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Using acoustics to estimate inspiratory flow rate and drug removed from a dry powder inhaler

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Abstract — **Morbidity and mortality rates of chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) are rising. There is a strong requirement for more effective management of these chronic diseases. Dry powder inhalers (DPIs) are one kind of devices currently employed to deliver medication aimed at controlling asthma and COPD symptoms. Despite their proven effectiveness when used correctly, some patients are unable to reach the inspiratory flow rate required to remove medication from the breath actuated devices and as a result, the medication does not reach the airways. This study employs an acoustic recording device, attached to a common DPI to record the audio signals of simulated inhalations. A rotameter was used to measure the flow rate through the inhaler while a milligram weighing scale was used to measure the amount of drug removed from each simulated inhalation. It was found that a strong correlation existed (R^2>0.96) when average power, median amplitude, root mean square and mean absolute deviation were used to predict peak inspiratory flow rate. At a flow of 30L/Min (mean absolute deviation=0.0049), it was found that 77% of the total emitted dose was removed from the inhaler. Results indicate that acoustic measurements may be used in the prediction of inspiratory flow rate and quantity of medication removed from an inhaler.**

I. Introduction

Chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) cause the death of more than four million people every year and affect hundreds of millions worldwide [1]. Asthma is an inflammatory disorder of the airways which causes the airways to become narrow, constricted and inflamed, while COPD is a heterogeneous disease that causes airflow limitation. Two of the main types of COPD are emphysema, which causes a weakening of the lung structure and chronic bronchitis, which causes an inflammation of the airways. Morbidity and mortality rates for asthma and COPD are projected to rise in the coming years [2]. Although there is currently no cure for asthma and COPD, when treated effectively symptoms of these diseases can be controlled.

Inhalers are handheld devices used to deliver medication to the lungs in the treatment of asthma and COPD. Many varieties of inhalers exist, although the two most popular types are the metered dose inhaler (MDI) and dry powder inhaler (DPI). MDIs deliver medication to the lungs in an aerosol spray form, while DPIs deliver medication in dry powder form. DPIs were designed to overcome coordination issues that some patients suffer when using MDIs. DPIs differ to MDIs in that they do not contain a propellant to deliver the medication, and are instead breath actuated. However, although breath actuation is one of the major advantages of DPIs, it is also ironically closely linked to a major disadvantage, which is that patients need to inhale with a full inspiratory effort in order to optimize drug delivery [3].

Despite the fact that a full inspiratory effort leads to effective disease management [4], many patients fail to reach the minimum inspiratory effort or peak inspiratory flow rate (PIFR) necessary to remove medication from their inhaler [5]. This minimum PIFR threshold is 30L/Min for DPIs. Failure to reach this PIFR means that patients may fail to obtain the intended total emitted dose (TED) from their inhaler, leading to decreased levels of drug lung deposition and clinical efficacy [6]. Every DPI has a unique resistance to airflow arising from its design which affects the PIFR, and subsequently the TED achievable by each patient. Patients will generate higher PIFRs in low resistance DPIs and lower PIFRs in high resistance devices. There exists a strong need to monitor patients PIFR and TED levels in order to objectively analyze their ability to correctly use their inhaler.

Previous studies have demonstrated a relationship exists between airflow and lung sounds [7, 8]. Most of the previous research in this area has focused on respiratory sounds originating at the chest wall and trachea. However, this relationship has never been investigated in inhaler sounds. The primary aim of this study was to investigate if acoustic measurements of inhaler use could be used to predict the flow rate and drug removed from a commonly used DPI. An inhaler compliance assessment (INCA) device, which can be used to record acoustic signals each time a Diskus™ DPI is used, was employed in this study. The ability to predict PIFR and TED can provide clinicians with objective measurements that may be useful in determining if a patient is capable of using their inhaler.

II. Hypotheses & Aims

The primary hypotheses tested in this study are: (1) the inhalation signal contains important information regarding

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the PIFR through the inhaler, (2) TED can be determined from the inhalation signal and (3) analysis of the (1) and (2) may be used to assess inhaler inhalation technique.

III. Methods

A. *Experimental Test Setup*

A test rig was designed to simulate inhalations in an *in vitro* environment (Fig. 1). The test rig employed an air vacuum to replicate patient inhalations. The flow rate of each inhalation was varied by controlling the power to the vacuum through a variable power supply. An on/off valve was used to vary the duration of each inhalation. PIFR was measured using a rotameter, while a specially designed fixture was used to hold the inhaler securely in place. The inhaler used was the Diskus™ DPI. An acoustic recording device, known as the INCA device, was bonded securely to the side of the Diskus™ in order to record the audio signal of each simulated inhalation. To measure the percentage of TED achieved for each inhalation a milligram scale was used to weigh the Diskus™ before and after each trial.

Simulated inhalations were carried out from 100L/Min to 40L/Min in steps of 10L/Min and from 40L/Min to 10L/Min in steps of 5L/Min. Tests were carried out for all of the aforementioned flow rates for inhalations of duration 0.5s, 1s, 2s and 3s. To address the issue of drug residue remaining in the mouthpiece of the Diskus™ and leading to inaccurate TED measurements, the device was cleaned out after every four trials using an air compressor gun.

B. *Acoustic Recording Device*

An INCA device (Fig. 2), manufactured by Vitalograph Ltd [9], was employed in this study. The INCA device enables the acoustics of inhaler use to be recorded for analysis. The device contains a microphone, microcontroller and battery. The microphone is a Knowles Acoustics SPM0204HE5 mini surface mount silicon microphone. The audio files are stored on the device from where they can be subsequently uploaded to a computer via a USB connection. The INCA device can be used in conjunction with the common Diskus™ inhaler. The INCA device starts recording the acoustics once the Diskus™ inhaler is opened and switches off when the Diskus™ is closed. The acoustics of inhaler use are recorded as mono WAV files, at a sampling rate of 8000Hz and bit depth of 8 bits/sample.

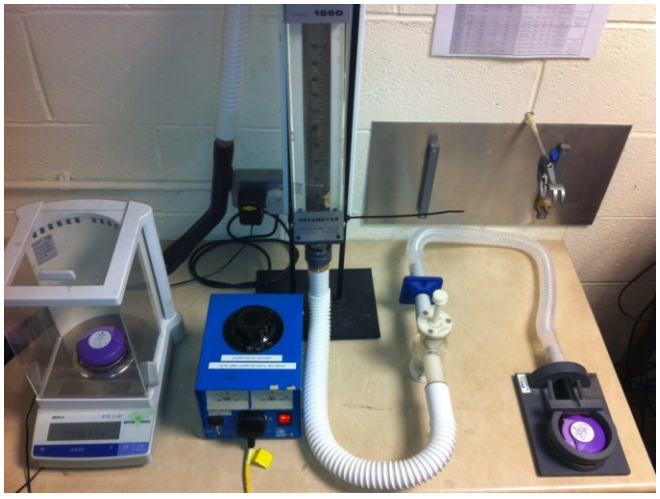

Figure 1: Test rig used to simulate inhalations in the in vitro experiment.

Figure 2: (Left) Internal components of INCA device, (Top Right) External view of INCA device and (Bottom Right) INCA device attached to Diskus™ inhaler.

C. *Data Analysis*

The inhalation audio signals were divided into 1,024 data samples with 50% overlap between successive segments. The window used to analyze each segment was a Hamming window, while a Fast Fourier Transform (FFT) was used to calculate the power spectrum of each segment. The median amplitude of the inhalations was calculated using a relative peak detection method. Peaks were defined as having a height greater than their nearest neighbor of 200. This method was chosen over calculating the mean value of the inhalation signal in order to reduce the effect of noise artifacts in the analysis.

In addition to calculating the median amplitude of the inhalation signals, the mean absolute deviation (MAD) and root mean square (RMS) of the signal was also calculated. MAD was calculated to see how much the inhalation signal varied from its mean and was calculated using the following equation (1):

$$MAD = \frac{1}{n}\sum_{i=1}^{n}|x_i - \overline{x}| \qquad (1)$$

The RMS or quadratic mean is a statistical measure of the magnitude of the variation in the inhalation signal. It was calculated using the following formula (2):

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

The average power of each inhalation was calculated over the frequency bands: 20-40Hz, 40-70Hz, 70-150Hz, 150-300Hz, and 300-600Hz, in addition to the frequency bands 70-300Hz, 70-450Hz, 100-300Hz, 100-450Hz and 150-450Hz respectively. These frequency bands were chosen as they were previously used in a study by Hossain and Moussavi [10], investigating the relationship between flow rate and average power in respiratory sounds.

IV. Results

Experimental results indicate that there is a strong correlation between flow rate and acoustics. The relationship between median amplitude, MAD and RMS to PIFR was best described using quadratic regression models. The coefficient of determination (R^2) was found to be 0.9767 between median amplitude and PIFR, 0.9675 between RMS and PIFR and 0.9784 between MAD and PIFR. Similarly there was a strong relationship between the average power of the simulated inhalations at the selected frequency bands and PIFR. The results of these correlations are demonstrated in Table I. Overall, it was found that MAD represented the best method of predicting PIFR, based on its R^2 value in this experimental study (Fig. 3).

The Diskus™ inhaler was weighed before and after each simulated inhalation in order to calculate the percentage of TED removed. The available weight in each dose of the inhaler was 13.05mg, which represented a TED of 100%. When PIFR was plotted against TED it was found that for a PIFR of 30L/Min at least 77% of the TED was extracted from the inhaler (i.e. 10.04mg of drug). For PIFR values of 35L/Min or greater the percentage of the TED removed through the simulated inhalations remained consistently high (92-109%). However, below 30 L/Min there was a dramatic decrease in percentage of TED removed (25% TED for a PIFR of 10L/Min). It was found that the duration of the inhalations did not significantly impact the amount of drug removed from the inhaler. The acoustics measurements obtained all provide a method of predicting PIFR in this simulated experiment. As these acoustic measurements relate to PIFR and TED is PIFR dependent, it is therefore possible to predict TED using from acoustics. To demonstrate this, a MAD value of 0.0049 would imply that 77% of the drug is removed from the mouthpiece of the inhaler, as this is the MAD value that corresponds with a PIFR of 30L/Min. To visualize this, MAD was plotted against TED as can be seen in Fig. 4.

Table I
Strength of linear regression models between PIFR and average power at range of select frequency bands.

Frequency Band (Hz)	R^2 Statistic
20-40	0.9725
40-70	0.972
70-150	0.963
150-300	0.9757
300-600	0.974
70-300	0.9732
70-450	0.9772
100-300	0.972
100-450	0.972
150-450	0.9779

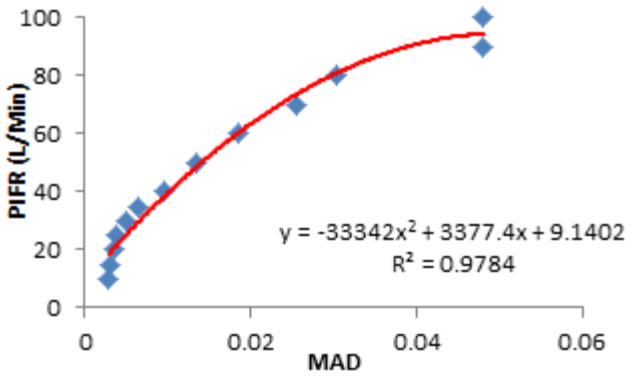

Figure 3: Relationship between PIFR and MAD.

V. Discussion

The aim of this study was to investigate if acoustic measurements could be used to predict the inspiratory flow rate and drug removed from a dry powder inhaler in an experimental test setup. Results have indicated that median amplitude, RMS, MAD and average power are strongly correlated with PIFR. It was found that quadratic regression models best described the relationship between median amplitude, MAD and RMS to PIFR, while linear regression models best described the relationship between average power and PIFR. MAD represented the best overall method of predicting PIFR. It was also demonstrated that TED is PIFR dependent, which indicates that it is possible to consequently predict TED using acoustic measurements. The strong level of correlation between the variables is a promising result as it proves the hypotheses that acoustics can be used to predict PIFR and TED, and that these variables may be used to assess inhaler technique.

A number of previous studies have been carried out into the relationship between respiratory sounds and flow. However, this study differs from previous studies in that the sounds analyzed are inhaler sounds. Inhaler sounds are a mixture of both respiratory sounds and sounds created by the inhaler device. The results support previous research which established that variations in flow rates affect the intensity and frequency distribution of sounds [7, 8]. A study by Hossain and Moussavi [10] indicated that average power had the strongest correlation with the airflow generated by subjects breathing, and that a power model best described this relationship in healthy adults and children. The same study by Hossain and Moussavi [10] also found that the optimum

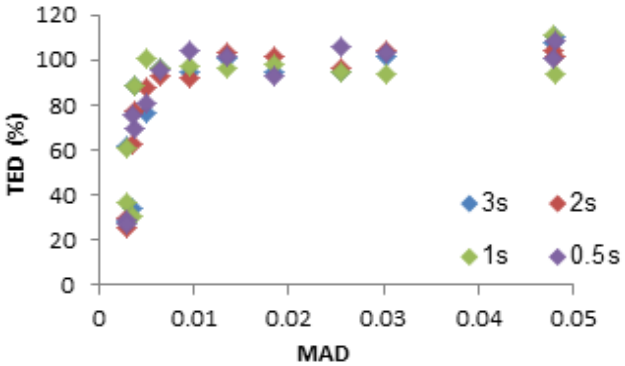

Figure 4: Demonstration of how MAD can be used to predict TED.

frequency band to calculate average power to be 150-450Hz. The experimental study presented here found that MAD exhibited the strongest correlation with simulated inspiratory flow (R^2=0.9784). Of the frequency bands investigated in this present study, it was established that the 150-450Hz frequency band provided the strongest correlation with inspiratory flow through an inhaler device. In the study presented here, quadratic regression models best described the relationship between median amplitude, MAD and RMS to PIFR. A number of studies [8, 10] have indicated that a power regression model best describes the relationship between spectral power and flow in respiratory sounds; however, in this study it was found that a linear model best described the spectral power data in inhaler sounds. Reasons for this variation may be due to the turbulence created by the inhaler device, the fact that the current study employed an experimental model to simulate inhalations opposed to actual patients, and that this study investigated flow values between 10-100L/min (typical inhaler flow range) , as opposed to the flow of breaths which range between 30-180L/Min [8,10].

A number of previous *in vitro* studies have been carried out investigating the relationship between PIFR and TED [11, 12]. Such studies have found that for a PIFR of 30L/Min as little as 50% of TED is delivered while this can drop as low as 25% at a PIFR of 20L/Min. The results of the current study are in agreement with previous research in this area. In the current study TED was found to be 77% at a flow rate of 30L/Min, while TED dropped to 25% for a flow rate of 10 L/Min. Inhalations are judged to be clinically effective above a flow rate of 30L/Min. U.S. FDA draft guidelines require all inhalers to deliver 75%-125% of the claimed label dose [13]. This study proves the hypothesis that acoustic measurements such as MAD, RMS, etc. can be used to predict TED.

This study has some limitations due to its experimental nature. Inhalations were simulated using an air vacuum, while PIFR was controlled using a variable power supply. A number of factors can influence the amount of drug removed from a DPI and the probability of the medication reaching the distal pathways of the lung. Such factors include PIFR, rise or ramp rate of the inhalation and total air volume inhaled. In this study an instantaneous ramp rate is used which is not fully representative of actual inhalations which have a more gradual ramp rate. There may also have been slight variations in the PIFR measured by the rotameter, and the actual PIFR at the mouthpiece of the Diskus™ inhaler. However despite these limitations, this study has a number of important findings.

The ability to accurately predict PIFR and TED values from an inhaler using acoustics would have a number of benefits for both clinicians and inhaler users. Current methods of assessing patient inhaler technique are limited in that clinicians make subjective decisions on a patient's ability to use their inhaler. Effective inhalations are primarily dependent on the flow rates achieved which cannot be measured during inhaler use. Therefore a method of predicting PIFR during inhaler use may be highly beneficial. Actively measuring TED would also help clinicians understand if patients are getting the full amount of medication from their inhaler and if they are capable of using their inhaler device. This type of quality feedback may encourage patients to improve their inhaler technique, which in turn may improve the clinical efficacy of the inhaler medication.

VI. Conclusions

In conclusion, it has been demonstrated that it is possible in an experimental trial to predict flow and drug removed from an inhaler device using acoustics. Being able to predict such values provides clinicians with important objective measurements on patients inhaler use. Acoustic monitoring of inhaler use is a non-invasive and simple method of observing patient inhaler technique. The next stage of this research will involve testing the hypotheses in a study using actual patient inhalations. With the use of the INCA device this may open the window for real time monitoring of patients suffering from asthma and COPD, and the possibility of predicting exacerbations.

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