

Airway resistance variability and response to bronchodilator in children with asthma

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Running head: Bronchodilation and variation in airway resistance

Abstract

Variability of airway function is a feature of asthma spanning timescales from months to seconds. Short-term variation in airway resistance (Rrs) is elevated in asthma and is thought to be due to increased variation in the contractile activation of airway smooth muscle. If true, then variation in Rrs should decrease in response to bronchodilators, but this has not been investigated.

Using the forced oscillation technique, we measured Rrs and variation in Rrs from 4 to 34 Hz in 39 children with well-controlled mild to moderate asthma and 31 healthy controls (7-13 yrs) before and after an inhaled bronchodilator (200 µg salbutamol) or placebo.

In agreement with other findings, we found that baseline Rrs at all frequencies and standard deviation of Rrs (SDRrs) below 14 Hz were elevated in asthma while neither FEV_{1.0} nor FEF_{25%-75%} were different compared with controls. We found that SDRrs changed the most of any measure in asthma, and this was the only measure that changed significantly more in children with asthma following bronchodilator ($p < 0.005$).

These results show that like airway narrowing, short-term airway variability of resistance may be a characteristic feature of asthma that may be useful for monitoring response to therapy.

Key words: airway resistance, asthma, asthma severity, bronchodilator, children, forced oscillation technique, variation.

Introduction

The forced oscillation technique (FOT) to measure impedance of the respiratory system is being used increasingly to assess lung function. This is especially the case in young children or in adult populations where spirometry is infeasible as FOT does not require a learned manoeuvre (1-5).

Airway resistance (Rrs) is the most widely reported measure, however this has been shown to be more variable than FEV₁ in terms of measurement repeatability, day-to-day measurement variation and week-to-week measurement variation (6;7). Here we examine if this variability may be functionally important and possibly indicative of airway pathology. Indeed, asthma is an episodic disease leading to variation in symptoms and lung function tests that occur over time scales from minutes to hours, days, months and even years (8).

Recently we demonstrated that variation of Rrs recorded over 15 minutes was elevated in adult asthma, and in healthy individuals was increased following the administration of a contractile agonist (9). These data suggested that increased variation in asthma was due to increased activity of the airway smooth muscle (9). If true, then airway variation should be reduced in response to bronchodilators in asthma, and therefore could be useful as a measure of the effect of a bronchodilator in reducing airway diameter variation. To confirm this hypothesis, we measured FEV₁, Rrs and variability of Rrs at baseline and following bronchodilator administration (BD) in asthmatic and healthy children as controls.

Methods

Population

Asthmatic subjects were diagnosed with asthma by a physician based on their symptoms at an average age of diagnosis of 3.39 (SE 0.38) yrs. The asthmatic children were recruited and tested at Camp Treasure Chest, a camp for asthmatic children sponsored by the Nova Scotia Lung Association. Control children had no history of lung disease or respiratory complaints and were tested at the IWK Health Center, Pulmonary Function Lab in Halifax, NS, Canada. The children's parents signed a written informed consent form prior to the start of any study procedures and the study was approved by the research ethics board of the IWK Health Centre.

Study Design

Subjects withheld all short- and long-acting beta-2 agonist medications on the day of their participation in the study. The test protocol followed for each child began with three 1-minute FOT measurements (described below in FOT) with 20-40 second breaks after each minute. The breaks allowed the subject to swallow or cough if desired, which occurred occasionally. This established a baseline FOT measurement and was followed by baseline spirometry (below) followed by another FOT measurement to assess any changes that may have occurred from the deep inspirations and forced expirations associated with spirometry. A bronchodilator (BD) was then administered (200 µg salbutamol) by metered dose inhaler (MDI). Fifteen of the control children were given a placebo inhalation (propellant-only MDI) instead of a BD as a control. FOT measurements were made at 4-5 min intervals following BD, and spirometry

measurement at 12-15 minutes was made, followed by three 1-minute post BD FOT measurements with short breaks in between, as performed during baseline FOT. These final three 1-minute FOT and spirometry measures were used to assess changes due to a BD and to compare these results between patient populations.

Spirometry

Flow-volume curves were recorded with a portable, pneumotachograph-based spirometer (PrestoFlash, Burdick, Inc., Milton, WI) to determine FEV₁ and FEF_{25-75%}. The spirometer was calibrated daily with a calibrated syringe. Acceptance of flow volume curves was according to ATS criteria for children (10). Results were expressed as the percentage of predicted values according to Knudson et al. (11).

FOT

FOT measurements were made using a custom-built FOT device (Fig. 1) constructed at Dalhousie University. Subjects spontaneously breathed through a mouthpiece (FreeFlow, SensorMedics, CA, USA) and bacterial filter (Collins DC-1, Ferraris Respiratory, CO, USA) wearing nose clips, cheeks clasped in their hands, while comfortably seated with the head in a neutral position. The device used a loudspeaker to produce low-amplitude pressure oscillations (approximately ± 1 cmH₂O) with frequency range > 50 Hz. A Fleisch pneumotachograph with differential pressure transducer (TD-05-AS, SCIREQ, Montreal, Canada) with CMRR measured to be greater than 60 dB was used to measure flow and a pressure transducer (TD-05-AS, SCIREQ) was used to measure pressure at the patients' airway opening. Both signals passed through a signal conditioner (SC-24, SCIREQ) for anti-alias filtering with 6-pole Bessel filters (cut-off

100 Hz) and were sampled at 700 Hz. A bias fan provided a constant flow of approximately 12 L/min of fresh air via long, high inertance, stiff walled tubes (1.9 cm x 176.5 cm length). Flow and pressure were calibrated weekly and the device was verified with a 5 cmH₂O/l/s constant flow resistor (Hans Rudolph, MO, USA).

We designed a signal with low crest factor (peak-to-peak amplitude/SD (12)) composed of frequency components of 4, 6, 10, 14, 22, 26 and 34 Hz of 1 second duration which was repeatedly applied at the patient's airway opening during spontaneous breathing. The frequencies were higher than breathing to avoid contamination from the breathing frequencies and are the prime numbers multiplied by two to largely eliminate harmonic distortion from any non-linearities (13). The magnitude of pressures at 4, 6 and 10 Hz was increased by 3.6, 2.4 and 1.4 times respectively to improve signal to noise ratio.

Data Analysis

Figure 2 is an example of the pressure and flow data obtained from one subject. For both pre BD and post BD FOT measurements, three 1 minute data sets were concatenated to give 3 minutes of pressure and flow data. The impedance to airflow measured at the transducer (Z_{meas}) was derived at each of the input frequencies from either 1-second non-overlapping blocks or 4-second, 75% overlapping blocks of the pressure and flow signals according to

$$Z_{meas} (f_i) = \frac{P(f)}{\dot{V}(f)}, \quad (1)$$

where f_i denotes calculation at one of the 7 frequencies ($i = 1 \dots 7$), and $P(f)$ is the Fourier transform of pressure and $\dot{V}(f)$ is the Fourier transform of flow. Thus Z_{meas} was

a time-series of 180 points. One second blocks were used for calculation of standard deviation as described below to capture as much variation as possible, while 4-second blocks were used for calculation of median resistance which provided a small improvement in estimation of median Rrs (<5%) particularly at low frequencies.

The impedance of the FOT system proximal to the patient was compensated for by measuring closed system (mouthpiece blocked) and open system (mouthpiece open to atmosphere) impedances ensuring coherence greater than 0.99 and computing Zrs (14). The resistance to airflow, Rrs was calculated as the real part of Zrs (Figure 2b) and the reactance was not analyzed in this study. Standard deviations of resistance (SDRrs) were evaluated at each oscillation frequency from the time-series of Rrs as

$$SDRrs(f_i) = SD(Rrs(f_i)) \quad (2)$$

where SD denotes calculation of standard deviation.

Pressure and flow data that appeared to be associated with glottis closure, swallowing or episodes of irregular breathing were discarded. We also discarded Rrs values greater than 5 standard deviations above the mean, as well as rare negative Rrs values likely caused by the subject's breathing occasionally generating flow components which contaminated the signal frequencies. One-second blocks of pressure and flow were discarded until coherence calculated over a 16-second window was greater than 0.9 for all data analyzed (15). Furthermore, we estimated noise amplitude at a frequency from the average amplitude of the pressure and flow spectra at neighbouring non-signal frequencies (e.g. for 10 Hz we used the average of 8, 9, 11 & 12 Hz) and rejected cycles with any component having signal to noise ratio (SNR) less than 10.

Statistical Methods

Rrs, SDRrs, FEV₁ and FEF_{25-75%} were tested for normality in each patient population using Shapiro-Wilk normality tests as well as normality plots. Baseline measurements of FEV₁, FEF_{25-75%}, Rrs and SDRrs were each compared between the two patient populations using unpaired t-tests. The effect of a BD was assessed between asthmatics and controls using a separate one-way repeated measures ANOVA for each of FEV₁, FEF_{25-75%}, Rrs and SDRrs measures. The difference between placebo and BD administration in controls was assessed with another separate one-way repeated measures ANOVA for each of FEV₁, FEF_{25-75%}, Rrs and SDRrs measures. The effect of a BD was also assessed in asthmatics classified by severity according to the GINA guidelines (16), and in controls with a one way repeated measures ANOVA and Games Howell post hoc tests. All statistical tests were done using SPSS 10.1 statistical software. Statistical significance was determined by $p < 0.05$, unless otherwise stated.

Results

The results are organized into baseline comparisons between asthma and control subjects first, followed by comparisons of the effect of a BD between populations as well as subpopulations of asthma classified according to disease severity. Shapiro-Wilk normality tests and normality plots indicated that spirometry and FOT measurements were all approximately normally distributed.

There were no significant differences in age or height between asthmatic and control subjects (Table 1), and asthmatic subjects were slightly heavier ($p=0.045$). The subjects with asthma were taking different medication combinations as follows: 7 were taking as needed short-acting beta-2 agonist (SABA) alone (salbutamol 200 µg), 13 were

taking inhaled corticosteroid (ICS) plus as needed SABA (fluticasone propionate 125-250 µg twice daily + salbutamol 200 µg), 4 were taking a leukotriene receptor antagonist (LTRA, montelukast 5-10 mg daily) plus as needed SABA, 15 were taking combination ICS plus long-acting beta-2 agonist with as needed SABA, half also taking a LTRA (8 of 15 taking fluticasone propionate 200-500 µg daily/salmeterol 50 µg daily and 7 of 16 budesonide 200-400 µg daily/formoterol 12 µg daily).

Baseline Comparisons

There was no difference in baseline measures of percent predicted FEV₁ between asthmatic and control subjects (p=0.509), being 98.4% (SE 2.4) and 100.6 % (SE 2.1) of predicted values respectively. There was a larger but still not significant (p=0.105) difference between baseline FEF_{25-75%} measures, being 85.5% (SE 3.2) and 94.4% (SE 4.6) of predicted in asthmatic and control subjects respectively. Thus, neither FEV₁ nor FEF_{25-75%} distinguished between the asthmatic and control subject groups at baseline.

At baseline, Rrs was higher in asthmatics at all frequencies (p<0.001), and SDRrs was also higher in asthma at 4, 6 and 10 Hz (p <0.001, p=0.035 and p = 0.018, respectively, Figure 3). Rrs was constant across frequencies in control subjects, but a decreasing dependence with frequency was detected in asthmatics as a significant negative slope. There was no change in Rrs or SDRrs before and after the FEV₁ manoeuvre.

Effect of a Bronchodilator

The subjects with asthma were well controlled at the time of measurement. Breathing frequency and tidal volume by integrated flow was not changed with BD in any

group. In response to BD, only two of the 39 asthmatic children showed changes in FEV₁ exceeded 12%, a threshold indicating clinically significant reversibility (17) and only one of these subjects had a greater than 20% increase in FEF_{25-75%}.

The FOT measures of Rrs and SDRrs were divided into three frequency ranges to simplify analysis: the average of 4 Hz and 6 Hz measurements were considered low frequency, the average of 10 Hz and 14 Hz were considered middle frequency and the average of 22 Hz, 26 Hz and 34 Hz were considered high frequency. Within asthmatic subjects there was considerable overlap between pre- and post-BD Rrs, SDRrs and FEV₁ measures (Fig. 4). Comparing pre-BD measures within Fig. 4 as well as middle frequency values using linear regression, FEV_{1.0} was weakly linearly correlated with Rrs, with $r^2 = 0.20, 0.16$ and 0.21 ($p = 0.0117, 0.0260, 0.009$) for low, middle and high frequencies respectively, while FEV₁ was not correlated with SDRrs at any frequency range. Rrs was better correlated with SDRrs with $r^2 = 0.40, 0.41, 0.39$ ($p = 0.00016, 0.00013, 0.00022$) also at low, middle and high frequencies, respectively. Asthmatic subjects with higher SDRrs values were clustered at lower FEV₁ (panels C&D) and higher Rrs (panels E&F).

The response to BD between control and asthmatic subjects in Rrs, SDRrs, % predicted FEV₁ and FEF_{25-75%} are summarized in Figure 5. No measure changed in controls given a placebo. FEV₁ and FEF_{25-75%} increased significantly in controls (3.1% SE 1.3% and 12.7% SE 1.9% respectively) and asthmatics given a BD (4.8% SE 0.7% and 7.8% SE 2.8%, respectively). These increases were small and not clinically significant, and were not significantly different between control and asthmatic children.

Rrs decreased significantly at all frequencies in both asthmatics and controls given a BD but not differently between groups (Figure 5). Similarly, SDRrs decreased

significantly at all frequencies in both asthmatics and controls given a BD, but in this case, SDRrs changed significantly more in asthmatics than controls at low and middle frequencies but not at high frequencies. Thus the change in SDRrs due to BD at low and middle frequencies distinguished between control and asthmatic subjects, while the changes in Rrs and FEV₁ due to BD did not.

Since the children with asthma differed in their severity and therapy, we also examined the difference at low frequencies in response to BD measured by FEV₁, Rrs, and SDRrs based on asthma severity according to the step in daily medication regimen by the GINA guidelines (16). In this study there were 17 subjects with mild persistent asthma, 16 with moderate persistent asthma which were sufficient for analysis, but only 7 with mild intermittent asthma and none with severe persistent asthma. Repeated measures ANOVA with Games-Howell post hoc tests revealed significant differences amongst asthma severity in both baseline measures and responses to BD. At baseline, mild persistent asthmatics had lower FEV₁ and FEF_{25-75%} than both moderate asthmatics and control subjects, in contrast to the lack of difference when all asthma groups were grouped together described above. For the FOT measures, although Rrs of all asthma groups were higher than control (Fig. 6, inset), there was no difference in Rrs between mild persistent and moderate asthma. This was in contrast with baseline SDRrs where only SDRrs of mild asthma was higher than control and there was no significant difference between control and moderate asthma (Fig. 6, inset). Furthermore, similar to the grouped data in Figure 5, there were no differences in response to BD measured by spirometry or Rrs when subjects were split according to asthma severity, but the change in SDRrs due to BD was more in mild asthmatics than both moderate asthmatics and controls.

Discussion

The principal findings of this study are that 1) variations in Rrs were greater in children with asthma and 2) administration of a BD caused a greater decrease in variation of Rrs in asthmatics compared to controls; and 3) the reduction in variability of Rrs exceeded the change Rrs or FEV₁ following BD. These findings have significant implications for airway function in asthma.

Spirometry and Rrs

In all subjects, baseline measures of FEV₁ and FEF_{25-75%} were within the normal range as commonly found in stable subjects with asthma (18;19). Only 4 asthmatics had FEV₁ less than 80% of predicted (20;21). We found that Rrs was significantly elevated in asthmatics compared to controls as previously reported in adults and in children (9;22;23) at all frequencies, and showed similar frequency dependence (Fig. 3) to previous studies (24-26). Additionally, baseline Rrs values corresponded well to previous values obtained in asthmatic children (27;28), but were slightly higher than those previously obtained in healthy children (3;28;29).

Healthy children and well-controlled asthmatic children do not show much change with BD in spirometric measures, which we also found (30). Furthermore, while we found that Rrs decreased in asthma in response to a BD, it also decreased similarly in the healthy children by an amount consistent with previous results (28). Thus neither the BD response in FEV₁ nor Rrs distinguished between children with and without mild to moderate asthma, likely due to the fact that the asthma subjects were well controlled. While Rrs and FEV₁ have been used to assess bronchodilator function and have been used

to distinguish disease (28;31), there is no consensus on either the sensitivity or the correlation between methods in bronchodilator testing (15).

Variation in Rrs

While it is well established that variation in airway function is a central feature of the disease, this is largely based on long-term variability of airway obstruction from several diurnal measurements of FEV₁ and PEFr over several weeks or months of measurement (32;33). Indeed, high diurnal variation of PEFr is associated with a higher risk for exacerbation (32). Long-term variation has also been assessed by FOT showing that within day and between day variability in Rrs is elevated in asthma (34). Short-term variability in the time scale of minutes similarly finds Rrs to be elevated in both adult and childhood asthma (9;35), in agreement with our findings. Despite the similarities, it is unknown if the mechanisms responsible for long-term variation in lung function are the same as those for short-term variation.

There are several sources for variation in Rrs in addition to airway smooth muscle activity (9), including but not limited to episodic movement of the glottis, changes in lung volume which act to dilate or narrow airway diameters, and noise at the transducers particularly due to breathing. Unlike mean Rrs, the effects of noise on SDRrs cannot be reduced by averaging. However, we minimized the effects of breathing noise by shunting most of the breathing through the bias tubes which provided a low resistance at breathing frequencies, thereby decreasing flow and pressure swings due to breathing (Fig. 2). In our case, noise was never more than 10% of the signal as described in Methods. We used a perturbation signal and analysis window of 1 second duration to estimate Rrs which, although this improved signal to noise ratio compared to shorter windows, limited the

ability to track rapid variation in Rrs. This likely led to the decreasing frequency dependence of SDRrs and possibly the lack of sensitivity of SDRrs to differences between groups and to BD-induced changes at high frequencies (Figs. 3 and 5). Longer windows and the presence of the upper airway shunt tend to underestimate breath-by-breath variation in Rrs (36). Shorter windows would improve the ability to track Rrs, but lead to overestimates of SDRrs from increased noise contamination. This suggests that fewer or single signal frequencies should be employed to improve signal to noise ratio and enable shorter estimation windows.

A strong determinant of Rrs and thus SDRrs are the changes in lung volume and flow that occur with breathing. Rrs changes with dilation and renarrowing associated with breathing, but also with alterations in upper airway geometry associated with the glottis (9;36;37). Rrs also changes with flow associated with turbulence and other effects, and in anaesthetized children can change 2-fold with a 3-fold change in flow under isovolume conditions (38). Agonists can modulate the volume dependence of Rrs (39;40), which may have contributed to the changes in Rrs and SDRrs in asthma and with BD. However, the effects of a BD on median Rrs were similar in both groups and we did not observe any changes in tidal volume with bronchodilator or between asthma and control. Differences in Rrs could also be attributed to changes in FRC which we did not measure (9;39).

If changes in airway smooth muscle activation are reflected in variation of Rrs, this can occur either by modulation of lung volume dependence as described above, or by directly altering airway diameter and thus airway resistance. The latter effects of bronchodilator on Rrs are well established and reproduced here (Fig. 5 and 6), supporting the idea that some of the variation in Rrs reflects variation in airway smooth muscle activity and is potentially useful in understanding airway pathology. However, for the

resistance to vary randomly and frequently, from breath-to-breath and even possibly within breaths, temporal variations in airway constriction must be occurring in a spatially heterogeneous fashion through the airway tree. It is now known that airway narrowing during constriction is markedly spatially heterogeneous, particularly in asthma, either inferred from FOT impedance data, or directly by imaging methods (41-44). It is reasonable to expect that these effects vary temporally as well as spatially, leading to variations in Rrs impedance data as suggested by this and other studies (9;35). Temporal variation in airway diameter has yet to be examined however with imaging methods.

Effect of a Bronchodilator

In support of the notion that some of the variation in Rrs is due to changes in smooth muscle activation, we previously found that variation in Rrs was increased in asthma and could be increased with methacholine administration in subjects with asthma (9). We reasoned that if this were true, then SDRrs should decrease in asthmatic subjects that were administered a bronchodilator as we report here for the first time.

We further found that SDRrs and the response to BD were significantly different amongst subjects with different degrees of asthma severity based on the current step in daily therapy prescribed according to GINA classification (16). However, our sample is small and it is likely that some subjects were at a higher step in therapy relative to their symptoms. Also, the distinction of severity is problematic once treatment is initiated and some of the differences we observed may be due more to therapy than to severity and Indeed, in a 20-month cross-over study by Taylor et al (45), asthma symptoms and variation in PEF were higher in asthmatic subjects that received short-acting beta agonists compared to subjects that received long-acting beta agonists (LABA). We similarly found

that asthmatics that were not taking LABA, but were taking inhaled corticosteroids and could be classified as mild persistent asthma were the most variable, with highest baseline SDRrs and greatest decrease in SDRrs with BD. In contrast, subjects that received LABA with corticosteroids and could be classified as moderate persistent asthmatics had the lowest baseline SDRrs of the asthma subjects and the smallest decrease with BD, perhaps indicating LABA may contribute to reduced variability similar to reduced exacerbations reported in some other studies (45;46). While a prospective study is needed to confirm a relationship of short-term variation in Rrs to long-term variation in airway function and symptoms, this may be important, especially since it has been recently shown that fluctuation analysis of variation in airway function can predict the risk of asthma exacerbations (8).

Geometric Considerations

Due to the nonlinear inverse 4th power law dependence of airway resistance on diameter, a change in SDRrs can be shown to be due to either a change in the standard deviation of airway diameters, but also due to a change in *average* airway diameter, with no change in diameter variation. If one assumes the time-averaged diameter d_0 of an airway is perturbed by some random variation $s(t)$ such that diameter = $d_0 + s(t)$, then normalized to the average diameter we can write $R/R_0 = 1/(1 + s/d_0)^4$ where R_0 is the resistance at the average diameter. If there is bronchodilation with no change in the percent variation of airway diameter, which is the case for constant s/d_0 (constant coefficient of variation), then the change in SDRrs of the airway is equal to the change in Rrs (indicated by the arrow in Fig. 7). This could conceivably occur with sufficient decreases in airway stiffness with little change in load. Also possibility is dilation without

a change in airway diameter variation which predicts a greater decrease in SDRrs than Rrs (demonstrated by numerical simulation giving the thin lines in Fig 7). Any additional decrease in variation would lead to even larger decreases in SDRrs. This analysis implies that SDRrs is a more sensitive measure than Rrs to the effects of a BD.

This geometric dependence of SDRrs on Rrs predicts that SDRrs should be correlated with Rrs. Indeed, in Fig. 4 they are mildly correlated ($r^2 \sim 0.4$). However, in response to BD we found different behaviours: some subjects decreased Rrs more than SDRrs, but most subjects decreased SDRrs more than in Rrs, with a few subjects decreasing SDRrs substantially with very little change in Rrs (Figure 7). Also, amongst asthma classifications, a greater proportion of mild persistent and moderate persistent asthmatics decreased SDRrs more than Rrs. The greater change in SDRrs than Rrs with BD implies, that while BD usually dilated the airways, it may also function to calm the airways, reducing the tug-of-war between airway constriction and dilation (9).

In conclusion, like recently visualized spatial heterogeneity in asthmatic airways, measurement of SDRrs by FOT may provide a window onto temporal variation in airway function. It is an easily performed method that is more sensitive than both Rrs and FEV₁ for evaluating the effect of a bronchodilator, but its dependence on changes in lung volume needs further investigation before studies are developed to evaluate its clinical utility.

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Table 1. Subject characteristics in asthmatic and control children

| | | Asthmatic | Control |
|----------------------------|---------------|------------------------|------------------------|
| N | | 39 | 31 |
| Gender | Male | 25 | 13 |
| | Female | 15 | 18 |
| Age (yrs) range | | 9.90 (SE 0.16) 8-12 | 9.93 (SE 0.32) 7-13 |
| Height (cm) | | 137.35 (SE 1.57) | 141.72 (SE 2.34) |
| Weight (kg) | | 43.63 (SE 2.21) | 36.55 (SE 1.65) |

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Figure 1: The FOT device creates oscillatory pressure at the loudspeaker which is transmitted to the patient airway via a mouthpiece. Fresh air is supplied by a bias fan to the patient via long, high inertance tubes which shunt much of the low frequency breathing prior to the pneumotachograph and pressure transducers.

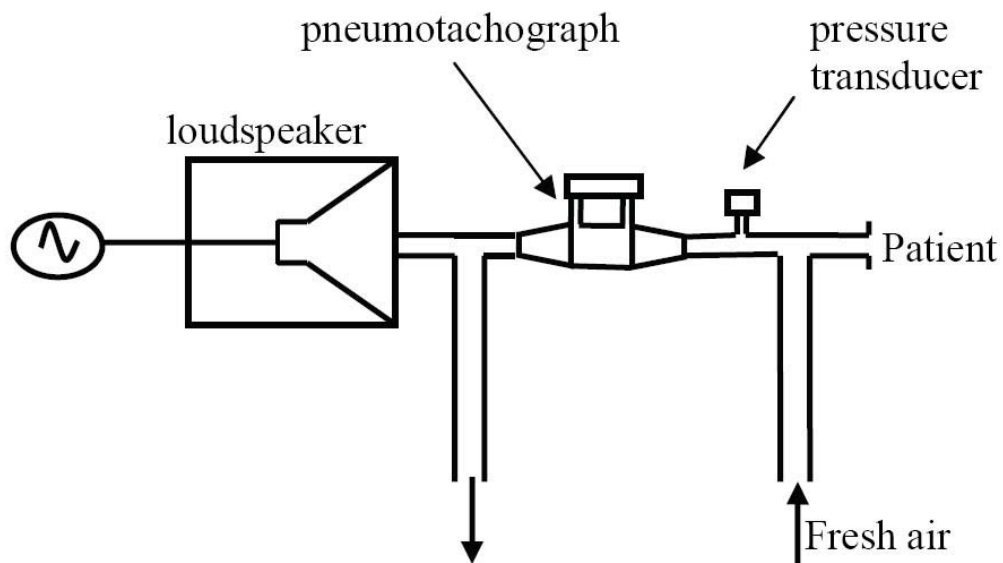


Figure 2: Flow and pressure contained 7 frequencies repeating every second from 4 Hz to 34 Hz. Panel A shows 10 seconds of baseline pressure (—) and flow (—) recorded from one individual. Panel B shows 150 seconds of baseline Rrs from a subject calculated once per second from 4 Hz (—) and 34 Hz oscillations (—).

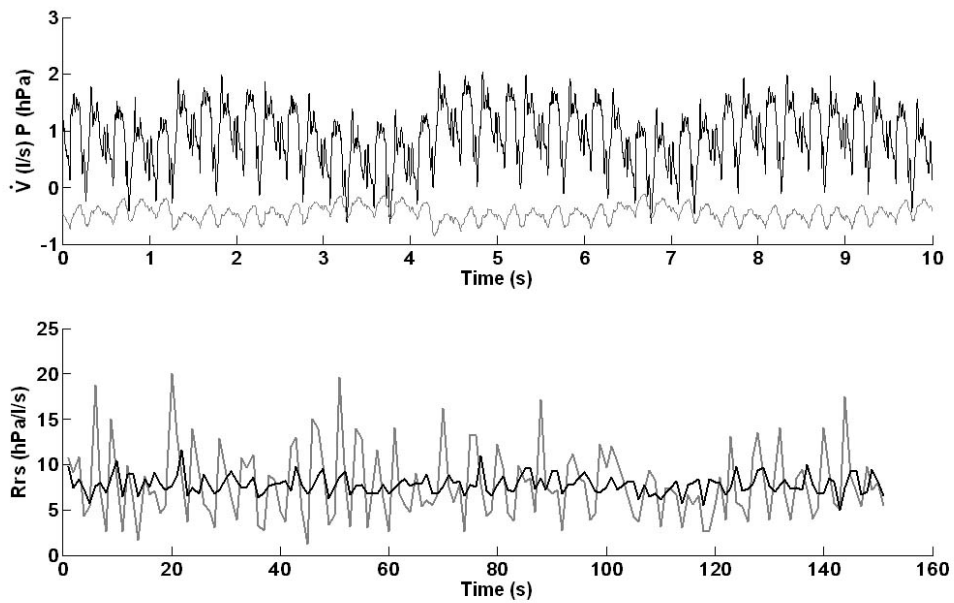


Figure 3: Median baseline Rrs (upper panel) and SDRrs (lower panel) in asthmatics (■, n = 39) and control subjects (□, n = 31). At baseline, Rrs was elevated in asthma at all frequencies compared with control ($p < 0.001$), while SDRrs was elevated in asthma below 14 Hz ($p < 0.04$) compared to controls. Error bars indicate SE.

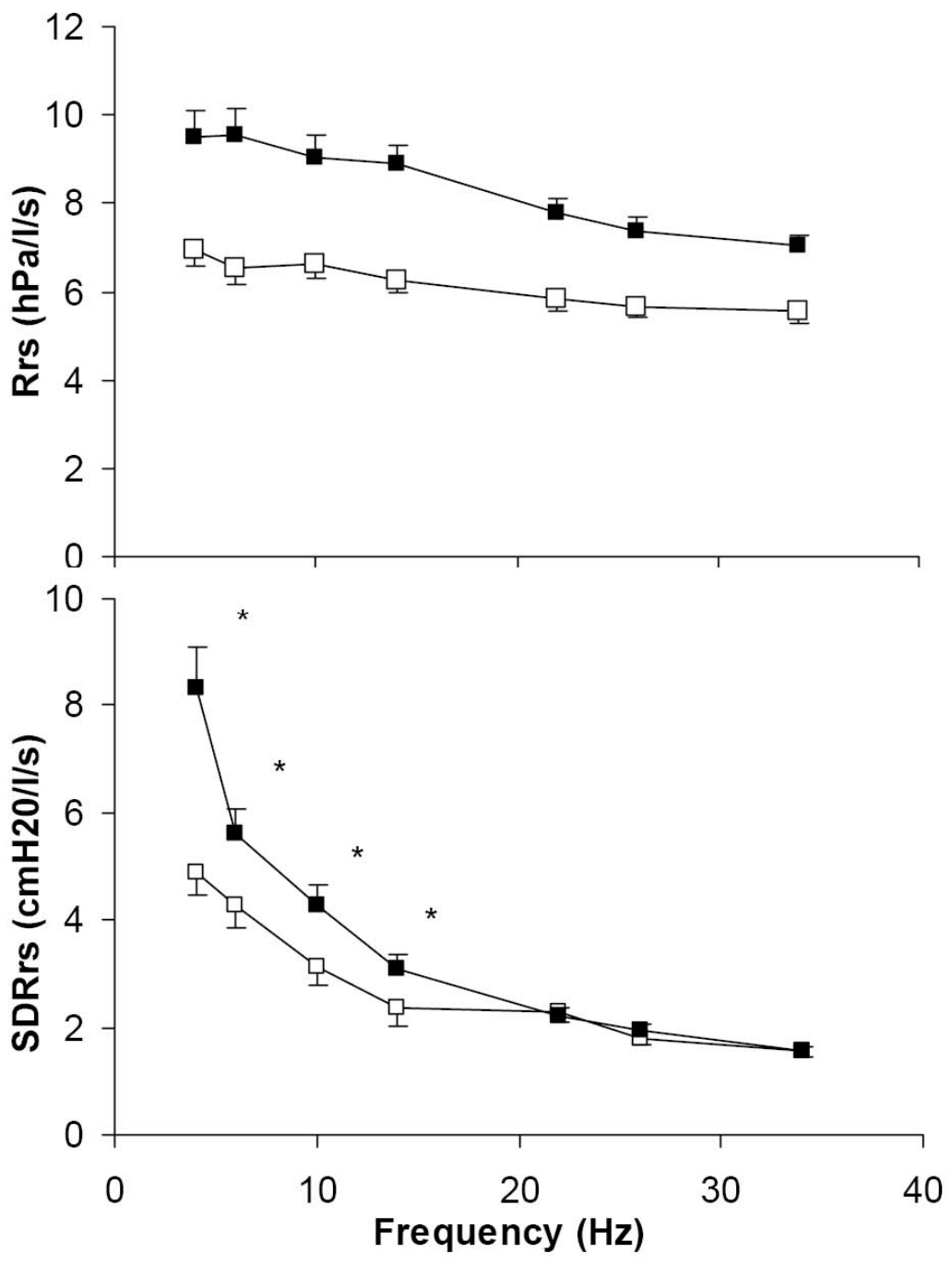


Figure 4: Baseline (\blacklozenge) and post bronchodilator (\square) values for each asthmatic child from low frequencies (left) and high frequencies (right). Values from different subjects overlap substantially for all parameters Rrs, SDRrs and FEV_{1.0}.

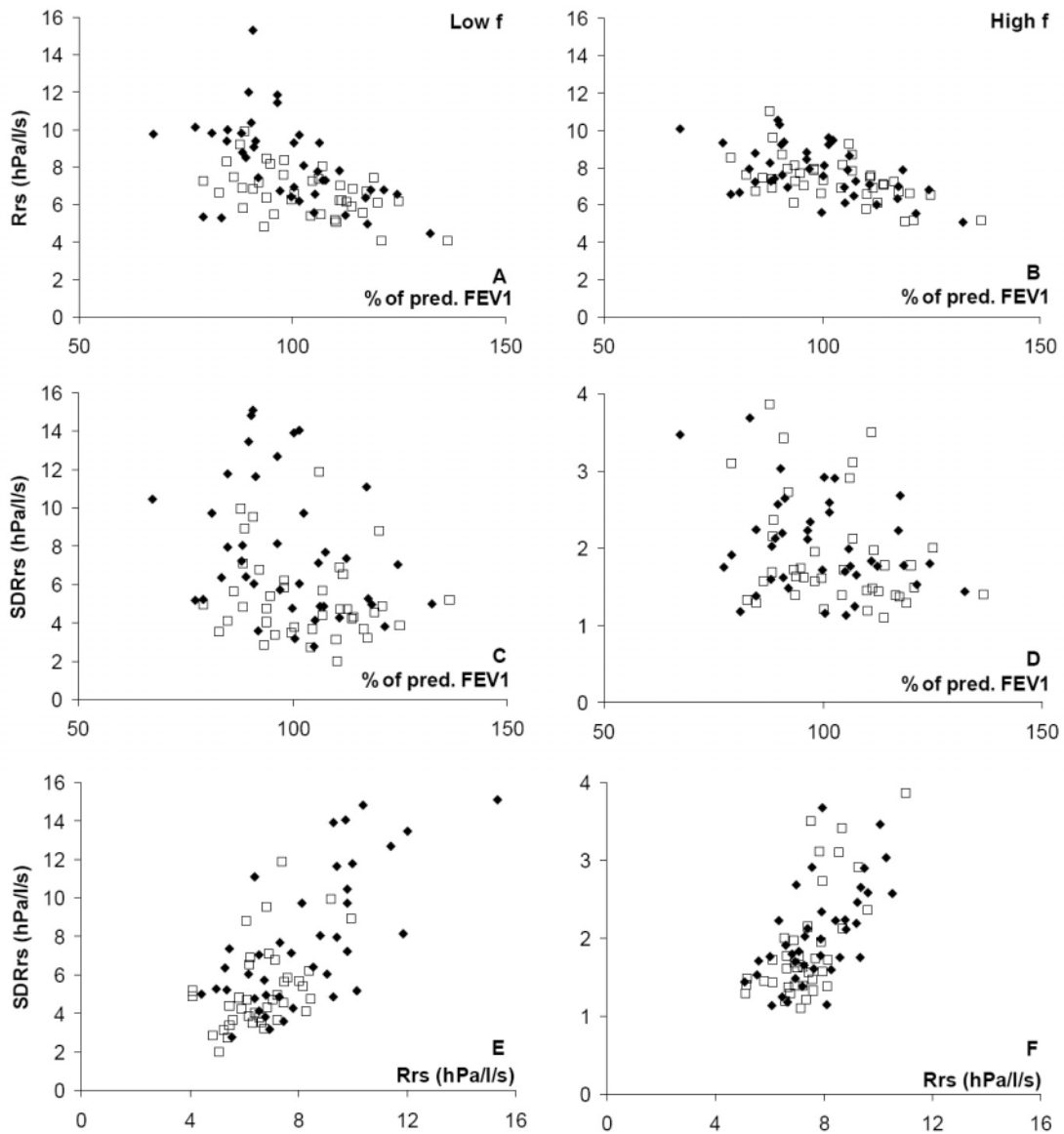


Figure 5. Comparison of the effect of a bronchodilator (BD, 200 µg salmeterol) measured by spirometry (% predicted FEV₁ and FEF_{25-75%}) and FOT (Rrs and SDRrs at low medium and high frequencies L, M and H, respectively) in asthmatic subjects (n=40, ■), control subjects given a BD (n=16, ▒) and control subjects given a placebo (n=15, □). BD increased FEV_{1.0} and FEF_{25-75%}, and decreased Rrs at all frequencies in both control and asthmatic subjects (* p <0.05). Comparing asthmatic and control subjects administered BD, only SDRrs decreased significantly more in asthmatics (# p<0.05). Error bars indicate SE.

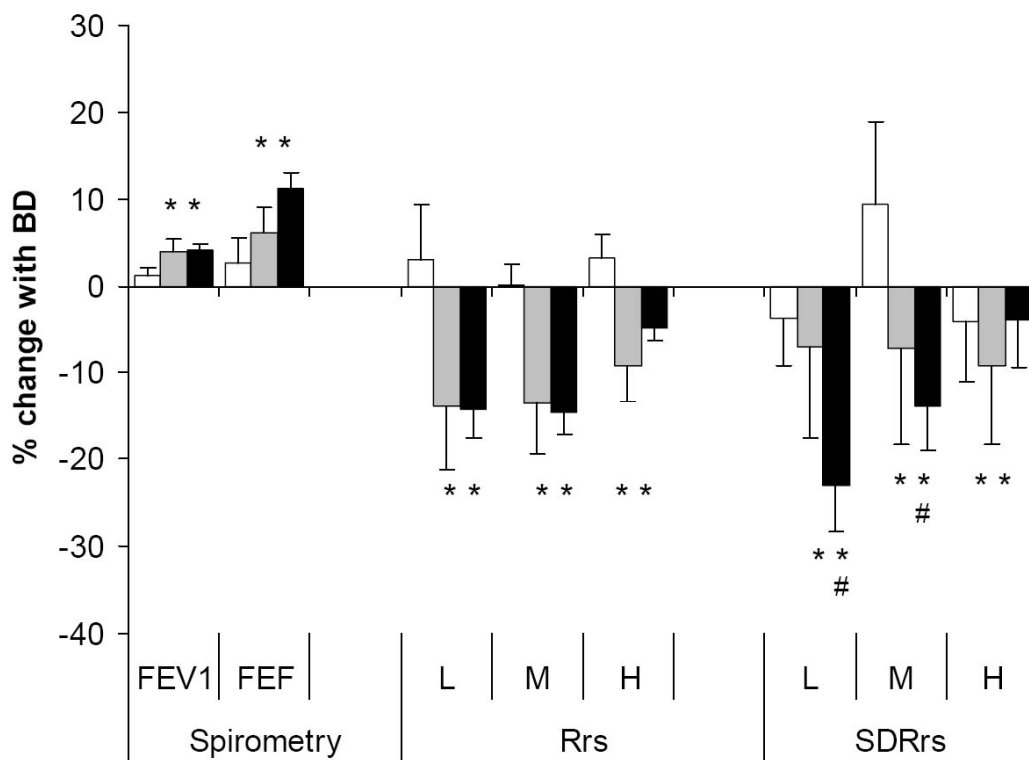


Figure 6. Percent change with bronchodilator administration classified according to GINA score for FEV₁, FEF₂₅₋₇₅, Rrs, and SDRrs with controls (n = 16, □), mild persistent asthmatics (n=17, ▒), and moderate persistent asthmatics (n=16, ■). Inset shows baseline values. Only significant differences between groups are shown with different letters indicating a difference (p<0.05).

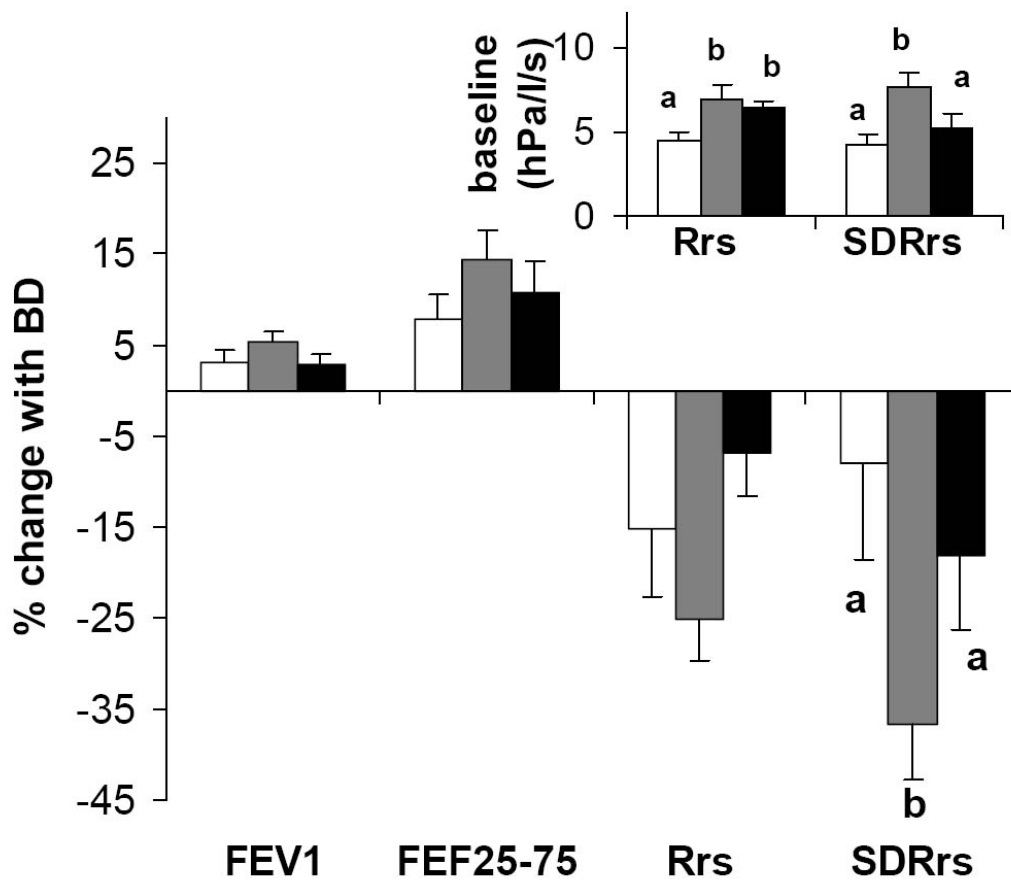


Figure 7. Individual percent change in SDRrs in all asthmatics plotted versus percent change in Rrs at low frequencies (□ intermittent, ◆ mild persistent, ▲ moderate)

asthma). The arrow indicates the line of identity analytically predicted for a single airway with an increase in mean diameter and no change in percent diameter variation (see text). The lines indicated by open circles and crosses are the numerically predicted relations for simple dilation up to 30% with no change in variation of airway diameters with Gaussian distributed diameters with SD fixed at 0.1 and 0.2 of baseline diameter, respectively. Most subjects were in the lower left quadrant, with most of these decreasing SDRrs more than Rrs.

