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ASSESSING CHANGE IN AIRWAY CALIBRE—MEASUREMENT OF AIRWAY RESISTANCE

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The need for tests to assess bronchodilatation or bronchoconstriction is of considerable importance in respiratory pharmacology. It can be approached either by measuring flow during conditions of maximal effort as discussed in the previous paper or by measurements of airway resistance under low flow conditions. Since the physiological basis of these two types of test is somewhat different they do not necessarily give the same information although in most situations there is general concordance. Each test is appropriate to different situations and the purpose of this article is to outline the main physiological factors underlying measurements of airway resistance and discuss the situations where these measurements may be more appropriate than measurements of maximum flow.

Physiological basis of airway resistance measurements (Raw)

The measurement of airway resistance is normally made under very low flow (quasi-static) conditions. Airway dimensions then approach those seen during breath holding and unlike the situation during maximal flow manoeuvres should not be subject to dynamic compression during expiration.

The value obtained for airway resistance is a composite value for the combined resistances of a great number of separate airways in series and parallel. As air flows in and out of the tracheobronchial tree the resistance at any distance from the trachea depends on the total cross-sectional area of the airways at that point. In normal subjects the decreasing size of individual airways distal to the trachea is more than compensated for by the increased number of airways at each generation so the total cross-sectional area is greatly increased towards the lung periphery. Consequently, during quiet breathing the major site of resistance in the lungs is in the trachea and large airways (Figure 1). The balance is different in patients with airways obstruction where the major resistance is in medium or small airways (Hogg, Macklem & Thurlbeck, 1968). It will be apparent from Figure 1 that a 50% increase in central airway resistance will have a much greater effect on total resistance than a 50% increase in the resistance of peripheral airways. Thus, measurements of airway resistance are more sensitive to changes in large airways and can be relatively insensitive to changes in small airways, the 'quiet area' of the lungs.

Airway resistance measurements (Raw) depend on both the size and number of patent airways. When there is a reduction in the number of parallel airways total cross-sectional area is decreased and airway resistance is increased, for example following a pneumonectomy when resistance is approximately doubled. During quiet breathing airway size depends on intrinsic airway factors such as bronchial muscle tone, mucosal oedema and secretions. It also depends on the airway distending pressure which cannot be measured directly but which under quasi-static conditions appears to be closely related to static lung recoil pressure (Butler, Caro, Alcala & DuBois, 1960; Mead, Takishima & Leith, 1970). Patients may therefore have increased airway resistance in the absence of intrinsic airway disease due to loss of lung recoil pressure (Leaver, Tattersfield & Pride, 1973).

Although changes in airway resistance may be due to changes in intrinsic airway factors or lung recoil pressure it is probably uncommon in the acute situation for drugs to have any appreciable direct effect on lung recoil pressure. However, large changes in lung elasticity can occur following both bronchodilatation and bronchoconstriction in patients with severe or acute asthma (Woolcock & Read, 1968; Gold, Kaufman & Nadel, 1967; Freedman, Tattersfield & Pride, 1975). The rapid changes in Raw seen in most bronchodilator and bronchoconstrictor studies are usually assumed to be largely due to changes in bronchial muscle tone. This is an assumption, however, since the tests will not distinguish changes in bronchial muscle tone from other factors affecting airway calibre such as mucosal oedema and bronchial secretions. These are perhaps more likely to be present when changes in Raw develop gradually.

Unlike measurements of forced expiration, measurements of airway resistance are unlikely to be affected by dynamic compression during panting nor in most subjects during tidal breathing though some

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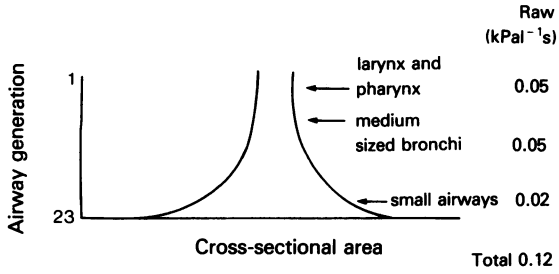

Figure 1 Diagrammatic representation of the increased airway cross-sectional area towards the periphery of the lung and increased airway resistance in the central air conducting passages. The figures on the right show the approximate distribution of Raw in normal subjects. They were calculated by Pride (1971) from the data of Hyatt & Wilcox (1961), Ferris, Mead & Opie (1964) and Hogg, Macklem & Thurlbeck (1968).

change in glottal size does occur between inspiration and expiration (Stanescu, Pattijn, Clement & van de Woestijne, 1972).

Relationship of Raw to lung volume and lung static recoil pressure (Figure 2)

Because airway resistance varies with lung volume the value of Raw will depend on the lung volume at which it is measured. It is therefore necessary to measure lung volume and if values are to be compared, measurements of Raw need to be corrected in some way for this. Airway resistance is in fact determined by lung recoil pressure rather than lung volume since lung recoil pressure approximates to airway distending pressure (Butler *et al.*, 1960; Mead *et al.*, 1970). However, under normal circumstances lung recoil pressure and lung volume change in a roughly linear manner in the middle range of lung volume (Figure 2a) so both show a similar relationship to Raw in the same subject. Because resistance is inversely proportional to the 4th power of the radius the relationship between resistance and both lung recoil pressure and lung volume is curvilinear (Figure 2b). Differences in the pressure volume curves between subjects and patients will obviously affect the absolute relationship of Raw to lung volume, as will any acute change in lung elasticity, if this were to occur following drug administration for example. Although correcting Raw for lung recoil pressure is physiologically more appropriate it is usually corrected for lung volume for convenience. Specific airway resistance (sRaw), the product of Raw and thoracic gas volume, corrects to some extent for lung volume though it is a less useful correction than sGaw (see below) because of the shape of the Raw/lung volume plot.

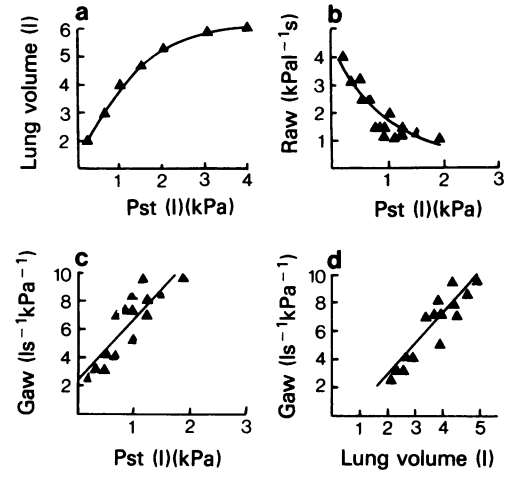

Figure 2 Values from one normal subject to show the relationship between lung volume, lung static recoil pressure (Pst(1)), airway resistance (Raw) and airway conductance (Gaw). Figure 2a shows the static lung pressure—volume curve and Figure 2b the curvilinear relationship between Raw and lung recoil pressure (a similar relationship exists between Raw and lung volume). In Figure 2c and 2d the more linear relationship between Gaw and lung recoil pressure and lung volume is shown. Note that the intercept in 2d would be between 0 and 1 litre lung volume. The scatter of results in 2b, 2c and 2d are typical of the scatter in individual measurements of Raw.

The reciprocal of airway resistance, airway conductance (Gaw), shows an approximately linear relationship to both lung recoil pressure and lung volume (Figure 2c and d) (Briscoe & DuBois, 1958; Butler *et al.*, 1959) and this conversion of Raw to Gaw makes the information more convenient to handle. A correction can then be made for lung volume by calculating specific airway conductance (sGaw).

$$\text{Gaw} = \frac{1}{\text{Raw}}$$

$$\text{sGaw} = \frac{\text{Gaw}}{\text{TGV}} \text{ when TGV = thoracic gas volme}$$

This will correct to some extent for lung volume but will only be truly independent of lung volume if the relationship between Gaw and lung volume is linear and if it goes through zero. Some deviation from linearity is well recognized (Butler *et al.*, 1960; Linderholm, 1963; Guyatt, Alpers, Hill & Bramley, 1967), though problems of reproducibility makes studies in individual patients more difficult to assess. In normal subjects the Gaw/TGV line usually approaches zero Gaw between 0 and 1 litres on the

volume scale (Briscoe & DuBois, 1958; Butler *et al.*, 1960; Guyatt & Alpers, 1968). In patients with airways obstruction the intercept at zero Gaw is more likely to lie between 1 and 4 litres lung volume (Butler *et al.*, 1960; Pelzer & Thomson, 1969; Leaver, Tattersfield & Pride, 1973).

Methods of measurement

In this review we describe three methods: the body plethysmograph measuring airway resistance; the oesophageal balloon method measuring lung resistance (airway and lung tissue resistance) and the forced oscillation technique measuring total thoracic resistance (airway, lung tissue and chest wall resistance). The relative contributions of airway, lung tisue and chest wall resistance to total thoracic resistance in normal subjects has been estimated at 60%, 1% and 39% respectively by Ferris, Mead & Opie (1964) though this probably underestimates lung tissue resistance (Marshall & DuBois, 1956). One reason for the variation in quoted values is that the different measurements of resistance are often made under different physiological conditions, e.g. panting versus quiet breathing or inspiration versus combined inspiration and expiration. In the majority of animal studies lung or total thoracic resistance has been measured whilst in man airway resistance is more likely to have been measured directly in the body plethysmograph. Any change in lung or total thoracic resistance is for most pharmacological studies assumed to be due to a change in airway resistance.

Other methods are available for measuring airway resistance, such as the interrupter method (Neergaard & Wirz, 1927; Mead & Whittenberger, 1954) but it is used less frequently and there is little work on the reproducibility. The sensitivity is less than that of the three methods described here (Frank, Mead & Whittenberger, 1971).

For each method we have attempted to assess the reproducibility of results from the literature. These vary with the laboratory, the apparatus and recording systems and the experience of the operator. The results quoted are a guide to the sort of reproducibility that can be expected but cannot be extrapolated to other workers and other laboratories.

Body plethysmography

Body plethysmography, first described by DuBois, Botelho & Comroe in 1956 to measure airway resistance, has the big advantage that thoracic gas volume is measured at the same time. Three types of plethysmograph may be used: constant volume, volume displacement and pressure-flow (see Freedman, 1979), though the volume displacement plethysmograph will not usually have an adequate frequency response for panting. The original method used a constant volume plethysmograph (Comroe, Botelho & DuBois, 1959) and since the principles are similar for each type, only this method will be described in any detail.

The subject sits in a closed box of approximately 600 litres and breathes the contained air through a heated pneumotachograph. The box pressure (Pb) is measured and displayed on the X axis of an oscilloscope. Airflow at the mouth ($\dot{V}m$) is displayed on the Y axis. The subject pants at 2–3 breaths/s which helps to keep the glottis open and the small tidal volume helps to minimize any drift in box pressure due to differences in temperature, water vapour saturation or RQ effects between inspired and expired air. An 'S' shaped line or loop is obtained on the screen and its slope ($\dot{V}m/Pb$) is measured, usually between 0 and 0.5 litre s^{-1} inspiration. Immediately after this measurement, the airway is occluded at the mouth while the subject continues to make panting efforts. Pressure at the mouth (Pm) is now traced on the oscilloscope Y axis and the slope of the resulting straight line (Pm/Pb) is measured. Thoracic gas volume is derived from this slope which is also used to calibrate the change in box pressure for the change in alveolar pressure (Palv) since Palv = Pm when the airway is occluded. Airway resistance (Raw) is the ratio of alveolar pressure to flow and is obtained from the ratio of slopes:

$$\text{Raw} = \frac{\text{Palv}}{\dot{V}m} = \frac{\text{Palv/Pb}}{\dot{V}m/Pb}$$

Technical points The pneumotachograph must be suitable for low flow readings and the transducers sensitive and linear over the appropriate pressure ranges. The pressure leak from the box needs to be checked periodically to ensure it will not interfere with box pressure measurements at 2–3 Hz. This is best done by measuring the signal from an oscillatory pump at different frequencies above and below the panting frequency.

The slope of $\dot{V}m/Pb$ and Pm/Pb are usually displayed on an oscilloscope and the angle of the slope can be measured directly by protractor. Alternatively, the slope can be recorded on paper or tape to be read later or fed directly to a computer. An X–Y plotter does not usually have an adequate frequency response for direct readings if the subject is panting though it can be used to record from a magnetic recording replayed at a slower speed. Using a protractor directly is convenient for routine use but will introduce errors since the angles of the slopes must be read rapidly. Observer bias will inevitably be introduced, either a tendency for repeat measurements to conform to previous readings or, more importantly, anticipating the effects of drugs in

pharmacological trials. Because the tangent of the angle is used to calculate Raw a small difference in slope of 1° around the 45° mark will give an error of about 3.5% in the value of sGaw. The capacity for observer error is therefore large and for pharmacological studies it is essential that the observer is unaware of the drug given to the subject. For detailed studies it is preferable that the results are recorded and coded to be read blind subsequently in a careful, unhurried manner. Computer analysis of the data should exclude observer bias but technical difficulties have precluded its widespread use so far.

Panting v *quiet breathing* Airway resistance can be measured during quiet breathing or during panting as recommended originally by DuBois *et al.* (1956). They suggested that panting would minimize temperature, water saturation and RQ effects to insignificant levels and would improve the signal to drift ratio, the drift being due to thermal changes in the box. They also outlined certain disadvantages related to the non-physiological nature of panting but felt these were likely to be of lesser importance. Measurements of laryngeal or upper airway resistance have usually shown a small reduction during panting (Hyatt & Wilcox, 1961; Ferris *et al.*, 1964; Spann & Hyatt, 1971), presumably related to the increased size of the glottis (Stanescu *et al.*, 1972; Baier, Wanner, Zarzecki & Sackner, 1977).

Panting involves both an increased frequency of breathing and a decreased tidal volume. In normal subjects upper airway resistance falls slightly as respiratory frequency is increased (Spann & Hyatt, 1971) and as panting volume is reduced (Stanescu *et al.*, 1972) the latter probably because of reduced turbulence. However, when panting was compared to quiet breathing in the body plethysmograph there was no difference in Raw in normal subjects (Peset, Quanjer & Tammeling, 1969) though a small reduction (12%) was seen in patients with chronic bronchitis similar to that seen in a similar group of patients by Barter & Campbell (1973). This may reflect a frequency dependent reduction in Raw in patients with airways obstruction with unequal time constants in the lung. A more controversial study showed an increased resistance during panting but neither the type of panting nor the measurement of Raw were those in common practice (Jaeger & Otis, 1964).

Reproducibility Although airway resistance is a sensitive measurement, its reproducibility is not particularly good. A mean value of Raw is usually obtained from three to ten separate readings. The variability of these individual readings is rarely quoted but can be estimated by calculating the coefficient of variation, i.e. the standard deviation expressed as a percentage of the mean. Calculations for published data (Table 1) show that mean values for the coefficient of variation lie between 10% and 20% but the range is large.

The value used for Raw and sGaw is usually the arithmetic mean though the distribution of values is not known. We have found that values for mean sGaw vary little whether they are calculated as the mean of individual sGaw values, by calculating sGaw from mean Raw and mean TGV values or from log transformation of all sGaw values. The results differ by less than 1% in most normal subjects and although the difference may be larger in patients it is still likely to be small.

A much greater error occurs if an inadequate number of measurements are made. In twelve normal subjects we compared mean sGaw from three measurements with that from ten measurements, after discarding the first two traces. On average there was a 5% difference in the two values (range 0.5–11%) though the overall means for the group were the same.

The main cause for the variability is the difficulty in measuring the slope of $\dot{V}m$ on Pb. Careful setting of the amplifier gains will minimize noise and optimize

Table 1 Variability of individual readings of Raw and sRaw measured in the body plethysmograph

Author	*Range of coefficient of variation*		*Number of subjects*	*Number of readings per subject*
	sRaw	*Raw*		
Lord & Edwards (1978)		11–26%	8 (normal)	6
Zedda & Sartorelli (1971)	1–28%	1–43%	3 (normal)	4–7
	2–32%	1–39%	2 (asthma)	4–7
	3–17%	9–35%	3 (chronic bronchitis)	4–7
Lord & Brooks (1977)		20–51% (computer) 18–37% (manual)	12 (normal)	7

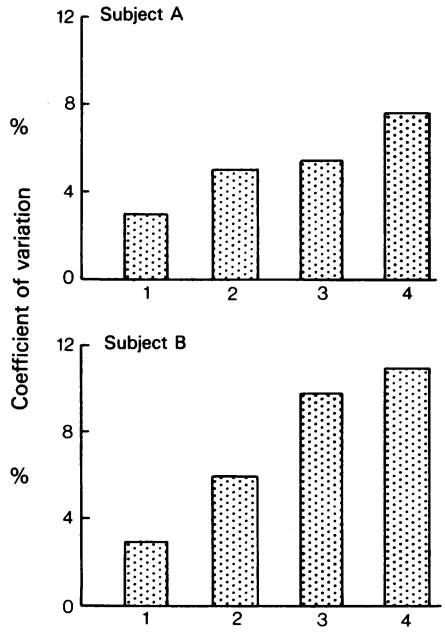

Figure 3 The coefficient of variation for four observers (1–4) reading six sets of ten readings from two subjects. All traces were read blind from a paper record. Observer no. 1 had read 20–30 plethysmograph traces a week on average for 4 years, whilst observer 4 had been reading traces for only a few months. Observers 2 and 3 were of intermediate experience.

the angle of the slope. Because the tangent of the angle is used a 1° error at an angle of 80° would give an error of 11% compared to 3.5% at 45°. There is little information about the best way of measuring the angle of the slope. A comparison of a direct reading from the oscilloscope using a protractor with a computer analysis measuring the angle of the slope between two points of flow (not the angle of the slope of the trace) showed no significant difference in the variability though on repeat readings the computer was more consistent (Lord & Brooks, 1977). The flow at which the slope is measured may be important since the same computer analysis found a coefficient of variation of 22% when the slope was measured at a flow between zero and 0.5 litre s^{-1} and 11% when the interval was between 1 litre s^{-1} expiration and 1 litre s^{-1} inspiration (the deceleration phase of expiration and acceleration phase of inspiration) (Lord & Edwards, 1978). Most manual methods, however, take tangents to the loop at a stated flow rate, usually 0–0.5 litre s^{-1} inspiration.

The values obtained by different observers reading the same slopes have been shown to differ (Guyatt *et al.*, 1967; Lord, Brooks & Edwards, 1977). Studies in our department on slopes recorded on light sensitive paper and read blind at a later date showed that reproducibility correlated closely with the experience of the observer reading the slopes (Figure 3) (Ranawaya, unpublished observations). The mean values also differed slightly between observers with some observers consistently tending to read higher than others.

The technique of the subject may be important since panting has been shown to reduce the difference in Raw between inspiration and expiration (Stanescu *et al.*, 1972) and repeated measurements may lead to a training effect with improved reproducibility (Pelzer & Thomson, 1966).

Oesophageal balloon technique

This method was introduced by Mead & Whittenberger in 1953. Transpulmonary pressure is measured as the difference between oesophageal and mouth pressure with oesophageal pressure measured from an oesophageal balloon representing pleural pressure. A signal proportional to volume is subtracted in order to correct for lung elastic recoil pressure and the resulting pressure is displayed on an oscilloscope against airflow at the mouth. The resulting S-shaped trace is used to derive pulmonary resistance. The main problem with this method is the need to use an oesophageal balloon which, because of its discomfort, makes it less suitable for pharmacological studies. The resistance measured is a combination of inspiratory and expiratory resistance at varying flow rates.

Variability There is little information about the reproducibility of this technique, since it is particularly unsuitable for repeated or protracted measurements. Frank *et al.* (1971) found that the variance during quiet breathing was consistently higher than that seen with either the plethysmographic or forced oscillation methods. Their quoted values give coefficients of variation in the order of 50%. They attribute this to problems in measuring oesophageal pressure because of cardiac oscillations. The variance was much improved by panting.

Forced oscillation

Since this technique was first described by DuBois, Brody, Lewis & Burgess (1956) to measure total thoracic resistance it has undergone various modifications, both to the apparatus and the methods of data analysis. Sine-wave oscillations are normally applied at the mouth and the resulting sine-wave flow and pressure measured at the mouth. The oscillations are usually applied by a loudspeaker connected to a tube through which the subject breathes, though a

valveless pump may be used instead. A low resistance, high impedance side tube is usually incorporated to connect the system to atmosphere and air is drawn through the apparatus at a constant flow rate to prevent build-up of carbon dioxide. The flow signal therefore, consists of a constant bias flow, normal respiratory cycle and superimposed oscillations. The bias flow signal may be removed electrically. Several techniques have been used to separate the forced oscillations from the respiratory cycle. The simplest is to make measurements at points in the respiratory cycle where flow is relatively constant; mid inspiration, mid expiration, or during pauses between expiration and inspiration. Alternatively, the respiratory events can be electrically filtered. The analysis depends on the assumption of a model of the combination in series of resistance, inertance and compliance of the respiratory system which is believed to apply in subjects without airways obstruction (Otis, McKerrow, Bartlett, Mead, McIlroy, Selverstone & Radford, 1956; Mead & Milic-Emili, 1964; Mead, 1969).

To measure resistance the components of the applied pressure oscillations due to compliance and inertance need to be eliminated and this is most simply achieved by finding the resonant frequency of the thorax (usually 5–8 Hz), when compliance and inertance pressures cancel out since they are of equal magnitude and opposite sign (180° out of phase). The oscillating pressure wave is then due to resistance only. In practice, pressure and flow are displayed on an oscilloscope and the frequency of oscillation is adjusted until a straight line is obtained. This is the resonant frequency and resistance is the slope of the line $Pm/\dot{V}$. Other methods of analysis do not require measurements at resonant frequency (Grimby, Takishima, Graham, Macklem & Mead, 1968; Goldman, Knudson, Mead, Peterson, Schwaber & Wohl, 1970), but the values obtained may be different in some circumstances (Landau & Phelan, 1973).

Reproducibility Although good reproducibility is claimed (Mansell, Levison, Kruger & Tripp, 1972) information on the forced oscillation technique is limited. Mean coefficients of variation calculated from the data from ten normal subjects and seventeen patients with airways obstruction were 3.5% and 6.5% respectively and in the normal subjects repeat measurements 2–4 weeks later were within 20% of the first value (Fisher, DuBois & Hyde, 1968).

Normal values

The distribution of Raw, Gaw and sGaw in the normal population

There is relatively little information about how these measurements are distributed in the population though all are likely to be non-normal. In a small study values of Raw showed a small skew distribution (McDermott & Collins, 1965) whilst in a larger study of 82 normal subjects aged 17–82 years both Gaw and sGaw approximated more closely to a log normal distribution (Pelzer & Thomson, 1966). This study contained twice as many men as women and just over one-third were smokers.

In a large survey of 752 men both Gaw and sGaw also fitted a normal distribution better after log transformation (Guyatt & Alpers, 1968). The population in this study was, however, deliberately weighted to include both more non-smokers and more patients with symptoms of chronic bronchitis than would have occurred in a random sample.

Table 2 shows mean values selected from the literature. None of the papers intended to define normal values from a representative population sample so sampling errors may affect the mean values. The largest series for instance by Guyatt & Alpers (1968) showed a mean Gaw value of 1.13 litre^{-1} cm$^{-1}H_2O$ equivalent to Raw of 0.89 cmH_2O litre^{-1} s^{-1}, which is outside the range quoted in Table 2, reflecting their particular selection of subjects.

Normal values for children in SI units are based on prediction formulae according to height or thoracic gas volume.

Total respiratory resistance = 0.0981 (antilog (1.877–0.89 height)).
(Mansell *et al.*, 1972).
Gaw = 1.63 TGV + 0.71
(Zapltal, Samanek, Tuma, Ruth & Paul, 1972).

Effect of age, sex, smoking habits, posture and height

Any change in airway resistance due to other factors must take change in lung volume into account. sGaw is similar in men and women and, in non-smokers, does not alter with age (Pelzer & Thomson, 1966). However, smokers and ex-smokers without other evidence of airways obstruction show a decline in sGaw with age (Guyatt & Alpers, 1968).

There is a reduction in both Gaw and FRC when normal subjects change from a seated to a supine position but no change in sGaw (Linderholm, 1963). Both Gaw and TGV show a positive correlation with height, reflecting the larger airways and larger lung volumes. Pelzer & Thomson (1966) found sGaw to be independent of height whilst Guyatt & Alpers (1968) found a small negative correlation, suggesting that tall people may have slightly lower values of sGaw.

Diurnal variation

The coefficient of variation of Raw measured at hourly intervals throughout the day in three normal subjects ranged from 7% to 23% (Zedda & Sartorelli,

Table 2 Mean values and range of mean values selected from the literature for airway resistance (Raw), specific airway conductance (sGaw), lung resistance (RL) and total thoracic or respiratory resistance (Rrs)—all values in SI units*.

Number of subjects	*Mean Raw*	*Mean sGaw*	*Mean RL*	*Mean Rrs*	*Range*	*s.d. (range)*	*Age (range) years*	*References*
293	0.13	—	—	—	0.09–0.17	0.02–0.06	16–90	1, 2, 4, 5, 6, 8, 9, 12.
242	—	2.4	—	—	2.1–3.1	0.6–0.8	19–90	14, 10, 15, 16, 17. 19.
82	—	—	0.21	—	0.15–0.24	0.05–0.08	18–90	4, 7, 8, 12.
277	—	—	—	0.24	0.22–0.26	0.01 0.06	18–79	3, 6, 8, 11, 13, 18.

References

1. Blide, Kerr & Spicer (1964).
2. Briscoe & DuBois (1958).
3. Brody, Wander, O'Halloran, Conolly & Schwertley (1963).
4. Butler, Caro, Alcala & DuBois (1960).
5. DuBois, Botelho & Comroe (1956).
6. Fisher, DuBois & Hyde (1968).
7. Frank, Mead & Ferris (1957).
8. Frank, Mead & Whittenberger (1971).
9. Guyatt, Alpers, Hill & Bramley (1967).
10. Jaeger & Otis (1964).
11. Jiemsripong, Hyatt & Offord (1976).
12. Linderholm (1963).
13. Mansell, Levison, Kruger & Tripp (1972).
14. Nadel & Comroe (1961).
15. Pelzer & Thomson (1966).
16. Peset, Quanjer & Tammeling (1969).
17. Skinner & Palmer (1974).
18. Sobol (1968).
19. Watanabe, Renzetti, Begin & Bigler (1974)4).

* Resistance values have been converted from cmH_2O $litre^{-1}$ s to SI units, (kPa $litre^{-1}$ s) using a conversion factor of 0.0981 and sGaw has been converted from s^{-1} cmH_2O^{-1} to s^{-1} kPa^{-1} using a factor of 10.2.

1971). Values at 07.00 h were consistently higher as noted by Hruby & Butler (1975). In 33 normal men no difference was found between measurements made at 10.00–11.00 h and 16.00–17.00 h (Zedda & Sartorelli, 1971). Diurnal variation can therefore be minimized by avoiding measurements early in the morning (Guyatt *et al.*, 1967; Graham, Heime & Constantine, 1967). Patients with airways obstruction show greater variability throughout the day (Zedda & Sartorelli, 1971; Hruby & Butler, 1975).

Day to day variation

This appears to be of a similar order to the diurnal variation. The coefficient of variation calculated from up to 55 measurements of sGaw for each of 3 normal subjects studied in the body plethysmograph over several months gave values between 12% and 17%. Studies over 5 days using the forced oscillation technique gave a mean coefficient of variation for total respiratory resistance of 8% which was identical to that seen throughout the day (Hyatt, Zimmerman, Peters & Sullivan, 1970). Both studies also carried out measurements of day to day changes in patients with airway obstruction but these will obviously be greatly influenced by patient selection.

The use of airway resistance measurements in clinical pharmacology

For the majority of pharmacological studies in patients with airways obstruction flow measurements such as the FEV_1 are most appropriate since they are simple, have good reproducibility and adequate sensitivity for this purpose. Airway resistance measurements offer two advantages which are valuable in certain situations. Firstly, they avoid a

full inspiration or forced expiratory manoeuvre which can alter the underlying airway calibre at a given lung volume and secondly they can provide increased sensitivity.

In normal subjects resting Raw measurements are not affected by a previous deep inspiration, but this manoeuvre will attenuate the reduction in Raw following a bronchoconstrictor stimulus such as histamine (Nadel & Tierney, 1961). In asthmatic patients a forced expiratory manoeuvre or deep inspiration can cause bronchoconstriction which is usually transient but may be more marked in occasional patients (Simonsson, Jacobs & Nadel, 1967; Gayrard, Orehek, Grimaud & Charpin, 1975; Mackay, Mustchin & Sterling, 1978). These manoeuvres may also alter the subsequent response of an asthmatic patient to an inhaled bronchoconstrictor agent (Orehek *et al.*, 1975). Airway resistance measurements circumvent these problems and may be preferable for studies of bronchoconstrictor agents in normal subjects and for studies wishing to investigate or involve patients who bronchoconstrict after a forced expiration.

Airway resistance is a more sensitive test than most measurements of flow, though less reproducible. The increased sensitivity is essential for studies of normal subjects and may be valuable for selected studies in some patients.

Resting vagal tone to normal airways ensures that they are not fully dilated though this can be overcome by both anticholinergic drugs and β-adrenoceptor agonists (Butler *et al.*, 1960; McFadden, Newton-Howes & Pride, 1970; Bouhuys & van de Woestijne 1971; Skinner & Palmer, 1974; Ingram, Wellman, McFadden & Mead, 1977). These drugs will normally cause an increase in sGaw of between 50% and 100% though occasional normal subjects show little or no

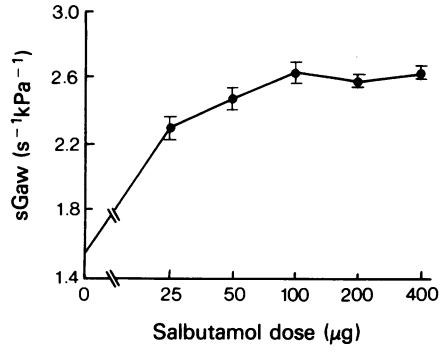

Figure 5 The salbutamol dose-response curve for one normal subject. sGaw is plotted against the cumulative dose of inhaled salbutamol. This plot is the mean of 3 separate days ± s.e. mean.

effect. This bronchodilatation is not reflected in flow measurements which show little change (Figure 4) though the reasons are not entirely clear (see Pride, 1979). Airway resistance measurements provide the necessary sensitivity for studies in normal subjects and the relatively poor reproducibility can be overcome by taking several readings (Figure 4). A mean of 10–12 readings will usually provide consistent results as shown for example in the salbutamol dose-response curve in Figure 5. This approach has opened up a considerable potential for studying drugs in normal subjects who offer many advantages for pharmacological research—greater availability of subjects, little spontaneous change in airway calibre and freedom from the effects of other medication which may interact with the drug under investigation. They may also provide a greater margin of safety as for example with β-adrenoceptor

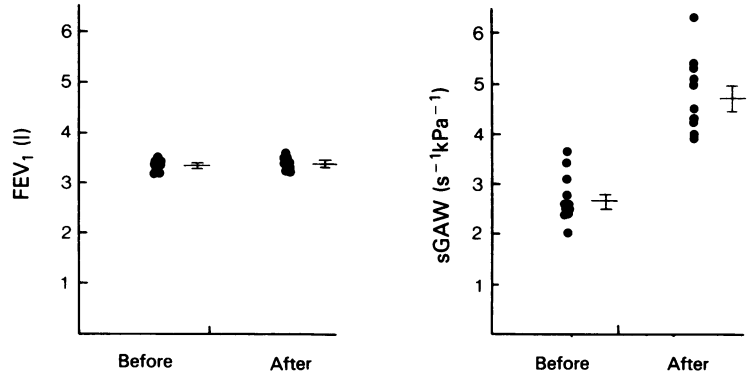

Figure 4 Sensitivity and reproducibility of the FEV_1 and sGaw in one normal subject. Ten measurements of FEV_1 and sGaw were made in one subject before and after 200 μg salbutamol. The scatter of individual points is given with the mean and s.e. mean. The FEV_1 is reproducible but is unable to detect any bronchodilatation. sGaw is sensitive but a large number of measurements must be taken to overcome the relatively poor reproducibility.

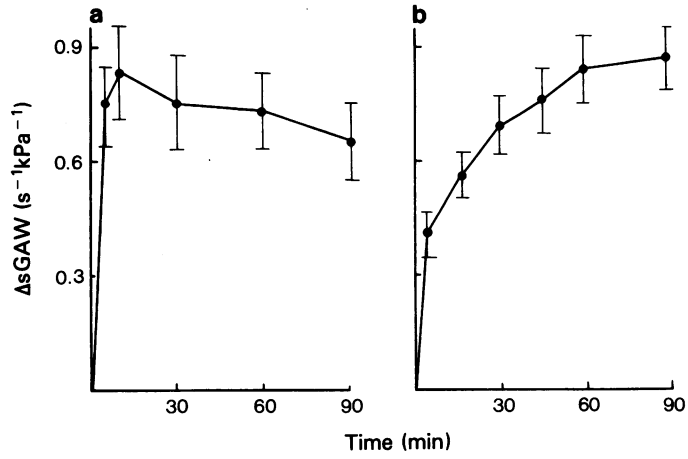

Figure 6 The mean time course for the change in sGaw after (a) 200 μg salbutamol (six subjects) and (b) 40 μg ipratropium bromide (eight subjects). Mean ± s.e. mean. (Gribbin, Baldwin & Tattersfield, 1979; Dhillon & Tattersfield, unpublished).

blocking drugs. Three examples of the ways in which the greater sensitivity of Raw has been used to study the effect of drugs in normal subjects are outlined below:

Example 1. Time course and dose-response studies.

The relative stability of airway calibre allows more detailed pharmacological studies to be carried out and this can be particularly useful for changes lasting over a long period of time. The time course or dose-response characteristics of bronchodilator drugs can be initially investigated in normal subjects (Figures 5 and 6). Although the results do not necessarily apply to patients there is generally good agreement and they provide useful preliminary studies on which to base appropriate studies for patients.

Example 2. Quantitative assessment of bronchial β-adrenoceptor blockade.

Normal subjects can be used to study certain drugs such as β-adrenoceptor blocking drugs which may be potentially dangerous for patients with asthma. The amount of bronchial β-adrenoceptor blockade following a β-adrenergic receptor blocking drug can be assessed by measuring the displacement of the salbutamol dose-response curve as shown in Figure 7 (Gribbin, Baldwin & Tattersfield, 1979). This allows a quantitative assessment of bronchial β-adrenoceptor blockade whereas previous methods have been only semiquantitative and the majority have involvllved asthmatic patients. With normal subjects it is possible to assess thehe cardioselectivity of β-adrenoceptor blocking drugs more accurately.

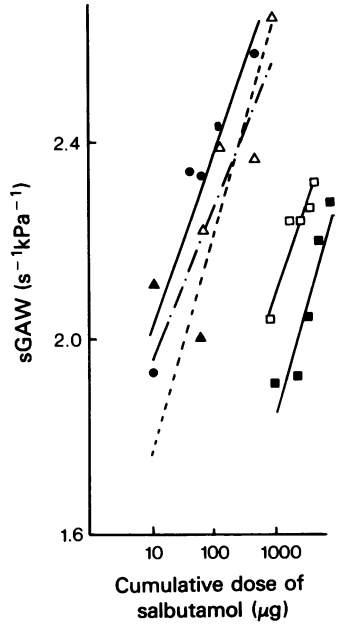

Figure 7 The salbutamol dose-response curve plotted on a log scale before (control ●) and 2 h after practolol (100 (△) and 200 (▲) mg) and propranolol (40 (□) and 80 (■) mg). All tests were carried out on separate days. The shift to the right of the dose-response curve is a measure of the amount of bronchial β-adrenoceptor blockade following each drug.

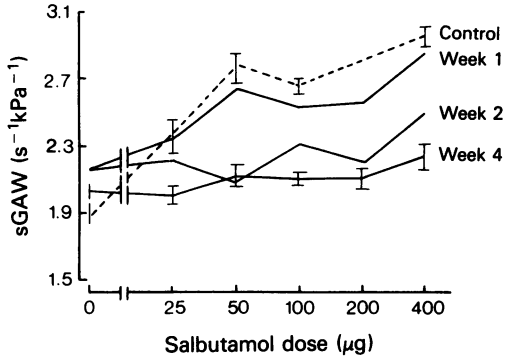

Figure 8 Dose-response curves to salbutamol from one normal subject taking increasing doses of regular inhaled salbutamol (1,600 μg a day by week 4). The response to salbutamol is attenuated after the larger doses of salbutamol demonstrating the development of resistance.

Example 3. Investigating physiological differences between normal subjects and patients.

Studies in normal subjects have shown that the bronchodilator response to salbutamol is progressively reduced if subjects take regular inhaled salbutamol in large doses (Figure 8, Holgate, Baldwin & Tattersfield, 1977). A similar study in patients with mild asthma not taking any other treatment found no evidence of any reduction in the response to salbutamol (Harvey & Tattersfield, 1978) indicating differences in β-adrenoceptor responsiveness between normal subjects and patients with asthma which are unlikely to be due to treatment.

The increased sensitivity of airway resistance measurements may be useful for certain studies in asthmatic patients such as detailed dose-response studies. They can also be used to detect small changes in response to a bronchoconstrictor agent so that larger doses of a potentially dangerous agent need not be given. The next article will discuss challenge studies in more detail. They will allow comparison of normal subjects and asthmatic patients though the results may be difficult to interpret if baseline values of Raw are dissimilar (Benson, 1975). Care must also be taken in dose-response studies where there has been a change in baseline airway resistance, for example following β-adrenoceptor blocking drugs in patients with asthma. Any shift to the right of a subsequent dose-response curve to a β-adrenoceptor agonist will then be due to both the pharmacological effect of bronchial β-adrenoceptor receptor blockade and to the mechanical effects of starting from a lower baseline. The shift of the dose-response curve cannot then be used to assess bronchial β-adrenoceptor blockade quantitatively. Similar problems occur with the bronchodilation following atropine in normal subjects and this can make assessment of the role of the vagus difficult to interpret (Benson, 1975).

The dose of an inhaled drug reaching bronchial receptors directly will only be a small fraction of the dose administered, usually less than 10% (Davies, 1975). The actual dose cannot be estimated easily but fortunately this is not important for most studies. What is important is that the same drug is given by an identical technique so that the same proportion of drug is inhaled on each occasion. If reproducible dose-response curves can be obtained it is reasonable to assume that the dose of drug reaching the receptors is fairly constant. Whether the dose plotted on the dose-response curve is the dose administered on that occasion or the cumulative dose will depend on the pharmacokinetics of the drug in question but is again relatively unimportant since the fraction of each dose reaching the receptors will be unknown but it should be consistent. Problems occur when comparing different groups of patients since deposition of aerosol may be more central in patients with airways obstruction. Following bronchodilatation with a drug such as atropine, the distribution of a second inhaled drug may be more peripheral and changes in Raw may reflect greater access of the drugs to more peripheral receptors. These problems may be circumvented for some drugs by carrying out intravenous dose-response studies which in our experience with salbutamol produce slightly more reproducible dose-response curves in normal subjects though the difference is not large (Holgate *et al.*, 1977). Whether the advantages of more precise dosage outweigh the increased convenience and safety of inhaled drugs depends on the study in question.

Conclusions

When compared to simple flow measurements resistance measurements are more sensitive but less reproducible. They are also more complicated to carry out and require more expensive apparatus. Most experience has been gained with the body plethysmograph which measures airway resistance and lung volume. The oesophageal balloon technique is considerably less convenient for the patient, does not measure absolute lung volume and appears to be less sensitive than the other two methods. The forced oscillation technique may be more reproducible than the body plethysmograph and might be of value for pharmacological studies though it again does not measure lung volume.

The increased sensitivity of resistance measurements can be valuable in clinical pharmacology and allows detailed studies to be carried out in normal subjects and patients. The measurement does not

require a preceding inspiration, nor a forced expiration, and this is an advantage in some situations.

The main problem with resistance measurements is their relatively poor reproducibility. This can, however, be minimized and we would suggest the following precautions are taken for detailed pharmacological studies using the body plethysmograph—in addition to careful calibration of the apparatus.

(1) A large number of readings are taken to obtain a mean value. Ideally the number should depend on the variability of the measurements under the conditions of the experiment. Ten measurements or more are probably necessary and this should produce a standard error of the mean of less than 10%.
(2) All traces are recorded on paper or tape and read carefully later. Alternatively, the results can be fed directly to a computer. All traces for each measurement should be coded and read blind with the same observer reading all the traces for one subject.
(3) All the readings should be averaged to obtain a mean sGaw after discarding the first two readings. Raw, Gaw and sGaw are probably not normally distributed in the population and this needs to be borne in mind when comparing two groups of patients. Unless the distribution is normalized non-parametric statistical analyses should be used.
(4) Subjects should be studied at the same time of day preferably avoiding the very early morning. They will need some practice in panting before the study and should avoid cigarette smoking, caffeine and any bronchoactive drugs.

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