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Research Article

Comparison of the Measurement of Obstructive Pulmonary Disease Using Spirometry, Plethysmography and Aerosol Dispersion Techniques

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Abstract

Aerosol dispersion in the lung is caused by differences in the product of the resistance and compliance between inhalation and exhalation of the various pathways in the lung. The test of aerosol dispersion, itself, consists of a tidal-volume, relaxed, breathing maneuver with an aerosol bolus delivered at a selectable volume before the end of inhalation. The exhaled concentration distribution is then analyzed as an indication of changes in ventilation of the lung. Changes in ventilation due to disease appear as changes in either the Half-Width (the volume differential between the volume at which half the maximum concentration on the rising portion of the exhaled concentration profile occurs and the volume at which half the maximum exhaled concentration occurs on the declining portion) of the exhaled pulse and/or the Volume Mode Shift (a shift in the volume at which the exhaled concentration mode occurs). Aerosol dispersion has previously been shown to correlate with pulmonary function measurements. When aerosol dispersion is used to derive standard clinical pulmonary function values we have termed the technique Aerosol Spirometry. Aerosol Spirometry has been found to be a powerful tool in the differential diagnosis of chronic obstructive lung disease with higher sensitivity and specificity than conventional lung function parameters for assessing patients with chronic bronchitis, cystic fibrosis and asthma.

Testing a group of patients with mixed diagnoses of asthma, bronchitis and emphysema with a new, personal Aerosol Spirometer has demonstrated a comparability between standard forced exhalation spirometry, plethysmography and Aerosol Spirometry. Design of the new device has allowed the device to be successfully operated by nursing students and also by patients, alone, achieving results not significantly different from those of a skilled operator and correlated with standard clinical pulmonary function tests. The size and cost of the device along with its proven operability may allow in-home monitoring of pulmonary diseases with greater sensitivity and reliability.

Keywords: *Aerosol Dispersion; Aerosol Spirometry; Obstructive Lung Disease; Plethysmography; Asthma*

Abbreviations

β: Mixing parameter signifying the apparent volume in which mixing occurs; COPD: Chronic Obstructive Pulmonary Disease; ERV: Expiratory Reserve Volume; FEV_1: Forced Expiratory Volume in the first second of exhalation; FVC: Forced Vital Capacity; HW: Mixing parameter called Half-width, the volume or time differential occurring at half the maximum exhaled concentration points; IC: Inspiratory Capacity. Called a capacity because it is the sum of two lung volumes: IC = Inspiratory Reserve Volume +Tidal Volume; p: Mixing parameter signifying the extent of mixing; Raw: Airway Resistance; SVC: Slow Vital Capacity; SGaw: Specific Airway Conductance; Stdev: Standard deviation

of the exhaled particle concentration distribution; TGV: Thoracic Gas Volume; TLC: Total Lung Capacity; VMS: Mixing parameter, called Volume Mode Shift, volume shift in the exhaled concentration mode as a result of nonhomogeneous mixing; V_p: Volume of penetration of the aerosol bolus, the volume difference between bolus injection and inhalation end volume

Introduction

Aerosol dispersion in the lung is caused by differences in the product of the resistance and compliance between inhalation and exhalation of the various pathways in the lung [1,2]. In healthy individuals there is relatively little intersubject variability in those differences in resistance and compliance which, in turn, leads to consistent values in healthy subjects for aerosol dispersion. There are, however, significant changes in aerosol dispersion, well beyond those seen in healthy individuals, for subjects with obstructive lung disease, especially asthma and bronchitis. These aerosol dispersion changes are due to changes in resistance or compliance in diseased portions of the lung. Axial diffusion in conductive airways and convective mixing in alveoli, resulting in irreversible particle transport, are believed to be the major determinants of bolus dispersion. The variability and asymmetry of the branching airway network, leading to asymmetric flow splitting at airway bifurcations, has, as well, been shown to enhance the effect of irreversibility and the resulting dispersion of the inhaled bolus [3].

Aerosol dispersion is measured using submicrometer-size droplets of corn oil inhaled in a narrow pulse through a photocell which measures the concentration of both inhaled or exhaled aerosol (Figure 1) as a function of breathing volume as described previously [1].

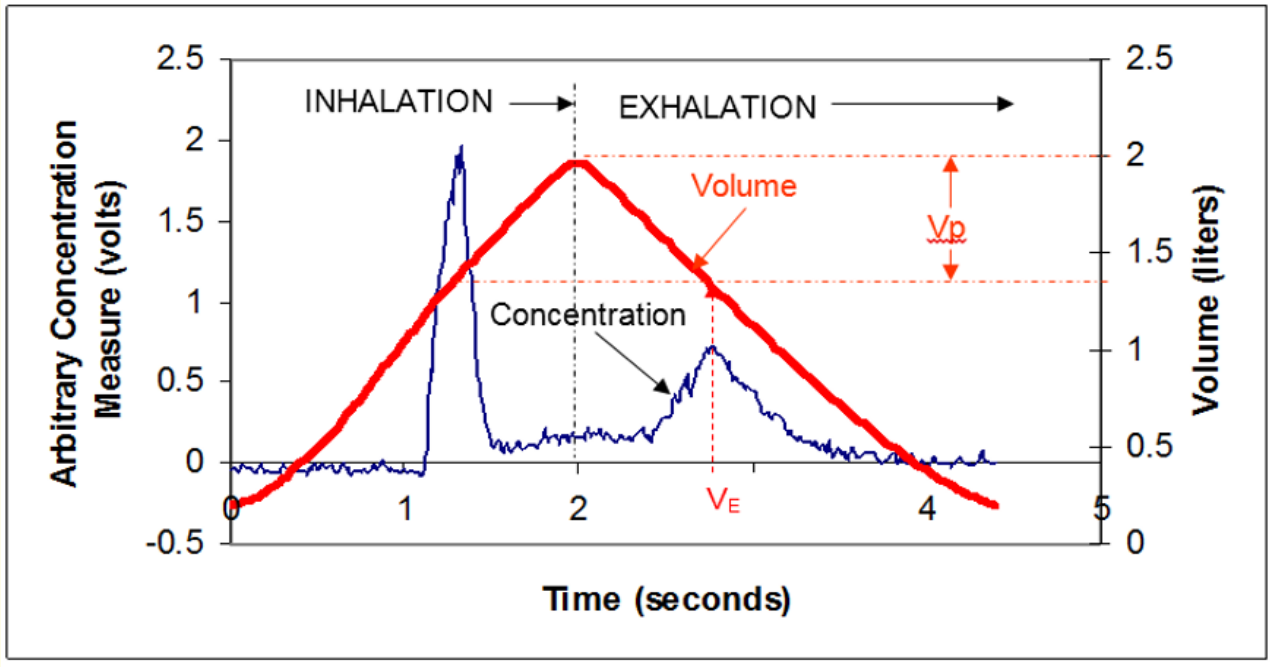

Figure 1: *Test results from a 2.0 liter tidal volume maneuver with approximately a 0.6 liter (600 cc) volume of penetration (Vp). As mentioned in figure 1, VP = VE and in this case VE = VM.*

Changes in ventilation due to disease appear as changes in either the Half-Width (the volume differential between the volume at which half the maximum concentration on the rising portion of the exhaled concentration profile occurs and the volume at which half the maximum exhaled concentration occurs on the declining portion) of the exhaled pulse and/or the Volume Mode Shift (a shift in the volume at which the exhaled concentration mode occurs) [4]. The test itself consists of a tidal-volume, relaxed, breathing maneuver with an aerosol bolus (0.7 μm aerodynamic equivalent diameter) delivered during approximately 5 milliseconds of an assumed 2 to 3 second inhalation at a selectable volume before the end of inhalation.

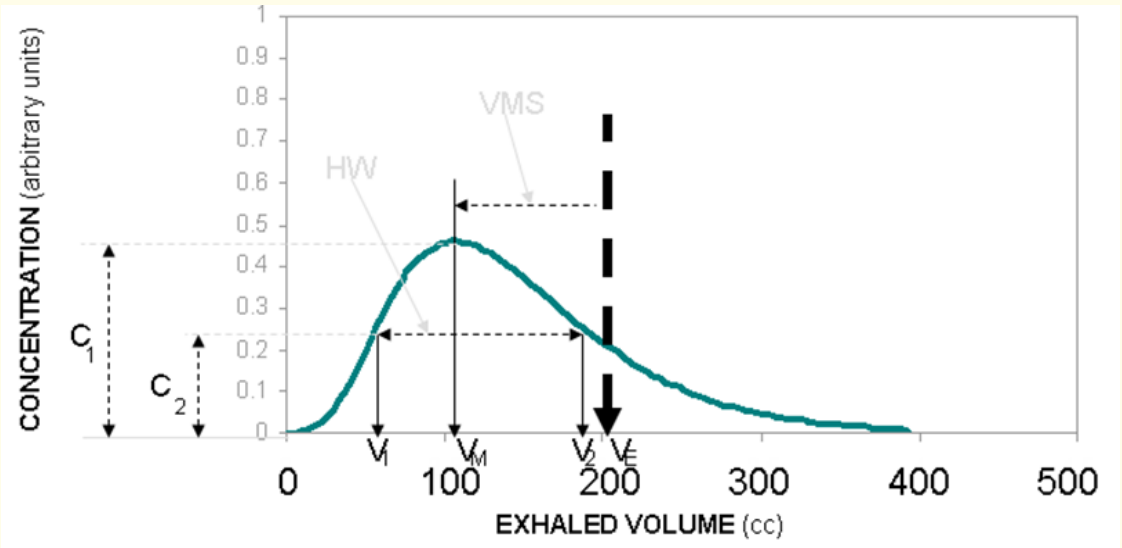

Figure 2: *Idealized, exhaled aerosol concentration profile as a function of exhaled volume. In this case, a 500 cc tidal volume was taken with a pulse of aerosol introduced 200 cc before the end of inhalation (not shown). The half-width (HW) was determined by taking the volume difference (V2 - V1 = 180 - 50 = 130 cc) at half the maximum concentration (C2 = 0.5 C1). The volume mode shift (VMS) is the difference between the expected mode volume (VE) and the actual mode volume (VM), that is (VE - VM = 200 - 100 = 100 cc). The expected mode volume (VE) is set by the volume at which the aerosol pulse is introduced relative to the end of inhalation (200 cc as stated above), which is also called the volume of penetration (Vp).*

Both inhaled and exhaled concentrations of aerosol are monitored using a photometer in-line in the breathing stream. Analysis of the Half-Width (HW) and Volume Mode Shift (VMS) of an idealized exhaled concentration profile is shown in figure 2. For proper analysis it is desirable that the entirety of the inhaled aerosol be exhaled. This is achieved through the selection of the appropriate aerosol size to reduce impaction, sedimentation and diffusion losses, as well as through the delivery of the aerosol in a pulse only in the last few hundred cubic centimeters of the inhaled volume. Values such as FEV_1/FVC percent predicted used in detecting known alterations in the lung with values that correlate with standard flow-volume spirometry pulmonary function are able to be derived from aerosol dispersion [5]. In carbachol induced bronchoconstriction, Aerosol Spirometry results also correlated with changes in airway conductance [6]. Aerosol dispersion values also correlate with flow-volume spirometry values in patients with cystic fibrosis with values changing in proportion to the change in severity of the obstruction [7,8]. Thus aerosol dispersion values expressed in terms of the correlated values from either plethysmography or standard flow-volume spirometry will be termed Aerosol Spirometry to signify the different way in which the values were obtained in an attempt to avoid confusion with the other methods mentioned. Throughout this paper the more commonly used form of spirometry, requiring a maximal forced exhalation and measuring both the flow and volume exhaled during that maneuver will be termed flow-volume spirometry to distinguish it from Aerosol Spirometry.

From the viewpoint of the utility of the test for ease of use with the patient as well as sensitivity and specificity of the test for disease, Aerosol Spirometry is at least as sensitive as standard flow-volume spirometry. Aerosol Spirometry has been found to be a powerful tool in the differential diagnosis of chronic obstructive pulmonary disease (COPD) with higher sensitivity and specificity than conventional lung function parameters for separating patients with chronic bronchitis from those with chronic bronchitis and emphysema [9]. Aerosol bolus dispersion was found to be altered in asthmatic children with respect to healthy controls. This modification is primarily expressed by an increase in standard deviation and skewness of the exhaled aerosol boluses [10]. Aerosol Spirometry can distinguish morphometric changes caused by emphysema from those caused by fibrosis [11]. In lungs with airway obstructions, the exhaled bolus exhibits a decreased dispersion with respect to healthy subjects, whereas in emphysematous lungs the respective half-width of the peak is increased. Mode shift and skewness of the bolus are influenced significantly by the modified lung architecture, enhancing the diagnostic meaning of the bolus technique [12]. Aerosol Spirometry results are also independent of the tidal volume used in testing [13] as well as total lung capacity - even as much as those between children and adults [14]. It is also independent of the breathing rate used in testing [15,16]. Those last three features, then, make the test useable for the patient at home with only minor training prior to use. This, in turn, led to the testing described below. Both flow-volume spirometry and plethysmography have been shown to correlate with Aerosol Spirometry [7,17].

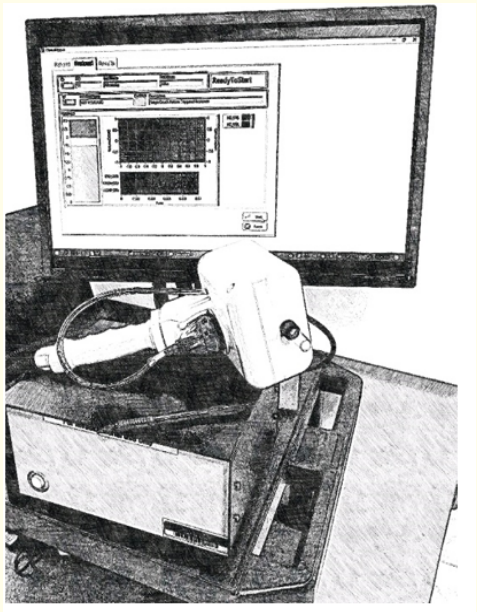

Figure 3: *Aerosol Spirometer, consisting of a compressor (at base of picture) for the nebulizer and a handheld unit (on top of compressor) into which the subject can breathe while having both volume of air and aerosol concentration measured. The two piece unit (without the video screen, which was used primarily for initial training) is intended for home use.*

One of the earliest evaluations of pulmonary change due to disease using the aerosol dispersion test was reported by McCawley., *et al* [18]. The test was used to evaluate the differences in response between a group of smokers and non-smokers. A subsequent evaluation [15], showed that though there was no significant difference in flow-volume spirometry between a group of 19 smokers and 19 non-smokers, aerosol dispersion showed a highly significant difference between the groups. This finding was confirmed by other researchers [19] whose data suggested that cigarette smoke-induced variations of lung function are also detectable in clinically asymptomatic smokers.

Even in cases of normal flow-volume spirometry, aerosol dispersion was able to discriminate between healthy smokers and nonsmokers. Since flow-volume spirometry showed only minor differences between both groups, the researchers concluded that aerosol dispersion was superior to flow-volume spirometry in the detection of early disturbances of lung ventilation in healthy smokers. Mean values of flow-volume spirometry and dispersion in smokers and nonsmokers showed a high reproducibility of the data obtained at the beginning of the study as well as at the end of the observation period. Their data further confirmed that parameters of pulmonary gas exchange and gas mixing (i.e. dispersion) are affected by cigarette smoke at an earlier time than parameters of breathing mechanics (i.e. flow-volume spirometry). Anderson., *et al.* [20] found exhaled bolus dispersion to be significantly increased in smokers compared with nonsmokers. Volumetric mean shift was significantly different in smokers at shallow lung depths, with the center of bolus mass occurring later in exhalation. The percent predicted FEV_1/FVC ratio in smokers was significantly inversely correlated with dispersion at deeper lung depths and with mean shift at all lung depths. Smokers with abnormal flow-volume spirometry (n = 4) or an abnormal single-breath nitrogen test (n = 7) had significantly increased dispersion compared with smokers with normal pulmonary function tests. Aerosol bolus inhalation also bears a certain potential for the diagnosis of emphysematous structures and, if applied with sufficient accuracy, also for the distinction of single manifestations of emphysema. The successful use of this technique, however, may require that all statistical bolus parameters and particle deposition be subjected to a detailed evaluation [21]. This latter evidence would then point to the need for a multiple regression analysis of the bolus parameters preferably compared to standard pulmonary function.

Materials and Methods

An Aerosol Spirometer (RAPID™, RMTI, 3501 Silverside Road, Naamans Building, Suite 202, Wilmington, DE 19810) (Figure 3), similar to that described previously [15] was used to test individuals with a prior, physician-diagnosed asthma, selected from patients at West Virginia University Hospital who had a scheduled visit to their pulmonary physicians. Twenty-four subjects were selected from asthmatic adults, 21 to 75 years in age, on the basis of their expected level of pulmonary function. Subjects, however, were not excluded for having multiple diagnoses of lung disease, specifically, bronchitis and/or emphysema (COPD). Subjects followed an IRB approved protocol because the RAPID™ is not yet FDA approved, with written, informed consent given before testing began. Subjects were paid for their participation and selected in order to cover a broad a range of pulmonary function values distributed over the range expected to be seen in practice. The selected patients first performed Aerosol Spirometry, then, their scheduled flow-volume spirometry, to determine their percent predicted FEV_1/FVC ratio, and plethysmography to determine airway resistance.

For the regression analysis, 24 patients were tested. Only patients who showed a statistically worse than predicted pulmonary function value were compared to Aerosol Spirometry to reduce noise and better establish the applicable relationship for a disease induced signal in each piece of equipment. Between 5 and 6 of the total number of patients qualified for each standard pulmonary function value used as the independent variable. It is not always the same patients for each of the independent variables considered since not all of the patients suffered purely from asthma. This was considered to better reflect the nature of the type of patient commonly seen.

The Aerosol Spirometry test, itself, begins with the patient breathing on an 8 mm diameter tube connected to an aerosol photometer and a two-way valve. At the reverse end of the photometer from where the subject is breathing, a pneumotachograph is attached to a pressure transducer to record flow, which is then electronically converted to volume. The volume is displayed on a computer screen as a vertical, moving bar, graduated at 100 cc intervals up to 2000 cc and visible to the test subject. The test subject was allowed to breathe at their own normal tidal breathing rate to a designated volume of one liter. A valve triggered at a preset volume and delivered approximately a 50 cc pharmaceutical grade corn oil aerosol bolus into the breathing stream of the patient. A volume of penetration of approximately 400 cc for the aerosol bolus injection was used. Prior to testing with the actual injection of an aerosol bolus, the subject was instructed by the nursing student administering the test on the proper techniques for breathing. The subject was instructed to take a deep, cleansing breath, well in excess of their normal tidal volume and then exhale to the point of a relaxed lung volume by sighing. This brought the

subject to their Functional Residual Lung Capacity, for the start of the test [13]. Without the aerosol being triggered, the subject was then allowed to take as many breaths as they desired until they and the student administering the test concluded the subject was comfortable achieving the one liter volume. Achievement of the correct volume was necessary to achieve the approximate desired volume of penetration, which must be predicted from the yet-to-be achieved end volume during the test. The subject then took five breaths of aerosol at the required volume of penetration, pausing between each breath to repeat the cleaning breath and sigh, with the nursing student prompting them to achieve the desired tidal volume, when it seemed necessary. Following the first five breaths, the nursing student stopped prompting the patient, who, continued pausing between each breath for a second set of five breaths.

Calibration of equipment in the Pulmonary Function lab is done on a routine basis using accepted standards and written quality control procedures. Calibration of the Aerosol Spirometer was done using a factory calibrated, commercial, aerosol photometer for aerosol monitoring calibration. The calibration of the pneumotachograph and associated pressure transducers were checked daily against a 3 liter calibrated syringe to assure the device would remain within tolerance. Failure to achieve the desired calibration level, +/- 5% for the flow measurement system, had it happened, would have resulted in suspension of testing until the problem was corrected. This might be important if the equipment was used at the patient's home, although the addition of built-in critical orifices available for flow calibration should help maintain adequate calibration. Student nurses performed the testing under the supervision of the authors. All equipment operators had to demonstrate that they fully understood the operation of the Aerosol Spirometer by passing a standard oral exam on the operation of the equipment given by the PI or one of the Co-I's and based on the instruction manual for the equipment supplied by the company manufacturing the equipment. Earlier versions of the Aerosol Spirometer have been compared against the device which was described by Heyder., *et al.* [4] and used to obtain many of the results referenced here. No significant differences were found between the two devices when testing the same asymptomatic individual multiple times over a 30 year period.

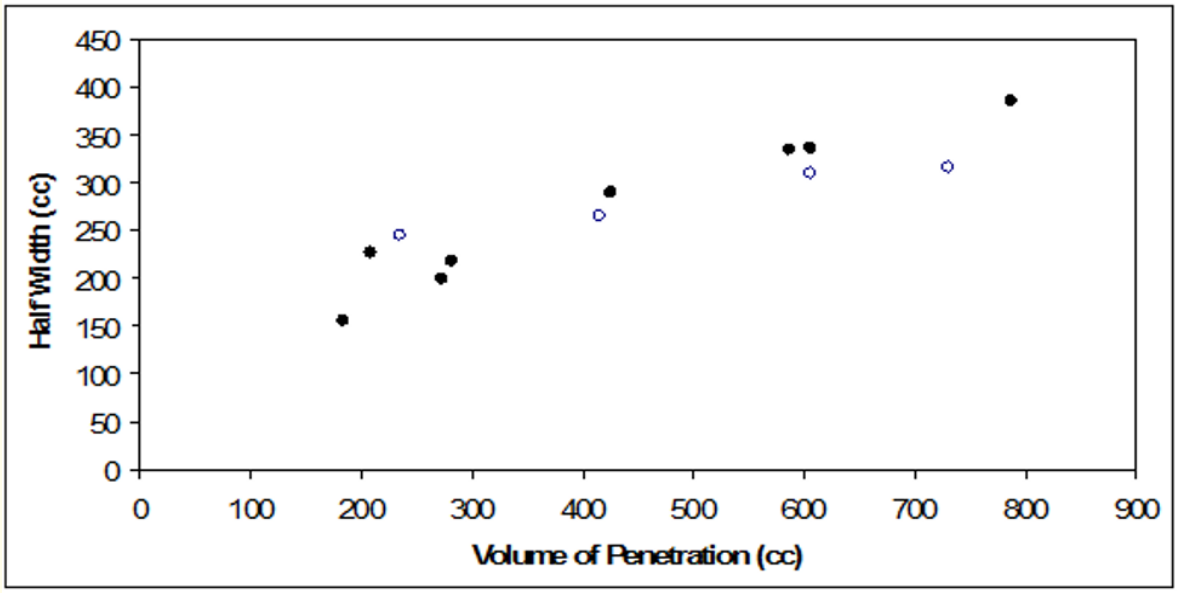

Figure 4: *Comparison of aerosol dispersion measurements between the GSF (4) aerosol spirometer-type device (o) and the RAPID™ Aerosol Spirometer (•) for the same subject.*

Results and Discussion

Testing with the new Aerosol Spirometer, shown in figure 3, has demonstrated a comparability between flow-volume spirometry, plethysmography and Aerosol Spirometry (Table 1) using regression analysis and Pearson's correlation coefficient (r^2).

Independent Variable	Dependent Variables	Number of Subjects	r^2
FEV1	β/p/Stdev	6	0.77
Raw	p	5	0.91
Raw	β/p/HW	5	0.99
SVC	β/p/V_p	5	0.99
IC	β/p/V_p	5	0.84
TLC	β/p/V_p	5	0.98
TGV	β/p/V_p	5	0.96

Table 1: *Regression analysis.*

The correlation coefficients are similar to those shown in figures 4 which were done with the earlier instrument described by Heyder., *et al* [4].

Table 2 shows the results of the statistical analysis examining the question of whether the Aerosol Spirometer can be used without operator assistance. There is no statistically significant difference in the results as a group between when the nursing students operate the Aerosol Spirometer and guide the subject through the breathing maneuver and when the patient performs the testing without assistance. Table 1 on the other hand demonstrates that when the nursing students operate the equipment they are able to achieve correlation coefficients that are a sufficiently reliable reflection of standard pulmonary function testing.

Values of aerosol dispersion parameters for subjects when being coached						
Parameter	**β**	**p**	**Vp**	**Mean of Exhaled Concentration Profile**	**Standard Deviation of Exhaled Concentration Profile**	**HW**
Average of 24 Subjects' Results	1.023	8.069	0.502	1.168	1.219	0.388
Standard Deviation of 24 Subjects' Results	0.218	4.301	0.083	0.190	0.187	0.147
95% Confidence Interval	0.092	1.816	0.035	0.080	0.079	0.062
Values of aerosol dispersion parameters for subjects when NOT being coached						
Parameter	**β**	**p**	**Vp**	**Mean of Exhaled Concentration Profile**	**Standard Deviation of Exhaled Concentration Profile**	**HW**
Average of 24 Subjects' Results	0.963	8.375	0.489	1.172	1.237	0.370
Standard Deviation of 24 Subjects' Results	0.133	4.125	0.115	0.155	0.202	0.157
95% Confidence Interval	0.056	1.742	0.049	0.066	0.085	0.066

Table 2: *Mean values and confidence intervals of aerosol spirometry parameters achieved by patients with and without supervision. No significant difference between being and NOT being coached for all parameters.*

To describe the underlying mechanics for aerosol dispersion, mixing theory derived for reactor vessels was suggested by McCawley to surmount problems encountered in small-scale mixing [1,15]. This is similar to the approach Ultman [22] took in applying network theory to this problem. This type of modeling derives from first principles underlying the mechanism of aerosol dispersion. The model parameters from the McCawley method, p and β, correspond in that order to the extent of mixing, which may be thought of as similar to the standard deviation of the exhaled particle concentration distribution or the HW (p) and the apparent volume in which mixing occurs (β) which may be thought of as similar to the mean of the exhaled particle concentration distribution or the VMS, as discussed previously [1]. However, the McCawley parameters are more standard and widely used in the chemical and electrical engineering field, allowing access and cross-reference to that older and even more substantial body of literature and experience [23-25]. Both plethysmography and flow-volume spirometry appear to be correlated with Aerosol Spirometry under conditions likely to be found outside the clinic and inside patients' residences. A positive finding of the study is that the technique appears to be robust enough to achieve significantly correlated results without resort to analysis of more complex mixing scenarios. More complex mixing parameters, of course, may still be of use for more detailed clinical analyses, but that is speculation beyond the scope of the current paper. The analysis derived from the Aerosol Spirometer is also robust enough that it can be derived from data obtained using trained novices (nursing students) or patients alone with no significant difference in the results. It could be speculated that the increased sensitivity of aerosol dispersion may counterbalance the noise generated by using the test in a cruder fashion than has been done previously.

Limitations of the study include the small population size used, though earlier work on this topic has used populations as small [20]. Additionally, the variability in the volume being breathed and the consistency of the breathing rate was not as tight as in previous studies. However, it may better represent how the device can be practically used. It also demonstrates that results achievable under those circumstances are still sufficient to show comparability with standard pulmonary function.

Conclusion

Given the substantial difference between the new and possibly personal Aerosol Spirometer and the original aerosol dispersion device [4] in both size and cost, it is important to note that the preliminary comparison of the results achievable with either device is similar. The ease with which the test can be done, allows the patient to breathe at their own selected rate with minimal guidance. This should be of note for the improvement of adherence to pulmonary function testing outside of clinical settings and subsequent control of pulmonary disease symptoms. The work to date suggests the next step as in-home trials in larger populations to determine the possibility of broadening the utility of this method.

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Conflict of Interest

M.McCawley received stock from RMTI for intellectual property leading to the development of the RAPID™ Aerosol Spirometer.

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