly into two treatment groups (control, lesion). When the pigs were 7 days old, all piglets underwent surgery to suture one radio opaque bead (1.8 mm, sterling silver, Riogrande, Albuquerque, NM) on their hyoid and one on their thyroid. In addition to receiving the hyoid and thyroid beads, the lesion pigs' right RLN was transected with a 2 mm segment removed, ligated in two places, and the ends displaced to ensure that the nerve remained lesioned for the duration of the experiment [5]. At this age, they can maintain a stable body temperature, which allows them to be transported from CMU housing to the lab which is not temperature controlled, where feeding recordings took place. The second age was chosen because 17 days is just prior to when pigs wean to solid food. We collected data longitudinally from 15 control pigs (11 from one litter, four from the other), and lesion data from nine pigs (4 from one litter and five from the other). Following the conclusion of data collection, pigs were euthanized with Fatal-Plus (1 ml/10 lb), and the absence of regrowth of the lesioned RLN was confirmed via dissection.

Videofluoroscopy

We collected videofluoroscopic data, while measuring respiration using a plethysmograph around the pigs' thorax (MLT 1132, ADInstruments, Colorado Springs, CO). Barium (E-Z-Paque, E-Z-EM Inc, NY) was mixed in with the pig formula to visualize milk processing during videofluoroscopy (IDDSI level = 1 [23]). The fluoroscope (GE9400 C-Arm, 80 kV, 4MA) recorded images at 100 fps (XC 1 M digital video camera, XCitex, Cambridge, MA). The plethysmograph signal was recorded on a 16/32 Powerlab (ADInstruments) at 10 kHz. During these recordings, piglets were permitted to feed until satiation. A video sequence lasted from 40 to 600 s with 50 to 1000 swallows. Data were collected when the piglets were 7 days (younger, equivalent to 1–2 months of human development) and 17 days (older, equivalent to 6–9 months of human development).

Data Processing and Extraction

Swallows were identified in blinded sequences. Evaluators were trained to apply the IMPAS scale on a standardized set of swallows until intra and inter rater reliability rates of 90% were achieved. One person (BS) rated each swallow on the Infant Mammalian Penetration–Aspiration Scale (IMPAS), and statistical analyses were performed on IMPAS scores of individual swallows [2]. IMPAS scores range from 1 to 7, and are assigned as follows: (1) normal swallow, (2) penetration with clearance, (3) minimal penetration without clearance, (4) penetration of a larger amount without clearance, (5) aspiration with successful clearance, (6) aspiration with unsuccessful clearance, (7) aspiration with no attempt to clear. The video image files were aligned with frame precision to the digital files containing the plethysmograph signal.

Statistical Analyses

The variables in this study included two independent/classifying categorical variables: age (7/17 days) and lesion (lesion/control) and one categorical response/dependent variable: IMPAS (1–7). Because we tested whether differences in inspiration delay predicted IMPAS score, we treated this continuous variable as a predictor or independent variable. We used different tests for different specific hypotheses, as follows (SYSTAT 13):

H1 χ^2 analysis of age (7/17 days) vs. IMPAS

H2 χ^2 analysis of lesion status vs. IMPAS

H3 χ^2 analysis of age and lesion status vs. IMPAS (interaction)

H4 Multiple logistic regression of IMPAS (response) on inspiration delay (independent)

We used multiple logistic regression [to test whether the delay to the onset of inspiration was a predictor of IMPAS score (Hypothesis 4)]. It is multiple because IMPAS takes on more than two values. Logistic regression measures the impact of a unit increase in the continuous independent variable on the probability that the dependent variable will go from one outcome level to another. Thus, two values are reported for each logistic regression. The first is the coefficient or parameter estimate for the independent variable, in this case: delay. The coefficient is the estimated or predicted increase in the odds of a specific value of the dependent variable (IMPAS) per unit increase in the independent variable, or delay. The odds ratio is the probability/odds that for a given increase in the delay, what increase we will see in the odds of a specific IMPAS score. We used an IMPAS of 1 for the basis of comparison. We calculated a logistic regression for each age/treatment group (older/younger and intact/lesion). This study included a total of 442 swallows in 18 individual animals.

Results

Impact of RLN Lesion on Swallow Safety

We observed no IMPAS scores of 4–6. In looking on the impact of postnatal age and RLN lesion on swallow safety, we found the main difference between groups was that young lesioned pigs had more incidences of penetration without clearance than the other groups. Young lesioned pigs had a greater number of swallows involving penetration without clearance than young control pigs and older pigs (regardless of lesion status), which all had similar rates of penetration without clearance (Fig. 1, χ^2 value = 23.60, $p = 0.005$). Additionally, there were swallows of all IMPAS scores in each of the four groups (Table 1), and the frequency of IMPAS scores were qualitatively similar between groups. All four groups had safe swallows (1 or 2 IMPAS) approximately 50% of the time and experienced aspiration (IMPAS score of 7) approximately 15% of the time (Table 1). Penetration without clearance (IMPAS 3) occurred approximately 30% of the time.

Interaction Between IMPAS and Aerodigestive Coordination

For three groups, younger control, older control, and older lesion, the results for the logistic regression found no significant relationship between IMPAS score and delay in inspiration (Tables 2 and 3). The overall model fit was not significant ($p > 0.2$ in these models). The parameters for the logistic regressions were not significant for these models, and the 95% confidence intervals included 0.0. The 95% confidence intervals for all odds ratios were wide, and included 1.0, indicating equal likelihood for the comparison. The non-significant coefficients and wide CI for odds ratios are interpreted to mean that changes in the delay of the start of inspiration were not likely to produce a change in IMPAS.

However, for the younger lesion age group, there were significant coefficients for delay and significant odds ratios. For the comparison of IMPAS 2 to IMPAS 1 and IMPAS 3 to IMPAS1, the coefficients were negative values and were significant ($p = 0.04$ and $p = 0.02$, respectively). The coefficient for IMPAS 7 to IMPAS 1 was marginal at $p = 0.07$. The 95% confidence intervals for the odds ratio

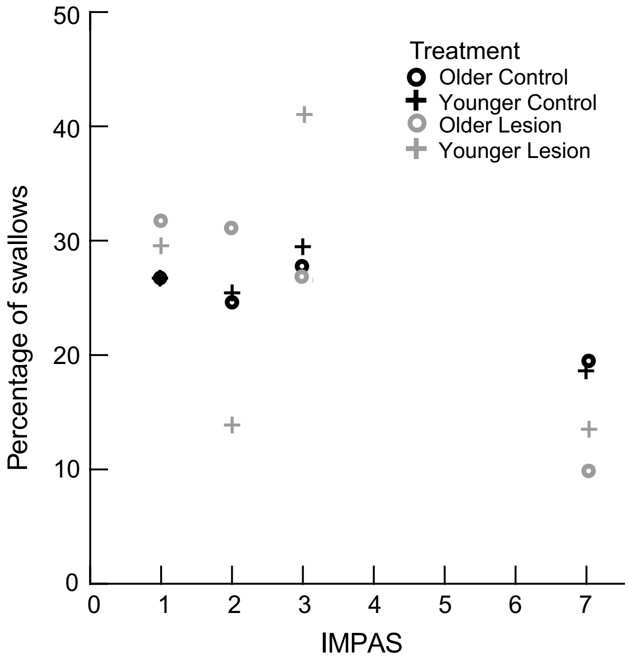

Fig. 1 The percentage of swallows classified as safe (1), with penetration with clearance (2), without clearance (3), or with aspiration (7) in younger and older infant pigs with (gray) and without (black) RLN lesion. There is little difference in the distribution of IMPAS scores for older animals. In younger animals with lesion, the decrease in 1′s and 2′s is nearly equivalent to the increase in 3′s

estimates were less than 1.0 for the 1–2 and 1–3 comparisons. The 1–7 comparison included 1.0. The negative coefficients and odds ratios less than 1 indicate that an inverse relationship existed, so that as the delay decreased, the odds of a higher IMPAS score increased in this group.

Discussion

The Impact of Age and Lesion on Swallow Safety

We found that younger lesion pigs exhibited differences in IMPAS compared to younger control, older lesion, and older control pigs. This difference was marked by a decrease in cleared penetrations (IMPAS 2) and an increased amount of penetration without clearance (IMPAS 3) compared with the other three groups (Fig. 1). These results refute our hypothesis that there would be an impact of age or lesion (H1 and H2), but support our hypothesis that there would be an interaction between age and lesion (H3). One pattern in the younger animals was that the percentages of aspiration (IMPAS 7) were the same with and without lesion. However, the reduced occurrence of 1′s and 2′s with lesion was nearly equivalent to the increase in 3′s in these animals. That is, while young lesioned animals had fewer successful and safe swallows (reduced IMPAS of 1 and 2), these swallows are offset by an increase in IMPAS-3′s, but not 7′s. This suggests that an RLN lesion may have acute impacts on the ability of infants to clear their airway of residue following a swallow, despite the fact that it is not directly involved in sensation above the vocal cords. Whatever the cause of full aspiration is in these infants, it appears to occur at the same rate in infants with and without an RLN lesion.

RLN lesion has been shown to have acute impacts on tongue kinematics and bolus formation, as well as increase the rate of dysphagia [21]. However, our study is the first to document longitudinal changes in performance following RLN lesion through time, and in doing so we demonstrate that the impact of RLN lesion decreases with time, as older lesioned pigs performed similarly to older control pigs. As the nervous system of infants is highly plastic [24, 25], these results suggest that some mechanism of neural control can

Table 1 The percentages and (number) of safe and unsafe swallows by age and treatment

	IMPAS 1	IMPAS 2	IMPAS 3	IMPAS 7
Younger control (N = 311)	37.63% (108)	26.48% (76)	20.91% (60)	14.98% (43)
Younger lesion (N = 182)	30.34% (54)	15.73% (28)	38.20% (68)	15.73% (28)
Older control (N = 287)	25.72% (80)	30.23% (94)	27.97% (87)	16.08% (50)
Older lesion (N = 178)	30.22% (55)	26.92% (49)	28.02% (51)	14.84% (27)

Table 2 The mean (in seconds) and standard deviation of delay with age, treatment, and IMPAS

	IMPAS 1	IMPAS 2	IMPAS 3	IMPAS 7
Younger control	0.030 (0.026)	0.028 (0.022)	0.033 (0.014)	0.036 (0.015)
Younger lesion	0.093 (0.053)	0.022 (0.014)	0.069 (0.055)	0.044 (0.040)
Older control	0.056 (0.029)	0.047 (0.020)	0.053 (0.022)	0.055 (0.022)
Older lesion	0.061 (0.040)	0.054 (0.039)	0.068 (0.042)	0.066 (0.032)

Table 3 Logistic regression results indicating that at age 7, lesion pigs were more likely to have higher IMPAS scores with shorter inspiration delays

		Estimate	*P*	95% CI	Odds ratio	Odds 95% CI
Younger control	2 vs 1	0.2 ± 1.5	0.86	− 2.7 to 3.2	1.3 ± 1.9	0.1–24.7
	3 vs 1	− 0.7 ± 1.6	0.65	− 3.9 to 2.4	0.5 ± 0.8	0–11.4
	7 vs 1	1.1 ± 1.8	0.55	− 2.5 to 4.7	3.0 ± 5.5	0.1–110.1
Younger lesion	2 vs 1	− 3.9 ± 1.9	**0.04**	**− 7.6 to 0.2**	**0.02 ± 0.04**	**0–0.8**
	3 vs 1	− 3.3 ± 1.5	**0.02**	**− 6.2 to 0.5**	**0.04 ± 0.05**	**0–0.6**
	7 vs 1	− 3.4 ± 1.9	0.07	− 7.0 to 0.3	0.04 ± 0.07	0–1.4
Older control	2 vs 1	0.1 ± 1.5	0.94	− 2.8 to 2.9	1.1 ± 1.6	0.1–19.7
	3 vs 1	0.2 ± 1.5	0.88	− 2.7 to 3.2	1.3 ± 1.9	0.1–23.7
	7 vs 1	0.1 ± 1.7	0.97	− 3.4 to 3.5	1.1 ± 1.9	0–32.2
Older lesion	2 vs 1	− 1.2 ± 1.9	0.5	− 4.9 to 2.5	0.3 ± 0.5	0–11.7
	3 vs 1	2.0 ± 2.0	0.3	− 1.9 to 5.9	7.6 ± 15.2	0.1–388.6
	7 vs 1	1.9 ± 2.4	0.4	− 2.9 to 6.7	6.6 ± 16.1	0.1–790.3

Bolded values indicate statistical significance

be coopted to compensate for the role of RLN lesion through development (Fig. 2).

The Impact of RLN Lesion on Aerodigestive Coordination

Similarly, we found no effect of RLN lesion on the aerodigestive coordination of older pigs, but that there was an effect on young pigs (Table 3). In young lesioned infants, as the delay of inspiration relative to the swallow decreased, the likelihood of experiencing penetration also increased (Table 3). Despite these differences, the rate of aspiration was similar across all four groups, including intact, healthy animals.

Aspiration events in all four groups were largely silent events that were only detected in review of blinded measurement of videofluroscopic films and occurred in approximately 15% of all swallows. Thus, if only one to three swallows were recorded, which is common in clinical settings, there is a large chance that aspiration would not be observed even when it is occurring. Furthermore, the fact that even otherwise healthy pigs aspirated at a similar rate to those with an RLN lesion suggests that, if generalized to human infants, the occasional aspiration in infants may be a normal occurrence, that aerodigestive coordination may not be the only factor influencing the rate of aspiration, and that interventions should be prescribed when an infant is showing other signs of pathophysiology (i.e., reduced growth), in addition to dysphagia.

Our results also highlight the importance of longitudinal studies for understanding how the sensorimotor system involved in safe feeding responds to nerve damage. Although nerve lesion did impact the relationship between safe swallows and aerodigestive coordination in young animals, by the time these animals were close to weaning at 17 days of age (6–9 months human development), differences in IMPAS score between control and lesion pigs were negligible. One possibility for this is that the highly labile nervous system of infants may allow a unilateral lesion to have a decreased impact on performance as other branches of nerves may take over the role of the lesioned nerve. Similarly, previous work in a rat model has found that animals can recover following RLN lesion [14]. This is relevant clinically, as it highlights the importance of monitoring infants which experience RLN lesion specifically (often through ductus arteriosis surgery [11, 12]) shortly after surgery, with interventions designed for modulating the acute effects of lesion, as long-term effects may be reduced. This is especially critical because in clinical settings, RLN lesion often occurs with other comorbidities (for example, poor baseline aerodigestive coordination in preterm infants [26]), and also in that the infant nervous system matures at a rapid rate, and performance for most motor tasks, including feeding, improves with age [26, 27]. Additionally, the plastic nature of the infant neural system suggests that in general, a diagnosis of dysphagia at one time point during infancy may not apply throughout nursing, as with time, it is possible that incidences of aspiration may reach levels of healthy infants.

Limitations of the Current Study

One limitation of this study is that this is not a paired study. This reduces the power of the study, although with c-sections we had a large number of individuals with sufficient power to detect the potential impact of RLN lesion on performance. Finally, although these results show that RLN lesion is not the only factor influencing the rate of aspiration in infant pigs, we did not document other measures of feeding performance which are known to be impacted by RLN lesion, such as oropharyngeal kinematics [21]. This study tested the isolated impact of RLN lesion on aerodigestive function using a longitudinal

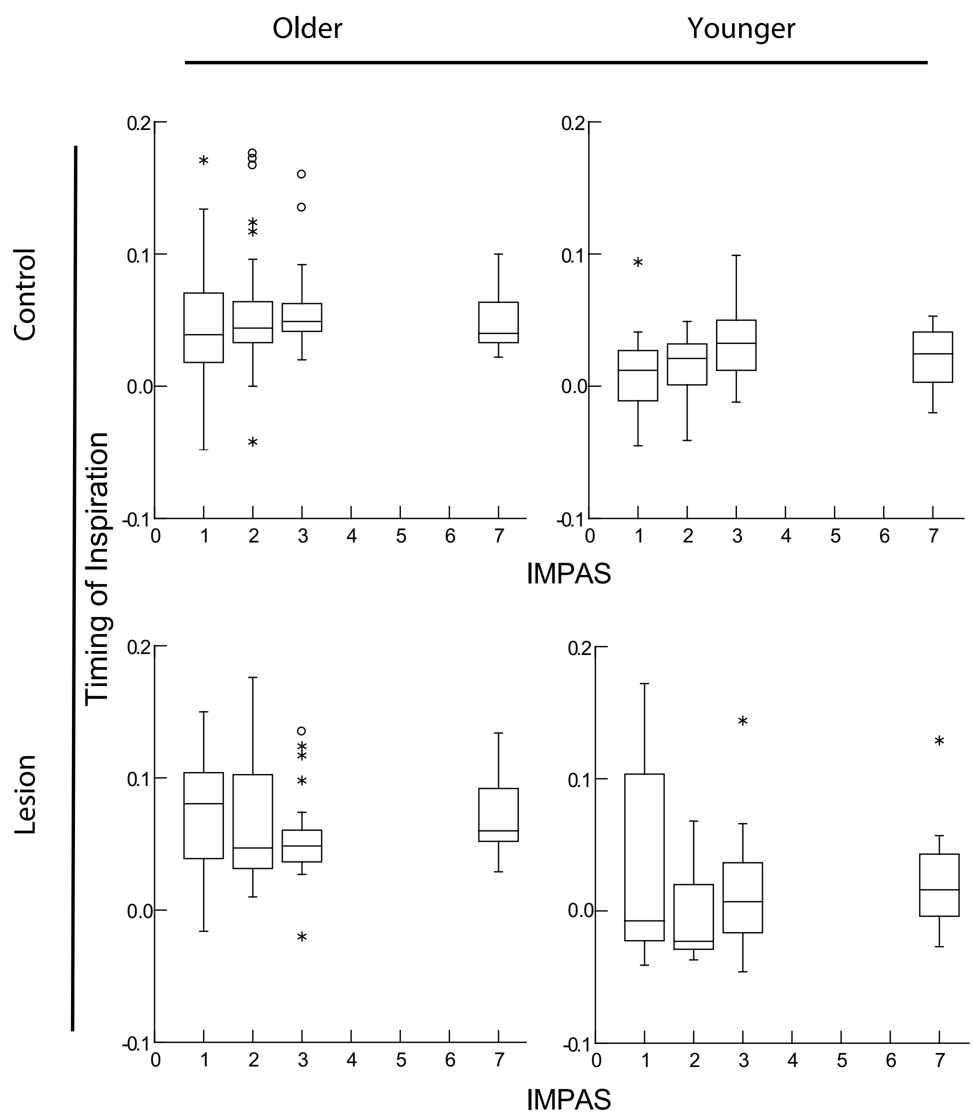

Fig. 2 The box plots shows the timing between the end of a swallow and the start of inspiration and IMPAS for two ages (young, old) and two treatment groups (control, lesion). The asterisks are outliers. IMPAS had no impact on the relationship between the timing of inspiration relative to the swallow and IMPAS in younger and older control and older RLN lesioned pigs

model to clarify the specific impact of RLN lesion over time. While this is advantageous for determining the impact of lesion on performance, it is also a limitation in that lesioned individual were randomly selected and were otherwise normal. In many human patients with RLN lesion, the situation is more complex with significant other comorbidities [11, 12]. Future studies will hopefully integrate and apply these results to more clinically multifaceted situations.

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Compliance with Ethical Standards

Conflict of interest The authors declare no competing interests.

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