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## Oral and respiratory control for preterm feeding

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### Abstract

**Purpose of review**—Feeding competency is a frequent and serious challenge to the neonatal intensive care unit survivors and to the physician–provider–parent teams. The urgency of effective assessment and intervention techniques is obviated to promote safe swallow, as attainment of oral feeding for the preterm infant/newborn is one of the prerequisites for hospital discharge. If left unresolved, feeding problems may persist into early childhood and may require management by pediatric gastroenterologists and feeding therapists. This review highlights studies aimed at understanding the motor control and development of nonnutritive and nutritive suck, swallow, and coordination with respiration in preterm populations.

**Recent findings**—Functional linkages between suck–swallow and swallow–respiration manifest transitional forms during late gestation and can be delayed or modified by sensory experience and/or disease processes. Moreover, brainstem central pattern generator (CPG) networks and their neuromuscular targets attain functional status at different rates, which ultimately influences cross-system interactions among individual CPGs. Entrainment of trigeminal primary afferents to activate the suck CPG is one example of a clinical intervention to prime cross-system interactions among ororhythmic pattern generating networks in the preterm and term infants.

**Summary**—The genesis of within-system CPG control for rate and amplitude scaling matures differentially for suck, mastication, swallow, and respiration. Cross-system interactions among these CPGs represent targets of opportunity for new interventions that optimize experience-dependent mechanisms to promote robust ororhythmic patterning and safe swallows among preterm infants.

### Keywords

apnea; bolus; brainstem; central pattern generation; nonnutritive suck; nutritive suck; preterm; respiration; swallow

### Introduction

Feeding competency is a frequent and serious challenge both to the neonatal intensive care unit (NICU) survivors and to the physician–provider–parent teams [1–3,4•,5]. Since 1980, the rate of prematurity has increased from 9.5 to 12.8% of all live births in the United States [6]. This underscores the urgency of effective assessment and intervention techniques to promote safe swallow and oral feed function, as attainment of oral feeding for the preterm infant is one of the prerequisites for hospital discharge. If left unresolved, such feeding problems may persist well into early childhood and manifest as oral feeding aversion and long-term feeding difficulties and require management by pediatricians and pediatric gastroenterologists [7,8,9•]. Indeed, more than 40% of patients followed in feeding disorder clinics are former preterm

infants [2]. Early feeding problems may contribute to significant delays in the emergence of other oromotor behaviors, including babbling, and speech-language production [10–12].

Infants who manifest stable cardiopulmonary function are introduced to oral feeding around 33–34 weeks postmenstrual age (PMA). At this age, the sucking pattern shows resemblance to that of term infants with rhythmic alternation of suction and expression, the principal motor components of nutritive suck [2]. Sensorimotor control of oral feeding involves multiple central pattern generators (CPGs) to coordinate suck–swallow and swallow–respiration, and the spatiotemporal integration and coordination of all three rhythmic motor behaviors to achieve safe feedings (Fig. 1). The infant’s behavioral state and organization during feeding, environment, positioning, and caretaker’s approach in handling the infant are regarded in the context of neurodevelopmental care and significantly affect feed performance and development [13].

## Sucking

There are two basic forms of sucking, including nonnutritive sucking (NNS) when no nutrient is involved (i.e., pacifier or finger) and nutritive sucking when a nutrient such as milk is ingested from a bottle or breast. Lau [2,3] defines mature nutritive sucking to include the rhythmic alternation of suction (negative intraoral pressure that draws milk into the oral cavity) and expression, which is characterized by the compression and stripping force applied by the tongue against the nipple to eject milk into the mouth.

Mature sucking is attained sequentially into the following five primary stages: (Stage 1) arrhythmic expression with no suction, (Stage 2) transition to rhythmic expression and appearance of arrhythmic suction, (Stage 3) emergence of rhythmic suction, (Stage 4) progression to an alternating pattern of suction and expression, with concomitant increases in suction amplitude and duration of sucking bursts (Stage 5). This sequential development of nutritive sucking is correlated with postmenstrual age and oral feeding performance defined by Lau [2] as the rate of milk transfer (ml/min) and the ability to complete their feeding within a 20 min feed session.

NNS indirectly provides benefits to the attainment of oral feeding skills. For example, a pacifier offered during gavage feeding improved feeding tolerance, accelerates the transition from tube to oral feed, increased weight gain, reduced length of stay, predictive of feeding readiness/feeding problems [2,14], improves breastfeeding scores [15•], and increases gastric motility (tachygastric) [16•]. The observation of an apparently mature NNS pattern with alternating suction and expression does not guarantee the production of a mature pattern of suck during bottle feeding [17]. For such infants, the coordination necessary for suck–swallow–respiration to support safe oral feeding is likely underdeveloped.

During NNS, the demands on swallowing are minimal, as the infant need only handle their own secretions. Thus, NNS and respiration can operate independently from one another. However, during nutritive swallow, swallowing occurs frequently and the suck–swallow–respiration event must be closely linked (dependent on each other) to avoid aspiration. Immature nutritive swallow does not reflect immature sucking ability only, but may also reflect the state of coordination of suck–swallow–respiration. NNS provides a good index of fundamental suck skills, but is not inclusive of the additional coordinative skill set produced by additional CPGs involved in airway protection during nutritive feeds [2].

## Swallowing

With neuromuscular maturation, the swallowing process becomes more rapid and adaptable in handling larger and more varied bolus sizes [2]. More rapid swallowing rates are correlated

with higher tongue force and higher intrabolus pressures to propel the bolus to the posterior pharynx and trigger the swallowing reflex. Such observations reinforce the close link between sucking and swallowing and suggest the operation of a dynamic neural sensorimotor control mechanism to sense and allocate activity patterns among at least three brainstem pattern-generating networks to achieve safe swallow. Driving intraoral and pharyngeal sensory afferents mediated by the trigeminal and glossopharyngeal system during suck can initiate or modulate a swallow [18,19••]. Safe swallowing occurs with the proper timing of the epiglottis, aryepiglottic folds, and true vocal folds to effect tracheal closure to prevent tracheal penetration/aspiration into the lungs [2]. Penetration and aspiration may occur prior to swallowing due to poor bolus formation, during swallow due to incomplete laryngeal closure, or following a swallow because of residual liquid or bolus material pooled around the valleculae and pyriform sinuses due to poor pharyngeal clearance.

Many preterm infants have respiratory issues, including respiratory distress syndrome (RDS), chronic lung disease (CLD) that require oxygen supplementation ranging from a few days to more than 2 months during hospitalization in the NICU. Ororhythmic pattern development for suck may be disrupted in these infants who are routinely subjected to abnormal tactile stimulation of sensitive peri-oral and intra-oral tissues during extended periods of intubation and cannulation. Trussing the lower face and nostrils with tubes and tape also restricts the range and type of oral movements. In animal models, the combination of sensory deprivation and motor restriction has been shown to disrupt the development of sensorimotor areas of the brain, including motor cortex and cerebellum. This is consistent with the notion of a critical period during late gestation and early postnatal life, when manipulation of the trigeminal sensory field to treat RDS may significantly alter the structure and function of the developing brain, delay attainment of oromotor skills such as NNS, and may negatively impact the transition to oral feeds [20•–22•].

Preterm infants with bronchopulmonary dysplasia also demonstrate sucking and feeding difficulties [23,24•,25••]. Compared with healthy controls (~29 weeks GA), preterm infants with severe bronchopulmonary dysplasia (BPD) (~27 weeks GA) demonstrated significantly lower performance on several suck variables, including suck pressure and suck frequency, short suck burst duration, feeding efficiency, and also manifested the lowest frequency of swallows and the longest periods of deglutition apnea. The respiratory rate was highest among BPD infants, accompanied by the largest decreases in O<sub>2</sub> saturation. Suck endurance and performance and/or coordination of suck–swallow–breathe are two important elements that can affect the feeding ability of an infant. Mizuno *et al.* [24•] found that deglutition apnea events lasted longer while BPD infants performed the swallow. Less frequent sucking with weak pressure in infants with severe BPD resulted in less swallowing when compared with infants without BPD, or with mild-to-moderate BPD. The decreased scaling in motor output may provide the BPD infant with a compensatory mechanism to avoid longer deglutition apnea. Poor feeding abilities and the integrity of the suction/expression pattern are biomarkers for brain development and function [10].

Healthy preterm infants normally experience decreasing episodes of apnea during oral feeding. As pointed out by Lau [2], baseline respiratory rates among preterm infants range from 40 to 60 breaths/min or 1.0–1.5 s per respiratory cycle. The duration of a swallow event that results in airflow interruption is of the order of 350–700 ms. The close temporal relation between the respiratory cycle and swallow–apnea during oral feeding leaves little time to successfully integrate respiration. Given the demands on coordination of the milk bolus during suck–swallow–respiration, it is not surprising that some healthy preterm infants manifest episodes of desaturation, apnea, or bradycardia during oral feeds.

Coordination of suck–swallow–respiration is attained when the child or infant can take oral feedings with no overt signs of aspiration, oxygen desaturation, apnea, or bradycardia, and demonstrate a ratio of 1 : 1 : 1 or 2 : 2 : 1 suck : swallow : breathe [2]. From a systems control viewpoint, close interactions/functional linkages exist between suck–swallow and swallow–breathe [26]. These interactions were documented in bottle-feeding preterm infants who had no major medical issues and were born less than 30 weeks GA and followed from 34 to 42 weeks PMA and compared with term infants studied between 1 and 3 weeks postnatally. Bolus size, suck and swallow rates, strength of suction, and rate of milk transfer increased during this period. Suck–swallow coordination was attained when infants were introduced to oral feeding at 34 weeks PMA. Next, the timing of swallows was indexed relative to the phase of respiration (Fig. 2). The frequency of occurrence of swallow–respiration was mapped when infants were taking one to two and six to eight oral feeds per day and when term infants were 1 and 2–3 weeks postnatal age. Lau [2] observed that as the infants matured, swallowing occurred at a safer phase of respiration (i.e., start of inspiration or end of expiration when airflow is minimal or zero). Coordination of suck–swallow–respiration is attained with a consistent suck–swallow ratio (1 : 1 or 2 : 1) and a safe swallow–respiration index location (start of inspiration or start of expiration).

### Integration of breathing into swallow

The integration of respiration–chest wall dynamics into ororhythmic suck–swallow efforts is highly variable in preterm infants [27]. Respiratory rhythms during feeding undergo developmental changes concurrent with maturation [28,29]. Gewolb and colleagues [23,29, 30], using instrumental measures correlated to aeroingestive function, have demonstrated developmentally regulated individual differences in swallow and breath rhythms and in the coordination of these rhythms.

Real-time measurements of aeroingestive parameters have been used effectively to differentiate low-risk from high-risk populations, including preterm infants with bronchopulmonary dysplasia [23,30–32], and term infants exposed to maternal substance abuse [33] with respect to their attainment of rhythmically coordinated feeding. In the hierarchy of infant feeding, swallow influences respiratory efforts (as in obligatory deglutition apnea). The Gewolb research team also found that breathing rate and tidal volume were reduced in term infants with the onset of feeding, and that the pattern of respiratory airflow became more irregular. The phase relationship between swallows and breaths changed frequently during feeding in both term [34] and preterm infants [29], although there were periods of stability during which the phase relationship became more regular. Developmentally regulated changes in phase relationship were also noted. Breathing efforts appear to be the last function integrated into a successful feeding episode.

On the basis of digitized recordings of pharyngeal pressure, nasal thermistor airflow, and thoraco-abdominal strain gage outputs [27], several specific and interesting respiratory patterns were observed during the transition from immature to more mature feeding episodes in 34 preterm infants (26–33 weeks GA, study at 32–40 weeks PMA). Infants were studied weekly on two or more occasions from initiation of bottle feeding (using breast milk or preterm formula via bottle). Exceptional patterns of feeding-adapted variations of respiration were observed, including breathing during swallow, alternating blocks of suck-swallow and respiration efforts, nasal airflow without thoracic movement, modulation of respiratory phase relationship against swallow rhythm, and paired rhythms with swallow : breath ratios of more than 1 : 1. The excessive compliance of the infant chest wall may account for some of the observed paradoxical chest wall movements. Some of these strategies were developmentally regulated. Alternating blocks of suck–swallow and respiratory efforts were only seen in the earliest (32–33 weeks PMA) studies. In contrast, coordination and phase relations of suck–swallow and breathing

stabilized over time, as did the percentage of synchronized nasal and thoracic respiratory efforts, which increased significantly after 36 weeks PMA compared with synchronization at 32–33.9 and 34–35.9 weeks PMA. There was also a significant positive correlation between percentage synchronization and PMA. The strategies and patterns noted by Vice and Gewolb [27] further clarify the developmentally regulated coordination of suck, swallow, and respiration into a mature pattern of infant feeding, and may be predictive of those infants with short-term and long-term feeding or developmental difficulties.

## Safe oral feeds

Safe and successful oral feeding implies minimal risk of aspiration and requires proper maturation and coordination of sucking, swallowing, and respiration [5,25••]. This is crucial for feed dynamics in the infant, as the anatomical pathway for air and nutrient share the same pharyngeal tract. The swallow must occur during a safe phase of the respiratory cycle. Amaizu *et al.* [4••] hypothesized that oral feeding difficulties result from different rates of maturation (development) for a given CPG, which they term synchronization of muscles operating within a specific CPG, and the process of coordination among the suck, swallow, and respiration CPGs. Each of these three rhythmic motor patterns is regulated by a bilateral network of interneurons known as a CPG [35••]. These are localized to pontine and medullary regions of the brainstem reticular formation (central gray). Their working premise involves two levels, including the appropriate functional maturation and synchronization of the individual muscles implicated within each centrally patterned function, and the safe coordination between muscle subsystems of these different functions. On the basis of a cohort of 16 medically stable preterm infants (26–29 weeks GA), specific feeding skills were monitored as indirect markers of the maturational process of oral feeding muscle subsystems, including oral feeding efficiency defined as the rate of milk intake (ml/min) equivalent to the total volume transferred minus volume lost during a feeding, perioral muscle maturation reflecting an infant's ability to latch onto the nipple tightly to achieve lip seal (defined as the proportion of milk leakage to total volume taken during oral feed expressed as a percentage based on weighing the bib before and after the feed), measures of suck maturation determined by assignment of sucking stage (1 [immature] to 5 [mature]), rate (number of sucks/s) and suction : expression ratio, suction amplitude (mmHg), rate and slope (mmHg/s) to evaluate the synchrony of the suck musculature and rhythmicity of suction and/or expression components. The suck : expression ratio is used as an index of coordination between lip–tongue muscle systems used to generate nipple compression and negative intraoral pressure (suction) and the anterior–posterior stripping motion of the tongue tip along the flattened nipple against the palate. A 1 : 1 suck : expression ratio corresponds to full-term mature stage 5 characterized by a rhythmic alternating pattern of suck : expression ratio. Maturation of swallow was evaluated by the rate of swallows per second and was considered an indirect marker of the synchrony of the swallow muscles and rhythmicity of the SwCPG. Maturation of the suck–swallow implies the coordinative action between two CPGs and was assessed by the computation of the suck : swallow ratio and the corresponding time intervals (in seconds) between peak suction to onset of swallow and peak E to onset of swallow. Amaizu *et al.* [4••] noted that the time interval between peak expression and the onset of swallow was necessary to account for when infants only used the expression component of the suck, as this is the predominant pattern when infants are introduced to oral feeds. These outcomes serve as markers for the coordination between suck and swallow muscle subsystems, and the temporal relation between the end of suck and activation of the swallow muscles. Finally, coordination between the swallow and respiratory CPGs is assessed as the percentage occurrence of swallow at specific phases of respiration, including the start of inspiration-end of exhalation (start I), during inhalation (i), at end inspiration-start exhalation (end I), during exhalation (e); while interrupting inhalation (ii) and/or exhalation (ie), and/or during deglutition apnea greater than 2 s [26]. Unsafe swallow–respiration events were defined

as those that occurred during deglutition apnea and inhalation, and correlated with oxygen desaturation and aspiration, respectively.

Coefficients of variation (COVs) were used to index functional stability among these parameters. Results showed that feeding efficiency and related skills improved, some decreased, and others did not change. Components of sucking, swallowing, respiration, and their coordinated activity matured at different times and rates. Differences in functional stability of particular outcomes confirm that maturation levels depend on infants' gestational rather than PMA [4••].

Rate of milk intake increased significantly as infants progressed from one to two oral feeds/day (~34 weeks PMA) to six to eight oral feeds/day (~38 weeks PMA) ( $1.9 \pm 1.0$  versus  $4.3 \pm 1.8$  ml/min, respectively) and milk loss decreased significantly over the same period ( $22 \pm 14$  versus  $10 \pm 7\%$ , respectively) [4••]. This outcome suggests some degree of immaturity, as full-term infants at 1-week of life averaged  $7.1 \pm 1.3$  ml/min [26]. These measures of oral feed efficiency were correlated to advancement in suck stage, suck rate, suck amplitude, and suck slope, with no discernible changes observed in swallow and suck–swallow outcomes. For these preterm infants, the suck : expression ratio remained less than 1 ( $0.76 \pm 0.25$ ) at approximately 38 weeks PMA, indicating these infants still relied on the use of an immature sucking pattern dominated by expression. In general, infants born at the earlier (26/27 weeks GA) exhibited greater variability than their 28/29 weeks GA counterparts. This finding suggests that birth GA may be a more significant factor on oral feeding skills than PMA. This study also found that swallowing occurred more frequently during deglutition apnea and inhalation when infants were at the one to two oral feeds/day stage, and became predominantly deglutition apnea upon advancing to six to eight oral feeds/day. With rhythmicity as an essential requirement, swallowing should occur at a preferred phase of the respiratory cycle that minimizes the risk for aspiration [26]. Further study is needed to fully characterize the developmental processes of individual rhythmic motor patterns, such as suck, swallow, and respiration in the context of oral feed. As Amaizu *et al.* [4••] noted, comparison of the infant's performance at the six to eight oral feeds/day level with that of full-term infants during their first week of life is necessary.

Preterm infants can modify the dynamics of their suck to regulate the rate of milk transfer to match their level of suck–swallow–respiration coordination [36]. Sensory feedback is essential in maintained volumetric control of nutrient to match the spatiotemporal dynamics of the suck–swallow–respiratory CPGs. The notion that experience or training enhances sucking skills is supported among several studies using nonnutritive oral stimulation. When training is offered prior to the introduction of oral feeds, the attainment of independent oral feed is accelerated [37,38,39•,40••,41••].

Thus, nonnutritive and nutritive swallowing apnea may occur at one of the following four stages in breathing, including expiration, inspiration, at the transition between inspiration and expiration, or the transition between expiration and inspiration [4••,34,42]. Infant nutritive [26,43] and nonnutritive swallows [42] may also occur during respiratory pauses that last between 3 and 15 s.

### **Advanced swallow assessment technologies**

The brainstem plays an important role in breathing–swallowing coordination (BSC); however, the role of suprabulbar structures is unclear during the first year of life [12,35••]. Nonnutritive swallowing occurs frequently during sleep in infants and is vital for fluid clearance and airway protection. Swallowing is also associated with prolonged apnea in some clinical populations. A recent study examined the temporal relations between swallowing, respiratory pauses, and arousal in six preterm infants at term using multichannel polysomnography and a pharyngeal

pressure sensor [44•]. Results showed that swallows occurred more frequently during respiratory pauses and arousal than during control periods. Most swallows occurred after the respiratory pause onset and were linked to arousal from sleep; thus, the swallow does not appear to trigger the pause in respiration. Swallows not associated with the respiratory pause were observed consistently during the expiratory phase of the respiratory cycle. Nixon *et al.* [44•] concluded that swallowing and associated arousal may serve to protect the airway during sleep with medically stable preterm infants manifesting the mature pattern of respiratory–swallow coordination at term.

Studies on the dynamics of pharyngoesophageal motility have benefited from the application of pharyngo-UES-esophageal micromanometry in human preterm neonates and infants [7, 9•,45–47]. Esophageal micromanometry has also proven effective in evaluating the relation between spatial (height) and temporal (duration) characteristics of acid reflux events (AREs) in preterm and term infants with chronic lung disease [9•]. On the basis of a sample of 511 AREs from nine preterm infants, 80% of AREs were found to reach the distal esophagus compared with other esophageal segments. One-third of AREs were associated with symptoms and the average acid clearance time was significantly prolonged with symptomatic AREs versus nonsymptomatic AREs by 3.5-fold. This finding suggests that the presence of the acid in the esophagus leads to the expression of symptoms (i.e., cough, gag, arching head and neck) and implies that aversive stimulation of sensory and motor fibers is involved in the pathogenesis of such symptoms.

### **Entrainment of oromotor central pattern generators to promote the transition to oral feed in preterm infants**

Oral stimulation strategies have proven beneficial in developing oral feeding skills in preterm infants [37,38,39•]. An entrainment cutaneous stimulus delivered to healthy term infants through 6 months of age was shown to produce harmonic entrainment (1 : 1) of NNS [48]. This approach is consistent with contemporary ideas on the role of sensory-driven neural activity and critical periods [49,50] during late gestation and early infancy in the formation of functional ororhythmic and deglutition networks. Recent studies of oromotor entrainment in premature infants who have endured prolonged periods of orosensory deprivation secondary to respiratory distress syndrome have demonstrated the potent therapeutic effects of patterned orocutaneous pulse trains in developing NNS ‘burst-pause’ patterning [40•,41•]. The intraluminal pressure of a pneumatically coupled silicone pacifier was dynamically modulated at 1.8 Hz in six-cycle burst trains at an amplitude of 275  $\mu\text{m}$  interspersed with 2-s pause periods. The unique orosensory experience offered by the ‘motorized pacifier nipple’ is physiologically salient and spectrally patterned to resemble the spatiotemporal features of the NNS burst. This form of stimulation serves to entrain the activity patterns of populations of mechanoreceptors located in the lips, tongue, and jaw of the preterm infant. The synchronous pattern of sensory flow encoded by trigeminal primary afferents project relay in the chief trigeminal sensory nucleus and project to the ventroposteromedial nucleus of the thalamus ( $\text{VP}_m$ ), and subsequently relayed to orofacial regions of the sensorimotor cortex [51]. Descending neuromodulatory inputs are presumed to influence the firing patterns of facial, trigeminal, and hypoglossal motoneurons. The richness of the somatic sensory experience offered by an entraining pacifier nipple presents new and exciting neurotherapeutic applications for the habilitation of the suck CPG during late gestation. Inputs to the trigeminal system have also been observed to prime swallow circuits and drive gastric motility. Use of a mechanical entrainment stimulus also has the distinct advantage of being safe, pleasurable, and salient to developing brainstem ororhythmic CPGs. Therapeutic exposure to patterned orocutaneous events generates neural activity, which, in turn, exerts trophic effects on the formation and strengthening of central projections underlying orofacial motor control.



## Conclusion

Preterm infants with respiratory and neurological disorders coordinate their breathing, nonnutritive, and nutritive swallows in a different way compared with their healthy counterparts. Postswallow apnea and postswallow inspiration occur more frequently in infants suffering from respiratory disease than in healthy infants. Prematurity is a major factor leading to feeding and swallowing issues and may be further complicated by insults to the developing nervous system. There is a significant predictive relation between disordered breathing–swallowing coordination and adverse outcomes (e.g., aspiration) in infants that may negatively impact neurodevelopmental outcomes.

## References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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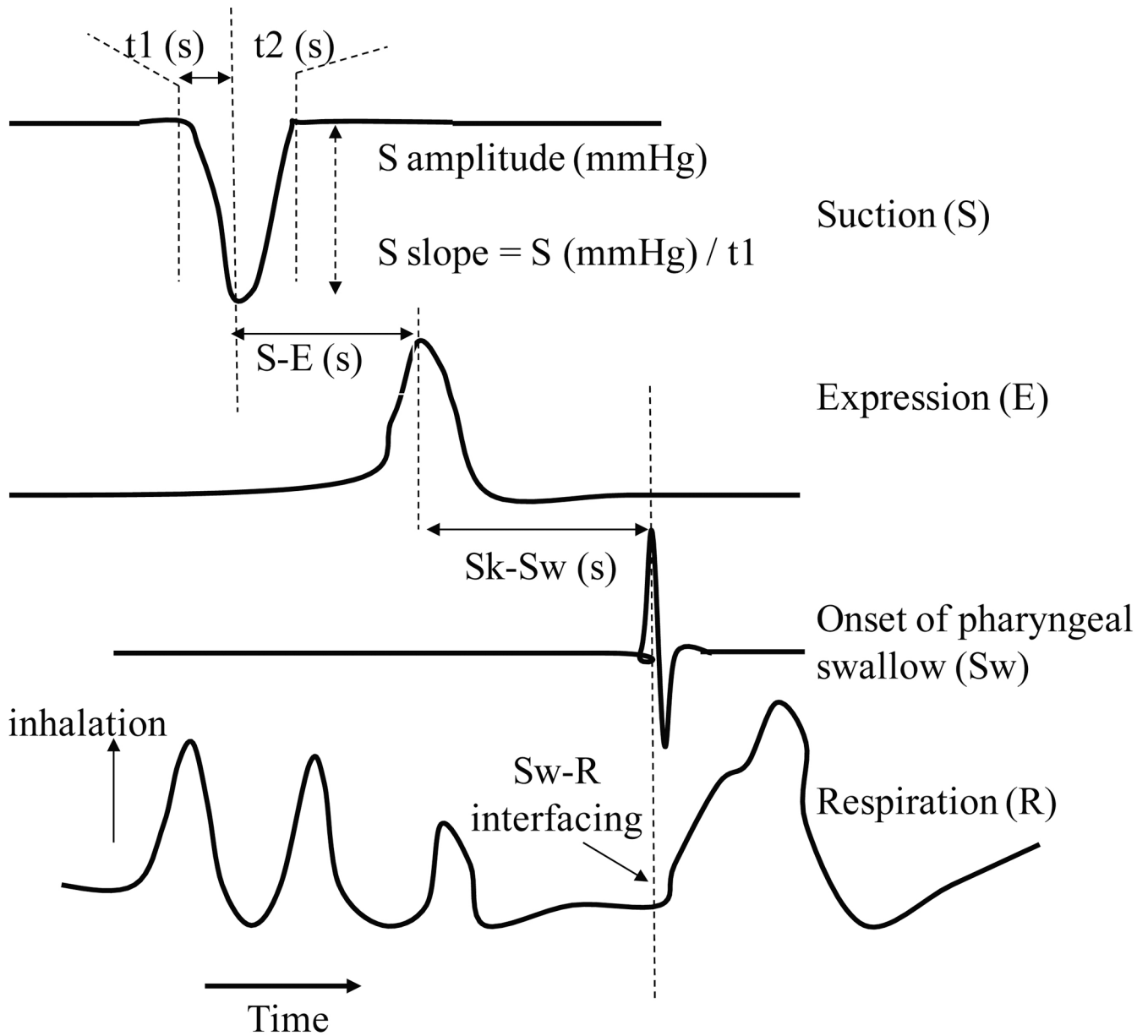
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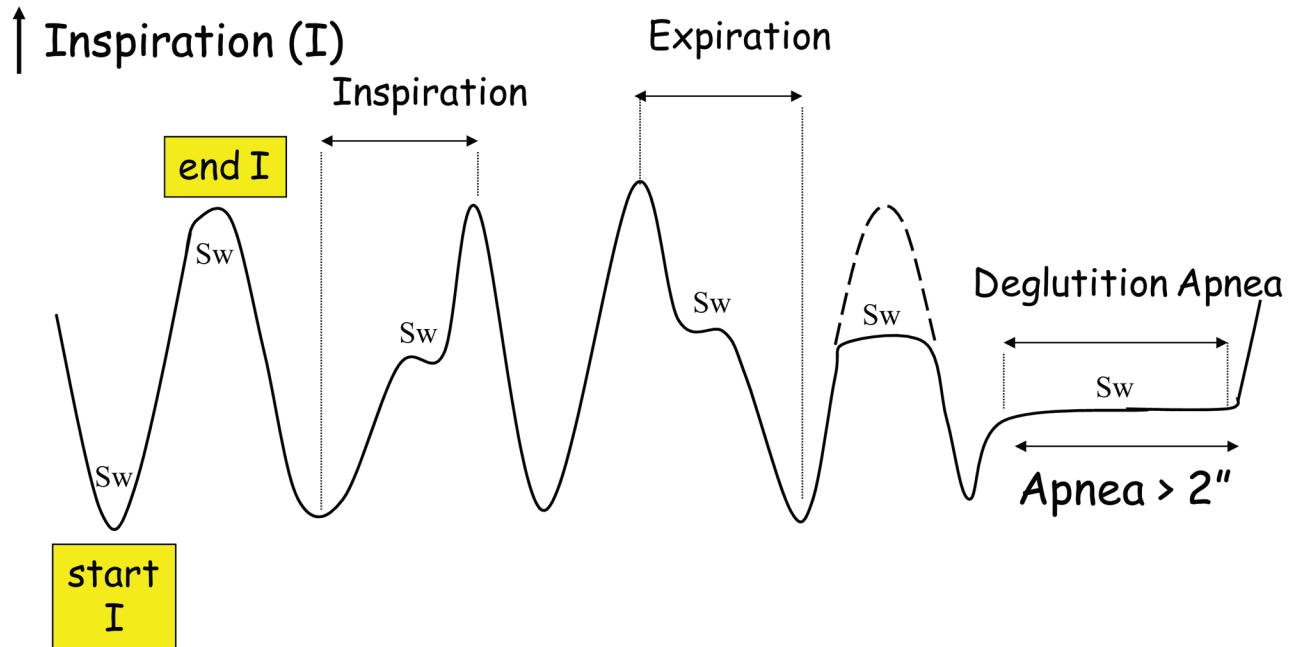
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**Figure 1.** Schematic representation of the simultaneous pressure recordings of sucking (suction and expression components), onset of swallowing, and respiration (upward deflection: inhalation) over time. Dotted lines on each tracing delineate measures of time interval (s) gr1 Swallow–respiration interfacing were identified by the time at which onset of pharyngeal swallowing and a particular respiratory phase occurred. The example shown by the dotted line between swallow and respiration is that of a swallow occurring at the beginning of inhalation. Reproduced with permission from Amaizu *et al.* [4••].

# Swallow-respiration interfacing



**Figure 2.**

Schematic representation of swallow-respiration interfacing, including swallow at start inspiration/end expiration; swallow at end of inspiration/start expiration; swallow during inhalation position, swallow during exhalation; swallow interrupting inspiration; and a swallow episode when respiration is halted (>2 s) gr2 The yellow highlights indicate interface locations corresponding to safe swallows. Reproduced with permission from Amaizu *et al.* [4••].