Measurement of airway mechanics in young children

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Introduction

Measurement of pulmonary function is an important tool for the diagnosis and monitoring of respiratory diseases. The gold standard of pulmonary function testing (PFT) is the maximal expiratory flow volume (MEFV) curve. However, only children aged 6-8 years and older can be expected to perform reproducible forced respiratory manoeuvres. In younger children MEFV measurements are rarely performed, because these children lack co-operation, but also show diminished reproducibility and reliability of results.

There are little alternatives in this age group. The clinical evaluation of lung function by auscultation appears to be an extremely insensitive indicator of bronchial obstruction. For instance a fall in oxygen tension of 33% may occur in young asthmatic children without audible wheeze. Probably at least 30% fall in FEV1 is necessary before wheezing is heard.

Between infancy and school age only methods that do not require sedation (unlike e.g. baby body plethysmography, VmaxFRC measurement by the squeeze jacket method) and are not invasive (unlike airway pressure measurement using pitot static probe or oesophageal balloons) are widespread applicable. In small children they should only require passive co-operation. Tidal breathing analysis and resistance measurement by the interrupter technique or (impulse) oscillation technique all appear to fulfil these requirements. The accuracy of these methods, i.e. their relationship to true airway resistance is not well known. These measures may be considered as indices of lung function.

In this chapter general principles of pulmonary and especially airway anatomy, development and physiology are discussed, followed by an overview of the different available methods to measure airway mechanics. The tidal breathing technique is comprehensively discussed in the next chapter.
1. General principles of respiratory mechanics

Modelling of the respiratory system

The respiratory system can be considered as a physical model, i.e. a collection of physical components interacting with one another and with the environment. Most real life systems, such as the respiratory system are nonlinear, but they can be simplified to linear models under certain conditions. A linear model has useful properties that makes analysis easier.

The most simple model of the complex respiratory system is that of a single balloon on a pipe. The relationship between the pressure applied at the opening of the model \( P(t) \) and the volume in the model \( V(t) \) during emptying of this balloon can be described as a first order model:

\[
P(t) = E.V(t) + R.V'(t)
\]

where \( E \) = elastance of the balloon, \( R \) = resistance of the pipe and \( V' \) = flow through the opening. Using regression analysis one can calculate \( E \) and \( R \) from \( P(t), V(t) \) and \( V'(t) \).

If this model is applied to the respiratory system, the values of \( R \) and \( E \) reflect the \( R \) of the airways and the \( E \) of the respiratory system, whereas \( V(t) \) is the volume increase from functional residual capacity (FRC), i.e. where \( P(t) \) at mouth opening is zero.

In other words the passive deflation of the respiratory system is characterised by a volume-time profile determined by \( E \) and \( R \).

In vivo measurements show that the lungs can not be seen as a single compartment and when one reports a single airway resistance or elastance value, the underlying assumption that this is the one and only value for these parameters is never satisfied in real life, especially in non healthy subjects.

Nevertheless, the majority of respiratory mechanics are represented by this simple linear, single compartment model.

Using this model there are three important components:

1. time constant (\( \tau \))
2. compliance or elastance
3. resistance
The relationship of these parameters is given by the equation:

\[ \tau = C \times R, \quad \tau = R/E \]

**Time constant of lung emptying**

The time constant (\( \tau \)) describes the expiratory airflow generated by the elastic properties of the respiratory system (balloon)\(^9\). During passive emptying the time to reduce by 63% is known as the time constant of the respiratory system (Figure 1). In healthy adults \( \tau \approx 0.5 \) sec. This allows the lung to empty to FRC at each expiration. In infants with normal lungs \( \tau = 0.3 \) sec and in infants with stiff 'hyaline membrane' lungs \( 0.1 \) sec\(^10\). In obstructive airway disease increasing \( R \) (with or without decreasing \( E \)) increases \( \tau \), leading to a need for longer expiration time.

![Figure 1. Time constant (\( \tau \)) of lung emptying. \( V = \) lung volume.](image)

**Elastance and compliance**

When forces are applied to elastic structures such as the lungs, these structures will resist deformation by an opposing force in order to return to their relaxed state. This opposing force is called elastic recoil. The pressure needed to overcome elastic recoil, the elastic recoil pressure (\( P_{el} \)), depends on the lung volume above or below the equilibrium volume. The \( P_{el} \) divided
by the lung volume gives a measure of the elastic properties of the lung tissue and is called elastance (E):

\[ E = \frac{P_{el}}{V} \]

The slope of the volume (V) versus pressure (Pel) gives the reciprocal of elastance, i.e. compliance (C).

\[ C = \frac{V}{P} \quad C = \frac{1}{R} \]

The phenomenon that elastance and compliance depend on the volume history of the lung is called hysteresis. Expiration and inspiration are represented by different pressure-volume curves. Actually this is the failure of tissue to follow identical paths of response during in- and expiration as shown in Figure 2. Hysteresis depends on visco-elasticity and plasticity of the lung. It is important to know that during tidal breathing hysteresis is negligible, which is functionally desirable because the area of the hysteresis loop represents energy loss from the system. This also means that in all PFTs during tidal breathing hysteresis will hardly influence results.

\[ Figure 2. \text{Hysteresis in the pressure volume curve of the lung. The area contained within the curve represents the energy lost in the system. } V = \text{volume, } P = \text{pulmonary pressure, } d = \text{change.} \]
Resistance

Resistance is expressed as changes in pressure divided by changes in flow:

\[ R = \frac{dP}{dV'} \]

In other words, the flow (V’) measured at the mouth depends on the driving pressure (i.e. the pressure difference between alveoli (P_{alv}) and mouth (P_{mo})) and the airway resistance (R_{aw}):

\[ V' = \frac{(P_{mo} - P_{alv})}{R_{aw}} \]

If mouth pressure is 0 (i.e. atmospheric pressure), driving pressure is alveolar pressure.

Alveolar pressure is determined by two components: elastic lung recoil pressure (P_{el}) and intrathoracic or pleural pressure (P_{pl}). P_{el} is the pressure caused by the elastic properties of the lung, resulting in volume reduction of the lungs. P_{pl} results from the influence of breathing muscles on the thorax. During inspiration these forces counteract (P_{alv} = P_{pl} - P_{el}) during expiration they work together (P_{alv} = P_{pl} + P_{el}).

Airway resistance (R_{aw}) can be considered the sum of peripheral airway resistance (peripheral intrathoracic airways < 2 mm diameter; R_{awp}), central airway resistance (large intrathoracic airways > 2 mm diameter; R_{awc}) and extrathoracic airway resistance (especially glottis; R_{ext}).

\[ R_{aw} = R_{awp} + R_{awc} + R_{ext} \]

In healthy persons R_{ext} accounts for 50% of total R_{aw} and R_{awp} accounts for about 15% of R_{aw}. R_{awp} and R_{awc} are influenced by lung volume, i.e. by P_{el}. Higher lung volumes give higher P_{el} and therefore increase airway diameter. With increasing volumes during inspiration the increased P_{el} is counteracted by P_{pl}, resulting in increased radial distending force. This distending force is the transmural pressure and is the difference between pressure in (P_{in}) and outside (P_{out}) the airway.

During breathing arrest the pressure inside the airways (P_{in}) equals atmospheric pressure and transmural pressure (P_{tm}) equals P_{el}. 

![Image of a baby]
Airway diameter is sigmoidally related to $P_{tm}$ of the intrathoracic airways. This results in volume dependency of $R_{aw}$. At higher lung volumes $R_{aw}$ decreases. The specific relation between $R_{aw}$ (or its reciprocal conductance $G_{aw} (=1/R_{aw})$ and volume is mirrored by the specific $R_{aw}$ ($s_{R_{aw}}$) and specific $G_{aw}$ ($s_{G_{aw}}$).

$$R_{aw} = R_{aw} / V \text{ and } s_{G_{aw}} = G_{aw} / V$$

Dynamics of breathing

The forces produced by respiratory muscles should overcome the elastic, flow resistive and inertial properties of the lungs and chest wall to produce ventilation.

The inertance is the “resistance of the respiratory system to acceleration”. During tidal ventilation inertance is negligible. 90% of pressure is required to overcome the elastic forces, only 10% to overcome flow resistant forces. The elastic properties, compliance and resistance, are the main determinants. Frictional resistance to airflow acceleration to airflow accounts for 1/3 of the work during quiet breathing. The magnitude of pressure loss, due to friction depends on the pattern of flow, which can be laminar (streamlined) and turbulent. This depends on the properties of the gas (viscosity, density), velocity of airflow and the radius of the airway. In general there is laminar flow in small peripheral airways and turbulent flow in larger central airways.

The pressure gradient required to maintain laminar flow through a tube is given by Poiseuille’s law:

$$P = V' \cdot (8\eta l / \pi r^4)$$

$P = \text{pressure}$, $V' = \text{flow}$, $l = \text{length}$, $r = \text{radius}$ of the tube, $\eta = \text{viscosity}$ of the gas.
Viscosity of air is low (0.000181 poise). Because resistance = pressure/flow, it is clear that the most important determinant of resistance in small airways is the radius raised to the fourth power in the denominator of the equation.

Flow limitation

Expiratory flows are limited throughout most of the forced expiratory manoeuvre11-13. Above a certain expiratory effort expiratory flow is independent of the applied pleural pressure. During forced expiration, the driving pressure for air flow is determined by the sum of elastic lung recoil pressure and actively applied pleural pressure. As the actively applied pressure is also applied to the airway walls it is only the elastic recoil pressure at any lung volume that allows pressure inside the airways to be higher than that outside the airways. During forced expiration flow-related frictional and convective accelerative intrabronchial pressure losses occur. At some point along the airways from the alveoli to the mouth, the flow-related pressure losses will equal the lung elastic recoil pressure and the difference between the intrabronchial and extrabronchial pressures will be zero. This point is called the equal pressure point (EPP)(Figure 3). Downstream, i.e. mouthward from this point airways are compressed by the pressure surrounding the airway wall which will be greater than the decreasing intrabronchial pressure, thus leading to dynamic compression of the airway lumen.

Following this theory, MEFV measurements can be considered the blue print of the mechanical properties of the lung parenchyma and airways and explains the high reproducibility within one subject of the MEFV curve. The shape of the MEFV curve is determined by the variable site of the flow limiting segment. This site is normally located in the central intrathoracic airways14-16, especially the lobar and segmental airways17,18 during forced expiration and does not move beyond the subsegmental airways19.
The force generated by the respiratory muscles must overcome the total respiratory resistance ($R_{rs}$), consisting of resistances of the lung ($R_L$) and chest wall ($R_{cw}$) and the resistance to gas flow through the airways ($R_{aw}$).

$$R_{rs} = R_{cw} + R_L + R_{aw}.$$ 

The contribution of $R_{cw}$ and $R_L$ to $R_{rs}$ is not completely clear. In adults and older children $R_{cw}$ and $R_L$ represent only 10-20% of $R_{rs}$. Polgar and String reported that in newborns $R_L$ averaged 24% of $R_{rs}$, almost twice that in adults, but other investigators found almost identical values for $R_{aw}$ and $R_{rs}$, so only small contributions of $R_{cw}$ and $R_L$. Largely because of different techniques of measurement, absolute values for resistance in infants and children remain unsettled and values in different age groups can hardly be compared.

The upper airway

The upper airway consists of the passages between airway opening and larynx. Normally this is the nasal passage (from nostrils to the posterior ending of the nasal septum), the nasopharynx (from end of nasal septum to lower border of the palatum molle) and the pharynx (from soft palate to glottis). When breathing orally, it also includes the mouth. Breathing through the nose causes much greater resistance than breathing through the mouth. There are important anatomic features that have to be considered in the phase of gas transport through the upper airways. The axis of the nose to that of the trachea is 90%. Cross sectional area of the airways increase from anterior nares, containing hairs to large turbinated airways, than decreases again in the nasopharynx and the rest of the airways. The nose accounts for 50% of total respiratory resistance, although there is marked variation among subjects and the contribution is less in children than in adults. Most of this is accounted for by the first 2 cm of the nasal passage. Under normal conditions 15-50% of airway resistance is accounted for by oral cavity, pharynx and larynx. The individual contribution of these three elements was studied by Schiratzky in 1965. She found that the larynx
accounts for 25% of the total airway resistance and oral cavity for 30% \(^7\). Similar findings were presented by Pressman and Kelemen \(^8\). These results show that especially the angulation of the airway results in decreased air transport capacity.

Several studies showed that the orifice between the vocal cords represents an important resistance to air flow and significantly influences total airway resistance \(^25,29,30\). Vocal cords move apart during inspiration and close somewhat during expiration \(^31\). During panting the glottis stays wide open \(^32\). This technique is used when performing body plethysmography.

Stanescu et al. found significant correlations between glottis opening, lung volume and flow rate. The variation of glottis opening with lung volume was larger during expiration. The glottis opening was greater during panting than during tidal breathing. As a result airway resistance (from the glottis) was smaller during panting at comparable lung volumes. This indicates that, to reduce the influence of the glottis during airway resistance measurement, panting is a suitable method \(^33\).

The cricothyroid muscle is especially active during inspiration, contributes to vocal cord abduction and thereby causes the airway to open \(^34\).

Infants are believed to be obligatory nasal breathers \(^35\). Indeed, when both nose and mouth are open infants, but also most older subjects are exclusively nasal breathers \(^36\). However research by Rodenstein et al showed that during nasal obstruction tight apposition of the soft palate and tongue occurs, but that after a mean of 8 (range 1-30) seconds oral breathing was initiated. The older and more awake the child, the earlier switch to oral breathing occurred. This switch occurred by detaching the soft palate from the tongue \(^37\). So, infants, children and adults only prefer nasal breathing but at all ages oral breathing is possible.

When the temperature of inspired air falls below 7° C there is a marked rise in resistance caused by vascular engorgement. Also changes in body posture alter resistance through hydrostatic effects on vasculature. Going from vertical to horizontal position increases resistance. Resistance through both nasal passage is not similar and varies in 3-4 hour cycles.

The pharynx is the most compliant region of the upper airways and negative pressures tend to collapse the airway. This is prevented by the tone of the airway muscles, but can cause tremendous resistance in subjects with anatomic abnormalities or muscle dysfunction or during REM sleep. Even minimal mucosal thickening in the nose or mild oedema of the larynx
or trachea in infants may cause significant increases in resistance. Both the measurement and the degree of airflow resistance is influenced by the breathing pattern. During spontaneous breathing 80-90% of breathing of most people is nasal\textsuperscript{38,39}. Only during exercise they shift to oral breathing and at maximal exercise about 60% of breathing is orally. However some people show combined oronasal breathing and few people persist nasal breathing even at maximal exercise\textsuperscript{40}. During oronasal breathing inspiratory nasal airflow is greater than expiratory nasal airflow. Using a mouth piece will wedge open the mouth and this will influence oral airflow resistance values. Probably respirologists have obtained falsely low oral resistance values using mouthpieces. The opening of the lips and the position of the tongue against the palate will influence airflow obstruction. If nasal airflow increases there is more turbulent flow with exponential increase in airflow resistance\textsuperscript{41}.

The lower airways

The diameter of the lower airways is caused by a balance of forces distending and forces narrowing the airway. Narrowing forces are bronchial smooth muscle contraction, mediated by efferent autonomic nerve control. Sympathetic impulses relax, parasympathetic impulses constrict these muscles. Constriction can also develop as a reflex caused by irritants (dust, smoke, cold), hyperventilation, embolisation of vessels and some vaso-active agents (acetylcholine, histamine, bradykinine). Airways dilation may occur as a reflex to increased blood pressure (baroreceptors in carotid sinus) and sympathomimetic agents (epinephrine, isoproterenol).

Airway resistance is lung volume dependent and increases when lung volume decreases from functional residual volume (FRC) and approaches infinity at residual volume. It is especially the decrease in lung elastic recoil that is responsible for this increase. This recoil provides a tethering effect tending to increase airway diameter. Thus older children with bigger lungs have increased elastic recoil and thereby lower airway resistance. That’s why the measurement of airway resistance and it’s reciprocal airway conductance are normally corrected for lung volume. The resultant is the specific airway resistance ($sR_{aw}$) or conductance ($sG_{aw}$), which is remarkably constant regardless of age or height.
An extra narrowing force to airways exists during forced expiration, when there is dynamic airway compression caused by pleural and peribronchial pressures. This effect is counteracted by the intraluminal pressure and the tethering action of the surrounding lung (Figure 3).

Small airways

The contribution of small airways (< 2 mm diameter) to total resistance in adults is only some 20%, caused by the very vast number of small peripheral airways, providing a large cross sectional area for flow. That is why small airway disease may severely impair ventilation of distal air spaces but go undetected by total airway resistance measurement. However, in children small peripheral airways may contribute up to 50% of the total airway resistance. This proportion does not decrease until about 5 years of age. This increases the value of resistance measurements in small children, who can be severely affected by small airway diseases (e.g. bronchiolitis).
3. The influence of growth and development on airway mechanics

Developmental anatomy and physiology of the respiratory system

The respiratory system is in a continuous process of development from early embryonic stages to young adulthood. As with height and weight, children show a constant and rapid growth of lung volume and lung function parameters. This growth however shows a wide variety within and between individuals. Therefore normal values of pulmonary function parameters are often presented as referenced by standing height, sex and sometimes weight. However also age, arm-span, body composition, sitting height and even ethnicity influence lung function parameters. Some steps in the development of the lung that bear particularly influence on lung function during (early) childhood and on the pattern of respiratory disease are discussed below.

Respiratory system development

In humans the lungs begin to form at 21-24 days of gestation as a bud of the primitive foregut. During the first, i.e. pseudoglandular phase this process evolves rapidly resulting in complete formation of all the airways through the terminal bronchioles by week 16 of gestation. This branching process of the airways is more or less dichotomous. Only then the first gas-exchanging units are formed (canalicular phase). From 26 weeks, during the final or alveolar (or terminal sac) phase lungs prepare for gas exchange by formation and growth of type II pneumocytes, secreting surfactant. About 50 million alveoli are present at birth in a term infant. After birth new alveolar formation is thought to continue especially until 2, but probably even until 7 years of age. At this stage the number of alveoli has increased to about 300 million. From then alveoli only grow by enlargement. Airways continue to grow in length and diameter with remodelling of the peripheral airways from week 16 of gestation, but do not increase in number.

Postnatal growth of the airways has been studied in only a limited number of anatomic investigations. One study describes the infant’s airway as a
miniature of the adult one, but another study suggests that peripheral airways increase in size relative to the central airways after the fifth year of life.

Smooth muscle is present in the airways of the foetus early in development and extends from the trachea to the alveolar ducts in newborns as in adults. Smooth muscle content appears to remain relatively constant in airways of a given generation and mechanisms controlling airway tone in the neonate are comparable to the adult. Cartilage is present in the bronchi at about 25 weeks of gestation and its distribution is similar to that of adults. Increased cartilage develops in the first years of life, thereby contributing to the stiffening of the airways observed in the first months of postnatal life.

Although collagen and elastin are important in airway morphogenesis and branching, the interstitium of the human lung contains little collagen and elastin during late gestation and at birth. From birth elastin and collagen formation increase. The changing ratio of elastin and collagen probably contributes to the change in volume-pressure relationships in the developing lung. However little is known about the organisation and development of these tissues at various stages of lung growth and in various regions of the lung.

Considerable structural changes occur in the chest wall, particularly during early postnatal life. The ribs, oriented in a horizontal plane, slant in a progressively caudal direction to the downward slope seen in adults. Also the ossification of ribs, sternum and vertebrae and muscle mass development contribute to changing volume pressure relationships during childhood. In adults, the functional residual capacity (FRC) is mainly set passively by the balance between elastic recoil of the lungs and chest wall. However in newborns the high compliance of the chest wall would cause nearly complete collapse of the lungs, if not actively counteracted by glottic narrowing or interruption by the onset of inspiration. Probably, the major function of the Hering Breuer reflex in young children might be the termination of the expiratory process before lung volume gets too small. Once the chest wall has become stiff enough to counteract elastic recoil of the lungs, this reflex is reduced and may disappear from the age of 1 year. Then passive characteristics appear to determine end-expiratory lung volumes. The easy collapsibility of the rib cage is advantageous in utero to prevent pleural effusion and during birth, when it allows deformation of the chest during passage of the birth canal and expulsion of fluid before the first breath. After birth it diminishes metabolic demands but a decrease in collapsibility is nec-
necessary to decrease the need for outward recoil of the lung, necessary to maintain lung volume.

Respiratory function development

It may not be surprising that the remarkable change of respiratory structures also has significant functional implications. Lung volume and volume-pressure relationships (e.g. pulmonary compliance) reflect parenchymal (air space) development, and airflows and pressure-flow relationships (resistances and conductances) reflect airway development. But the relationships are not as direct as they might seem.

Figure 4. Deflation volume-pressure curves of the lung at different ages (obtained from studies on excised lungs). With increasing age up to young adulthood the curves become straighter and at a given lung volume elastic recoil pressure is greater. The curve from elderly subjects resembles that from a 7 year old.
Pulmonary compliance depends on the number of air spaces expanded, the size and geometry of the air spaces, the characteristics of the surface lining layer and the properties of the lung parenchyma that change with growth and maturation. This is represented by changes in the shape of the volume-pressure curve. These curves, when normalised by expressing volumes as the percentage of the maximal observed lung volume, are more curvilinear in infants than in older children (Figure 4).

This reflects immature air spaces rather than mature alveoli and probably the differences in elastin-collagen ratio with age. The lung volume at which airway closure occurs is higher in younger children (7 years) and elderly adults than in older children and younger adults. In infants higher collapsibility is illustrated by atelectasis in dependent regions.

The configuration of the relationship of maximal expiratory flow and lung volume (maximal expiratory flow-volume (MEFV) curve) is similar in the child and in the elderly; in both age groups there is linearity of F-V curves compared to younger adults, compatible with decreased elastic recoil. Pressure-volume relationships of the total respiratory system show comparable developments as those of the lung in young children in that they are more curvilinear in infants. However in 2-16 year children the shape of these curves is constant. This means that there is a constant relationship between the increasing elastic recoil of the lung and the increasing recoil of the chest wall. Overall the total respiratory system becomes stiffer with increasing age, especially in children under 5 years of age.

Chest wall compliance corrected for body (i.e. also lung) size is 50% greater in infants under 1 year compared to infants over 1 year of age. In infants chest wall compliance is threefold greater than lung compliance but in older children and adults these values are virtually equal.

The changes in resistance of airways, lungs and total respiratory system are substantially but also variably influenced by the upper airway resistance, notably from the glottis. Although in adults this may comprise over 50% of measured resistance, studies by Hogg et al, who partitioned airway resistance by means of a retrograde catheter technique into central and peripheral components, showed that in children up to 5 years of age the contribution of peripheral airways to respiratory resistance is greater than in adults. This increases the usefulness of resistance measurements in children, especially during small airway disease. On the other hand it diminishes the usability of this parameter to reflect changes during development of normal subjects. This also affirms that the infant’s tracheobronchial tree is
not simply a miniature of the adult one\textsuperscript{48}, but that the contribution of peripheral airways to the total changes with age. Data on compliance and resistance collected in children 3 weeks to 15 years of age support the relatively greater increase in lung parenchymal growth relative to airway growth throughout childhood\textsuperscript{65}. Although the increase in total alveolar content increases the absolute compliance, the changes in shape of the volume pressure curve suggests that to some extent maturation makes the lung relatively stiffer. Indeed with increase of parenchymal volume relative to airways, there is a decrease in specific conductance and rate of lung emptying.

In daily practice, however, individual variability in airway size and lung volume are probably more important indicators of lung disease than maturational changes. Some studies found indications of inter-individual differences in the interaction between parenchyma and airway growth\textsuperscript{66,67}, which is presumably genetically determined. There is increasing epidemiological evidence that diseases in early childhood, e.g. wheezing with lower respiratory infections, is linked to physiologic indicators of lung and airway size, already established in early infancy\textsuperscript{68-70}.

4. Techniques for the measurement of resistance in spontaneously breathing young children

It is important to realise that several measures or resistance are used in daily practice. Several techniques measure different kinds of resistance, that are not completely interchangeable. Specific techniques have been developed for measurement of $R_{aw}$, total pulmonary resistance ($R_{tot} = R_L + R_{aw}$) and active or passive respiratory system resistance ($R_{rs} = R_{aw} + R_L + R_{cw}$) (Table 1).

During measurement of resistance, pressure is measured at the two endings of an open tube, in case of the lungs at the mouth and at the alveoli and corresponding flow is recorded. Measurement of alveolar pressure is difficult. With most techniques pressure and flow are measured at the mouth and alveolar pressure can be measured at the mouth after airway occlusion when equilibration of alveolar and mouth pressure occurs.
A. Respiratory system resistance (Rrs)

Respiratory system resistance (Rrs) can be measured, using active and passive techniques.

1. Active measurement: active breathing against occlusion

Measurements of active Rrs can be performed in infants during quiet breathing under sedation or spontaneous sleep. Simultaneously airway pressure, volume and air flow are measured. After a normal breath the airway is occluded at end expiration. During the following occluded inspiratory effort, repetitive measurements of pressure can be related to flow and volume measured during the preceding breath. From these relations elastance E, compliance C (i.e. 1/E) and resistance Rrs can be calculated. Inspiratory resistance measured in this way represents about 70% of expiratory resistance during infancy.

2. Passive measurements: airway occlusion, oscillation and interrupter techniques

2.a. The airway occlusion technique

The basis of the airway occlusion technique is that after airway occlusion at end-inspiration the Hering Breuer reflex causes apnoea, both inspiratory

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Table 1. Measurement of resistance in humans. Techniques that are possible in spontaneously breathing pre-school children are presented in bold, techniques possible in infants in italics.

<table>
<thead>
<tr>
<th>Respiratory system resistance</th>
<th>Total pulmonary resistance</th>
<th>Airway resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_{rs} = R_L + R_{aw} + R_{cw} )</td>
<td>( R_{tot} = R_L + R_{aw} )</td>
<td>( R_{aw} )</td>
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*Active breathing against occlusion*

*Airway occlusion technique*

| Intra-oesophageal balloon | Body plethysmography |

Forced oscillation technique (FOT)

Impulse oscillation technique (IOS)

Interrupter technique
and expiratory respiratory muscles relax and a passive expiratory flow-volume curve can be analysed after release of the occlusion. Also in children and adults changes in the mechanical properties of the lungs and thorax can be demonstrated by the measurement upon purely passive expiration curves. This, however is only possible under complete apnoea, inflating the lung to a known alveolar pressure and than permitting deflation by elastic recoil only. During this expiration the pressure of recoil is approximately proportional to lung volume added to FRC. Flow will only be retarded by frictional resistance, lung tissue resistance to movement and the pressure required to overcome inertia. Flow decreases with time during expiration. Inertia is negligible.

In the single breath occlusion technique (Figure 5), the airway is occluded at end inspiration, with the subsequent expiration occurring passively. A passive expiratory flow volume curve is then constructed. The slope of the linear part of the passive flow volume curve is equal to the reciprocal of the

![Figure 5. Calculation of the respiratory compliance (Crs) and resistance (Rrs) using the single breath occlusion technique. Paoocc airway opening pressure following occlusion; Pao pressure at the airway opening; τrs expiratory time constant.](image-url)
time constant of the respiratory system ($\tau_{rs}$) during expiration. Respiratory system resistance ($R_{rs}$) can be calculated by dividing $\tau_{rs}$ by $C_{rs}$.

In the multiple breath occlusion technique (Figure 6) pressure is measured at the mouth during brief airway occlusions performed on multiple breaths, at different volumes above FRC and the individual measurements are plotted as volume vs. pressure. The slope of the line of “best fit” is the compliance of the respiratory system.

\[
\text{Slope} = \frac{V_{occ}}{P_{ao}} = C_{rs}
\]

Figure 6. Calculation of compliance of the respiratory system using the multiple-breath occlusion technique. $V_{occ}$ volume at which occlusion is made, $P$ pressure, $P_{ao}$ pressure at the airway opening, $C_{rs}$ compliance of the respiratory system.

2.b. Oscillation techniques

2.b.1. Forced oscillation technique (FOT)
Total pulmonary resistance can be measured in infants and children by the forced oscillation technique. This measurement includes tissue viscous resistance of lungs and chest wall. A sinusoidal pressure applied at the upper airways changes the airflow and resistance can be calculated. When the forced oscillations are applied at the so-called resonance frequency of the
lung (5-7 Hz in children\textsuperscript{73}), it is assumed that the force, required to overcome elastic resistance of the lung and the force required to overcome inertia are equal and opposite.

The forced oscillation technique (FOT) was introduced by Dubois et al\textsuperscript{74}, to characterise respiratory impedance (Z\textsubscript{rs}) and its two components reactance (X\textsubscript{rs}) and resistance (R\textsubscript{rs}) over a wide range of frequencies\textsuperscript{75}.

The general set up of the oscillation system is shown in figure 7. Flow oscillations, generated by means of a loud speaker are applied at the subject’s mouth and superimposed on normal breathing (Figure 8). A large bore impedance tube directs the oscillations to the patient without offering any resistance to spontaneous breathing. Fresh air bias flow prevents rebreathing of the expire.

The driving pressure, either sinusoidal (single frequency) or composite (multiple frequencies), results in flow oscillations, the magnitude and phase of which are determined by the resistive, elastic and inertial properties of the respiratory system (Figure 9). The resulting pressure and flow signals are recorded at the mouth using a pressure transducer and a pneumotachometer and analysed. These signals are, in general, waveforms containing several frequencies. For each of these frequencies, the ratio of pressure to flow can be considered (i.e. the impedance), which is a complex number of the magnitude of pressure to flow and about the phase shift between these sig-
Most often this complex number is represented by its real part, the respiratory resistance \((R_{rs})\) and its imaginary part, the respiratory reactance \((X_{rs})\).76-79

With the random noise or pseudo random noise method oscillations of different frequencies are analysed and frequency dependency of resistance and reactance can be found.76,80 Microprocessor techniques allow analysis of the complex signals by Fourier transformation.80-82

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**Figure 8.** General principle of FOT and IOS. A wave form pressure signal causes flow changes superimposed on the tidal breathing pattern.

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**Figure 9.** A sinusoidal pressure wave causes a flow wave that is analysed using Fourier analysis. From the relationship of pressure and flow changes resistance \((R)\) and reactance \((X)\) can be calculated.
In children and obstructive patients the resistance is frequency dependent, with higher $R_{rs}$ at lower frequencies. The fact that during inspiration the vocal cords are more open than during expiration makes measurements, obtained during inspiration more appropriate. From clinical studies it appears that $R_{rs}$ at low frequencies allows the best discrimination between healthy subjects and various obstructive conditions. $X_{rs}$ is mainly determined by the elastic and mass-inertial properties of the airways, lung tissue and chest wall. At low frequencies the elastic properties dominate (negative $X_{rs}$), at higher frequencies the mass-inertial forces take over (positive $X_{rs}$). The frequency at which $X_{rs}$ crosses zero is called the resonance frequency (RF). In obstructive airway disease $X_{rs}$ deviates to more negative values and therefore the RF will be reached at higher frequencies. Both the $X_{rs}$ and RF are useful indices in establishing positive reactions to provocation tests.

The estimation of $R_{rs}$ and $X_{rs}$ can be made in several ways but, in principle, the two are determined by the amplitude and the phase of mouth pressure and flow at a given frequency. In the multiple frequency technique the use of Fourier transformation algorithm enables the assessment of the frequency dependency of $R_{rs}$.

2.b.2. The impulse oscillation technique (IOS)

An alternative method for FOT uses an impulse oscillation system (IOS, 5-35 Hz). In this technique an impulse (a rectangular wave form), rather than a pseudorandom noise signal (a mixture of several sinusoidal wave forms) is applied by a loud speaker. Also the data processing and analysis (the so called Fourier analysis) is different.

There are recommendations for measurement of respiratory input impedance by means of forced oscillations but the IOS technique has not been standardised against the recommendations stated in this publication.

2.c The interrupter technique (Rint)

The interrupter technique is a non-invasive method to measure airflow resistance. It was first described by Von Neergaard and Wirz in 1927. During sudden occlusion of the airway pressure changes at the mouth. The interrupter technique is based on the premise that, during this transient interruption of the tidal airflow, alveolar pressure and mouth pressure equilibrate within a few milliseconds. The alveolar pressure can therefore be derived from the measurement at the mouth immediately after interruption. If the flow is measured immediately prior to interruption, the ratio of flow to pressure changes gives the interrupter resistance (Rint). Difficulties
in interpreting the post-occlusion pressure tracing has delayed the further introduction of this technique and until recently the interrupter technique has never been widely accepted as a clinical tool. Also other technical considerations (e.g. the discussion if post-occlusion flows instead of pre-occlusion flows should be used) have delayed general acceptance. However, recent studies have unravelled the factors which influence the post-occlusion mouth pressure tracing and the physiologic basis of this technique. Also the introduction of a small portable device to measure interrupter resistance has caused a revival of the interrupter method technique.

When the airway is occluded at the mouth airflow ceases and there is an initial large and rapid increase in mouth pressure succeeded by a smaller and more gradual one (Figure 10). Approximately 5 msec after actuation of the valve, closure is complete. The initial change in flow is caused by the rapid equilibration of alveolar and mouth pressure. This is due primarily to mouth pressure jumping to meet pre-occlusion alveolar pressure. However, alveolar pressure changes immediately after occlusion due to transference of chest wall pressure. In paralysed subjects the second pressure change is caused by stress relaxation of the lung tissue and chest wall. If this is the case in awake spontaneously breathing humans is not known but the influence of respiratory muscles is probably less during expiration compared to inspiration. However, other authors suggested the use of inspiratory values to minimise the influence of glottic aperture.

During brief interruption of airflow the estimate of mouth pressure (Pm0) is more influenced by glottic resistance during expiration than during inspiration.

The time course of the post-occlusion pressure tracing is influenced by the compliance of the upper airways (especially cheeks) and gas in the lungs, the resistance of the airways and the inertia of the system. Both increased airway resistance and upper airway compliance prolong the equilibration time from about 40 msec in normals up to >100 msec. Most devices use interruption times of 100 msec. Only after 150–250 msec active breathing against the occluded valve occurs. Back-extrapolation of the post-occlusion pressure tracing to the time of valve closing is considered by most authors to be the best method to approximate the resistive pressure drop across the airways at the time of interruption. For this the pressure trace between 40 and 80 msec or 30 and 70 msec are advised (Figure 10). This is late enough to allow equilibration of mouth and alveolar pressure in most patients and early enough to prevent active breathing against the valve.
B. Total pulmonary resistance ($R_{tot}$)

Oesophageal balloon

Before the introduction of the bodyplethysmograph in 1956 total lung resistance measurement was only performed in specialised centres, using oesophageal balloons to measure transpulmonary pressure. $R_{tot}$ can be measured by placement of an intra-oesophageal balloon or catheter. Oesophageal pressure is related to flow changes at midtidal lung volumes. A balloon is positioned in the distal part of the oesophagus. During tidal breathing pressure and volume changes can be measured and from these compliance and resistance can be calculated. This technique is of course not useful in general practice, but is frequently used in animal studies. It is assumed that elastic forces are equal but opposite at points of equal volume during inspiration and expiration. $R_{tot}$ is conventionally calculated at the midtidal volume points during inspiration and expiration by dividing differences in oesophageal pressure at those points by the corresponding absolute difference between the in- and expiratory flow (Figure 11).

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Figure 10. Interrupter resistance. During tidal breathing short interruption of airflow ($V'$) causes changes in respiratory system pressure that can be measured at the mouth ($P_{mo}$). $P_{mo}$ is computed by back-extrapolating a line drawn through two points, centered at 30 and 70 msec (which are blocked averages of pressure during 10 ms) to the point at 15 msec from start of occlusion ($t = 0$).
Airway resistance ($R_{aw}$) in both adults and older children is most commonly measured using body plethysmography. The method is based on the assumption that when a shutter occludes the tube airflow ceases and the mouth pressure equilibrates to alveolar pressure. At BTPS conditions $R_{aw}$ can be determined from the difference between alveolar pressure ($P_{alv}$) and airway opening pressure ($P_{ao}$), divided by airflow ($V'$).

A sitting person in an airtight box breathes spontaneously through a tube connected to a pneumotachometer, measuring airflow ($V'$) and plethysmographic pressure ($P_{box}$). Simultaneous changes in $V'$ and $P_{box}$ are recorded on an x-y oscilloscope and the slope of this relationship is recorded ($V'/P_{box}$). After occlusion of the airway changes in volume (recorded from $P_{box}$) and mouth pressure ($P_{m}$, which reflects $P_{alv}$) are monitored. Provided that the ratio of lung volume to plethysmographic gas volume remains constant, the $P_{alv}$ corresponding to a given $P_{box}$ remains constant whether or not flow is interrupted. Thus derivation of $R_{aw}$ is obtained by dividing the slope of $P_{m}/P_{box}$ by the slope of $V'/P_{box}$.
\[ \text{R}_{aw} = \text{dPalv}/V' = \text{dPm}/V' = (\text{dPm}/\text{dPbox})/V'/\text{dPbox} \]

Higher lung volumes show lower resistance. Because this technique measures resistance and volume simultaneously resistance can be related to lung volume and specific airway resistance (\(sR_{aw}\)) or its reciprocal conductance (\(sG_{aw}\)) can be calculated. Airway conductance (\(G_{aw}\)) is linearly correlated to lung volume (\(sG_{aw} = G_{aw}/\text{FRC}\)) and is therefore regularly determined in older children and adults (Figure 12).

Plethysmographic measurements of resistance are dependent on the assumption that pleural pressures are homogeneously applied to all lung fields. If not, the Pm does not reflect Palv.

The plethysmograph is recording volume changes of intrathoracic gas. In a closed system pressure changes in the airways caused by in- and expiratory movements lead to volume changes in the airways.

Compared to spontaneous breathing during panting higher frequencies and higher flows are applied. Both methods gave similar values in healthy subjects\(^{100}\), but in patients with obstructive airway disease higher values were found during spontaneous breathing. However other investigators found slightly increased values during panting\(^{101}\). During panting the glottis will open (decreased resistance), there may be turbulent flow during panting in obstructive patients (increased resistance) and there is higher breathing frequency (lower resistance). The total sum of these factors will determine if resistance during panting is higher or lower.

Important issues in the interpretation of airway resistance measured by body plethysmography are:

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Figure 12. The relationship of airway conductance (\(G_{aw}\)) and resistance (\(R_{aw}\)) with lung volume (\(V\)).
1. This $R_{aw}$ represents especially resistance of extrathoracic and central airways and hardly peripheral airways.
2. Panting is especially difficult for children and the closing of the flow pressure loop performed to calculate resistance impairs the reliability of results.
3. Laminar versus turbulent flow at different lung volumes impairs the applicability of this technique in patients with high airway resistance.
4. The difference between inspiratory and expiratory flow pressure curves impairs reliability of this technique. Especially in patients with high airway resistance the expiratory loop is irregular.

5. Feasibility of different techniques to measure airway mechanics in children

During pulmonary function measurement in young children no active co-operation nor co-ordination may be expected. Also only testing during spontaneous breathing allows for application of the technique in all day practice. The minimal age above which these measurements are possible depends especially on the ability to passive co-operation. This may vary in individual children.

Obtaining lung function measurements in young children presents a great challenge and very rarely produces reliable results when conventional methods are used. That’s why all possible disturbances that influence reliability should be kept to a minimum. Co-operation of the children can only be optimal, not perfect. Instruction to the child has to be made as simple as possible in a positive encouraging atmosphere, because real passive co-operation is essential for reliable and reproducible measurements. The child is sitting upright and, if possible, a mouthpiece and nose clip are used. Only in the smallest children tight fitting face masks should be used.

Several studies evaluated applicability of pulmonary function tests in young children. A summary of these studies is presented, together with important technical considerations.
Rrs measurements

1. Active measurement

This technique has only been applied in infants, not in older children. In adults it was only studied under halothane anaesthesia.

2. Passive measurement

2.a. Airway occlusion technique

This technique depends on the Hering Breuer reflex. Therefore it is possible in infants but very difficult in older children who lack this reflex and will normally react to airway occlusion with active counteracting by trying to “blow away the occlusion”. Considerable training is needed for older children to relax their respiratory muscles, in order to obtain quasi static pressure volume curves. These methods are only applicable when a linear expiratory flow-volume relation is obtained, i.e. when \( \tau_{rs} \) is constant. In obstructed airway disease curvilinear flow-volume relations demonstrate significant heterogeneity of \( \tau_{rs} \). In these children the interpretation of results is hampered if not impossible.

2.b. Oscillation techniques

This method can be used in children from 3 yrs of age onwards\(^3,75,102\). The use of forced oscillation in children has been limited by some practical problems encountered when applying this technique and by the lack of user-friendly commercially available equipment. Major technical problems are caused by the interference of applied oscillations with spontaneous breathing, by air leak around the mask or mouthpiece and by upper airway compliance. The breathing frequency causes loss of coherence from the forcing function, which means that no useful data are obtained at frequencies below 4 Hz. Air leak results in overestimation of resistance because mouthpiece or masks acts as an extra resistance parallel with the respiratory system. This air leak occurs especially in obstructed patients. Compliance of the upper airways acts as a shunt compliance in parallel with the respiratory system. Especially at higher frequencies this causes shunting of the applied forces and overestimation of resistance and underestimation of inertance (higher resonance frequency). Here again airway obstruction increases this confounding. The cheeks and floor of the mouth should be supported by an assistant, but variation in this support will enable variable results.
In infants the usefulness of this technique is further reduced by the fact that there is considerable variation of $R_{aw}$ during the respiratory cycle and there is no international standardisation of the technique as is in older children and adults, in whom measurements are standardised to a flow rate of 0.5 L/sec.

Therefore it is not unexpected that Phagoo et al, but also other investigators, found that the forced oscillation technique is a rather unreliable method to find bronchial responsiveness to challenge with methacholine. This method combines great baseline variability with low sensitivity and unsustained increase in $R_{aw}$ with rising obstruction4103-106. This is especially caused by the need to breath against the oscillating column of air, the mandatory length of quiet breathing, consistent breathing required to obtain a measurement and the importance of maintaining a consistently patent upper airway.

2.c. Interrupter technique

Feasibility studies were performed recently and reported in several publications. Our study on feasibility is discussed in chapter 6 of this thesis. The resistance measurements obtained in awake spontaneously breathing children are only a gross approximation of airway resistance. There are many variables that can affect the final value obtained with the interrupter technique, e.g. air leak around mask or mouth piece, compliance of the cheeks, airflow rate at interruption, lung volume at the time of interruption, the time and point in the respiratory cycle of flow interruption, the type of interrupter device and especially criteria for selecting and back-extrapolating the post-occlusion pressure tracing to the time of valve closing. The ideal interrupter device should have a solid state piezoresistive pressure transducer. Shutter closure must be as rapid as possible to prevent air leak during closure107. Most young children prefer the face mask108. Dead space of the device should be as small as possible and the compliance of the upper airways must be minimised by applying gentle support to the cheeks. This decreases equilibration time significantly. The effect of uncontrolled tongue position and mouth movements, variation in glottic aperture, head or neck movements should be prevented as much as possible.

After comparison of several different ways of back extrapolation of post-occlusion mouth pressure tracings, a linear back extrapolation was the least variable and most sensitive in children and is recommended for standard use103 although a comparable study by the same authors in adults showed that a smooth curvilinear back extrapolation was the most sensitive in
adults\textsuperscript{109}. Also the number of interruptions averaged, the criteria for rejecting individual post-occlusion pressure curves and software used for analysis are not yet standardised. It should be possible to define the precise flow at which valve closure occurs. There is hardly any quality control for interrupter devices. There should be a possibility to store and display pressure and flow curves. Acceptance criteria for these curves should be defined and standardised.

Carter stated in 1997 that, after standardisation, evaluation of normal values, reproducibility and standard differences we will really know the $R_{\text{int}}$ its ultimate clinical potentials\textsuperscript{110}. Technical considerations as mentioned above and the moment of airway occlusion in the respiratory cycle were recently studied by an ERS working group. Only after standardisation of these factors application in daily practice can be advised.

A study by Sly et al. showed the applicability in infants\textsuperscript{111}. Several studies have evaluated the applicability in (pre) school children\textsuperscript{85,112-114}. In 3–12 year old children, both normal and diseased, the technique proved to be applicable\textsuperscript{89}. Both children and parents prefer this technique to the forced expiration technique. Changes in airway obstruction could be assessed, caused both by disease and by pharmaceutical intervention\textsuperscript{85,112-115}.

Feasibility defined as the ability to complete two measurements 15 minutes apart, before and after bronchodilation was found in 53%, 71% and 91% of 2, 3 and 4 year old wheezy children respectively. The total session took about 25 minutes\textsuperscript{112}. The same authors also found that inter observer variability was rather low, indicating that training of the pulmonary function technician should not be difficult.

Merkus et al. found no problems in applying the interrupter technique in school children with asthma and CF\textsuperscript{116}.

Phagoo applied the technique without problems in 3 year old children after some practice\textsuperscript{117}, but in infants with a history of wheeze Chavasse et al. could only apply the technique in 15 out of 26 patients, partly because of low flows that failed to trigger the interrupter valve\textsuperscript{118}.

Total pulmonary resistance ($R_{\text{tot}}$)

\textbf{Oesophageal balloon}

For the measurement of pulmonary resistance using oesophageal balloons subjects should voluntarily undergo balloon introduction through nose and
throat. Active co-operation is required unless the procedure is performed under anaesthesia. These premises do not allow wide spread use of the technique, especially not in children. Therefore this technique is not used in daily practice.

**Airway resistance (R_{aw})**

**Bodyplethysmography**

Body plethysmography is routinely possible in most pulmonary function laboratories. This method requires a complex equipment and is time consuming\textsuperscript{119}. The specific technical requirements and the expensive equipment limit the use of this technique to specialised laboratories. This technique can be used in younger children but requires sedation. Recently bodyplethysmographic measurements were also applied and validated in children accompanied by an adult during bodybox measurements\textsuperscript{120}. Nowadays, after many years of clinical experience this technique has been technically adapted, so that the actual measurement has become relatively easy for the pulmonary function technician.

Bodyplethysmography has several limitations when applied in young children. Young children have a tendency not to blow against a closed valve, restricting volume measurement and thereby resulting in unreliable measurements with increased intra-individual variability\textsuperscript{121}.

### 6. Reference values

**Respiratory system resistance (R_{rs})**

1. **Active measurements**

This approach has only been applied to infants. The mean (±SD)value of R_{rs} in a group of healthy neonates averaged 45 ± 21.6 cm H\textsubscript{2}O/(L/s). These values are comparable to the estimated passive inspiratory R_{rs} in the same infants\textsuperscript{122}. 
2. Passive measurements

2.a. Airway occlusion technique

The mean (+SD) values of $R_n$ reported in a group of healthy newborns amounted to $58.7 \pm 27.0$ cm H$_2$O/(L/s) (121). It is assumed that inspiratory resistance represents approximately 70% of expiratory resistance during infancy71.

Table 2. Reference values of $R_{aw}$ and $R_n$.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Ref.</th>
<th>sex</th>
<th>age</th>
<th>Regression equation</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>plethysmography</td>
<td>122</td>
<td>M/F</td>
<td>4-18</td>
<td>$R_{aw} = 1.660 \times 10^{-3} H^{-1}$</td>
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<td></td>
<td>121</td>
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<td>$R_{aw} = 5.15 \times 10^{-3} H^{-1}$</td>
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<td></td>
<td>124</td>
<td>M/F</td>
<td>0-5</td>
<td>$R_{aw} = (68.205 + 4.109 H) \times 10^{-3}$</td>
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</tr>
<tr>
<td>ocillometry</td>
<td>125</td>
<td>M/F</td>
<td>3-17</td>
<td>$R_n = 10^{0.266 - 0.089 H}$</td>
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<tr>
<td></td>
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<td>$R_n = 2.42 - 1.27 H^{-0.7}$</td>
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<td>3-10</td>
<td>$R_n = 6.79 \times 10^3 H^{-1.93}$</td>
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<td></td>
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<td>$R_n = 2.22 \times 10^5 H^{-2.17}$</td>
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<td>M/F</td>
<td>2-16</td>
<td>$R_n = 9.2 \times 10^{-3} - 34.1 H^{-0.85}$</td>
<td>-0.89</td>
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<td>129</td>
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<td>3-18</td>
<td>$R_n = 13.92 - 0.0635 H$</td>
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<tr>
<td></td>
<td>130,131</td>
<td>M/F</td>
<td>2.25-12.5</td>
<td>For abundant equation see references</td>
<td></td>
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<td>132</td>
<td>M/F</td>
<td>3-17</td>
<td>$R_n = 11.122 - 2.759 \log S$</td>
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<td>3-17</td>
<td>$R_n = 6.221 - 1.547 \log S - 0.040 A$</td>
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<td>$R_n = 6.225 - 1.349 \log H - 0.040 A$</td>
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<td>M/F</td>
<td>3-17</td>
<td>$R_n = 8.705 - 1.945 \log H$</td>
<td>-0.81</td>
</tr>
</tbody>
</table>

$R_{aw} = kPa/L/s$, measured at frequency $x$; $R_{aw} = kPa/L/s$; $sG_{aw} = 1/(kPa.s)$; $sR_{aw} = kPa.s$, $H =$ standing height in cm; $H^*$ = standing height in m; $S =$ sitting height in cm; $A =$ age in years.
No normal values for older children are available. In adulthood, as in infants, similarity between active and passive measurements exists.

2.b. Oscillation techniques and body plethysmography
Several authors have studied FOT and IOS parameters in healthy subjects. Most authors use regression equations for resistance versus height (Table 2). Ducharme among others found that height is the best predictor for total respiratory resistance in children at 8, 12 and 16 Hz. Because standing height is easier measured than sitting height and the latter does not add anything extra, standing height should be considered as the main predictor. In- and expiratory $R_{rs}$ have been shown to be equal. $R_{rs}$ decreases with growth.

2.c. Interrupter technique
Until recently no reference values were reported in literature for Rint. Reference values are subject of chapter 6 of this thesis. In this chapter other recent publications of reference values are discussed.

Reference values have only recently been established for specific age groups. The range is wide and therefore a single measurement in any individual is of limited value.

McKenzie et al presented reference values based on measurements in 48 healthy pre-school children. For the age group 2-5 years they found: logRint = -0.078 x age(yrs) + 0.24. Because height did not better predict Rint the authors preferred age, which is simpler to determine.

Klug and Bisgaard presented reference data for 2-7 year old healthy children, using a face mask. Merkus presented reference values in pre school children using a mouth piece. Lombardi et al presented reference values in pre school children. They used a card board mouth piece and nose clip, valve closure occurred at peak expiratory and peak inspiratory flow, but they did not support the cheeks. Although the latter is generally accepted as essential to minimise the influence of upper airway compliance using this technique, they found no differences between supporting and not supporting the cheeks. Also in contrast to other studies they found no differences between inspiratory and expiratory values. Significant correlations with age, height and weight were found for inspiratory Rint but only height was independently correlated with expiratory Rint.
Total pulmonary resistance ($R_{\text{tot}}$)

Using the approach as described earlier $R_{\text{tot}}$ was found to average 21 (SD 4) to 29 (SD 13 cm H2O/L/sec in healthy newborns\textsuperscript{31}, with similar values found during the first 2 years. When corrected for lung size the specific expiratory conductance was reported to be relatively high in newborns compared to older infants and children\textsuperscript{137}. Conductance values were significantly linearly correlated with height:

$$G_{\text{tot}} = 0.000475 \times \text{height} - 0.0079 \quad (r = 0.937).$$

($G_{\text{tot}}$ in L/(cm H2O.sec), height in cms)

However, despite numerous reports of dynamic lung mechanics in healthy infants and children, none are based on large enough populations of subjects either studied longitudinally or cross sectionally to be considered as reference values.

Airway resistance ($R_{\text{aw}}$)

Reference values derived from bodyplethysmographic measurements of airway resistance are presented in Table 2. Best correlations are found between $R_{\text{aw}}$ and height.

7. Comparison of different techniques

Different techniques to measure resistance consider different aspects of anatomy and physiology of the respiratory system. Therefore direct and perfect correlation between individual techniques can not be expected. Correlations with other measures of pulmonary function such as FEV\textsubscript{1} may be expected to be even worse, because not only other physiology but also other parameters are concerned. The relation of resistance measurements with FEV\textsubscript{1} is discussed in the next paragraph of this chapter. Here several techniques for resistance measurement are compared.
Comparison of oscillation techniques, Rint and body plethysmography

Methodological considerations

With all techniques considering resistance measurement, flow is measured at the mouth, but the location of pressure measurements varies. With body-plethysmography the difference between alveolar pressure and mouth pressure is the driving pressure for flow. Thus the measured resistance represents only airway resistance ($R_{aw}$).

With the oesophageal balloon the pressure difference between mouth and pleura is measured. The measured resistance therefore gives the total lung resistance ($R_{tot}$), composed of both airway resistance ($R_{aw}$) and resistance of lung tissue ($R_{L}$) ($R_{tot} = R_{aw} + R_{L}$)

Both forced oscillation and interrupter technique measure pressure change over airways, lungs and chest wall, i.e. they measure the resistance of the total respiratory system ($R_{rs}$) ($R_{rs} = R_{aw} + R_{L} + R_{cw}$). The indices derived from IOS and FOT are, in principle, comparable.

$R_{rs}$ is expected to be higher than $R_{tot}$ and $R_{aw}$. $R_{int}$ and $R_{5}$ are expected to be comparable.

Studies comparing values in healthy subjects.

In animal studies values of $R_{int}$ were higher than those measured with bodyplethysmography, probably due to a contribution of chest wall rigidity and the glottis to airway resistance\textsuperscript{50,138}. The latter is reduced by the panting manoeuvres performed during bodyplethysmography.

Both interrupter and oscillation techniques measure total respiratory system resistance but the oscillation method can show frequency dependency. With lower frequencies the tissue deformation factor can be distinguished and with higher frequencies the gas inertia factor. In healthy persons the most representative resistance values are found with frequencies around 10 Hz. These values correlate well with those found with the interrupter method\textsuperscript{139}. Hellinckx et al. found resistance and reactance measured by IOS similar but not identical to those provided by the FOT\textsuperscript{140}.

Phangoo et al. showed in their study that the method of back extrapolating post interrupter pressure changes considerably influences the correlation between $R_{aw}$ and $R_{int}$ values. When back extrapolation of the post occlusion pressure was performed from 100 msec post occlusion to mid occlu-
tion pressure, Rint showed good correlation with R\textsubscript{aw}, with other methods Rint significantly exceeded R\textsubscript{aw} measured with bodyplethysmography\textsuperscript{109}. R\textsubscript{rs} determined by the oscillation technique correlates well with airway resistance\textsuperscript{73,81} and with total lung resistance\textsuperscript{141,142}. R\textsubscript{rs} measurements reveal significant frequency dependency especially in young children and in subjects with airway obstruction, probably reflecting inequality of the distribution of ventilation. In young children this is probably not an indicator of abnormal airway function, supported by the finding of frequency dependency in healthy young children\textsuperscript{130}. Klug and Bisgaard also presented normal values for IOS, Rint and sR\textsubscript{aw} in 2–7 year old children. Mean values of sR\textsubscript{aw}, Rint, R\textsubscript{rs5}, X\textsubscript{rs5} and Z\textsubscript{rs} in children were 1.09, 1.04, 1.38, -0.5, 1.48 kPa/L/s in the under 5 group and 1.13, 0.9, 1.18, -0.37 and 1.23 in the over 5 group. Surprisingly the best correlations were found for all parameters with weight compared to age or height (although not significant). As could be expected there was no correlation between sR\textsubscript{aw} and either age, height or weight. The authors presented linear regression equations for all techniques\textsuperscript{113}.

**Studies comparing values in diseased subjects.**

In a recent study evaluating the agreement between Rint and R\textsubscript{aw} in children with asthma and cystic fibrosis (CF) Rint was found to underestimate R\textsubscript{aw}, especially in children with severe airway obstruction\textsuperscript{143}. In these patients equilibration times are probably longer than 70–80 msec, and in these patients the extrapolation method underestimates true resistive pressure drop across the airways and thus airflow resistance\textsuperscript{87}. Substantial differences between Rint and R\textsubscript{aw} have also been found in individual patients\textsuperscript{94}. In obstructed patients longer equilibration times may be required to prevent underestimation of resistance.

In a recent study IOS was validated against the FOT and body plethysmography in children. Klug and Bisgaard found good correlations of IOS with both whole body plethysmography\textsuperscript{85} and also the correlation with results of FOT is acceptable\textsuperscript{144}. These results were recently confirmed in adults. Klug and Bisgaard found that both Rint and IOS techniques revealed abnormal results in 44% (Rint) and 8% (R\textsubscript{rs5}) of asymptomatic asthmatic 2–5 year old children but the outcome after 1.6 to 4.5 years was unrelated to baseline pulmonary function. Hence lung function measurement using IOS or Rint is not helpful in identifying children with a poor prognosis\textsuperscript{145}. 
Studies comparing feasibility.

In a study by Klug and Bisgaard, IOS, Rint and sRraw values could be obtained in 80% of all children, and almost 100% of children above 5 years of age113.

Studies comparing reproducibility

Most studies on the reproducibility of different techniques applicable in (young) children were recently performed in research centres in Great Britain and Danmark.

In a study in school children Bridge et al. found that the coefficient of variation (CV) of Rint was 11%, higher than Rrs (9%), FEV1 (5%) and PEF (5%)146. From the same centre results were presented describing repeatability of Rint in 3 year old children with an intra subject CV of 13% (ranging from 4-35%) compared to 1,6% (0,4-3,2%) for PtcO2117.

In a Danish study in 4-6 year old children reproducibility was much better for FEV1 (CV =5%) compared to sRraw (CV =13%), Rrs5 (CV = 10%), Xrs5 (CV = 17%) and Rint (CV = 12%)3.

In 2-4 year old asthmatics the reproducibility findings were more or less comparable to the former study: better for Rint (8%), sRraw (9%) and Rrs5 (10%) than for Xrs5 (16%)85.

The same authors also compared IOS, interrupter technique and whole body plethysmography in healthy 2-7 year old children and found that the repeatability was age independent and best for Rint (CV = 8.1%) compared to Rrs5 (10.2%), Zrs (10.8%) and sRraw (11.1%). For all parameters no significant sex differences were found and frequency dependency was confirmed113.

In a recent study Klug et al. compared within observer and between observer variability of the interrupter technique (Rint), impulse oscillation (Rrs5 and Xrs5) and whole body plethysmography (sRaw) in 2-6 year old children and found that the within subject standard deviation (SD) was not significantly different in observers but the between observer variability was greater for Rint than for the other parameters147.

Reproducibility of the oscillation technique has shown to be dependent on the support of cheeks and mouth floor, is strongly related to the patience of the investigator and can vary from 5-20%73,78,128,129.

Phagoo et al. compared the interrupter technique with forced oscillation and transcutaneous oxygen tension (PtcO2) measurement in 5 year old
asthmatic children during methacholine challenge. The lowest variability was found for PtcO2 (CV = 1.2%) compared to Rint (12-15%) and Rrs (12%)\textsuperscript{103}. The CV for inspiratory and expiratory Rint values are similar in children\textsuperscript{146}.

Bridge and McKenzie evaluated the Rint in expiration and inspiration in 2.5-5 year old children and found that expiratory Rint was significantly higher (mean 4%), but no significant differences were found for the CV of inspiratory and expiratory values, nor for bronchodilator response. Mean and median of 5-10 values contributing to a measurement were similar. The authors recommend to use the median\textsuperscript{148}.

Of course these findings on reproducibility should be taken into account when judging changes in the parameters in disease or after interventions of any kind.

Several confounders that have been discussed before may be responsible for the relative lack of reproducibility of resistance measurements in general, e.g. a switch from nasal to oral breathing or vice versa in young children using a face mask, changes in breathing patterns, respiratory muscle activity, tongue movements, glottic aperture etc.\textsuperscript{116}.

The use of a face mask with inner mouthpiece versus mouth piece with nose clip in 4-7 year old children resulted in comparable repeatability (CV = 11% for both) but in higher Rint values (p = 0.0002). This might be due to another breathing pattern, more rapidly and with greater tidal volumes. Maybe also a more turbulent flow in the mask because of a small ridge at the connection with the mask mouthpiece added to this higher value\textsuperscript{3}.

**Studies comparing sensitivity**

The sensitivity to detect changes in airway resistance (e.g. after intervention) can be expressed as the sensitivity index (SI):

\[
SI = \frac{(R \text{ after intervention} - \text{baseline } R)}{\text{within subject SD of baseline } R}
\]

or:

\[
SI = \frac{(R_{\text{post}} - R_{\text{pre}})}{SD_{R_{\text{pre}}}}
\]

In adults the SI for measurement of the response to bronchial challenge is significantly smaller for Rint(1.9-3.1) than for R\textsubscript{aw} (10.5)\textsuperscript{109}.
Bisgaard and Klug found in 21 4-6 years old children that the order of sensitivity of different techniques to assess airway obstruction was $Z_{ios} > sR_{aw}$ > FEV$_1$ > Rint. Parallel changes in all parameters were found but $Z_{ios}$ was significantly more sensitive than FEV$_1$.$^3$ It should be stated that they performed interruptions using a pneumotachometer and they measured mouth pressure during the last part of interruption during inspiration and measured flow directly after occlusion. This is another technique than used during later studies.$^3$

In another study in school children SI was not significantly different for Rint (3.5), R$_{rs5}$ (3.6), PEF (3.0) and FEV$_1$ (2.4)$^{14,6}$. Phagoo et al found a SI for Rint of 3 in 3 year old children compared to 16 for PtcO2. They found better sensitivity for detecting bronchodilator response (SI = 4.9%) than for detecting induced bronchoconstriction in asthmatic children. In up to half of the children a significant decrease in PtcO2 was not detected by Rint, in only 1 of 12 subjects bronchodilation was not found.$^{117}$

In a recent study Rint was measured to distinguish pre school children with recurrent wheeze from those with recurrent cough and healthy peers. Rint was significantly higher in wheezers and coughers did not differ significantly from normals. The bronchodilator response defined as the ratio between pre bronchodilator Rint and post bronchodilator Rint differed significantly between all three groups (wheezers 1,40, coughers 1,27 and normals 1,07). A bronchodilator response of >1,22 had a specificity and sensitivity for wheeze of 80% and 76% respectively.$^{115}$

In a study by Klug and Bisgaard X$_{rs5}$ was significantly more sensitive to induced bronchoconstriction than sR$_{aw}$, FEV1, R$_{rs5}$ and Rint. In patients with subclinical bronchoconstriction after provocation, this subclinical increase in muscle tone was detected by IOS, Rint and sR$_{aw}$ but not by FEV$_1$ or PtcO2.$^1$ In another study the same authors compared IOS and interrupter technique with body plethysmography in 2-4 year old asthmatic children at baseline, during bronchoprovocation and after bronchodilation. In this study the sensitivity was best for sR$_{aw}$ and X$_{rs5}$. Both were significantly more sensitive than Rint and R$_{rs5}$ (4%). Measurements during an asthma exacerbation yielded comparable results. In the latter study improvement after bronchodilation was best determined with PtcO2.$^{85}$ Both studies indicate that both Rint and R$_{rs5}$ are less useful for determination of reversible airway obstruction than X$_{rs5}$ (unless worse reproducibility) and sR$_{aw}$. The usefulness of X$_{rs5}$ was supported by results of Buhr et al.$^{149}$ and Duiverman et al.$^{83}$

Phagoo et al. compared the interrupter technique with forced oscillation.
and transcutaneous oxygen tension (PtcO2) measurement in 5 year old asthmatic children during methacholine challenge. PtcO2 was significantly more sensitive than the other methods to find airway responsiveness (SI = 18.9 compared to 4.2 (Rint) and 4.6 (Rrs)117. Important possible causes for the relative lack of sensitivity of Rint are retarded pressure equilibration in the presence of airway obstruction (underestimation of Rint), inhomogeneity of airway patency and extrathoracic airway compliance (underestimation of Rint). Their conclusion was that because of its simplicity the interrupter method provides a better method for assessing airway obstruction in this age group compared to the oscillation method117. Buhr and colleagues found comparable sensitivities for FOT and sRaw (SI = 8.2 and 12.0 respectively) to detect bronchial responsiveness in school children induced by carbachol149. In adults, Rint shows a close correlation to airway resistance (Raw) measured by whole body plethysmography (r = 0.86). The methods were equally sensitive in detecting changes in airway resistance following bronchodilation94.

8. Comparison of resistance measurements with MEFV curves

Evaluation of airway calibre can be performed either by measuring airway resistance during spontaneous breathing or by indices obtained from a forced expiration. Tests of forced expiration, such as PEF and FEV1 are widely used especially because of their simplicity and reproducibility. However there are several disadvantages of forced expiratory manoeuvres. They require full co-operation and co-ordination of the patient, which can not be expected from young children. Forced expiration parameters appear to be less sensitive to changes in airway calibre than are resistance measurements. Also the deep inspiration necessary for these tests is known to influence bronchial tone119,150,151.

Forced expiration manoeuvres and resistance measurements during tidal breathing represent different physiologic parameters. Therefore the relationship between resistance and maximal expiratory flow volume (MEFV) parameters is expected to be not very significant. In the first place, it is important to realise that FEV₁ is not a measure of airc-
ways resistance but of airway patency. Resistance is especially determined by the patency of (upper (large)) airways, both intra and extrathoracic. Maximal expiratory flow is especially influenced by patency of lower (smaller) airways and also by lung compliance. Lower airway obstructive disease can present with normal airway resistance and severely reduced FEV₁. Spirometry assesses the combined interaction of lung recoil and airway resistance and can not distinguish which of these has caused a specific change in lung function. That’s why specific measurement of airway resistance is required to assess what change in spirometry is due to changes in airway resistance, and not to changes in elastance.

Secondly, it should be stated that FEV₁ is a useful measure of airway obstruction, not because it represent a specific physiologic entity, but rather because it correlates with changes in airway calibre.

Nevertheless comparison of both methods gives significant correlations, probably caused by an important common mechanism, namely the airway obstruction.

In a study by Duiverman et al they found favourable sensitivity of the oscillation technique compared to FEV₁ in revealing short term changes in the bronchial status either during bronchial provocation tests or after administration of bronchodilators.

Mijnsbergen et al. found the correlation of Rint with FEV₁ to be somewhat higher in asthmatic than in CF patients (r = -0.74 versus -0.58). As in adults, also in children changes in Rint (and its reciprocal Gint) correlated with changes in FEV₁ and Rₛₜₐₜ measured by body plethysmography. The linear correlation of Gint and FEV₁ showed a r=0.77 (p<0.001). The curvilinear correlation of Rint and Rₛₜₐₜ showed a r=0.91 (p<0.001), but Rint was higher than Rₛₜₐₜ.

In their study Bridge et al. found significant correlations of interrupter conductance (Gint), the reciprocal of Rint, with FEV₁ (r = 0.837, p < 0.001) and peak expiratory flow (PEF) (r = 0.773, p < 0.001), as well as with Rₛ (r = 0.942, p < 0.001).
9. Final considerations

Although the functional evaluation of patients with lower airway obstruction is probably best performed using FEV\textsubscript{1}, resistance measurement can be applied when MEFV measurements are impossible (e.g. infants and preschool children, geriatric patients, myopathic or mentally retarded patients). The development of simple and easily available techniques to measure airway and respiratory system resistance might open new doors for diagnosis and follow up of these patient groups\textsuperscript{2,76,80,88}.

Different techniques measure different aspects of resistance. Only with bodyplethysmography the measured pressure causes hardly anything else but flow, so their relationship really gives resistance (only the inertia of gas should be overcome by alveolar pressure, but this is minimal and can be denied at breathing frequencies not exceeding 120/min). Also with the interrupter technique no correction for volume is necessary because no volume changes occur during this technique, so all pressure is applied to overcome respiratory system resistance. Interrupter resistance measurements are considered as only estimations of the resistance of the total respiratory system. Especially due to confounding variables and arbitrary choices that have to be made prior to the calculation of R\textsubscript{int}, absolute R\textsubscript{int} values have no general acceptance. With all other techniques only indirect resistances are measured\textsuperscript{3,154}.

Interrupter and oscillation technique, applied during tidal breathing, are not very burdensome. Therefore these techniques are suitable in both daily practice and in a laboratory setting or for research purposes. The availability of these techniques has come with devices, that are currently tested and presented by commercial manufacturers. Although this does encourage more widespread use of these techniques, it does not imply that standardisation of these techniques has been performed and e.g. reference values and a good relation to pathophysiology are available.

Several drawbacks of resistance measurements in young children can be mentioned. The paediatric lung is not a miniature of the adult lung and developmental changes significantly influence pulmonary function test results. Especially in infants with airway obstruction, airway occlusion does probably not lead to even distribution of airway pressure between mouth and alveoli. This might lead to inaccurate estimation or airway resistance.
Because specific techniques are only possible at specific ages or in specific patients (e.g. baby body box, squeeze jacket technique, airway occlusion technique) follow up studies using the same technique throughout life are nearly impossible. Until now no single pulmonary function test is applicable in spontaneously breathing children and adults of all ages. This impairs longitudinal studies on pulmonary function development from early infancy to late adulthood (i.e. “cradle to grave”). Many techniques are not yet standardised (interrupter technique, tidal breathing technique) and normal values are not available (for all patient/age groups). Comparison to the “gold standard” shows that the reproducibility is worse which impairs clinical applicability.

However, there are several aspects that make resistance measurements preferable.

In the first place, resistance parameters are measured during spontaneous quiet breathing, so without forced respiratory manoeuvres. Therefore these values might be more representative of normal breathing, i.e. daily life situations. Forced expiratory manoeuvres are hardly applied during all day activities, not even during exercise.

Secondly, resistance measurements and tidal breathing analysis require only passive co-operation and each measurement may be accomplished within short time. The methods are non-invasive, apart from a closely fitting mask, eventually equipped with a mouth piece. The general acceptance of these methods is therefore good among young children in whom the methods are used.

Thirdly, during childhood the most important pulmonary diseases have an obstructive character and especially peripheral airway resistance is better mirrored by resistance measurements in children than in adults. Also, changes after intervention or in disease are at least similarly reflected by these techniques compared to “gold standards”.

Finally, most criteria for pulmonary function tests as mentioned in Chapter 1 are met by the interrupter resistance, forced and impulse oscillometry (and tidal breathing analysis). Therefore these are useful alternatives for objective evaluation of obstructive airway disease in children.
References

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