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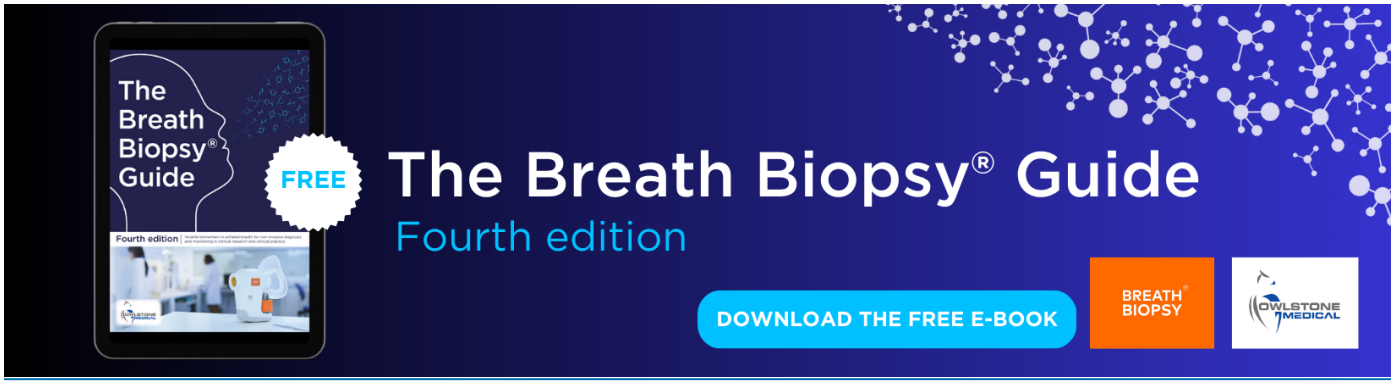

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A method of estimating inspiratory flow rate and volume from an inhaler using acoustic measurements

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Abstract

Inhalers are devices employed to deliver medication to the airways in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease. A dry powder inhaler (DPI) is a breath actuated inhaler that delivers medication in dry powder form. When used correctly, DPIs improve patients' clinical outcomes. However, some patients are unable to reach the peak inspiratory flow rate (PIFR) necessary to fully extract the medication. Presently clinicians have no reliable method of objectively measuring PIFR in inhalers. In this study, we propose a novel method of estimating PIFR and also the inspiratory capacity (IC) of patients' inhalations from a commonly used DPI, using acoustic measurements. With a recording device, the acoustic signal of 15 healthy subjects using a DPI over a range of varying PIFR and IC values was obtained. Temporal and spectral signal analysis revealed that the inhalation signal contains sufficient information that can be employed to estimate PIFR and IC. It was found that the average power (P_{ave}) in the frequency band 300–600 Hz had the strongest correlation with PIFR ($R^2 = 0.9079$), while the power in the same frequency band was also highly correlated with IC ($R^2 = 0.9245$). This study has several clinical implications as it demonstrates the feasibility of using acoustics to objectively monitor inhaler use.

Keywords: acoustics, asthma, COPD, inhalers, inspiratory flow rate, volume

S Online supplementary data available from stacks.iop.org/PM/34/903/mmedia

(Some figures may appear in colour only in the online journal)

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1. Introduction

Asthma and chronic obstructive pulmonary disease are two common types of chronic respiratory disease, characterized by airways obstruction. Prevalence of these two respiratory diseases has risen sharply over recent decades, creating a large economic burden due to treatment costs (Mannino 2002, Braman 2006). Obstructive airway diseases are primarily treated by delivering medication to the airways using inhalational devices. Medication efficacy is significantly dependent on the amount of drug reaching the small airways of the lungs. The medication in the inhalers is delivered to the respiratory tract via an inhalational maneuver. The clinical effect of inhaled therapy depends on the lung dose, its particle size distribution, the patient's inspiratory flow rate, inhaled volume and degree of airways obstruction (Sumby *et al* 1992). Several studies have highlighted that errors in inhaler technique may be as detrimental as the lack of temporal adherence (Crompton *et al* 2006, Nikander *et al* 2011).

The two main types of inhalers used are metered dose inhalers (MDIs) and dry powder inhalers (DPIs). DPIs are considered advantageous over MDIs since they avoid the use of propellants, and are instead actuated during the inhalation (Malmberg *et al* 2010). The elimination of propellants allows patient coordination issues to be overcome. However, a disadvantage of DPIs is that the particle size distribution of the aerosol generated depends on the inspiratory flow rate through the device (Nielsen *et al* 1997). This flow rate can vary depending on the resistance of the DPI being used and on a patient's inspiratory effort and inspiratory capacity (IC). The inspiratory flow rate influences the efficiency of removing particles of the drug formulation from the inhaler and it also affects the efficiency of de-aggregation of the particles and the fine particle dose that gets into the respiratory tract (Vidgren *et al* 1988). This correlates to an absolute peak inspiratory flow rate (PIFR) above 30 L min^{-1} and ideally above 60 L min^{-1} (Pauwels *et al* 1997).

Previous studies have demonstrated that the primary cause of poor clinical outcomes in inhaler therapy is due to the inability of patients to generate sufficiently high PIFRs through their DPI (Jarvis *et al* 2007, Wieshammer and Dreyhaupt 2008). Currently, the only methods available to clinicians for assessing inhaler technique are subjective checklist methods and the Clement Clarke *In-Check Dial*™. Subjective checklist methods give no indication of whether the patient had sufficient inhalational flow effort or IC to achieve adequate drug delivery. The *In-Check Dial* simulates the resistance of the main types of inhalers to give an estimation of the patient's PIFR. This method is quite effort dependent and may not correlate well with the *in vivo* PIFRs developed by the patient while using the actual inhaler device. There is a definite need for a device, which gives real-time feedback of inhalational technique and effort over a prolonged period of time.

This study aims to investigate if a relationship exists between inhaler inhalation sounds and airflow. Inhaler inhalation sounds are a mixture of both respiratory sounds and sounds created from turbulence in the inhaler. It is well known that a relationship exists between airflow and respiratory sounds. Most of the previous research in this area has examined the relationship between respiratory sounds generated at the trachea and on the chest wall to airflow. A relationship between airflow and sound amplitude was established by Shykoff *et al* (1988). Charbonneau *et al* (1987) also derived a formula for this relationship using mean amplitude and frequency to predict flow rates from respiratory sounds. Hossain and Moussavi (2004) again established a relationship between amplitude and airflow, but found that the average power in the frequency band 150–450 Hz provided a slightly stronger relationship with flow rate compared to mean amplitude in healthy subjects. Together these studies indicate that a definite relationship exists between airflow and respiratory sounds.

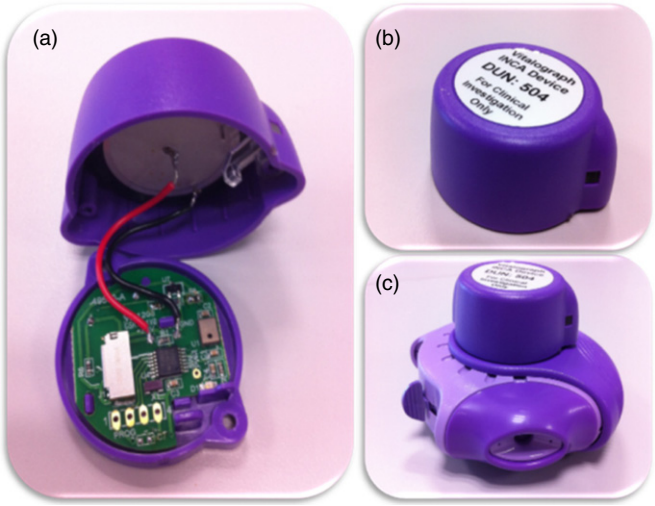

Figure 1. (a) Internal components of the INCA device, (b) external view and (c) the INCA device attached to the Diskus^{TM} inhaler.

The main objectives of this study were to investigate the relationship between temporal and spectral features of the inhalation signal and inspiratory flow rate and volume measurements in healthy subjects. It was hypothesized that features obtained from the inhalation signal could be used to estimate PIFR and IC. Three measurements of amplitude were used, in addition to the average power at a range of different frequency bands, in order to investigate which acoustic measurement had the best correlation with PIFR and IC. Using the inhalation signal to predict such inspiratory values would establish the feasibility to provide clinicians with new objective measurements on patient inhaler use.

2. Methods

2.1. Participants

Fifteen healthy volunteers between the ages of 18–40 years were recruited. Subjects were excluded if they had any cardiac, respiratory, hepatic, renal dysfunction, recent respiratory tract infection in the last six weeks, a greater than ten pack/year smoking history, a history of drug/alcohol abuse or a known sensitivity to Salmeterol or Fluticasone. Baseline spirometry was performed according to ATS/ERS recommendations (Miller *et al* 2005) to confirm that subjects had normal lung function.

2.2. Acoustic recording device

The recording device selected to obtain the acoustic signals of inhaler use was the INCA (Inhaler Compliance Assessment) device, manufactured by Vitalograph Ltd. The device (figure 1) primarily consists of a microphone, microcontroller and battery. The microphone is a Knowles Acoustics SPM0204HE5 mini surface mount silicon microphone. The audio files are stored on the INCA device from where they can subsequently be uploaded to a computer via USB connection. The INCA device can be used in conjunction with the common Diskus^{TM} inhaler (known as Accuhaler^{TM} in the United Kingdom). The INCA device starts recording the acoustic signal once the Diskus^{TM} inhaler is opened and switches off once the

Figure 2. Airtight container with the Diskus™ inhaler placed inside and INCA device attached on top.

Diskus™ is closed. The audio signals were recorded as mono WAV files, at a sampling rate of 8000 Hz and a resolution of 8 bits/sample.

2.3. Flow experimental design

A spirometer is a device that is capable of measuring the flow rates and volume of air inspired and expired by the lungs. Several studies have previously employed an airtight container to connect an inhaler to a spirometer in order to obtain flow measurements through an inhaler device (Magnussen *et al* 2009, Malmberg *et al* 2010). The airtight container ensures that all inspired air through the mouthpiece of the inhaler comes through the spirometer where it can be measured. In this study a clear PET (Polyethylene Terephthalate) container was used to act as an airtight adaptor between a Diskus™ inhaler and a spirometer. An empty Diskus™ inhaler was placed into the container (figure 2), which had a custom aperture cut for the mouthpiece, the INCA device and the spirometer connector. The mouthpiece was extended out 1 cm in length in order for subjects to get a good seal around the mouthpiece. The aperture for the INCA device was cut so that the position of the INCA device resembled that of real world use i.e. sitting flush on the Diskus™ inhaler; this limited the damping of the acoustic signal. Steinel Hybond 86 adhesive was used to seal any gaps and prevent any unintentional air from going in or out of the container. The container was submerged in a water bath before each test in order to verify that it was airtight. The end result was that air could only enter or exit via the inhaler mouthpiece and through the spirometer connector.

2.4. Spirometer employed

The spirometer used was the Vitalograph Pneumotrac (Model 6800) supplied by Vitalograph Ltd. This spirometer uses a Fleisch pneumotachograph for flow/volume readings. The specifications are presented below:

- Flow detection principle: fleisch type pneumotachograph
- Volume detection: flow integration sampling @ 100 Hz
- Accuracy when in operating range:

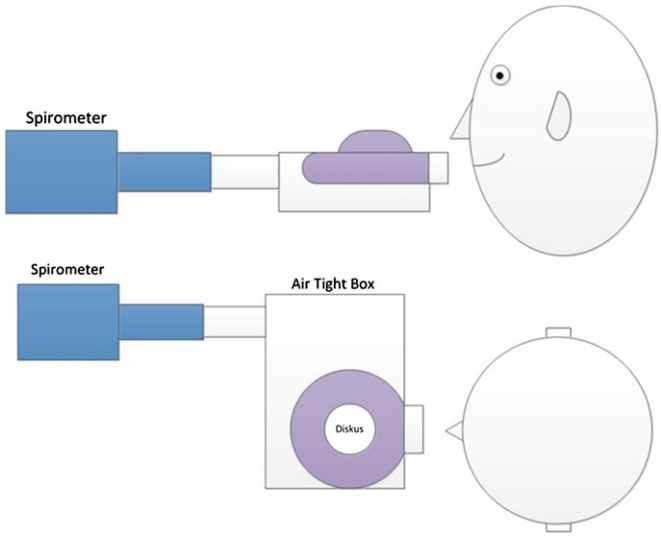

Figure 3. Preliminary experiment design showing the interaction between the subject, inhaler, airtight container and spirometer. Note: final container design shown previously in figure 2.

- Volumes: better than $\pm 3\%$ (max 8 L min^{-1} 0.05 L)
- Flows: better than $\pm 5\%$ (max 16 L s^{-1} /min^{-1} 0.02 L s^{-1})
- Linearity: $\pm 1\%$ in range 0.1 L s^{-1} to 16 L s^{-1}

- Resistance: $<$1.2 cm H_2O/L s^{-1} at 14 L s^{-1}
- Performance standards: BS EN ISO 23747: 2009 (BSI 2009), (Miller *et al* 2005).

2.5. Test procedure

The airtight container described previously was connected to the spirometer. Patients were instructed to exhale gently (to functional residual capacity) and then inhale at a variety of flow rates and volumes. Each patient performed this maneuver six to eight separate times. The airtight container was sterilized after each patient performed the test to ensure that no infections were passed between subjects. A graphical representation of the overall test set up can be seen in figure 3.

2.6. Inhalation signal analysis

The inhalation audio signals were divided into 1024 data samples with 50% overlap between successive segments. A Hanning window was used to analyze each segment, while a fast Fourier transform was used to calculate the power spectral density. Three measures of amplitude were employed in this study; median amplitude (MA), mean absolute deviation (MAD) of the amplitude and root mean square (RMS) of the amplitude. These three measures of amplitude were chosen in order to investigate which had the best correlation with PIFR and IC.

MA was computed using a relative peak detection method. Peaks of the inhalation signal were selected that were greater than their nearest neighbor by a minimum threshold height difference of 200. This method was chosen over calculating the mean value of the inhalation signal in order to reduce the effect of noise in the analysis. MAD is the mean of the absolute

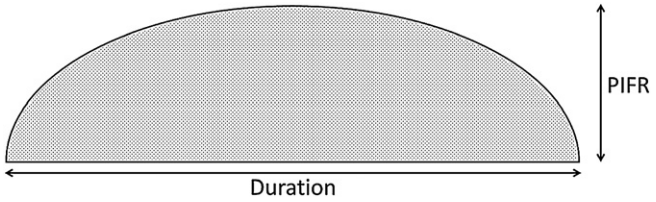

Figure 4. Area of semi-ellipse from which the volume or IC of an inhalation can be calculated.

deviations from the central value. This measure addresses the problem of calculating the mean from a sinusoidal measure and was calculated using the following equation (1):

$$\mathrm{MAD} = \frac{1}{n}\sum_{i=1}^{n} |x_i - \bar{x}|. \tag{1}$$

The RMS or quadratic mean is a statistical measure of the effective value of a signals amplitude, including the mean value. It takes into account sinusoidal waveforms and gives the equivalent non-varying power of a varying waveform. It is the square root of the mean of the squares of the values of either a discrete or continuously varying function. RMS has been used in a previous study, which investigated the volume-dependent changes in regional lung sound amplitudes (Kiyokawa and Pasterkamp 2002). It was calculated using the following equation (2):

$$\mathrm{RMS} = \left[\frac{1}{n}\left(x_1^2 + x_2^2 + x_3^2 + \cdots + x_n^2\right)\right]^{1/2}. \tag{2}$$

The average power (P_{ave}) of each inhalation was calculated in the frequency bands: 20–40 Hz, 40–70 Hz, 70–150 Hz, 150–300 Hz, and 300–600 Hz, in addition to 70–300 Hz, 70–450 Hz, 100–300 Hz, 100–450 Hz and 150–450 Hz. These frequency bands were chosen as they were previously used in a study by Hossain and Moussavi (2004) which investigated the best frequency band to estimate flow rate from respiratory sounds obtained from the chest wall.

In spirometry, the area under a PIFR—time curve equates to the volume of an inhalation or IC. Since acoustic measurements were used to predict the PIFR, integration could not be used to determine IC. Instead it was noted that the area under the curve of the inhalational sound waveform (inhalation volume) approximates that of the area of a semi-ellipse, described by the following equation (3):

$$\text{Inhalation volume} = \frac{1}{2} * \pi * A * \frac{B}{2} \tag{3}$$

where A = PIFR and B = duration (see figure 4). Values for MA, MAD, RMS and P_{ave} for each inhalation were employed to obtain predicted values for the mean PIFR. These predicted mean PIFR values and the actual duration of the inhalation were used to calculate a predicted IC value (equation (3)). The predicted values for IC were then compared to the actual IC values for each inhalation, as obtained from the spirometer.

2.7. Statistical analysis

Analysis was carried out using the statistical software Stata SE Version 12. This study was designed as a repeated measures study due to the fact that the samples were not independent. A Generalized least squares (GLS) regression model, which accounts for random effects intercept

Table 1. Summary of demographics and baseline lung function data from all subjects ($n = 15$).

Variable	Mean	SD	Range
Age (years)	25.9	4.2	22–35
Gender (males)	(9/15)		
Height (cm)	174.5	6.4	164–185
Weight (kg)	72.8	9.0	56–91
BMI[a] (kg m^{-2})	23.86	2.21	20.8–29.7
FEV1[b] (L)	3.98	0.58	2.79–4.85
FEV1[b] (%) predicted	99.33	5.33	92–110
FVC[c] (L)	4.90	0.73	3.41–6.24
FEV1/FVC ratio	0.81	0.06	0.70–0.91
PEFR[d] (L min^{-1})	547.6	103.7	384–744
FIVC[e] (L)	4.56	0.67	3.34–5.76
PIFR[f] (L min^{-1})	402.1	82.1	276–535

[a] BMI—body mass index.
[b] FEV1—forced expiratory volume in 1 s.
[c] FVC—forced vital capacity.
[d] PEFR—peak expiratory flow rate.
[e] FIVC—forced inspiratory vital capacity.
[f] PIFR—peak inspiratory flow rate.

at the subject level, was used to compare the acoustic parameters of MA, MAD, RMS and P_{ave} with measured PIFR and IC. The GLS model takes into account the correlation between the observations when calculating the regression model and was thus deemed appropriate for analysis of the data in this study.

3. Results

Table 1 presents the demographics and baseline lung function of the 15 healthy volunteers enrolled in this study. The ethnic origin of subjects was Caucasian for 93.3% (14/15) and Hispanic for the remaining 6.7% (1/15). All subjects had an FEV1/FVC ratio >0.7 and a predicted FEV1 > 89%, confirming normal baseline lung function according to ATS standards.

A total of 120 audio files were obtained from the 15 subjects. 17 audio files were discarded due to an INCA device formatting error. In this study the PIFR range of interest was between 0–100 L min^{-1} and a subsequent 17 audio files were omitted that had PIFR values greater than 100 L min^{-1}, leaving a total of 86 observations from the 15 subjects. For each inhalation the spirometer provided values for PIFR and IC. PIFR was compared to MA, MAD and RMS of the inhalation signal, while P_{ave} at several select frequency bands (described earlier) was also compared to PIFR.

It was found that MA, MAD and RMS were all highly correlated with PIFR ($P = 0.0000$) at a significance level of $\alpha = 0.05$. The coefficients of determination were found to be $R^2 = 0.8386$ for MA, $R^2 = 0.8340$ for MAD and $R^2 = 0.8320$ for RMS. P_{ave} for a range of select frequency bands was also calculated. Using a GLS regression model to compare PIFR to P_{ave} it was found that the relationship was also highly correlated for all of the frequency bands ($P = 0.0000$, $\alpha = 0.05$). It is worth noting that at higher powers, the GLS regression model will give PIFRs exceeding the maximum possible flow rate through the inhaler. The P_{ave} in the frequency band 300–600 Hz had the strongest correlation with PIFR, as the GLS regression model for this frequency band had an R^2 value of 0.9079. A complete analysis of the relationship between P_{ave} and PIFR for each of the frequency bands analyzed is presented in

Table 2. Correlation scores between P_{ave} and PIF.

Frequency band (Hz)	Coefficient of determination (R^2)
20–40	0.7865
40–70	0.7018
70–150	0.8067
150–300	0.8461
300–600	0.9079
70–300	0.8427
70–450	0.8746
100–300	0.8431
100–450	0.7018
150–450	0.8807

table 2. The overall results demonstrating the relationship between MA, MAD, RMS, P_{ave} and PIFR can be seen in figure 5. Individual plots of acoustic parameters versus PIFR for each subject with the associated GLS regression can be found in the online supplementary material (available from stacks.iop.org/PM/34/903/mmedia).

With the analysis of MA, MAD, RMS and P_{ave} it is possible to estimate IC. Figure 5 demonstrates that it is possible to estimate values for PIFR from analysis of the inhalation signal. IC can subsequently be calculated by using equation (3).

GLS regression demonstrated that IC can be estimated using MA, MAD, RMS and P_{ave} ($P = 0.000$, $\alpha = 0.05$). The coefficients of determination (R^2) for predicting IC were 0.9020 for MA, 0.9047 for MAD, 0.8989 for RMS and 0.9245 for P_{ave} in the frequency band 300–600 Hz. Figure 6 presents plots of actual IC versus IC estimated from MA (ICma), MAD (ICmad), RMS (ICrms) and P_{ave} (ICP_{ave}). GLS Regression outputs for each acoustic parameter and individual plots of calculated versus measured IC for each subject can be found in the online supplementary material (available from stacks.iop.org/PM/34/903/mmedia).

4. Discussion

The aim of this study was to investigate whether acoustic features of inhalations could be used to estimate PIFR and IC in 15 healthy subjects. The main results reveal that MA, MAD and RMS of the amplitude and P_{ave} at a range of different frequency bands all provided a robust method of estimating PIFR and IC. The high level of correlation between PIFR and IC from the acoustic measurements to the 'gold standard' method using spirometry is a promising result, suggesting that this approach may be used in future validation studies.

Several previous studies have investigated the relationship between respiratory sounds and airflow. Unlike earlier studies, which have investigated respiratory sounds recorded on the chest wall and trachea, this study focused on sounds generated during inhaler use. Inhaler sounds are a mixture of both respiratory sounds and sounds from the inhaler itself. The microphone was located in the INCA device, which was securely bonded to the inhaler in a location less than 5 cm from the mouth. The results of this study are in accordance with previous research which established that variations in flow are reflected in the intensity and frequency distribution of the sounds generated (Kraman 1984, Gavriely and Cugell 1996). A study by Hossain and Moussavi (2004) indicated that P_{ave} had the strongest correlation with flow rate from respiratory sounds. The results of the present study found that P_{ave} had the strongest correlation with flow rate from inhaler sounds. The same study by Hossain and Moussavi (2004) also reported that the optimum frequency band to calculate P_{ave} was 150–

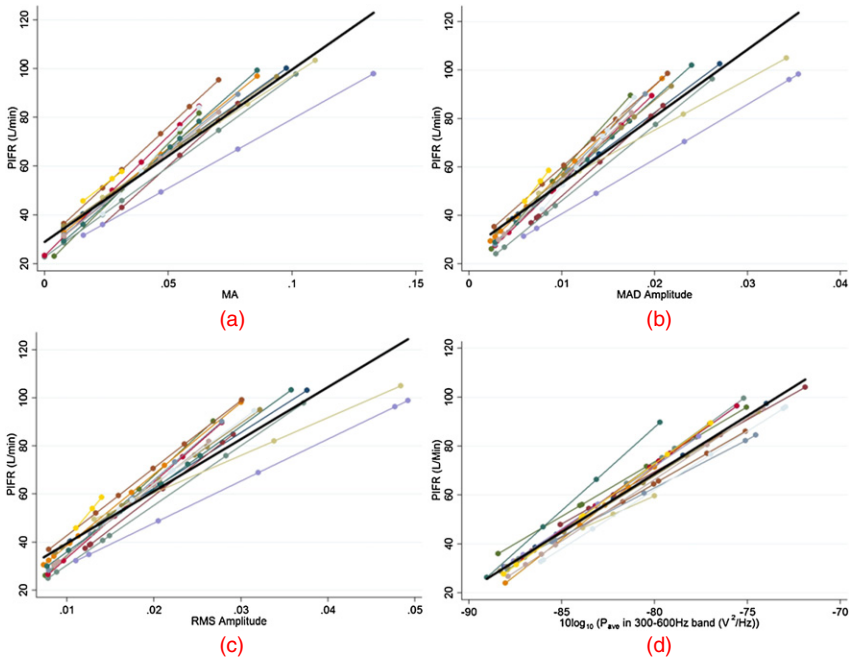

Figure 5. PIFR versus (a) MA, (b) MAD amplitude, (c) RMS amplitude and (d) average power (P_{ave}) in the frequency band 300–600 Hz. The plotted points are calculated PIFRs based on regression equation for each subject. The black line represents overall regression model equation.

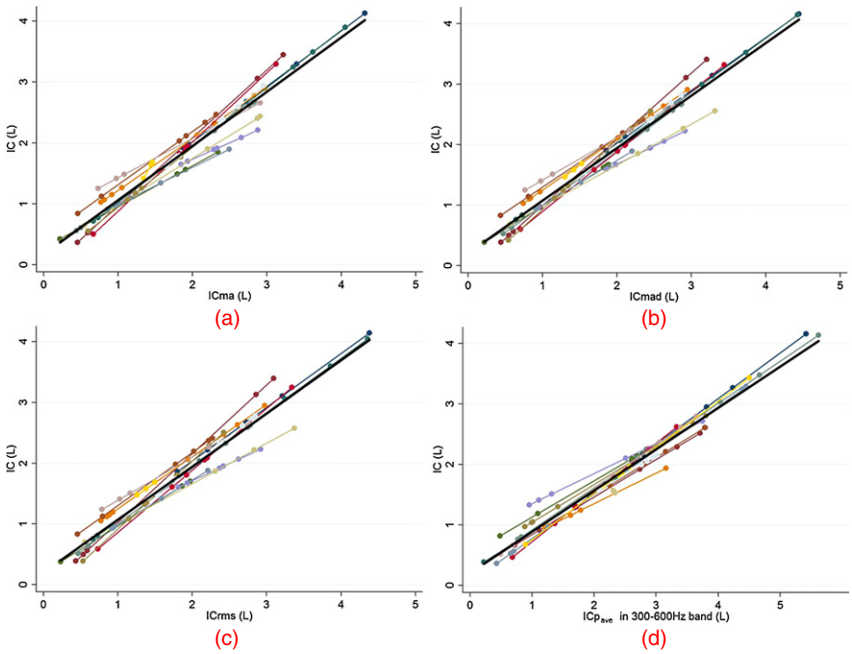

Figure 6. Measured IC versus IC calculated from (a) MA, (b) MAD, (c) RMS and (d) P_{ave} in 300–600 Hz frequency band. The plotted points are calculated ICs based on regression equation for each subject. The black line represents overall regression model equation.

450 Hz for healthy subjects, while in the present study we found this optimum frequency band to be 300–600 Hz for inhaler sounds. It is therefore clear to see that the sounds created by the inhaler are different in comparison to normal respiratory sounds. Inhaling through the narrow opening of the Diskus™ inhaler has created a shift in sound intensity towards higher frequencies.

The additional dead space volume of the airtight container adds additional resistance to the overall pathway of the spirometer. This means that a slightly greater patient effort is required in order to obtain PIFR and IC values that would have been reached without the airtight container. This could lead to values of MA, MAD, RMS and P_{ave} obtained being slightly higher than they should be for the corresponding PIFR and IC values. However, for the purposes of this study it was decided that the effects of the containers dead space is small enough to be negligible, given that the ranges studied were quite large (range of 100 L min^{-1} for PIFR and 3.54 L for IC). The additional dead space of the container also met ATS 2005 requirements for spirometry, in that the total dead space of the circuit was less than 350 ml. One point to consider in this study also is that if the sound is generated by the flow through the inhaler, the frequency content of the sound may be proportionally shifted to higher frequencies at higher flows. Further research is required to better interpret this effect on the results of this study and future inhaler based studies.

The current methods of assessing patients' inhaler technique are limited. At present clinicians make a subjective decision on whether a patient's inhalation is sufficiently adequate for their medication to reach their airways. However an effective inhalation is dependent on inspiratory flow rate, which cannot be measured subjectively. PIFR can be measured using a Clement Clarke *In-Check Dial*™ device (Janssens *et al* 2008, Amirav *et al* 2005), although this device is not widely used and when it is used, it is primarily in clinical environments. Additionally, the effort patients exert in front of the clinician may not correlate to the effort they put into using their inhaler on a day-to-day basis. The method we propose in this paper allows PIFR values from real world patient inhaler use to be acquired, in addition to IC values.

The objective of this study was to demonstrate the feasibility of using acoustic measurements to estimate PIFR/IC from inhalers. The regression models are inherently biased to the dataset used and hence cannot be used to estimate the 95% CI for a population of individuals. Nonetheless, the regression outputs in the online supplementary data (available from stacks.iop.org/PM/34/903/mmedia) show that the 95% CIs for the variables are actually relatively small, proving the potential of carrying out a validation study on a large population. There are numerous potential clinical applications for a system that can accurately predict PIFR and IC from patients' inhalations during inhaler use. A standard threshold could be put in place to inform clinicians whether a patient performed an effective or ineffective inhalation. PIFR and IC could also be monitored on a day-to-day basis, providing the opportunity to assess patients' respiratory condition over time. Monitoring PIFR and IC longitudinally may provide the opportunity to predict and prevent exacerbations before they take place. The method of calculating PIFR and IC as described in this study is independent of age and thus has many benefits for monitoring inhaler therapy. Analysis of PIFR may also show when narrowing of the airways occurs, while analysis of IC variations might be used to study dynamic hyperinflation, and monitor the drop in IC associated with exacerbations. Informing patients of their day-to-day PIFR and IC values may also encourage them to take better control of their respiratory disease, as they may come to realize that a greater effort is required on their part, in order to help deliver the medication to their airways. Such active feedback may provide the opportunity to improve the efficacy of the medication, reduce exacerbations and lower the frequency of admittance to hospital emergency departments.

5. Conclusions

In conclusion, it has been shown that acoustics can be employed to estimate the PIFR and IC values of healthy subjects' inhalations through a DPI device. It was found that P_{ave} in the frequency band 300–600 Hz provided the best acoustic measurement to predict PIFR, while P_{ave} in the same frequency band also represented the best method of predicting IC. The ability to use acoustic measurements to estimate PIFR and IC provides clinicians with new objective measurements that reveal the quality of a patient's inhaler inhalation effort. Such objective measurements may allow clinicians to reach a decision on a patient's ability to use their inhaler and also to provide feedback to a patient concerning their technique. Quality active feedback may encourage patients to improve their inhaler technique, which in turn may improve the clinical efficacy of inhaler medication, reduce the number of exacerbations, hospital admissions and ultimately prevent an increase in mortality rates.

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References

Amirav I, Newhouse M T and Mansour Y 2005 Measurement of peak inspiratory flow with in-check dial device to simulate low-resistance (Diskus) and high-resistance (Turbohaler) dry powder inhalers in children with asthma *Pediatr. Pulmonol.* **39** 447–51

Braman S S 2006 The global burden of asthma *Chest J.* **130** 4S–12S

British Standards Institution 2009 Anaesthetic and respiratory equipment. Peak expiratory flow meters for the assessment of pulmonary function in spontaneously breathing humans *BS EN ISO 23747: 2009* (London: British Standards Institution)

Charbonneau G, Sudraud M and Soufflet G 1987 Method for the evaluation of flow rate from pulmonary sounds *Bull. Eur. Physiopathol. Respir.* **23** 265–70 PMID: 3664016

Crompton G, Barnes P, Broeders M, Corrigan C, Corbetta L, Dekhuijzen R, Dubus J, Magnan A, Massone F and Sanchis J 2006 The need to improve inhalation technique in Europe: a report from the aerosol drug management improvement team *Respir. Med.* **100** 1479–94

Gavriely N and Cugell D W 1996 Airflow effects on amplitude and spectral content of normal breath sounds *J. Appl. Physiol.* **80** 5–13 PMID: 8847331

Hossain I and Moussavi Z 2004 Finding the lung sound-flow relationship in normal and asthmatic subjects *IEEE 26th Annu. Int. Conf. on Engineering in Medicine and Biology Society* pp 3852–5

Janssens W, VandenBrande P, Hardeman E, De Langhe E, Philps T, Troosters T and Decramer M 2008 Inspiratory flow rates at different levels of resistance in elderly COPD patients *Eur. Respir. J.* **31** 78–83

Jarvis S, Ind P W and Shiner R J 2007 Inhaled therapy in elderly COPD patients; time for re-evaluation? *Age Ageing* **36** 213–8

Kiyokawa H and Pasterkamp H 2002 Volume-dependent variations of regional lung sound, amplitude, and phase *J. Appl. Physiol.* **93** 1030–8 PMID: 12183500

Kraman S 1984 The relationship between airflow and lung sound amplitude in normal subjects *Chest* **86** 225–9

Magnussen H, Watz H, Zimmermann I, Macht S, Greguletz R, Falques M, Jarreta D and Garcia Gil E 2009 Peak inspiratory flow through the Genuair inhaler in patients with moderate or severe COPD *Respir. Med.* **103** 1832–7

Malmberg L P, Rytilä P, Happonen P and Haahtela T 2010 Inspiratory flows through dry powder inhaler in chronic obstructive pulmonary disease: age and gender rather than severity matters *Int. J. Chronic Obstruct. Pulm. Dis.* **5** 257

Mannino D M 2002 COPD epidemiology, prevalence, morbidity and mortality, and disease heterogeneity *Chest J.* **121** 121S–6S

Miller M R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Van Der Grinten C and Gustafsson P 2005 Standardisation of spirometry *Eur. Respir. J.* **26** 319–38

Nielsen K, Skov M, Klug B, Ifversen M and Bisgaard H 1997 Flow-dependent effect of formoterol dry-powder inhaled from the Aerolizer *Eur. Respir. J.* **10** 2105–9

Nikander K, Turpeinen M, Pelkonen A, Bengtsson T, Selroos O and Haahtela T 2011 True adherence with the Turbuhaler in young children with asthma *Arch. Dis. Child.* **96** 168–73

Pauwels R, Newman S and Borgstrom L 1997 Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers *Eur. Respir. J.* **10** 2127–38

Shykoff B E, Ploysongsang Y and Chang H 1988 Airflow and normal lung sounds *Am. J. Respir. Crit. Care Med.* **137** 872–6

Sumby B, Cooper S and Smith I 1992 A comparison of the inspiratory effort required to operate the Diskhaler inhaler and Turbohaler inhaler in the administration of powder drug formulations *Br. J. Clin. Res.* **3** 117–23

Vidgren M, Kärkkäinen A, Karjalainen P, Paronen P and Nuutinen J 1988 Effect of powder inhaler design on drug deposition in the respiratory tract *Int. J. Pharm.* **42** 211–6

Wieshammer S and Dreyhaupt J 2008 Dry powder inhalers: which factors determine the frequency of handling errors? *Respiration* **75** 18–25