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REVIEW

Body plethysmography – Its principles and clinical use

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^p This article is dedicated to the memory of the co-author Priv. Doz. Dr. Wolfgang Marek who died in October 2010. He was a passionate researcher and teacher and particularly engaged in the better implementation of physiological insight into clinical practice.

KEYWORDS

Whole-body
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Intrathoracic gas
volume;
Functional residual
capacity;
Specific airway
resistance;
Airway resistance;
Airway obstruction

Summary

Body plethysmography allows to assess functional residual capacity (FRC_{pleth}) and specific airway resistance ($sRaw$) as primary measures. In combination with deep expirations and inspirations, total lung capacity (TLC) and residual volume (RV) can be determined. Airway resistance (Raw) is calculated as the ratio of $sRaw$ to FRC_{pleth} . Raw is a measure of airway obstruction and indicates the alveolar pressure needed to establish a flow rate of 1 L s^{-1} . In contrast, $sRaw$ can be interpreted as the work to be performed by volume displacement to establish this flow rate. These measures represent different functional aspects and should both be considered.

The measurement relies on the fact that generation of airflow needs generation of pressure. Pressure generation means that a mass of air is compressed or decompressed relative to its equilibrium volume. This difference is called "shift volume". As the body box is sealed and has rigid walls, its free volume experiences the same, mirror image-like shift volume as the lung. This shift volume can be measured via the variation of box pressure. The relationship between shift volume and alveolar pressure is assessed in a shutter maneuver, by identifying mouth and alveolar pressure under zero-flow conditions. These variables are combined to obtain FRC_{pleth} , $sRaw$ and Raw .

This presentation aims at providing the reader with a thorough and precise but non-technical understanding of the working principle of body plethysmography. It also aims at showing that this method yields significant additional information compared to spirometry and even bears a potential for further development.

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Introduction

Body plethysmography is a well-established technique of lung function determination. Its frequency of clinical use appears to differ between countries, with the most intensive application in the German-speaking countries. The method

goes back to ideas developed and described by Bert (1878), Gad (1881) and Pflüger (1882) and was technically realized, as a volume-constant box, since the 1950s, especially by DuBois,⁴ Matthys¹⁸ and Ulmer.¹⁶ Subsequently the technique has been continuously improved to reach its current level of sophistication which extensively utilizes the power of

modern online data processing. Owing to this long tradition, detailed knowledge on the relevant physiological mechanisms involved, the measurement procedures being most adequate and the potential pitfalls has been accumulated.¹

Body plethysmography provides measures of the lung that reflect a multitude of functional and structural aspects. These measures have been demonstrated to confer clinical information that is independent from other functional information, especially in obstructive airway diseases. Currently the view on many diseases and their underlying mechanisms is changing by the increasing appreciation that significant progress in understanding requires a multi- rather than a unidimensional perspective. As the human ability for multidimensional viewing bears natural limitations, this also implies a need for comprehensive, integrative measures.

To match these needs body plethysmography appears to have a well-founded potential, in terms of both widespread application and the perspective of more detailed analyses, as not all of the information in principle provided by the method is currently considered. Therefore, proper understanding of its working principles, possibilities and limitations is essential in the interpretation of results in research and clinical practice.

It is, however, a common experience that a significant proportion of users do not have an in depth-understanding of the principle of body plethysmography and its implications for data interpretation. This situation could be improved by a comprehensive state-of-the-art description providing a detailed analysis on different levels of understanding, corresponding to the readers' needs and knowledge. The present article aims at explaining the working principles of body plethysmography in a precise manner, but without taking refuge to mathematical derivations that could be inaccessible to some readers or even counter-productive by providing only a formalistic understanding. For those interested, a mathematical derivation is supplied

in the appendix. Purely technical issues that might distract from the major message are mostly omitted.

Rationale of body plethysmography

Spirometry is considered the gold standard in lung function. It can, however, not provide information on, e.g., lung residual volume (RV) and total lung capacity (TLC), while body plethysmography allows to determine these and other characteristics, such as airway resistance and intrathoracic gas volume (ITGV).^{2–8} Moreover, these measures are recorded during breathing at rest and not by forced maneuvers. Given the differences in measuring conditions and information provided, body plethysmography and spirometry add to each other, and a complete measurement cycle of plethysmography even includes spirometry (Fig. 1).

Commonly, the determination of lung function by body plethysmography starts with breathing at rest, followed by the shutter maneuver. It is commendable to continue this with spirometric measurements. After opening of the shutter, an expiratory reserve volume (ERV) effort and an inspiratory vital capacity effort (IVC) are performed; this allows the computation of RV and TLC (for details see below). If possible, this should be followed by a prolonged forced expiration to determine the forced expiratory volume in 1 s (FEV₁) and the forced vital capacity (FVC). The spirometric data can be conveniently recorded by the same flow meter as used for resistance measurements. In this way information on lung mechanics during normal and forced breathing can be obtained in a single sequence of linked measurements (Fig. 1).

Principles of body plethysmography

Apparatus

The volume-constant whole-body plethysmograph is a chamber resembling a glass-walled telephone box in shape and volume (about 700–1000 L). During measurement the box is closed with an airtight seal, except for a small controlled leak that is used to stabilize the internal pressure by allowing for equilibration of slow pressure changes, e.g. due to warming-up. One pressure transducer serves to measure the pressure inside the box relative to ambient pressure, another one is placed close to the mouth for recording mouth pressure during a shutter maneuver. The shutter mechanism can be used to deliberately block the airflow by transient occlusion. Moreover, respiratory flow rate is recorded by conventional equipment, such as pneumotachograph, anemometer, or ultrasound measurement, all of which is calibrated via syringes delivering a defined volume.

Principle of measurement

The principle of measurement of the commonly used plethysmographs relies on detecting changes in box pressure in combination with either changes of mouth pressure or with flow rate under defined breathing conditions. These signals are evaluated in order to determine static lung volumes and airflow resistance.

The basic physical principle exploited by body plethysmography is the law of Boyle-Mariotte. For the present purpose this law can be concisely expressed as the statement

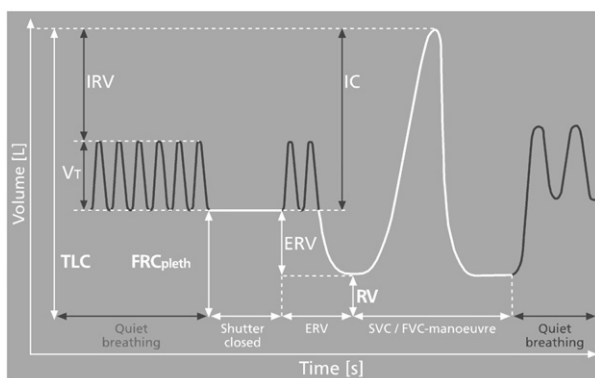


Figure 1 Volume-time display showing the following sequence: quiet breathing for recording specific airway resistance loops, a period when the shutter is closed for the determination of FRC_{pleth} , and subsequently a period during which the patient performs an expiratory reserve volume (ERV) maneuver, followed by a slow vital capacity maneuver (SVC) in order to determine inspiratory vital capacity (IVC) and to derive residual volume (RV) and total lung capacity (TLC). Commonly this is followed by a forced vital capacity (FVC) maneuver that also yields the forced expiratory volume in 1 s (FEV₁) and the maximum expiratory flows (MEFs) at different lung volumes.

Table 1 Short description of specific terms used in the text and figures.

Parameter	Abbreviation	Unit	Short description
Shift volume	ΔV (ΔV_{pleth} , ΔV_L)	mL	Change of volume by which the lung generates positive or negative alveolar pressure, i.e. deviation from the volume at which equilibrium of alveolar and box pressures would hold; represents a small part of tidal volume during free breathing
Alveolar pressure	P_{alv}	kPa	Mean pressure generated in the peripheral lung; provides the driving force for the airflow
Mouth pressure	P_{mouth}	kPa	Pressure measured at the mouth during the shutter maneuver; used as proxy for alveolar pressure under the zero-flow condition
Box pressure	P_{box}	kPa	Pressure measured in the body plethysmographic box during free breathing or the shutter maneuver; inversely related to alveolar pressure and generated by the shift volume
Flow rate	\dot{V}	L/s	Airflow rate measured at the mouth; also used to derive inspired and expired volumes by integration
Specific airway resistance	$sRaw$	kPa s	Inverse slope of the plot of flow rate versus box pressure (specific resistance loops); indicates volume- and resistance-dependent work of breathing needed in order to generate a reference flow rate of 1 L/s
Airway resistance	Raw	kPa s L ⁻¹	Flow resistance of the airways, i.e. ratio of alveolar driving pressure minus mouth pressure to flow rate; computed from $sRaw$ and FRC; indicates the alveolar pressure needed to generate a reference flow rate of 1 L/s
Intrathoracic gas volume	TGV or ITGV	L	Lung volume at which the shutter is closed (in principle deliberate); this closure is conventionally performed at the end of a normal expiration
Functional residual capacity	FRC_{pleth}	L	Lung volume at the end of a normal expiration, i.e. upon mechanical equilibrium of the opposite forces exerted by the lung tissue and thorax
Residual volume	RV	L	Lung volume reached upon maximum expiration
Total lung capacity	TLC	L	Lung volume reached upon maximum inspiration
Expiratory reserve volume	ERV	L	Volume of air exhaled by maximum expiration starting from FRC; used to derive RV from FRC
Inspiratory vital capacity	VC or IVC	L	Volume inspired starting from maximum expiration up to maximum inspiration; added to RV in order to obtain TLC
Expired (slow) vital capacity	EVC	L	Maximum volume that can be slowly exhaled after maximum inspiration; assessed in patients who can only inspire, and not expire, after opening of the shutter
Inspiratory capacity	IC	L	Volume of air that can be maximally inspired starting from FRC_{pleth} ; assessed either directly after opening of the shutter or by the difference IVC minus ERV
Tidal volume	VT	L	Volume of air moved during normal breathing; used to compute the mean volume at which specific resistance loops are recorded, by adding VT/2 to FRC_{pleth}

that for a fixed amount of gas in a closed compartment the relative changes in the compartment's volume are always equal in magnitude but opposite in sign to the relative changes in pressure. Thus one can infer relative volume changes from pressure changes and, even more, absolute volumes if the absolute volume changes are known. A summary of the terms used, their abbreviations and units, and a short description of their use is given in Table 1.

Definition of shift volume

The relevant changes during the breathing cycle can be described as follows. When inspiration from the end-expiratory lung volume is initiated by inspiratory muscles, thoracic volume increases. The increase in lung volume is

identical to that of thoracic volume, as the intrathoracic organs are incompressible. However, the airflow into the lung does not start immediately, since building-up of a pressure gradient is required to induce mass movement. It is important to understand that in general airflow lags behind the changes in lung volume, due to airway resistance. If the airways would have resistance close to zero, there would be virtually infinite flow, instantaneous pressure equilibration between the lung and the box, and no pressure gradient at all. Conversely, if the airways would be occluded during the inspiratory movement (which means infinite resistance), there would be a huge decrease in alveolar pressure but no flow. The decrease of pressure in response to the volume change would follow the law of Boyle-Mariotte, as the compartment would be closed.

In reality airway resistance is finite, thereby causing a nonzero pressure gradient. Airflow always tends to reduce pressure differences until equilibrium is reached. During inspiration, however, the continuing inspiratory movement of the thorax ensures that its volume excursion is slightly ahead of the equilibrating mass flow. When the thoracic, i.e. lung volume ceases to increase, alveolar and box pressure will rapidly reach equilibrium. As long as air is flowing, however, the increase in lung volume is slightly greater than the volume of air that has passed through the airways into the lung. This small difference represents a lag in mass flow during the breathing cycle and is called "shift volume".

Thus the shift volume corresponds to a deviation of volume relative to that which the same mass of air would occupy at equilibrium pressure. This deviation necessarily corresponds to a deviation of pressure from equilibrium. Specifically during inspiration it establishes the pressure drop in the lung as needed for inspiratory airflow. The magnitude of this pressure drop follows Boyle-Mariotte's law applied to the momentary lung volume and mass of air within the lung.

Moreover, the pressure drop is linked to inspiratory flow via the resistance of the airways that requires just this drop to establish the flow. At the end of inspiration, thoracic volume has increased by the amount set by the action of inspiratory muscles. While the muscles keep their tension for a short period of time, pressure equilibration via residual inspiratory flow occurs and the shift volume drops to zero. Finally, the inspired volume measured at the mouth equals the increase in lung volume, and both represent inspiratory tidal volume (VT_{in}).

Upon exhalation the situation is reversed. When the respiratory muscles relax, the elastic recoil of the lung starts to induce a decrease in lung volume. At the very beginning of exhalation, however, thoracic volume decreases but airflow has not yet started. Thus there is an increase in alveolar pressure and a nonzero shift volume. The pressure gradient initiates expiratory airflow, and the volume of gas in the lung decreases, with a short lag between the change in lung volume and expired volume, analogous to the situation during inspiration. The expiratory movement of the thorax continues until the recoil forces of lung and chest wall, which are opposite to each other, become equal. When the thorax movement ceases, pressure equilibrates, shift volume returns to zero and both the expired volume as measured at the mouth and the amount of volume reduction of the lung represent expiratory tidal volume (VT_{ex}).

This description should make clear that the dynamic pressure change within the lung corresponds to generation of a dynamic shift volume. This represents the part of volume change during breathing that is responsible for the decompression and compression of gas as needed for driving the airflow. In other words, the shift volume is the tiny, pressure-generating fraction of tidal volume. It is smaller than tidal volume by at least two orders of magnitude. To understand its definition and role is of utmost importance and will help in the interpretation of specific airway resistance.

Shift volume and box pressure

The shift volume provides the link to the box pressure that is at the heart of body plethysmography and allows the determination of two primary measures: thoracic gas volume and

specific airway resistance. Both measurements rely on the fact that the volume defect within the lung represented by the shift volume is necessarily equal in magnitude but opposite in sign to a volume defect in the body box. Thus, the shift volume in the box is the mirror image of the shift volume of the lung. This is the consequence of the fact that the box is hermetically sealed and has stable walls. Therefore, any change in lung volume must be equivalent to an opposite change in the free volume of the box outside the body, independent of the fact whether pressure equilibration has been achieved or not.

As the free volume of the box is known (total box volume minus body volume as estimated from body weight), Boyle-Mariotte's law is applicable and allows to derive the shift volume from the pressure change. Specifically, the relative change in the free box volume is equal but opposite in sign to the relative change in box pressure. This relationship can be used only because the box volume is known. In reality, the relationship is determined empirically by using a motorized pump that changes the volume in the body by defined amounts and by recording the concomitant changes in box pressure. It is important to understand that conceptually shift volume and change in box pressure are physically equivalent and interchangeable, and both might be used in diagrams without loss or gain of information. While for an initial intuitive understanding box pressure might offer the best approach, the physiological interpretation benefits more from shift volume. This is a major reason why the present description focuses on this measure.

Assessment of thoracic gas volume

Methodological approach

According to Boyle-Mariotte's law the unknown volume of a closed compartment can be determined if absolute changes of volume can be induced and the corresponding relative changes in pressure can be measured. Therefore, the determination of thoracic gas volume would be possible if the lung could be treated as a closed compartment and if one could measure the changes in alveolar pressure in parallel to the changes in volume.

In more detail this can be described as follows. The relative change in pressure is the ratio of the alveolar pressure change to the equilibrium alveolar pressure. Correspondingly, the relative change in volume is the ratio of the shift volume to the lung volume. According to Boyle-Mariotte's law the two relative changes are equal in magnitude. Thus, if one has measured the relative pressure change, one also knows the relative volume change. If additionally the absolute volume change has been measured, which is just the shift volume, then one can compute the absolute volume that produces the given relative change. The determination of absolute and relative pressure changes is equivalent as the reference pressure is always barometric pressure.

The question arises how to assess the change in alveolar pressure. This is determined by measuring the pressure generated at the mouth during respiratory efforts, while the airflow is blocked. The zero-flow condition implies mouth pressure to be equal to alveolar pressure, because occurrence of a pressure gradient and occurrence of airflow are necessarily linked to each other. To achieve this condition,

a shutter is used that prevents air from entering or leaving the lung (occlusion pressure maneuver). Normal inspiratory and expiratory efforts against the closed shutter lead to decompression and compression of the air in the lung.

Compared to the volume at equilibrium pressure, this air mass now occupies different volumes. Therefore a volume difference, i.e. shift volume, is generated. This is transmitted to the box through the movement of the thorax, as in the case of uninhibited airflow. Under the zero-flow assumption the change in alveolar pressure can be measured at the shutter as change in mouth pressure. Since shift volume (the amount of compression and decompression) and alveolar pressure change are proportional to each other, the result is a linear relationship between mouth occlusion pressure on one hand and shift volume or box pressure on the other hand (Fig. 2).

This relationship bears information on lung volume. When moving a plunger a certain distance (volume difference) in a short versus a long cylinder of given cross section, pressure change will be greater in the short cylinder. Translated to the lung: the larger the lung volume for a given shift volume, the smaller the pressure change. Conversely, the greater the pressure change, the smaller the lung volume must be relative to the shift volume. Therefore, in a large lung the occlusion pressure curve will be more flat, and in a small lung more steep.

Practical considerations

Obviously, the “thoracic gas volume (TGV)” determined in this way is that at occlusion; it is commonly performed at the end of expiration, i.e. under the condition of mechanical relaxation. This volume is the “functional residual capacity assessed by body plethysmography” (FRC, more specifically FRC_{pleth}). Occasionally the expression “intrathoracic gas volume (ITGV)” is used as synonym for FRC_{pleth} .⁸ In practical measurements there is a small deviation from this, as a small initial inspiratory volume has to be detected in order to reliably define the end of expiration, but the values reported by the commercially available equipment are corrected for this.

After the first occlusion maneuver, patients should continue to breathe normally until they have recovered from potential changes in FRC subsequent to the maneuver.

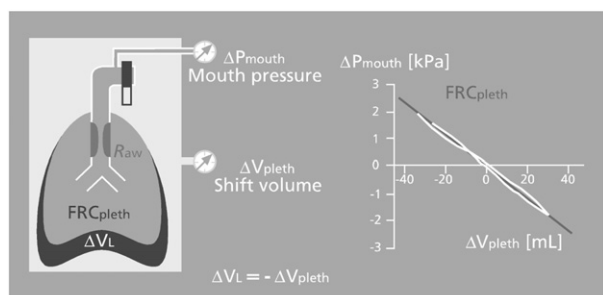


Figure 2 Mouth pressure (denoted by ΔP_{mouth}) versus shift volume (ΔV_{pleth}) during respiratory efforts against the closed shutter for determination of FRC_{pleth} . The plethysmographic shift volume is the mirror image of that of the lung (ΔV_L) (for details see text).

It is strongly recommended to perform at least one further occlusion maneuver. The values should be within 10% of each other. Depending on their difference, the operator can decide whether further measurements are necessary. In general, three or more measurements are recommended, of which at least two should be within 10% of each other. The median of the reproducible values is taken as final value. Since the maneuver might be perceived as exhausting by the patient, it should not be repeated more often than needed to obtain a reliable value. The occlusion maneuver is the part of body plethysmography which is most prone to artifacts of different kind leading to erroneous conclusions.

There are two ways to continue the measurement after the last occlusion maneuver. If possible, the patient should perform a maximal expiration to determine expiratory reserve volume (ERV) without potential for intermediate shifts in FRC. This should be followed by a maximal inspiration to determine inspiratory vital capacity (IVC) (Fig. 1). Residual volume (RV) can then be calculated as FRC minus ERV.⁸ Probably the best choice is to take median FRC and maximum ERV for this. Next, total lung capacity (TLC) is computed as the sum of RV and the maximal IVC from all satisfactory respiratory maneuvers. For patients with dyspnea it might be difficult to perform these linked maneuvers immediately after opening of the shutter. These patients should be allowed for a few cycles of quiet breathing before initiation of the ERV maneuver.

Patients with impaired lung function often perceive breathlessness during occlusion, and it is more comfortable and relieving for them to inspire than to exhale after the airstream interruption. Thus the alternative procedure is to ask the patients to perform a slow maximal inspiration after the reopening in order to determine inspiratory capacity (IC). Afterwards patients should perform a slow maximum expiration yielding expiratory vital capacity (EVC). TLC is then computed as the sum of FRC and IC, while RV is taken as the difference between TLC and EVC.

Clinical interpretation of FRC and derived indices

The assessment of TLC is considered indispensable in the diagnosis of restrictive disorders, which are defined as TLC being below the 5th percentile of normal values. A restrictive disorder can be suspected from spirometry when vital capacity (VC) is reduced and the ratio of forced expiratory volume in 1 s (FEV_1) to VC (FEV_1/VC , Tiffeneau; VC either FVC or IVC) is normal or elevated. It is definitely proven, however, only by a decrease in TLC.⁹ Recommendations for the diagnostic use of these indices have been given in the literature.^{2,7,8,10–12}

The determination of RV and $RV\%TLC$ also allows to judge upon the degree of lung hyperinflation. Values of RV or a ratio RV/TLC above the 95th percentile but below 140% predicted are indicative of mild, values between 140 and 170% predicted of moderate, and values above 170% predicted of severe hyperinflation. It is important to recognize that lung hyperinflation per se is not identical with the presence of emphysema but can have multiple other causes, especially due to the link between resistance and volume (see below). Severe hyperinflation, however, is regularly indicative of lung emphysema as being involved in

the disease. It also should be noted that in the presence of very severe airflow obstruction plethysmographic volumes tend to be overestimated, probably due to the fact that the pressure variations generated during the shutter maneuver are not properly transmitted to the mouth.¹³

If FRC is elevated but decreases after bronchodilator administration or in the course of the disease (e.g. after an exacerbation of COPD), this indicates beneficial effects on lung hyperinflation. Body plethysmography is capable of determining both the degree of lung hyperinflation and its changes by direct measurement of FRC that does neither rely on the proper performance of inspiratory maneuvers nor depend on possible changes of TLC.

Naturally, changes in FRC are inversely related to those of inspiratory capacity (IC), provided that there is no change in TLC. IC has been advocated particularly in intervention studies in COPD. It can be measured even during exercise, while body plethysmography normally does not allow the assessment of FRC under these conditions. In the sequence of maneuvers commonly performed in plethysmography, IC is not directly measured but derived from IVC and ERV, thereby involving two effort-depending maneuvers instead of one as in most spirometric IC determinations. Whether the correlation of FRC with indices of clinical state is weaker than that of IC measured at rest is not reliably known. The ratio IC/TLC is known to be a significant predictor of mortality in patient with COPD.¹⁴ The determination of IC during exercise is a separate issue involving mechanical responses rather than stationary states.

Specific airway resistance and airway resistance

Assessment of specific airway resistance

In the realm of mechanical flow, resistance is defined as the ratio of driving pressure to flow. The more pressure is needed for a given flow, the greater the resistance. Correspondingly, airway resistance (R_{aw}) is the ratio between the difference of alveolar and mouth pressure (the latter being essentially constant during unimpeded breathing) and the flow rate determined at the mouth. One of the goals of body plethysmography is the assessment of airway resistance, but it is of great importance to realize that the primary measure recorded is specific airway resistance ($sRaw$) which is, despite its name, not a resistance in the literal sense of the word.^{6,7}

As the alveolar pressure that is needed for the determination of the proper airway resistance is not available during free breathing, one could refer to a more easily available surrogate marker of airflow resistance. This can be done by relating flow rate to shift volume, or equivalently box pressure, which are directly measurable. This makes perfect sense, since the shift volume recorded during breathing represents that part of thoracic volume excursions which is needed to establish the driving pressure in the lung. It is not identical to the driving pressure but closely related to it.

The ratio of shift volume, or equivalently box pressure, to flow rate, expressed in suitable units, is called "specific

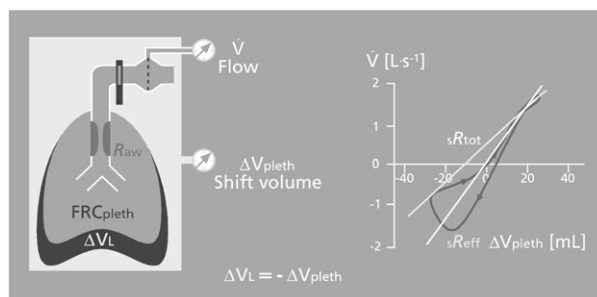


Figure 3 Tracing of specific airway resistance ($sRaw$) loop (half-tone, flow rate \dot{V} versus shift volume ΔV_{pleth}) in a patient with airflow obstruction. The white lines indicate the slopes representing two different types of evaluation: total $sRaw$ (sR_{tot}) and effective $sRaw$ (sR_{eff}) (for details see text).

airway resistance, $sRaw$ ". If airflow is plotted on the vertical axis versus shift volume on the horizontal axis (Fig. 3), closed curves are obtained. The reciprocal slope of these breathing loops represents specific airway resistance. In healthy subjects the curves are approximately straight lines, while in patients with respiratory diseases various patterns can be recognized that carry information on the particular disorder and are helpful in differential diagnosis (Fig. 4).

A more flat curve indicates an elevated shift volume relative to airflow and thereby an increase of $sRaw$. This is the primary measure provided by the body plethysmograph. It is incorrect to refer to these curves as "resistance loops"; they are "specific resistance loops". This is not simply a matter of parlance, since the distinction has major consequences for the interpretation of the data.

This can be understood as follows. If patients A and B show identical lung volumes and airway resistances, they will have to generate the same alveolar pressure change to produce the same airflow. This implies that their shift volumes are identical and thus the breathing loops, or $sRaw$, too. However, if the lung of patient A is twice as large as that of patient B, patient A will need twice the shift volume in order to generate the same change in alveolar

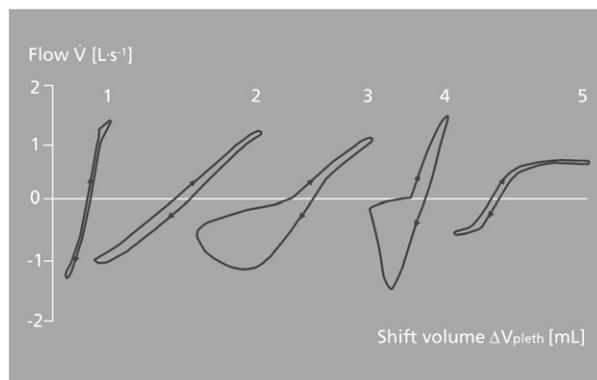


Figure 4 Schematic representation of specific resistance loops ($sRaw$) in a normal subject (1), a subject with increased large airways resistance (2), a subject with chronic airflow obstruction (3), a subject with obesity or diaphragmatic paralysis (4), and a subject with upper airway obstruction (5).

pressure. Thus the shift volume will be twice as large as in patient B, and $sRaw$ twice as high despite the fact that airway resistance is the same. One might interpret this situation by saying that patient A has to work twice as hard as patient B.

If, on the other hand, patients A and B have identical lung volumes, but patient A an airway resistance twice that of patient B, then patient A needs twice the alveolar pressure change to generate a given airflow. To achieve this, patient A needs twice the magnitude of pressure-generating volume changes, i.e. shift volume. Therefore the horizontal amplitude of the loop is twice as large, i.e. the loop is less steep than that of patient B and $sRaw$ twice as high. Again one might state that patient A has to work twice as hard as patient B. These examples illustrate that $sRaw$ depends on both lung volume and airway resistance. Conversely, this means that the breathing loops can be the same for different values of airway resistance, if it happens that the ratio of lung volumes is the inverse of that of resistances.

Determination of airway resistance and its relation to $sRaw$

To obtain airway resistance (Raw), information on alveolar pressure is indispensable, which is, however, not directly accessible. Fortunately, a relationship between alveolar pressure and shift volume is provided by the shutter curve obtained in the occlusion maneuver. This relationship allows the transformation of shift volumes into changes of alveolar pressure. Correspondingly the ratio of shift volume to flow rate, representing $sRaw$, can be transformed into that of alveolar pressure change to flow rate, which is just airway resistance, Raw . It turns out that this operation is mathematically equivalent to dividing $sRaw$ by FRC_{pleth} as determined in the occlusion maneuver (see next paragraph). Therefore Raw is the ratio of $sRaw$ to FRC_{pleth} . To account for the fact that the breathing loops are obtained at a mean lung volume higher than FRC_{pleth} , it is customary to correct for the tidal volume VT . Therefore FRC_{pleth} plus $VT/2$ is used in this calculation. Irrespective of these details, it is fundamental to recognize that the common notion of $sRaw$ being the product of Raw and FRC obscures the origin of these indices and has to be considered as a source of confusion instead of clarification.

Despite this, the formula is useful to understand the relationship between the three indices. A qualitative justification is as follows. If at a given lung volume Raw is doubled, shift volumes are twice as high for a given flow, and thus $sRaw$ is also doubled. Based on this reasoning, $sRaw$ must be proportional to Raw . If, on the other hand, lung volume is doubled at a given Raw , then again shift volume must be twice as high for a given flow, and $sRaw$ again be doubled. Therefore $sRaw$ must also be proportional to FRC_{pleth} . The proportionality to both Raw and FRC_{pleth} is exactly expressed by saying that $sRaw$ is equal to Raw times FRC_{pleth} , or that Raw is $sRaw$ divided by FRC_{pleth} .

Being not an airflow resistance in the literal sense, $sRaw$ still has a useful interpretation: it measures a specific work of breathing. This becomes clear when noting that mechanical work is defined as force times distance over which the force is working, or equivalently pressure times

volume change. Therefore, the work quantified by $sRaw$ is the work due to the changes in lung volume which is needed to maintain a flow rate of 1 L s^{-1} . In contrast, Raw involves pressure, i.e. force per unit area, to establish the flow rate of 1 L s^{-1} . Pressure can be large but work small, if the volume change is small. Conversely, work can be large despite pressure being small, if there is a large change in volume.

The mode in which $sRaw$ is assessed also has consequences for the reliability of measurements as compared to Raw . As noted above, $sRaw$ is independent from the shutter maneuver used to determine FRC_{pleth} . Thus errors and artifacts occurring in this maneuver affect the measured value of FRC_{pleth} , and consequently that of Raw , but not $sRaw$. Failure of this maneuver does not invalidate $sRaw$.

As a further feature, $sRaw$ is, within limits, independent from factual changes in FRC that might occur due to different causes. In smaller lungs or after voluntary decrease of FRC, airway resistance is likely to increase, while in larger lungs or after elevation of FRC, it decreases. Up to first order approximation, airway resistance and lung volume can be considered as inversely proportional to each other. This has the consequence that the product of Raw and FRC, which just represents the directly measured $sRaw$, is approximately constant, and in any case less sensitive to changes in volume than Raw . This stability mirrors the fact that the volume-related, flow-normalized work is the same under the two conditions. It also suggests that $sRaw$ can be expected to show less variation than Raw within both cross-sectional and longitudinal studies.

Practical considerations

The measurement of breathing loops should be performed under controlled conditions. Breathing frequency should be neither very low, since this amplifies the effects of noise and distortions in the breathing pattern, nor high, because this often leads to artifacts in the breathing loops as well as an involuntary rise of FRC. Slopes are commonly evaluated at flow rates in the range of 0.5 L s^{-1} ; this rate chosen for measurement should not be confused with the numerical reference rate of 1 L s^{-1} which corresponds to the units of pressure in Raw , or work in $sRaw$.⁴ Higher flow rates might cause artificially high values of $sRaw$ due to the increasing contribution of turbulent versus laminar flow regimes; commercial body plethysmographs usually allow for the selection of the flow range used for the computation of specific airway resistance. The best experiences have been gained with slightly enhanced breathing frequency at relatively shallow breathing. Several breathing loops should be recorded and the shutter maneuver should be initiated within short time after having obtained well-behaved loops, in order to ensure the proper association between loops and FRC. The median value of up to five technically acceptable loops should be taken.

Only in normal subjects breathing loops are straight lines, and there is effectively no question how to evaluate the slope. Obstructive diseases, however, not only lead to a flattening of the loop but also alter its form. Firstly inspiration and expiration may show different or changing slopes, and secondly there may be an opening of the loops that corresponds to a phase shift between flow and shift

Table 2 Alterations in body plethysmographic measures as observed in major disorders (see also Fig. 4).

	FRC	RV	TLC	<i>Raw</i>	<i>sRaw</i>
Obstructive airway diseases	Normal or elevated	Normal or elevated	Normal	Elevated	Elevated
Hyperinflation	Elevated	Elevated	Normal or elevated	Normal	Elevated
Restrictive disorders	Reduced	Reduced or normal	Reduced	Normal	Normal

volume, or equivalently mean alveolar pressure. An opening of loops is in particular generated by the differences in temperature and humidity between inspired and expired air. This factor is normally eliminated by a computational procedure that corrects for these asymmetries.¹⁵ However, the magnitude of correction appears to remain a critical technical issue, as there are also physiological factors causing an opening as a sign of inhomogeneous ventilation related to trapped air or pendelluft. It is well possible that a more detailed evaluation of the opening of loops will reveal valuable information particularly in COPD, but this issue remains open for future research. A brief summary of changes of plethysmographic measures observed in various disorders is given in Table 2.

In case of asymmetries or openings it becomes relevant by which procedure the loops are evaluated; this is particularly evident when they attain the form of golf clubs in their expiratory part, as often seen in emphysema on the basis of diminished elastic recoil and air trapping.^{7,16} Basically, there are two internationally recognized methods. The one proposed by Ulmer and coworkers^{17,18} relies on the maximum pressure, or equivalently shift volume, amplitude. For this purpose, the two points of the loop that represent the maximum shift volumes achieved during inspiration and expiration are identified (Fig. 3). If there is more than one maximum, the point associated with the greatest airflow is used. This amplitude (horizontal on the plot) is set into relation to the corresponding flow amplitude (vertical), thereby yielding "total specific airway resistance, sR_{tot} ".

The second method has been described by Matthys and coworkers.^{19,20} It aims at the determination of an average specific airway resistance. This is achieved not from the loops representing flow versus shift volume, but indirectly from loops representing the volume change due to airflow versus shift volume. If shift volume is taken as an equivalent of pressure, the integral of these loops has the dimension of work (pressure times volume change). The area of these loops is set into relation to the area of the corresponding flow-volume loops as obtained during tidal breathing. This sort of evaluation is equivalent to computing a weighted average over the breathing cycle. The modern software allows to depict an equivalent average slope within the standard loops and thereby to visualize the value. The slope thus obtained is termed "effective specific airway resistance, sR_{eff} ".

Corresponding to these specific resistances, airway resistances R_{tot} and R_{eff} can be obtained by dividing through FRC_{pleth} , or more precisely FRC_{pleth} plus $VT/2$, as described above.^{6,7} It is obvious that sR_{tot} represents the maximum value of specific resistance that can be sensibly defined, while sR_{eff} is more stable owing to the averaging procedure. Compared to sR_{eff} , the evaluation of sR_{tot} implies a greater

sensitivity to even slight deviations of the loops from a straight line, particularly at end-expiration. Thus, sR_{tot} may cover peripheral airway dysfunction to a greater degree than sR_{eff} and be more sensitive to changes in the bronchopulmonary system, but this issue has not been systematically clarified. The price paid is that sR_{tot} exhibits greater variability than sR_{eff} , as it relies on only two data points and is therefore more susceptible to measurement errors and artifacts that can occur in box pressure readings.

There is no international standard for the evaluation of $sRaw$ but we advocate sR_{eff} and R_{eff} against sR_{tot} and R_{tot} , since they are more robust¹ and the gain in robustness outweighs the potential loss in sensitivity. $sRaw$ determination during forced breathing is informative if a central airway stenosis is suspected, since the narrowing can be easily detected via the sigmoid-shaped breathing loop (Fig. 4).

Interpretation of (specific) airway resistance

It is prudent to evaluate both Raw and $sRaw$ in all instances. For example, one consequence of the relationship between Raw and FRC is that patients with COPD and severe lung hyperinflation may show only a moderate elevation of Raw associated with high FRC, while $sRaw$ is highly pathological. Analysis of the form of breathing loops provides relevant pathophysiological information. A steep curve at the first glance excludes a functionally relevant airflow obstruction, except at very low lung volumes. Any flattening indicates obstruction, which might be different for inspiration and expiration. If the procedure was performed correctly, an opening of the loop indicates an inhomogeneity of ventilation in terms of trapped air or pendelluft that can have a variety of causes, most importantly emphysema and bronchitis.

Typical examples are shown in Fig. 4. Reference values for body plethysmographic parameters are available from different sources, as well as recommendations regarding the categorization into degrees of severity of airway obstruction.^{1,2,9–11,20–23} One should always be aware, however, that (specific) airway resistance and its changes after interventions can largely dissociate from spirometric measures and thus categorizations of severity or responses are not equivalent.

In bronchodilator testing, the relative changes of FEV_1 are often smaller than the changes of FRC_{pleth} (ITGV), RV or $sRaw$, particularly in patients with airways collapsing at expiration. Noteworthy enough, the relative decrease of $sRaw$ following bronchodilator inhalation covers changes in both lung hyperinflation and airway resistance. Spirometry thus might underestimate the increase in bronchial lumen from smooth muscle relaxation, and body plethysmography is capable of detecting bronchodilator responses that would

be false negative when solely relying on spirometry. A reduction of R_{aw} or sR_{aw} by $\geq 20\%$ suggests partial reversibility, and changes by $\geq 50\%$ indicate reversibility with certainty, however systematic comparisons with other criteria in different disorders are lacking. Serial measurements of sR_{aw} also allow documentation of the time course of bronchodilation, i.e. onset of drug effect.

In bronchial challenges FEV_1 is often preferred because of its high reproducibility. Body plethysmography is recommended only in patients with spirometry-induced airway obstruction or those who are unable to perform the spirometry maneuvers as needed. Obviously, body plethysmography is particularly advisable when there is insufficient cooperation from the patient's side. It also seems advantageous in specific provocation tests with inhaled allergens, as bouts of coughing after allergen inhalation often do not allow to conduct a valid spirometry in time.²⁴ The provocation test could be considered as positive when specific airway resistance (sR_{eff}) has doubled and at the same time increased to ≥ 2.0 kPa s as a minimum value. Other criteria have also been used, such as a 35 or 40% fall in specific airway conductance (sG_{aw}) which is the reciprocal value of sR_{aw} .^{25,26}

If body plethysmography is used in combination with spirometry in routine bronchial inhalation challenges, experience shows that up to 20% of patients demonstrate a positive response in sR_{aw} without sufficient response in FEV_1 . The clinical significance of these discrepancies is not known. It suggests, however, that the sensitivity of inhalation challenges is raised if the outcome is assessed by these two different lung function indices. Furthermore this approach appears to be helpful in differential diagnosis regarding the assessment of the site of response, e.g. vocal cord dysfunction versus central or more peripheral bronchial obstruction. Overall, provocation testing by body plethysmography appears to be easier to perform and more sensitive than testing by spirometry.

Conclusion

The present analysis aims to demonstrate that body plethysmography is a technically demanding, physiologically nontrivial, highly informative, non-invasive method to obtain information on airway obstruction and lung volumes that is not available through spirometry.^{6,27,28} It normally takes no more than a few minutes to get reliable values. Importantly, the examination requires only a minimum of cooperation and in most cases is less bothersome for the patient than spirometry; the results obtained for sR_{aw} are virtually independent from the patient's cooperation. Moreover, in contrast to spirometry, it is an examination under physiological conditions, as the measurements are performed during quiet breathing. A closer inspection of the form of the breathing loops that represent sR_{aw} can yield valuable information on the type and even site of airway obstruction and the homogeneity of lung ventilation. Therefore, body plethysmography is an important, unique method for assessing the functional state of the airways. The method appears to be of particular value for characterizing the multiple, heterogeneous alterations occurring in patients with COPD. It also offers potential for further exploration and development.

Appendix. Mathematical relationships in body plethysmography

Shutter maneuver for the measurement of ITGV

Boyle-Marriott's law

Volumes are denoted by V and pressures by P . The following derivation focuses on the methodological principles and neglects secondary technical details. It particularly tries to elucidate the concept of shift volume which, according to the authors' experience, is cryptic to many users.

After a normal expiration or a voluntary expiration to a certain level with subsequent breath holding, the pressure in the lung, at the mouth and in the box is the ambient air pressure (barometric pressure, P_B). The corresponding lung volume is V_L .

If the shutter is closed and an inspiratory movement is performed, the volume of the lung increases (change ΔV), while the pressure decreases (change ΔP). ΔV corresponds to an uncompensated decompression or compression and is called "shift volume". Boyle-Marriott's law states that at constant temperature for a fixed amount of gas $P \cdot V = \text{const}$. If applied to both the initial state (left side of the following equation) and the final state (right side) it yields

$$P_B \cdot V_L = (P_B - \Delta P) \cdot (V_L + \Delta V). \quad (1)$$

For convenience the signs of ΔP and ΔV have been chosen in a manner that upon a change both are either positive or negative. Expanding the right side by multiplication leads to

$$P_B \cdot V_L = P_B \cdot V_L + P_B \cdot \Delta V - \Delta P \cdot V_L - \Delta P \cdot \Delta V.$$

As ΔP and ΔV are small compared to P_B and V_L , respectively, the product $\Delta P \cdot \Delta V$ is particularly small and can be neglected. The additional elimination of $P_B \cdot V_L$ on both sides of the equation yields

$$\Delta P \cdot V_L = P_B \cdot \Delta V,$$

which can be rearranged into

$$V_L = P_B \cdot \frac{\Delta V}{\Delta P}.$$

This expression shows how to compute the lung volume V_L , at which the shutter was closed. ΔP represents the change in lung (alveolar) pressure (ΔP_{alv}) during the respiratory efforts against the shutter. As there is no air flow that would lead to a pressure difference along the bronchi, it is assumed that the change in alveolar pressure is equal to that of mouth pressure (ΔP_{mouth}). Thus $\Delta P = \Delta P_{alv} = \Delta P_{mouth}$. ΔV is the shift volume, in this case the total change of lung volume (ΔV_L) due to movement of the thoracic wall ($\Delta V = \Delta V_L$). Inserting these specifications yields

$$V_L = P_B \cdot \frac{\Delta V_L}{\Delta P_{mouth}}. \quad (2)$$

Specific role of the plethysmographic box

The next step is to determine the shift volume ΔV_L by using the body box. If one applies Boyle-Mariotte's law (see formula (1)) to the box of volume V_{box} , the change in free box volume outside the body (ΔV_{box}) due to the subject's breathing efforts corresponds to a change in box pressure (ΔP_{box}). Repeating the steps leading to formula (2), one obtains for the box

$$V_{\text{box}} = P_B \cdot \frac{\Delta V_{\text{box}}}{\Delta P_{\text{box}}} \quad (3)$$

As the tissue can be considered as incompressible, the change in lung volume is numerically equal to the change of free box volume, but of opposite sign: $\Delta V_{\text{box}} = -\Delta V_L$. Inserting this into (3) and rearranging yields

$$\Delta V_L = -\Delta P_{\text{box}} \cdot \frac{V_{\text{box}}}{P_B} \quad (4)$$

which shows that the shift volume of the lung, ΔV_L , can be measured via ΔP_{box} . Moreover, inserting (4) into (2) and eliminating P_B results in

$$V_L = -V_{\text{box}} \cdot \frac{\Delta P_{\text{box}}}{\Delta P_{\text{mouth}}} \quad (5)$$

Thus the lung volume can be determined by the measurable quantities ΔP_{mouth} and ΔP_{box} . One should not be disturbed by the negative sign. For example, upon compression of the lung, ΔP_{mouth} is positive, while ΔP_{box} is negative, as the free box volume increases. Correspondingly the ratio of pressure changes is always negative, and therefore V_L positive.

The calibration factor for the ratio of the two pressure changes in formula (5) is the free box volume V_{box} , which is known, after subtraction of the patient's body volume. Due to a number of technical factors, an empirical calibration is still needed. This can be done by a motor-driven pump, which defines the relationship between ΔP_{box} and ΔV_{box} by inducing defined volume changes.

If one identifies the lung volume V_L with FRC_{pleth} (in clinical practice also often called *ITGV*) and replaces V_{box} by an empirical calibration factor K_P , formula (5) can be written as

$$FRC_{\text{pleth}} = K_P \cdot \left| \frac{\Delta P_{\text{box}}}{\Delta P_{\text{mouth}}} \right|, \quad (K_P \approx V_{\text{box}}), \quad (6)$$

whereby the vertical bars indicate that absolute values have to be taken.

The relationship between the volume changes of lung and box ($\Delta V_{\text{box}} = -\Delta V_L$) can also be directly inserted into formula (2) to express the lung volume via the measurable shift volume ΔV_{box}

$$FRC_{\text{pleth}} = K_V \cdot \left| \frac{\Delta V_{\text{box}}}{\Delta P_{\text{mouth}}} \right|, \quad (K_V \approx P_B), \quad (7)$$

whereby the empirical calibration factor K_V effectively represents the barometric pressure P_B . This shorter derivation illustrates that FRC_{pleth} can be expressed as a function of shift volume or box pressure in a fully symmetric manner. Box pressure is only a technical means to measure the shift volume.

Relationships (6) and (7) can be interpreted as follows. A given change in box pressure (ΔP_{box}) corresponds to a given change in box volume (ΔV_{box}) and a numerically equal but opposite change in lung volume. If this occurs at a lower FRC_{pleth} , the corresponding change in mouth pressure (ΔP_{mouth}) is larger, and the conventional shutter curve, in which mouth pressure is plotted vertically, is steeper (see Fig. 2). Conversely, a larger FRC_{pleth} would result in a more flat curve. It is irrelevant whether box pressure or shift volume are used on the horizontal axis.

The measurement of resistances

Determination of $sRaw$

The description of specific airway resistance $sRaw$ is somewhat intricate and, owing to its peculiar naming, prone to misleading interpretations. The present derivation aims at elucidating its physical meaning and relationship to airway resistance Raw .

Conventionally, a flow resistance is defined as ratio of driving pressure to flow rate and thus has the units of [kPa/(L/s)]. The specific airway resistance could be formally defined as the change in the measurable quantity box pressure (ΔP_{box}) relative to the measurable flow rate at the mouth (\dot{V}), with a deliberate scaling factor K_P .

$$sRaw = K_P \cdot \frac{\Delta P_{\text{box}}}{\dot{V}}$$

The factor K_P is conventionally chosen to be the same as the factor K_P for the determination of FRC_{pleth} (roughly corresponding to the box volume ($K_P \approx V_{\text{box}}$), see formula (6)). Boyle-Mariotte's law (compare formula (3)) implies that the relative changes of box volume and box pressure are the same ($\Delta P_{\text{box}}/P_{\text{box}} = \Delta V_{\text{box}}/V_{\text{box}}$). Therefore, $sRaw$ can be further written as

$$sRaw = V_{\text{box}} \cdot \frac{\Delta P_{\text{box}}}{\dot{V}} = P_{\text{box}} \cdot \frac{\Delta V_{\text{box}}}{\dot{V}} \quad (8)$$

This formula provides important insights. The first expression on the right side underlines that, due to the factor V_{box} , the units of $sRaw$ are [kPa s]. Thus $sRaw$ is not a resistance in the conventional sense; it does not involve a unit of volume as necessary for a flow rate.

The second expression on the right side demonstrates that $sRaw$ is proportional to the shift volume ΔV_{box} . In the shutter maneuver the shift volume is the change of lung volume resulting in compression or decompression in the absence of any flow. Under the conditions of free breathing, the shift volume represents only a small part of the volume change during tidal breathing. It is precisely the part used for induction of the pressure that is needed to overcome the resistance of the airways at a certain flow rate. Only this part results in a disequilibrium of pressures between alveoli and box.

Moreover, it is important to note that the product of pressure and volume change (see formula (8)) is work, and therefore $sRaw$ is sort of a flow-standardized volume-related work, which has far-reaching consequences for its interpretation.

Formula (8) also demonstrates that the slope of the well-known “breathing loops” represents $sRaw$ and that flow rate can equally well be plotted against box pressure or shift volume; it is merely a choice of labelling. The shift volume, however, has the advantage of being more suggestive for an adequate physiological interpretation of $sRaw$ (see text).

Determination of Raw

The airway resistance Raw is by definition the ratio of the true driving force of airflow to flow rate \dot{V} . The force is the change in alveolar pressure, ΔP_{alv} , or, more precisely, its difference to mouth pressure, which can be assumed as constant at tidal breathing. Thus, the units of Raw are those of a proper resistance, $[kPa/(L/s)]$ or $[kPa \cdot s \cdot L^{-1}]$.

$$Raw = \frac{\Delta P_{alv}}{\dot{V}} \quad (9)$$

In order to derive Raw from $sRaw$, the relationship between the changes of alveolar pressure and those of box pressure or shift volume must be known (see formula (8)). Fortunately this information is provided by the shutter maneuver used for the determination of FRC_{pleth} . It is implicitly assumed that the individual, volume-dependent relationship determined under the no-flow condition is also valid during free, unimpeded breathing.

To proceed, one formally expands the definition (9) by ΔP_{box} in numerator and denominator, or by ΔV_{box} , to obtain the two equivalent expressions

$$Raw = \frac{\Delta P_{box}}{\dot{V}} \cdot \frac{\Delta P_{alv}}{\Delta P_{box}} \text{ and } Raw = \frac{\Delta V_{box}}{\dot{V}} \cdot \frac{\Delta P_{alv}}{\Delta V_{box}},$$

whereby all ratios involved can be expressed through measurable quantities. To recognize this, formula (8) for $sRaw$ is to be solved for either $\Delta P_{box}/\dot{V}$ or $\Delta V_{box}/\dot{V}$. Inserting the results yields an explicit relationship between Raw and $sRaw$

$$Raw = \frac{sRaw}{V_{box}} \cdot \frac{\Delta P_{alv}}{\Delta P_{box}} \text{ and } Raw = \frac{sRaw}{P_{box}} \cdot \frac{\Delta P_{alv}}{\Delta V_{box}}.$$

The next step is to substitute suitable expressions for the two ratios involving the alveolar pressure change ΔP_{alv} . For this purpose one appropriately solves relationships (6) and (7), keeping in mind that during the shutter maneuver $\Delta P_{alv} = \Delta P_{mouth}$. After inserting the results and additionally the (ideal) values for the calibration factors K_P and K_V (see (6) and (7)), one obtains the relationships

$$Raw = \frac{sRaw}{V_{box}} \cdot \frac{V_{box}}{FRC_{pleth}} \text{ and } Raw = \frac{sRaw}{P_{box}} \cdot \frac{P_{box}}{FRC_{pleth}},$$

in which the quantities occurring in both the nominators and denominators can be immediately cancelled. The result of this formal footwork is the following basic equation for airway resistance

$$Raw = \frac{sRaw}{FRC_{pleth}}, \quad (10)$$

independently of the approach via box pressure or shift volume. Thus $sRaw$ and FRC_{pleth} are the primary quantities

needed to compute Raw . The often used, formally equivalent relationship

$$sRaw = Raw \cdot FRC_{pleth}$$

has the disadvantage of falsely suggesting $sRaw$ to be the result of Raw and FRC_{pleth} . This often leads to misinterpretations of these quantities and the reliability of their measured values.

Relationships (8)–(10) can be summarized as follows. $sRaw$ is a flow-standardized work and is assessed directly from the breathing loops, without requiring further maneuvers. The breathing loops are based on the shift volume, or equivalently change in box pressure. The relationship to alveolar pressure as determined in the shutter maneuver is then used to compute Raw from $sRaw$. This means dividing $sRaw$ through FRC_{pleth} . Raw is a true resistance, in contrast to $sRaw$. If the breathing loop corresponding to $sRaw$ becomes more flat, i.e. $sRaw$ greater, and/or if the shutter curve becomes steeper, i.e. FRC_{pleth} lower, then Raw becomes greater.

Conflict of interest

None.

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