Fast breaths, slow breaths, small breaths, big breaths: importance of vagal innervation in the newborn lung

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IT IS WELL ESTABLISHED that vagally innervated mechano-receptors in the lung influence respiratory frequency and the occurrence of spontaneous sighs (augmented breaths). Are these reflexes vitally important, or do they merely “fine tune” the respiratory pattern? The remarkable vitality and long-term survival of human patients and laboratory animals after denervation associated with lung transplantation argues for the former (3, 7). The rapid onset of severe respiratory failure following vagotomy in neonatal animals argues for the latter (5). In this month’s issue of *The Journal of Applied Physiology*, Lalani and associates (8) provide convincing evidence of the necessity of vagal pulmonary innervation for pulmonary function in lambs. This work extends earlier studies from their laboratory (15), which documented severe pulmonary failure at birth in lambs following denervation in utero. In the present work, the preservation of laryngeal innervation and absence of anesthesia eliminate confounding factors that were present in prior neonatal models. Moreover, the new study provides a wealth of physiological data that give important clues as to the cause of respiratory failure.

Why was respiratory function so disastrously compromised in the denervated lambs? To answer this, it is important to separate the early- from the late-occurring consequences of denervation. The earliest effects were slowed respiratory rate and decreased frequency of augmented breaths. These effects were associated with markedly decreased respiratory system compliance and prominent hypoxemia, which likely accounted for all later-occurring findings. Although the finer points of this generalization can be debated, the argument that extra pulmonary shunting and surfactant function were not the primary cause of the lambs’ demise (6) is accepted. What then is the explanation?

In their present study, Lalani et al. (8) focus on the maintenance of lung volume, a major theme in neonatal respiratory control for the past 25 years. Previous studies have discovered an array of interdependent, vagally mediated mechanisms that function to increase both average and end-expiratory lung volume in newborns of several species, including humans (11). Lalani et al. perform an excellent review of this literature; however, some additional comments may be useful. The traditional thinking has been that the newborn needs a “dynamically” elevated lung volume because its chest wall, unlike that of the adult, has minimum outward recoil (1, 11). To offset this, adductor muscles increase laryngeal resistance during expiration. As a result, various respiratory patterns, including expiratory breath holding and its variations (“grunting”), are common in newborns, especially those with compromised lung function. In addition, the diaphragm and inspiratory intercostal muscles may remain partially or “tonically” active during expiration, thus stiffening the chest wall. It is generally accepted that these expiratory airflow “braking” mechanisms, combined with a relatively rapid respiratory rate, keep end-expiratory lung volume above what it would be if allowed to deflate to passive functional residual capacity (FRC).

In Lalani and co-workers’ study (8), representative flow volume loops are shown for denervated and control lambs. The denervated lamb is shown to deflate to passive FRC, whereas the control lamb is shown to interrupt expiration with a breath before it reaches passive FRC. The passive expiratory time constant of the denervated lamb (slope of the flow volume curve, where volume is plotted as the ordinate) is shown to be much shorter than that of the control. Therefore, a shortened lung-emptying time combined with a prolonged expiratory time can explain the reduced lung volume in denervated lambs. The question of how laryngeal muscle activity might have affected this finding is not answered, as the larynx was bypassed to measure respiratory system mechanics. Did the denervated lambs grunt or perform breath hold maneuvers? This was not discussed in the study of Lalani and
colleagues; however, previous literature has suggested that laryngeal braking requires vagal feedback from the lungs (5, 11).

Lalani et al. (8) suggest that the low lung volume in denervated lambs resulted from decreased “tonic” activity in the diaphragm and/or inspiratory intercostal muscles. This may be the case, but some physiologists would likely take exception to this conclusion. Because the expiratory time constant is the product of respiratory system compliance and resistance, one cannot separate pulmonary compliance from chest wall compliance given the data provided. That is, decreased lung compliance producing rapid lung emptying, when combined with a prolonged expiratory time, is likely sufficient, in and of itself, to explain the lowered lung volume of denervated lambs. If this is so, just how important are expiratory braking mechanisms to neonatal respiratory function? Tonic diaphragm activity decreases during rapid eye movement sleep, but healthy newborns tolerate this very well, as do newborns with deficient expiratory braking mechanisms, such as those with tracheostomies or paralyzed inspiratory intercostal muscles (1, 12). In these examples, the ability to breathe rapidly plays a primary role in the maintenance of lung volume. However, the denervated lambs could not do this, a critical defect.

Is reduced lung volume alone a satisfactory explanation for respiratory failure in the denervated lambs? Probably not. In their study of lambs denervated before birth, Wong et al. (15) found that treatment with positive end-expiratory pressure had no beneficial effect on either lung compliance or hypoxemia. End-expiratory pressure should have corrected, at least partially, reduced lung volume. Mead and Collier’s (10) classic study in dogs and the study of newborn lambs by Williams and colleagues (14) clearly show that low lung volumes and transpulmonary pressures increase the tendency for alveoli to spontaneously collapse over time, a characteristic of all mammalian lungs and one that is fatal in 24–48 h if unchecked. The primary counterbalance to this progressive atelectasis is occasional spontaneous large lung inflations (augmented breaths or sighs), the primary stimulus for which are vagal pulmonary afferents.

In the present study by Lalani and colleagues (8), sighs were initially decreased in denervated lambs. The subsequent increase in frequency is somewhat surprising; however, it has been shown that, if one waits long enough after vagotomy, sighing returns (2). Why didn’t the increased sighing in denervated lambs reverse the atelectasis, increase compliance, and improve oxygenation? The authors suggest that, once the initial damage was done, subsequent sighs may have been inadequate. On this point further comment is warranted. The rate of sighs (breaths twice normal volume) finally attained at 20 h in denervated lambs (3.5 sighs/h) was quite low and did not equal that of control lambs soon after surgery (5.5 sighs/h). Furthermore, the peak sigh frequency in denervated lambs was remarkably lower than that of control lambs without surgery (13 sighs/h) or human infants (33 sighs/h) on the first day of life (13, 15). Furthermore, in human infants, sigh frequency during non-rapid eye movement sleep (48 sighs/h) increases during rapid eye movement sleep (65 sighs/h) when lung volumes are relatively low and the spontaneous rate of alveolar collapse is presumably increased (9). Finally, it has been noted that, in the absence of spontaneous sighs, not one but several large lung inflations in rapid succession may be required to fully restore compliance and eliminate intrapulmonary shunting (14). These observations provide strong, albeit indirect, evidence that not only are sighs required for preservation of pulmonary compliance, their frequency and force must match the degree of existing atelectasis and its ongoing rate of recurrence. Therefore, when vagal innervation (the primary stimulus for sighing) is absent, such as in denervated lambs, it is highly plausible, if not probable, that the magnitude and frequency of sighs cannot adequately restore existing atelectasis and cannot keep up with the increased rate of atelectasis secondary to low lung volume. Reflecting on the study of Lalani et al. as a whole, one can conclude that respiratory frequency, sigh frequency, and expiratory-making mechanisms all are interdependent in maintaining respiratory homeostasis in the newborn and that vagal afferents are critical in their interactions.

Having come to these conclusions, it is somewhat disconcerting that, unlike the previous study from the author’s laboratory (15), no evidence of atelectasis was found during examination of the denervated lambs lungs. It is possible that lung lavage or perfusion of fixation fluids reexpanded atelectatic alveoli. It is fair to say, however, that no single study can hope to solve all enigmas. Furthermore, the possible role of pulmonary neuroepithelial bodies is also unclear. These organelles, found in airways of newborns and vagally innervated subjects, are believed to function as oxygen-sensing receptors (4). Are these bodies important for respiratory control or for adjustment of ventilation-perfusion inequalities in newborn lambs? In regards to these possibilities, the door is left open for future studies.

REFERENCES


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