Respiration
Editor: H. Herzog, Basel

Separatum
Publisher: S. Karger AG, Basel
Printed in Switzerland

Editorial

Respiration 1993;60:1–8

Whole-Body Plethysmography in the Clinical Assessment of Infants with Bronchopulmonary Diseases

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Key Words
Infant lung function testing
Whole-body plethysmography
Wheezy bronchitis
Infant respiratory distress syndrome
Cystic fibrosis
Bronchial asthma

Abstract
Infant whole-body plethysmography offers a unique possibility of measuring end-expiratory resting level (thoracic gas volume; TGV), and hence lung volume in its close interrelationship to airway function (airway resistance; R_{aw}, its reciprocal value, airway conductance, G_{aw}). Therefore, this technique is a valuable aid for objective evaluation of lung diseases in infants. This article gives an overview of the physiological background of this particular measuring technique and its usefulness in the clinical routine. Plethysmographic data obtained in infant survivors of the infant respiratory distress syndrome (iRDS), in infants with cystic fibrosis (CF) and in the so-called 'wheezy infants' are presented. Special emphasis is given to the fact that in such infants the interrelationship between changes in end-expiratory resting level and the deficit in airway mechanics is of great importance and, consequently, for the determination of functional lung derangement in each particular case of lung disease, both TGV and the closely related R_{aw} and G_{aw} have to be evaluated. This recommendation has to be kept in mind when the different diagnostic tools for evaluation of treatment facilities are applied in this particular young age group of patients with lung disease. In children as in adult patients, inhalative treatment must be considered the mainstay of all therapeutic measures. However, in infants, the efficacy of such treatment regimens must first be evaluated by adequate functional investigations. Infant whole-body plethysmography offers one such possibility.

Introduction

Whole-body plethysmography, introduced in 1956 by Dubois et al. [1, 2] to be performed in adults, is an elegant method for measuring thoracic gas volume (TGV) and airway resistance (R_{aw}) and its reciprocal value, airway conductance (G_{aw}). A first technique to perform infant whole-body plethysmography was worked out by Geubelle et al. [3] in 1959 and shortly thereafter, Klaus et al. [4] and Nelson et al. [5] published plethysmographic measurements obtained in infants. In the following, this technique was used in infants with lung disease by Nelson et al. [5] and Auld et al. [6] who found that well babies in contrast to adults frequently have evidence of gas trapping, i.e. the

Held in part at the Postgraduate Course of the American Thoracic Society, Miami Beach, Fla., USA, May 17, 1992, and the Postgraduate Course of the European Respiratory Society, Vienna, Austria, August 29, 1992.

Received:
November 23, 1992
Accepted:
December 7, 1992

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0025–7931/93/0601–0001
$ 2.75/0

difference between plethysmographically measured TGV and functional residual capacity (FRC) determined by a gas dilution technique.

The plethysmographic technique is based on the fact that the driving pressure of airway mechanics is the alveolar pressure infered from the pressure change within the box. The corresponding airflow can be measured directly with an infant pneumotachograph or calculated from volume tracing. As the 'panting breathing technique' cannot be applied in infants a heated rebreathing system was developed by Stocks et al. [7]. This system enables the plethysmographic technique to be adapted for use in infants and standardized accordingly. It was possible to avoid artifacts due to problems of temperature and humidity adaptation, and the babies are strictly breathing under BTPS conditions during measurements of airway mechanics. In the meantime, R_{aw} and/or G_{aw} have been assessed by plethysmographic measurements from birth to adolescence [8–10]. Only a few studies, however, have measured TGV by whole-body plethysmography in a significant number of healthy infants and young children, the age range covered includes the first 12 months of life [8, 9, 11–15].

Definitions

FRC and TGV are defined as the volume of gas in the lungs at the end of a tidal breath (the so-called 'end-expiratory volume); in normal subjects, FRC and TGV are equal, at least in children after age 6 years and in adults. FRC is the volume of gas that communicates with the airways; TGV also includes the volume of trapped gas reflecting alveolar air space that is badly or not ventilated.

There are different kinds of airway resistance which can be measured in infants; they reflect different qualities of the viscoelastic behavior of the infant's lung. The resistance of the respiratory system (R_{rs}) is a reflection of the friction encountered by gas flowing through the airways and by tissue moving against tissue. It is defined as the change in pressure required for a unit change in flow (cm H_2O/l/s). R_{rs} is the sum of airway resistance (R_{aw}), lung tissue resistance (R_{lt}) and chest wall tissue resistance (R_{cw}). Lung resistance (R_L) is the sum of R_{aw} and R_{lt} [16]. Conductance is the inverse of resistance.

Finally, compliance reflects the elastic properties of the respiratory system and is defined as the change in volume per unit change in pressure (ml/cmH_2O). The compliance of the total respiratory system (C_{rs}) can be divided into compliance (C_L) and chest wall compliance (C_{cw}), where $1/C_{rs} = 1/C_L + 1/_{cw}$ [17].

Measurement Technique

Infant whole-body plethysmography requires no rebreathing of an inert gas, and no active cooperation on the part of the subject. The ingenuity of this technique is that, by measuring of two pressures during a few respiratory efforts against an occlusion at the mouthpiece performed by the sleeping baby and by mathematical application of Boyle's law, the physiological lung function parameters can be determined with high reproducibility [18]. This is presumably the reason why this lung function technique is highly appreciated by several pediatric pulmonary physiologists.

Equipment

Figure 1 shows the newly designed infant plethysmograph produced by the Jaeger Company (Würzburg, FRG) and in figure 2 a 'print screen' showing on-line curves of TGV and R_{aw} as well as on-line calculated lung function data is shown. The baby is asleep (chloral hydrate 80–100 mg/kg body weight) in supine position within the plethysmographic box. From the 4 signals, including flow (measured by a pneumotachograph), its integral the volume, the body-box pressure and the mouth pressure, typical curves can be obtained (box pressure-flow relationship, $\Delta Pm/\Delta Pb$ plot, $\Delta V'/\Delta Pb$ plot, volume), which enables one to calculate TGV (estimate of lung volumes), R_{aw} and G_{aw} (both estimates of airway mechanics) [1, 9].

Intrasubject Variability and Interindividual Sensitivity

The intra individual variability of repeatedly measured TGV and G_{aw} in 16 wheezy infants, age 1.9–14.9 (mean 9.2 ± 4.5) months, weight 3.5–11.5 (mean 8.1 ± 2.5) kg was evaluated in a previous study [18]. Mathematically, intrasubject variablity (RD) was computed as relative difference (RD) = $|Z1–Z2|/AZ$, where Z1 and Z2 are values of two measurements and AZ their average value) of paired measurements. Interindividual sensitivity (ΔSD-S) was calculated as differences of the standard deviation scores of values predicted [7] for paired TGV and G_{aw} measurements of all subjects. After baseline measurements (BLM), measurements were repeated 3 times at 5-min intervals. Means and standard deviations of RD and ΔSD-S comparing the repeated measurement with the preceding one, including last-to-BLM comparison, are given in table

1. Within the 15 min of repeated tests, RD for TGV varied within 9.3% and G_{aw} within 13.4%. For TGV ΔSD-S varied within the 1.6 SD range, and for G_{aw} within the 1.1 SD range. The conclusion of this study was that intrasubject variability (RD) and interindividual sensitivity (ΔSD-S) are quite acceptable for infant whole-body plethysmography. For pharmacodynamic studies, therefore, an improvement of 2 SD for TGV and/or G_{aw} could be considered as a significant response.

Physiological Background

Under the condition that flow is laminar, the resistance of an airway bears an inverse fourth-power relationship to its diameter [10]. Although in wheezy infants this may not be the case everywhere in the bronchial tree, this exponential relationship serves to explain the mechanism that as an airway narrows, a progressively greater change in resistance is expected for a given change in smooth muscle length (and hence inspiratory lung volume). Conse-

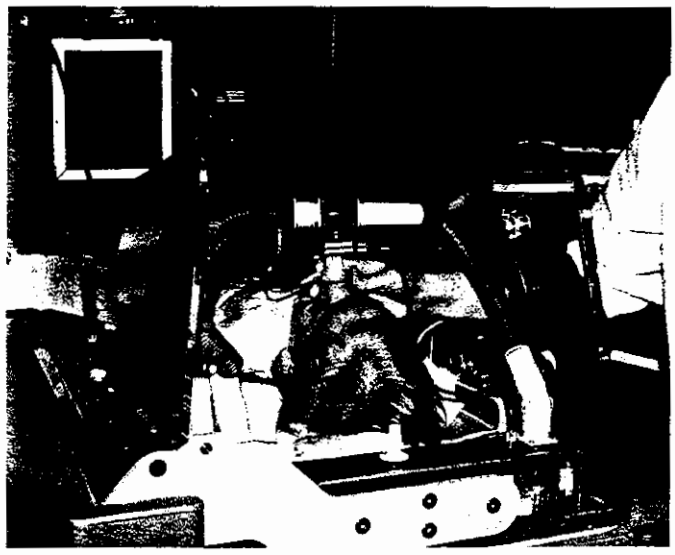

Fig. 1. The newly designed Master BabyLab (Jaeger Würzburg, FRG) with measurements head in place (containing heated pneumotachograph and mouth pressure transducer) attached to the BTPS unit.

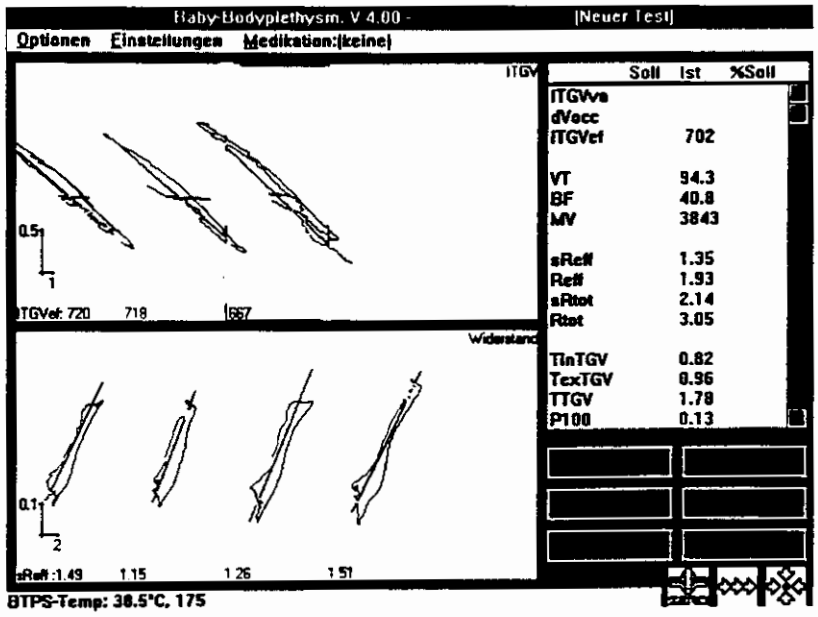

Fig. 2. 'Print screen' from the Master BabyLab PC showing the body-box pressure mouth pressure plot and calculation of TGV (top) and the body-box pressure flow plot reflecting R_{aw} (below). Right pannel: instantly measured lung function data.

Table 1. Intrasubject variability and interindividual sensitivity of whole-body plethysmographic measurements in 16 wheezy infants, evaluated by repeated measurements from baseline up to 15 min

	BLM	5 min	10 min	15 min	Last vs. BLM
TGV					
RD, %	5.1±4.5	8.6±5.6	8.4±10.0	4.5±5.7	9.3±7.3
ΔSD-S (SD)	0.9±0.8	1.5±0.9	1.4±1.4	0.8±0.9	1.6±1.2
G_{aw}					
RD, %	7.2±7.1	13.3±10.5	12.1±8.7	6.9±9.3	13.4±8.4
ΔSD-S (SD)	0.5±0.6	1.1±1.2	1.0±0.7	0.5±0.6	1.1±0.8

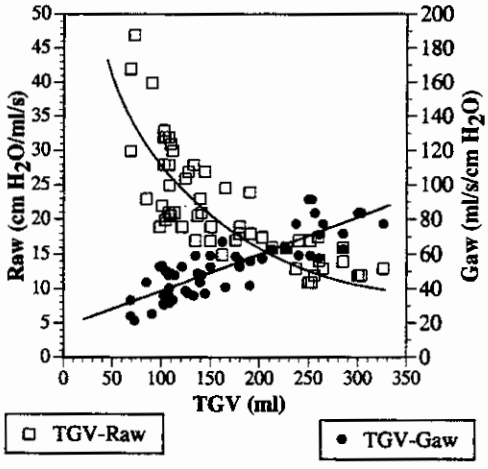

Fig. 3. Interrelationship between growing lung volumes (measured as TGV at end-espiratory resting level) and airway R_{aw} its reciprocal value, G_{aw}, in 56 healthy infants (age 2 days, 11.2 months).

quently, the bronchodilator response to β_2-agonists must be measured in children and especially in infants by methods that evaluate changes in airway function in relation to changes in resting end-expiratory level [19–22]. The potential influence of changes in functional residual capacity on airway function was recently reported by Maxwell et al. [23], who demonstrated that indices of partial expiratory flow maneuvers may underestimate the actual changes in airflow when changes in end-expiratory level are not taken into account. This was demonstrated for histamine-indued bronchoconstriction in recurrently wheezy infants, but the converse effect after bronchodilator inhalation is based on the same mechanism. A clear relationship between lung volume and airway caliber is found not only in children [2, 4], but also in healthy infants (fig. 3). This relationship is curvilinear between TGV and R_{aw}, and linear between TGV and G_{aw}. The data presented in figure 3 have been collected from a set of values in healthy infants and young children obtained from Stocks et al. [7], Dezateux [pers. commun., 1990] and unpublished data [1992].[1] Finally, the same relationship can be used to explain changes in the degree of pulmonary hyperinflation with concomitant changes in lung mechanics, as demonstrated in infants with bronchopulmonary disease [25–27]. The clinician is interested in following this relationship not only during normal lung growth, but more specifically in an attempt to modulate its evolution by adequate therapeutic measures in infants with lung disease. The great advantage of infant whole-body plethysmography is the possibility of measuring static lung volumes in relation to airway mechanics, and of obtaining objective evidence with respect to the reversibility and interdependence of clinical changes in these parameters [25–27].

Fields of Clinical Interest

One objective of infant lung function testing is to gain a better insight into the physiopathological mechanisms underlying various respiratory diseases in infancy. Premature infants may develop hyaline membrane disease requiring mechanical ventilation, a therapeutic measure which may lead to bronchopulmonary dysplasia (BPD) [28]. The major causes of BPD are not clear yet, nor is it clear why some survivors of hyaline membrane disease, with or without BPD, presented with abnormal lung function during adolescence and/or adulthood [29–33]. Besides oxygen toxicity and barotrauma [31, 32, 34, 35], which are commonly associated with the development of BPD

[1] The author thanks C.A. Dezateux (Unit of Epidemiology), M.E. Fletscher and J. Stocks (Portex Anaesthesia, Intensive Therapy and Respiratory Medicine Unit), Institute of Child Health, London, UK, for the support in collecting these data.

[36], prematurity either by itself or in combination with hyaline membrane disease [31, 32, 34, 35, 37, 38] are considered as possible reasons for later functional lung disorders. There is a need to have objective data showing the natural course of the disease, to know more precisely which risk factors are really involved, and to evaluate potential benefits of various treatments which are used by many clinicians without clear rational backgrounds.

One of the necessary preliminaries to an understanding of the disease process is the consideration of the first critical events in the airways of infants with cystic fibrosis (CF). With the micro-osmometer sweat-test technique [39] there is the possibility of detecting CF in early childhood. As a result of this early diagnosis, the question is whether these infants, who at this stage do not always have pulmonary symptoms, really have normal lung function. It has been shown previously that 5/24 infants with CF had normal lung function, 6/24 were hyperinflated (TGV > mean + 2 SD), 9/24 were of the mixed type (hyperinflation and bronchial obstruction: TGV and R_{aw} > mean + 2 SD) and 4/24 bronchial obstruction alone [19].

Another diagnostic group includes wheezy babies, i.e. all subjects with wheezy bronchitis, infants after viral bronchiolitis, and infantile asthmatics. It is widely accepted that wheezy bronchitis in infants represents part of the spectrum of early asthma in childhood, as it has been shown that infants who have more than one wheezing episode will frequently develop the typical picture of asthma in later childhood [40–42].

Evaluation of Drug Response

Although bronchodilator aerosols, whether administered by jet-type nebulization or by metered-dose inhaler (MDI), are common treatments for asthmatic patients, producing rapid and efficient relief of bronchospasm [43] at low doses [44] and avoiding adverse secondary effects [45, 46], the effectiveness of aerosol therapy in infants needed to be proven by objective lung function data. As objective evidence that β-adrenoreceptor agonists may be effective when given orally in infants younger than 18 months [25, 47] and improvement in clinical signs after topical administration by inhalation was provided [48–50], the question remained as to how β_2-agonists may induce changes in the degree of pulmonary hyperinflation, as well as concomitant changes in airway mechanics. Therefore, the response of lung function to salbutamol, topically administered by an MDI through a baby-adapted auxiliary device, the Babyhaler (Glaxo, Switzerland) was evaluated

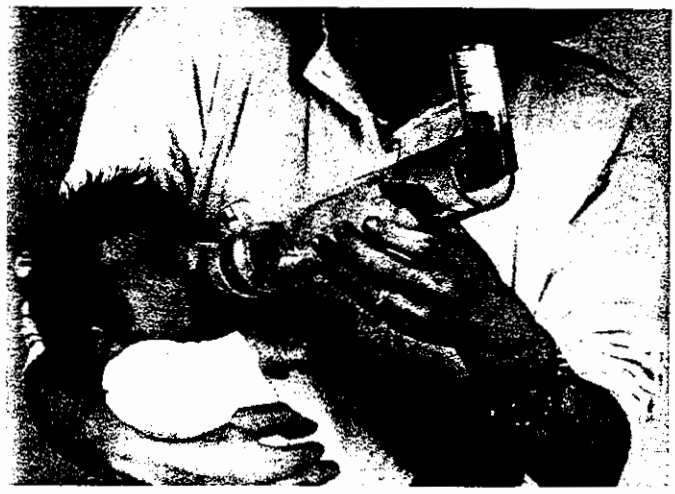

Fig. 4. Baby-adapted, double-valved auxiliary inhalation device (Babyhaler) for aerosol treatment with a β_2-stimulant from an MDI.

in 36 wheezy infants (1.6–25.2 months of age; median 8.1 months), in a double-blind, placebo-controlled study. The auxiliary device contains an air-chamber of 350 ml, two low-resistance valves, separating the inspiratory from the expiratory line. Such an aerosol treatment is shown in figure 4. Changes in the degree of pulmonary hyperinflation, estimated by TGV and/or in the degree of bronchial obstruction, estimated by G_{aw} were measured at 5-min intervals for up to 30 min. TGV and G_{aw} were expressed as standard deviation scores (SD-S) of values predicted, and patients whose TGV and/or G_{aw} improved by more than 2 SD were considered as responders [51]. From these data it becomes clear that the type of initial functional abnormality and the time course must be taken into account when studying drug efficacy. Significant improvement after inhalation with albuterol in comparison with placebo could be demonstrated by plethysmographic measurements. The study furthermore demonstrated that several methodological aspects are related to the kind of functional interrelationships by which lung function data should be evaluated in infants. Our data suggest that changes in both TGV (as an estimate of pulmonary hyperinflation) and G_{aw} (as an estimate of airway function) have to be considered in order to answer the question of whether or not drug response to adrenoreceptor agonists can be achieved and substantiated in infants.

To discuss plethysmographic data in relation to clinical patterns, lung function data of 118 infants with bronchopulmonary diseases including 36 survivors of iRDS, 30 infants with CF and 52 wheezy infants, some of which have not been published yet are presented in figure 5. Lung

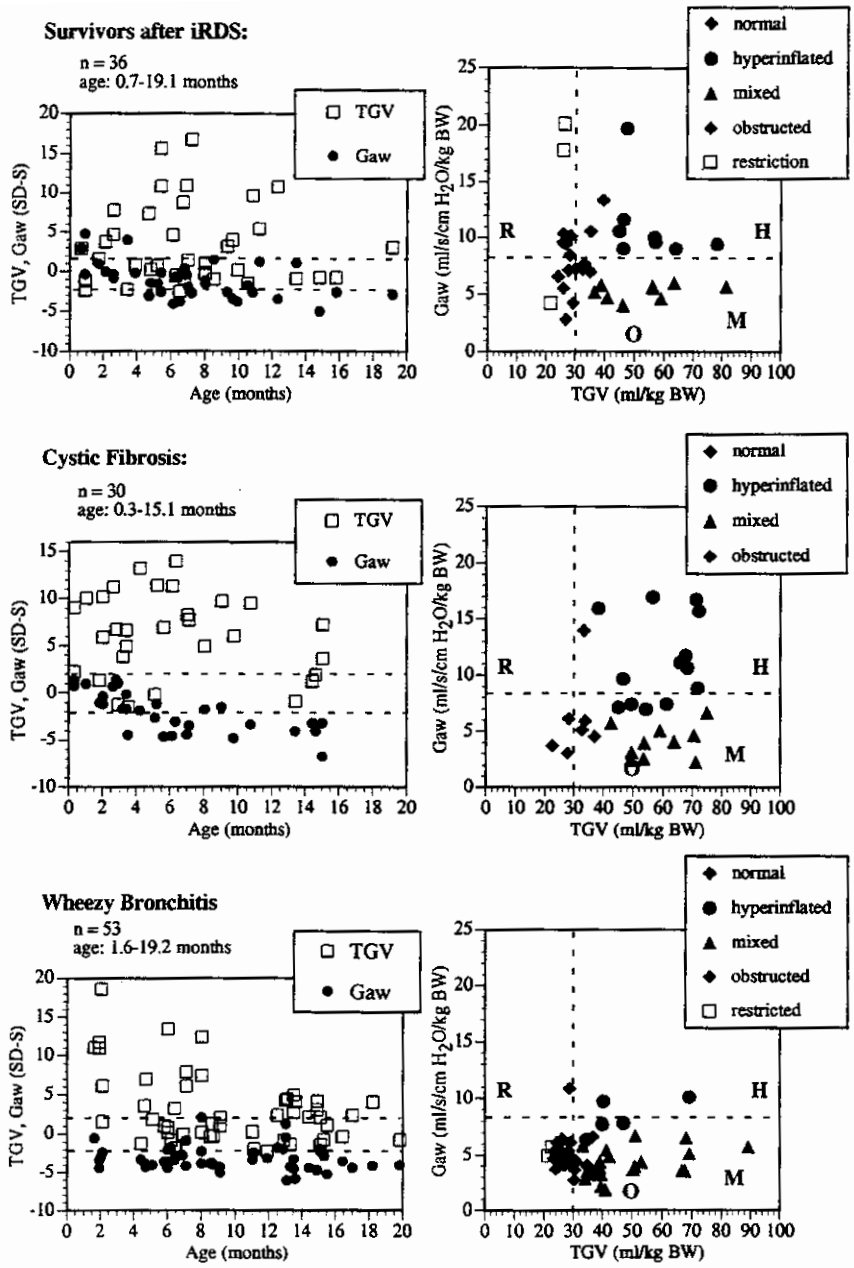

Fig. 5. Collection of lung infant plethysmographic data to show the degree of pulmonary hyperinflation (TGV) and the degree of bronchial obstruction (G_{aw}), both expressed as standard deviation scores (SD-S) based on a normal population in relation to age and as X-Y-plots to define different functional groups.

function data were expressed in SD-S in relation to age in the left pannel, and body-weight-corrected absolute values of TGV in relation to G_{aw} in the right pannel. One of the striking features of these plethysmographic data is the finding of consistent pulmonary hyperinflation especially in the first 10 months in all diagnostic groups. Whereas pulmonary hyperinflation seems to be the functional disorder predominantly detected in the first months of life, bronchial obstruction develops later on. The XY plot of TGV in relation to G_{aw} provides a synoptic representation to subdivide the subjects into different functional groups. According to the limits given by the mean ±2 SD of the TGV and the G_{aw}, 5 functional goups can be distinguished: pulmonary hyperinflation (H: TGV > mean +2 SD), pulmonary hyperinflation and bronchial obstruction (H&O: TGV > mean +2 SD and G_{aw} < mean −2 SD), bronchial

obstruction (O: G_{aw} < mean –2 SD), pulmonary restriction and obstruction (R&O: TGV < mean –2 SD and G_{aw} < mean –2 SD) and pulmonary restriction (R: TGV < mean –2 SD).

Limits of Infant Whole-Body Plethysmography

Although not supported by all author groups routinely performing infant plethysmography, there is an ongoing discussion about potential errors in measuring TGV [52–54]. In consequence, comments by Phelan and Williams [55] expressed doubts about the accuracy of the plethysmographic method in measuring TGV and R_{aw} in infants with airway obstruction. However, there are other studies in which such discrepancies have not been found, and multiple intrasubject measurement comparing TGV values before and after medication with oral [25, 47] or inhaled [26, 27] salbutamol have provided evidence that pulmonary hyperinflation as well as pulmonary restriction may be reversible. At least when additional radiologic findings support the functional data that a particular lung is definitely hyperinflated, it should be accepted that this is not an artifact. Numerous infants present with both increased TGV and R_{aw}, which cannot be explained by the mechanisms suggested for adults [54]. Provided that TGV tracings are absolutely superimposed (a condition that was carefully checked by the technician responsible for the measurements), there is minimal evidence to suggest that 'mechanical inhomogeneity' is present. Upper airway artifacts are easily detected from the resistance slope and mainly depend on the position in which the child's head is kept, the face mask tightly fixed on its face.

Conclusion

In conclusion, lung function testing in infants should be a valuable aid in making objective conclusions with respect to a particular case of lung disease. Infant whole-body plethysmography offers one such possibility enabling evaluation of the degree of pulmonary hyperinflation or pulmonary restriction in close relation with the degree of bronchial obstruction. Regarding new treatment facilities, there is a wide palette of different drugs, like β_2-stimulants, cromolyn, atropine derivates and topical steroids, which can be inhaled by improved inhalation techniques (spacer devices, breath-activated devices). However, most of these treatment regimens have not yet been satisfactorily investigated in infants.

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