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# Insight into Pulmonary Gas Trapping as an Index of Airway Responses in Small Laboratory Animals

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## Background

The majority of methods for measuring airway mechanics or pulmonary function in small laboratory animals are labor intensive, require specialized equipment and training, and have a low throughput. Hence, there is a need for a more rapid, simpler, user-friendly approach for assessing airway responses in rodent models of human lung diseases. One such method is pulmonary gas trapping or the excised lung gas volume (ELGV) measurement [1,2], a well-recognized technique for assessing airway mechanics in small laboratory animals [3]. Thus, a brief overview of the history of pulmonary gas trapping or hyperinflation will be discussed examining history of both qualitative and quantitative approaches and use in rodent models of human lung diseases.

**Keywords:** Airway responses; ELGV; Pulmonary gas trapping; Small laboratory animals

## Abbreviations

ELGV: Excised Lung Gas Volume; $C_{dyn}$: Dynamic Compliance; $R_L$: Total Pulmonary Resistance; Penh: Enhanced Pause

## History of Pulmonary Gas Trapping or Hyperinflation

### Qualitative assessment

Over one hundred years ago, Auer and Lewis [4] were the first to observe that lungs from antigen-sensitized, antigen-challenged guinea pigs failed to collapse upon opening of the thoracic cavity in contrast to lungs of normal guinea pigs after death (Figure 1). Further they noted the nearly fully distended lungs floated on water. Twenty-seven years later, Kallos and Pagel [5] found marked distension of lungs from guinea pigs that died during either inhaled antigen or histamine challenge. Examples of normal versus hyperinflated guinea-pig lungs are shown in Figure 2. The first attempt to quantitate lung distension following ovalbumin inhalation in antigen-sensitized guinea pigs was described by Eastham et al. who developed a graded subjective scale from 0 to 6 for assessing pulmonary hyperinflation of excised guinea-pig lungs [6]. Thus, the normal lungs would receive a 0 since the lungs collapsed after opening the thoracic cavity, while the hyperinflated lungs would receive at least a grade 4 because of the obvious visible distension. Drawbacks of the subjective grading scale for testing novel therapeutic modalities in treating lung disease include training of laboratory personnel for assessing pulmonary distension and potential bias unless scorers are blinded to treatment groups.

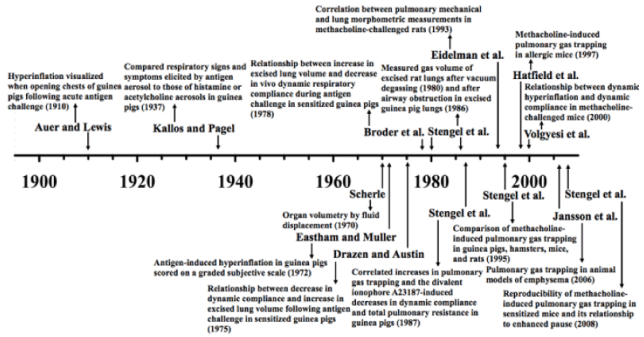


**Figure 1:** History of pulmonary hyperinflation or pulmonary gas trapping as an index of in vivo airway responses in small laboratory animals.

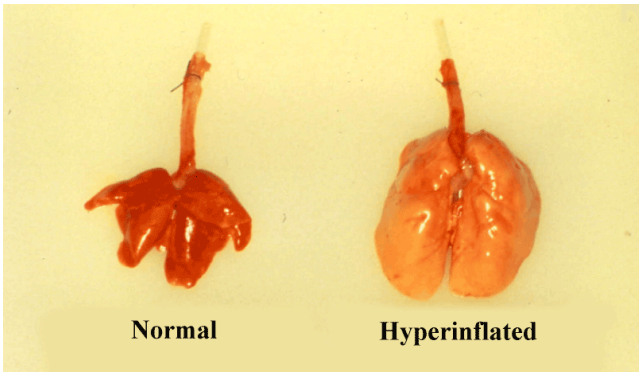


**Figure 2:** Normal and hyperinflated excised guinea-pig lungs.

Although Scherle [7] did not specifically examine lungs of non-sensitized or sensitized rodents following bronchoprovocation, the method he developed was the first demonstration of organ volumetry (i.e., rat liver) by fluid displacement using an analytical balance. This method is still used today to measure excised rodent lung volumes in small laboratory animal models of human lung disease [8-11]. However, this technique measures excised lung volume, not excised lung gas volume (ELGV) [1,2], which will be discussed below. In addition, lungs prepared for this measurement based on the method described by Scherle are first vacuum degassed and then instilled via the trachea with tissue preservatives to 20-25 cm fixation solution pressure [7,12]. Thus, determining buoyancy or volume displacement

of lungs is a two-step process involving weighing the lungs in air and then weighing the tissue-fixed lungs in liquid [7]. However, if lung volume was measured prior to tissue fixation, any fluid that might accumulate in the lungs as a consequence of bronchoconstriction or inflammatory processes such as increased airway secretions, peribronchial or interstitial edema, and/or cellular infiltration would likely contribute to the excised lung volume.

## Excised lung (relaxation) volume measurement

Another quantitative approach for measuring excised lung volume following antigen bronchoprovocation in sensitized guinea pigs involved submersing lungs in a graduated cylinder filled with fluid to determine lung volume displacement [13,14]. Following the immediate-type hypersensitivity response in guinea pigs, Drazen and Austen [13] found widespread airway narrowing that accounted for the decrease in dynamic compliance ($C_{dyn}$) and pulmonary conductance (pulmonary conductance is the reciprocal of pulmonary resistance) and increase in excised lung (relaxation) volume they observed. Similarly, Broder et al. [14] showed the decrease in total respiratory compliance and increase in lung volume following antigen challenge dose-dependently related to the sensitizing antibody guinea pigs received.

## Excised lung gas volume (ELGV) measurement

The two previous methods by Drazen and Austen [13] and Broder et al. [14] measured total lung volume, but could not distinguish between lung volume and lung trapped gas volume. While at West Virginia University, my colleagues and I developed a method using an analytical balance to measure the trapped gas volume following vacuum degassing of excised rat lungs [12]. Although not specifically related to the topic of this paper, vacuum degassing of excised rodent lungs provides for uniform volume history of lungs when performing multiple pressure-volume maneuvers [15]. Subsequently, at Eli Lilly and Company, we employed the same approach to measure the trapped gas volume in guinea pigs exposed to a variety of inhaled bronchoconstrictive agents that we called the excised lung gas volume (ELGV) measurement [1,2].

In brief, ELGV or postmortem pulmonary gas trapping is measured by Archimedes' principle and is based on the stable amount of air trapped within the excised lungs at a transpulmonary pressure of 0.0 cm $H_2O$. The lungs are attached by the tracheal cannula to a brass weight, then the lungs and brass weight are placed in a plastic cup, immersed in a beaker of saline on a stationary platform, and suspended from a hook at the top of the stirrup (Figure 3). By first taring the brass weight in saline, the lungs plus brass weight gives a negative weight display in grams that closely approximates the ml of air trapped in the lungs for both normal and hyperinflated lungs (Figure 4). Because lung tissue density is similar to that for saline, the volume of air trapped in the lungs can then be determined. Even when the thorax of a naïve guinea pig is opened, its lungs collapsed to the resting lung volume indicating a small residual volume of air remained in the lungs.

Although we made the density kit for measuring ELGV at West Virginia University and Eli Lilly and Company, many analytical balance manufacturers now provide a density kit as a relatively inexpensive accessory (ranging in cost from $300.00 to $1500.00). Only slight modifications to the density kit may be necessary to perform the ELGV measurement. However, if an investigator choses to make their own density kit, there are two crucial features of the stirrup: its weight and fulcrum have to be similar to those of the analytical balance weighing pan.

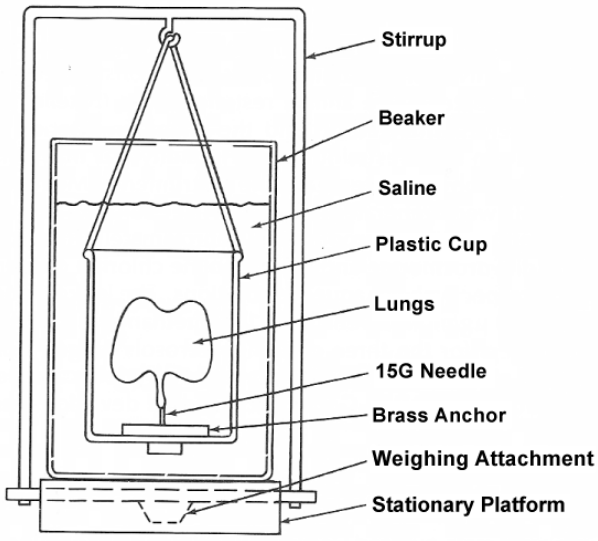


**Figure 3:** Diagram of the system constructed for excised lung gas volume (ELGV) measurements. The stirrup was connected to an analytical balance via its fulcrum or weighing attachment (modified from Silbaugh et al. [2]).

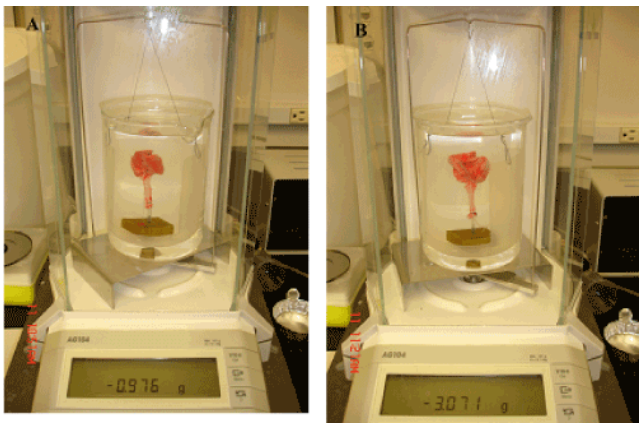


**Figure 4:** Examples of excised lung gas volume (ELGV) values of normal (panel A) and hyperinflated (panel B) lungs.

As shown in Figure 5, we found increases in ELGV or pulmonary gas trapping in the guinea pig to correlate highly with bronchoconstrictor agonist-mediated decreases in $C_{dyn}$ and increases in total pulmonary resistance ($R_L$), thus reflecting the physiological condition of the lungs at the moment the animal is euthanized [16-18]. Also, Eidelman et al. [19] observed a strong relationship between in vivo pulmonary mechanical and lung morphometric (mean linear intercept) measurements in methacholine-bronchoconstricted rats. They noted the increased in airspace size was indicative of the presence of pulmonary hyperinflation. In addition, using chest wall displacement for estimating a change in lung volume via a flex sensor,

Volgyesi et al. [20] reported an association between dynamic hyperinflation and decreases in Cdyn during methacholine challenge in naïve mice. Further, we found a correlation between in vivo enhanced pause (Penh) determined by whole-body barometric plethysmography [21] and ELGV in naïve mice challenged with methacholine [22]. Finally, we showed that the rank order of methacholine-induced increases in pulmonary gas trapping of naïve male A/J, BALB/c and C3H/HeJ mice [23,24] was similar to that observed for the same mouse strains using airway pressure-time index to measure airway responsiveness to acetylcholine [25]. Thus, collectively these investigations validate the use of pulmonary gas trapping in small laboratory animals for modeling pulmonary functional aspects of human lung diseases.

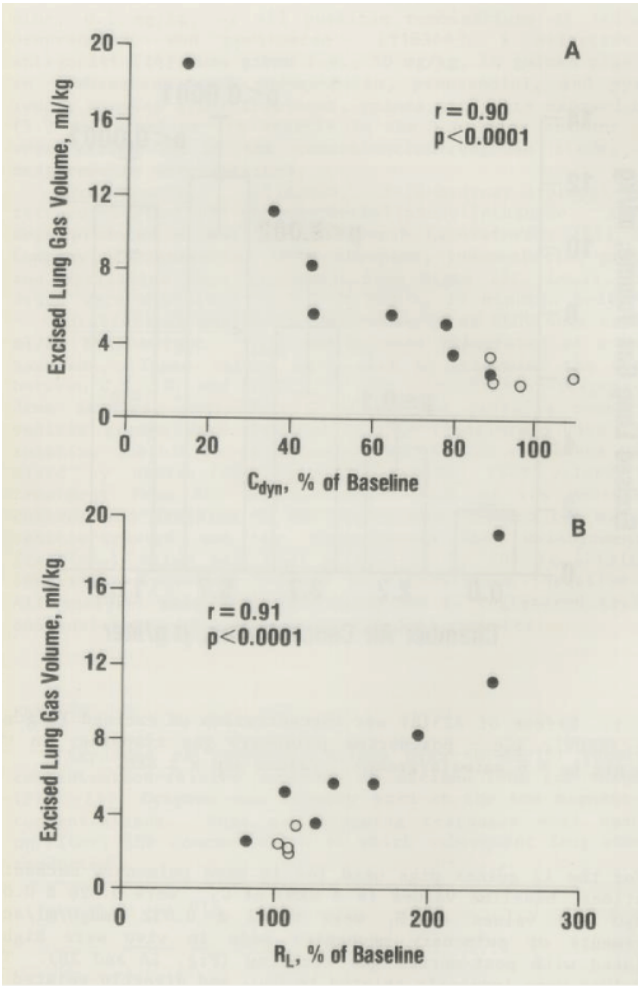


**Figure 5:** In guinea pigs, relationship of excised lung gas volume (ELGV) with $C_{dyn}$ and $R_L$ values obtained immediately prior to death. Pulmonary gas trapping was inversely related to $C_{dyn}$ (Figure 3A), while directly related to $R_L$ (Figure 3B). Each point represents one animal. Open circles-vehicle, closed circles- A23187 (modified from Stengel et al. [16]).

We found dose-related ELGV increases after methacholine bronchoprovocation in naive small laboratory animals [23]. When examining control ELGV values, they did not differ significantly among species, ranging from 1.50 ± 0.20 ml/kg for guinea pigs to 2 .75 ± 0.20 ml/kg for Brown-Norway rats. Thus, the resting gas volume in excised lungs when normalized by body weight was similar across species. Allometric analysis [26] between resting lung volume and the over 24-fold range of body weights of animals used in this study showed a linear relationship between those two variables. When expressing ELGV as a percent of control for each animal species, we found maximal response (Figure 6) and potency (Table 1) to inhaled methacholine in guinea pigs to be at least 2-fold and 11-1,395 times greater, respectively, than that observed for the other species.

Based on the methacholine-induced pulmonary gas trapping response in naïve mice, Hatfield et al. [27] were the first to demonstrate a significant increase in ELGV values of antigen-sensitized, antigen-exposed C57BL/6 mice compared to that of antigen vehicle-treated, antigen-exposed animals following a methacholine aerosol challenge. However, only one methacholine aerosol solution concentration was reported so there was no aerosol concentration- or dose-response information, indication of maximal pulmonary gas trapping, or reproducibility of the airway obstructive response in their mice. Similarly, Yiamouyiannis et al. [28] found increases in ELGV values to be significantly greater in ovalbumin-sensitized, ovalbumin-exposed C57BL/6 mice than that of control animals at both methacholine aerosol solution concentrations used in their study. Like Hatfield et al. [27], Yiamouyiannis et al. [28] did not provide information on either maximal or reproducibility of methacholine-induced airway obstruction in their animals.

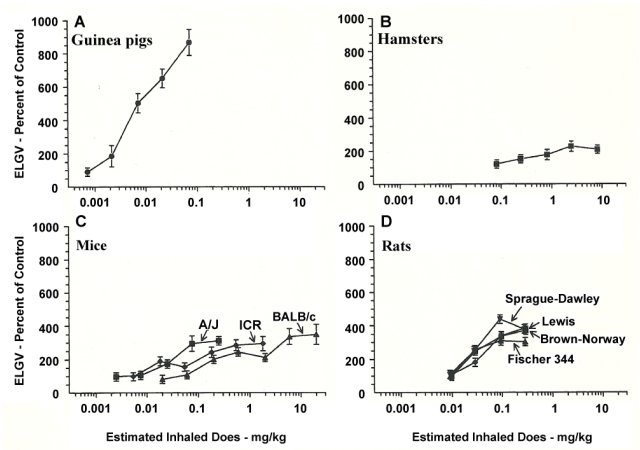


**Figure 6:** Comparison of methacholine-induced pulmonary gas trapping in guinea pigs (A), hamsters (B), mice (C), and rats (D). Increases in excised lung gas volume (ELGV) values produced by methacholine are as % control. Values are means SE of 4-6 animals/group (modified from Stengel et al. [23]).

From the results of those two studies, we examined reproducibility of methacholine-induced airway obstruction in ovalbumin-sensitized, ovalbumin-exposed BALB/c mice (Positive Control) versus ovalbumin-sensitized, sodium chloride-exposed animals (Negative Control) [22]. After establishing that dose-related increases in pulmonary gas trapping caused by inhaled methacholine in Negative Control mice was similar to what we observed previously in naïve BALB/c mice [23], we found maximum ELGV values of methacholine-challenged Positive Control mice to be 1.3-2.4 times greater than those of Negative Control mice. Additionally, we found the sensitivity to methacholine in Positive Controls [$ED_{200}$ (95% confidence interval) =

0.013 (0.0067-0.019) mg/kg] was 7.8 times greater than that observed Negative Controls [$ED_{200}$ (95% confidence interval) = 0.101 (0.033-0.340) mg/kg]. Next, we examined the relationship between pulmonary gas trapping and Penh in both naïve and sensitized mice [22]. In urethane-anesthetized naïve mice, we found changes in ELGV values correlated with changes in enhanced pause obtained immediately prior to death. In ovalbumin-sensitized mice, we observed remarkable stability in methacholine-induced pulmonary gas trapping when examining mean ELGV values of Positive and Negative Control mice from nine studies conducted over six months (Figure 7). In contrast, we found tremendous variability in mean enhanced pause values of methacholine-challenged Positive and Negative Control mice over a six-month period.

| Species | Strain | n | $ED_{200}$ ELGV, µg/kg (95% confidence interval) | Relative Potency |
|---|---|---|---|---|
| Guinea pig | Hartley | 25 | 1.6 (1.0-2.3) | 1 |
| Hamster | Golden Syrian | 25 | 2232.0 (769.0-3033.0) | 1,395 |
| Mouse | A/J | 25 | 26.0 (16.6-41.2) | 16 |
| | BALB/c | 48 | 359.0 (185.0-641.0) | 224 |
| | ICR | 30 | 71.9 (29.8-155.0) | 45 |
| Rat | Brown-Norway | 20 | 24.1 (17.0-32.0) | 15 |
| | Fischer 344 | 20 | 24.2 (12.1-38.6) | 15 |
| | Lewis | 20 | 28.8 (22.6-35.6) | 18 |
| | Sprague-Dawley | 20 | 17.2 (9.0-26.4) | 11 |

**Table 1:** Table showing relative $ED_{200}$ ELGV of methacholine producing pulmonary gas trapping increases in the guinea pig, hamster, mouse, and rat (from Stengel et al. [23]). Estimated inhaled dose of methacholine was calculated based on nebulizer solution concentration, usable nebulizer output, inhalation time, chambre airflow, minute volume, and animal body weight.

When using a method such as the ELGV measurement for assessing airway mechanical responses in animal models of human lung disease, I believe it is important to use established drug treatments as positive comparators. For instance, glucocorticosteroids are used in the treatment of asthma [29]. In two separate studies, we found both oral dexamethasone and inhaled budesonide reduced methacholine-induced pulmonary gas trapping and eosinophil and neutrophil recruitment in ovalbumin-sensitized, ovalbumin-exposed BALB/c mice [22,30]. Thus, the results with the glucocorticosteroids provide further validation of the ELGV measurement in a mouse model of allergic asthma.

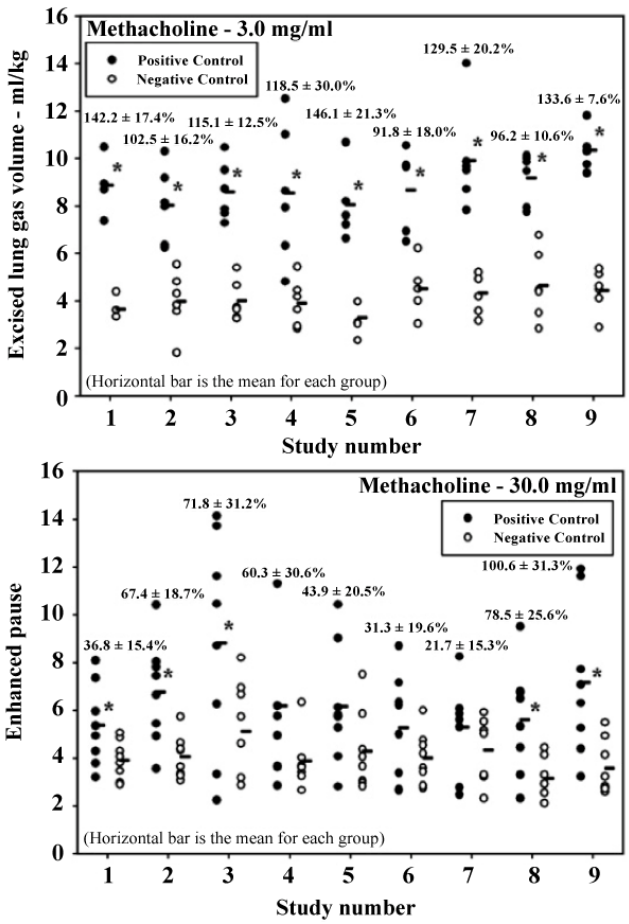


**Figure 7:** Indirect comparison in pulmonary gas trapping (upper panel) and enhanced pause (lower panel) of Positive and Negative Control mice produced by methacholine. For each method, intra- and inter-study variability was assessed in nine experiments performed over approximately 6 months. Each point corresponds to an individual animal, and the horizontal bar represents the mean for each group. One hundred mice (Positive Controls, n=50 mice, and Negative Controls, n=50 mice) were used to examine methacholine-induced pulmonary gas trapping, while 142 mice (Positive Controls, n=72 mice, and Negative Controls, n=70 mice) were used to examine enhanced pause following methacholine. The percentages listed in each figure represent the relative increase in excised lung gas volume and enhanced pause values of Positive Control mice compared to Negative Control mice. Asterisks indicate significant difference ($P<0.05$) between the mean excised lung gas volume or mean enhanced pause values for Positive and Negative Control mice (from Stengel et al. [22]).

## Use in rodent models of emphysema

Although the studies thus far described have shown the usefulness of pulmonary gas trapping in guinea pig and mouse models of allergic asthma, recently Jansson et al. [31] used the ELGV measurement to follow the progression of lung volume changes in genetic (pallid or tight-skin mice) or pancreatic elastase-induced (Wistar rats) animal models of emphysema. They noted as early as one and three months

after birth, ELGV values of tight-skin and pallid mice, respectively, were significantly higher than normal C57BL/6J mice. Morphometric analysis of lungs from pallid and tight-skin mice at four months after birth revealed significant loss of extra-alveolar tissue area and increases in intra-alveolar space compared to normal C57BL/6J mice. Likewise, Wistar rats receiving pancreatic elastase intra-tracheally showed statistically significant increases in ELGV, decreases in extra-alveolar tissue area and increases in intra-alveolar space seven days after instillation compared to rats receiving saline. Thus, measuring increases in ELGV may be useful for evaluating the development of emphysema-like lesions in animal models and the effectiveness of novel therapeutic agents for treating this human lung disease.

### Use of ELGV measurement in a non-lung disease study

With the recent development of transient receptor potential vanilloid 1 (TRPV1) agonists such as civamide [32] or SDZ 249-665 [33] for treating pain, a major concern of capsaicin analogues is increased airway smooth muscle contraction since the prototypical TRPV1 agonist capsaicin has been shown to cause bronchoconstriction in humans [34]. In a pilot study [35], we found that SDZ 249-665 caused dose-related ELGV increases following intravenous, but not oral administration in guinea pigs. Also, when given orally once daily for 7 days to guinea pigs, SDZ 249-665 significantly suppressed capsaicin-mediated increases in pulmonary gas trapping, but not airway obstruction caused by the muscarinic receptor agonist bethanechol. Although preliminary in nature, these results suggest the ELGV measurement may be useful for examining potentially adverse pulmonary adverse drug-related events [36] and for exploring the role of oral TRPV1 agonists in the down-regulation of TRPV1 channels in neurogenic inflammatory disorders [37].

## Summary

The ELGV measurement is a rapid and reproducible method for quantitating airway responses in small laboratory animals. In addition, it is easy to perform requiring only minimal training such as removing lungs from the thoracic cavity and reading the grams displaced on an analytical balance display. Further, the apparatus for measuring ELGV is much less expensive (hundreds of dollars) than the equipment for noninvasive or invasive pulmonary function measurements (tens of thousands of dollars) in small laboratory animals. Finally, investigators from academic [28,38,39], government [40], and pharmaceutical [27,41,42] laboratories have used the ELGV measurement to advance their research. Thus, I believe the ELGV measurement is a cost-effective alternative approach for assessing in vivo airway mechanics in small laboratory animals and for examining novel therapies for treating human lung disease.

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