**How Is Impulse Oscillation System Useful in Diagnosis and Differentiation of Interstitial Lung Disease?**

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**Abstract**

**Background:** The current study aimed to evaluate IOS findings and compare with body plethysmography in ILD to find and offer ways to determine the disease as well as predict lung tissue changes in addition to estimate the severity of lung parenchymal involvement.

**Materials and Methods:** Through a cross-sectional design, ILD patients above 18 years old enrolled the current study between Feb 2021 and March 2022 who had been absolutely diagnosed based on clinical manifestations and physical examination as well as chest X-ray and CT-scan in before admitted for body plethysmography and impulse oscillation test (IOS) through the current research.

**Results:** The percent of the predicted R5 was in strong indirect correlation with the percent of the predicted FEV1/FVC and MMEF but direct correlation with the percent of the predicted SRAW. Likely, R5-R20 had the same relationship with the named parameters. AX showed indirect correlation with FVC and the percent of the predicted DLCO and X5 directly correlated with FVC.

**Conclusion:** Our body box and IOS findings matched more or less to finally conclude that IOS may compete with body box in diagnosing and severity definition of ILD. Furthermore, the current study showed bigger absolute values of X5 in ILD but a final positive value of ΔX which is explained by higher X5 Inspiratory in ILD unlike emphysema. This discrimination between the named diseases is hopefully another strength point of IOS although the fact that more studies will be needed.

**Keywords:** Interstitial Lung Disease**,** Impulse Oscillometry System, Forced Oscillation Technique, Chronic Obstructive Pulmonary Disease, Body box

**Introduction**

Interstitial lung disease (ILD) is a group of lung diseases with various clinical and histopathological characteristics causing physiologic abnormalities and restricted ventilation. The disease is usually determined by a shifted pressure-volume curve to the right and down during exhalation to finally decreased vital capacity in spirometry. Decreased vital capacity is seen also in obstructive pulmonary disease and other conditions such as chest wall limitation, lung resection, respiratory muscle weakness or poor cooperation (1-3).

Forced Oscillation Technique (FOT) was first introduced by Dubois et al. (4) in 1956 to evaluate lung function using single-frequency sound waves in order to achieve better view of lung mechanism than simple spirometry. Later in 1975, Michaelson and colleagues (5) developed a technique that used multiple-frequency sound waves called Impulse Oscillometry System (IOS) as a variant of FOT to assess the mechanism of the lung in a passive manner requiring the least cooperation from patients. It works with sound waves through normal tidal breathing by evaluating air flow and pressure in the airways to ultimately measure respiratory resistance, reactance, and impedance (6). Thanks to its high sensitivity in airway resistance determination, FOT was used earlier in patients with obstructive pulmonary diseases. Furthermore, due to accurate indication of flow limitations by FOT, Dellaca et al. (7) clarified that reactance could be measured separately during inhalation and exhalation.

As far as our knowledge, although there is no published data in terms of inhaled-expiratory analysis of oscillometry in ILD, this technique failed to differentiate obstructive from restrictive lung diseases but it was useful to discriminate COPD from asthma which usually present similar degrees of airway restriction in spirometry (8).

Respiratory resistance is a component of lung impedance which includes the total resistance of oropharynx, larynx, trachea, small and large airways in addition to lung parenchyma and chest. This technique uses two prominent frequencies namely 5 Hz and 20 Hz as main indicators. The higher the frequency of the waves, the shorter the distance the waves travel into the airways.

Respiratory reactance is another part of lung impedance which reflects the properties of capacitation and inertance. Reactance at 5Hz frequency (X5) shows the elastic recoil in peripheral airways that decreases in fibrosis and hyperinflation to obtain higher negative values. Resonant frequency (Fres), another parameter, is defined by the frequency at which the airway interance and the peripheral capacitance of lung are equal and the overall reactance is zero in this point. Fres is normally ranged between 5-11 Hz increasing in peripheral obstructive conditions as well as fibrosis. Area of reactance (Ax), the space under the reactance curve, is a set of low frequency respiratory reactance located at a frequency between 5Hz and Fres.

The current study aimed to evaluate IOS findings and compare with body plethysmography in ILD to find and offer ways to determine the disease as well as predict lung tissue changes in addition to estimate the severity of lung parenchymal involvement. Also, we tried to introduce a more user-friendly module in this regard which needs the least patient cooperation instead of spirometry and body box that need active patients to achieve optimal results.

**Materials and Methods**

Through a cross-sectional design, ILD patients above 18 years old enrolled the current study between Feb 2021 and March 2022 who had been absolutely diagnosed based on clinical manifestations and physical examination as well as chest X-ray and CT-scan in before admitted for body plethysmography and impulse oscillation test (IOS) through the current research. Patients with coincident diseases which might affect pulmonary function tests like asthma, COPD, heart diseases, renal failure and respiratory tract infections were excluded. Demographics, current situation, manifestations, drug history, comorbidities and smoking habit were checked referring to the records. Then the suitable patients for body plethysmography and IOS were called to participate in our work.

**Body plethysmography (Body box):** Body plethysmography is a technique that evaluates lung function and shows many structural and functional aspects. This tool allows the evaluation of functional residual capacity (FRC) and specific airway resistance (sRAW) and can also determine the values of total lung capacity (TLC) as well as residual volume (RV). Measurements are based on the need to generate pressure to produce airflow. Body plethysmography, simply body box, is also suitable to assess air spaces which are not related to the bronchial tree in the lungs (9).

**Impulse Oscillation System (IOS):** Between the parameters, R5 and R20 are the first to present airway resistance at the frequencies of 5Hz and 20Hz, respectively. The former (R5) indicates total airway resistance while the latter (R20) shows the air resistance in large airways as far as the 20Hz wave could infiltrate. Rationally, R5-R20 indicates the resistance in small airways. As pointed out before, X5, always reported with negatives, is an index to show lung elasticity and compliance facing the sound waves at the frequency of 5Hz. Ax is another useful index relating to small airway patency, R5-R20 value and respiratory compliance. X5, Fres, and Ax have been proposed to determine the limit of expiratory flow.

**Statistics:** Normal distribution of the data was done using relevant tests like Shapiro before starting analysis. All the variables gathered in a questionnaire as described before. The confidence interval was 0.95 regarding type one error (α) = 0.05 with 0.05 significance to have the study power of 0.8. Central indices were measured by student t-test and the correlations were found using cross tables.

**Ethics:** The patients had been requested to give their informed consents to participate any research activity if agreed. There was no intervention throughout the study and we just reviewed participants’ hospital records to get necessary information before doing IOS. This study was approved under the code: 1400.685 in our center as university collaborating chronic respiratory disease research center (CRDRC). All the participants who experienced IOS test gave their informed consent and there was no charge for the tests. IOS evaluation was scheduled through serial physician visits to make no charge for commuting.

**Results**

Totally, 50 patients enrolled the current study including 32 (64%) males and 18 (36%) females with age mean ± SD of 55.54±14.01 years. BMI presents a total mean ± SD of 27.63±5.2. Demographics are illustrated in table 1.

**IOS findings:** The total mean of predicted percent of AX was reported 821 with the crude value of 10.21 to show eight-time increase of this parameter among ILD patients disregarding age, sex and BMI. On the other hand, the percent of the predicted R5 was 109.89% in average which it was 99.27% for R20. The crude value for “R5-R20”, as a very important index, was 0.78 CmH2O/l/s with 175.12% as predicted percent. Two other parameters for R5 namely R5IN and R5EX were measured to find 3.25 and 3.69 as their means, respectively to achieve their difference (R5EX-R5IN) of 0.44. These values were 2.58, 2.77 and 0.2 CmH2O/l/s for R20, respectively. For X5, inspiratory, expiratory, and “X5EX-X5IN” values were -1.413, 1.407 and 0.006, respectively, while the percent of the predicted X5 was measured 886.3±1282.5 (The findings are presented by table 2).

**Plethysmography findings:** The percent of the predicted FEV1% was found 69.82% among the participants in average and the mean for FVC was 64% of the predicted value. The ratio of FEV1/FVC had the mean of 88.5% of the predicted value as well. The percent of the predicted TLC, RV, MMEF, and DLCO were 69.77, 87.46, 95.13, and 52.89, respectively as can be seen in table 3.

**Correlations:** The current study attempted to compare the parameters of IOS and body box to find any significant correlations between them among ILD cases. In this matter, we figured out some relationships between the findings summarized in table 4 and table 5. The percent of the predicted R5 was in strong indirect correlation with the percent of the predicted FEV1/FVC and MMEF but direct correlation with the percent of the predicted SRAW (P values: 0.38, 0.001, and 0.005, respectively). Likely, R5-R20 had the same relationship with the named parameters (P values: 0.015, 0.007, and 0.006, respectively). AX showed indirect correlation with FVC and the percent of the predicted DLCO (P values: <0.001 and 0.005, respectively) and X5 directly correlated with FVC (P value: 0.012).

**Discussion**

This study tried to evaluate and compare the parameters of body box and IOS in patients with ILD to show the accordance of the two pulmonary function tests.

Decreased FEV1 and FVC whilst normal or a little bit increased FEV1/FVC ratio is basically expected in ILD as our participants showed. Likely, we found reduced TLC and DLCO and bigger AX values in our subjects.

Increased AX is a usual change in IOS when lung parenchyma is involved by diseases like ILD chiefly due to pronouncedly high sensitivity of AX to detect increased tissue resistance and failed lung compliance in this regard. Like Sugiyama’s performance, (10) our reported R5 and R20 were in normal range but higher in expiration to show no peripheral or proximal airway problems in our participants. Against our mean R5 of 109.89%, the mean R5 was reported 150% of the normal value by Naglaa et al. who justified this increase by blaming obstruction, which both is expected in ILD (11). However, R20 was normal in our work and Naglaa’s. On the contrary, R5-R20, as an indicator of peripheral airway resistance, was a bit higher than expected in ILD which is probably explained through three points. First, the specificity of IOS is not 100% in airway problem detection. Secondly, our participants might have degrees of undetected airway obstructive diseases as comorbidities such as HP, chronic eosinophilic pneumonia, and sarcoidosis despite of negative history in records. The last issue is that some patients might have common situations like mild asthma which were not diagnosed by ordinary evaluations. Sugiyama et al. got no significant difference between inhaled and exhaled values of R5-R20 but we found its values higher during exhalation (10). The indicator of peripheral airway resistance, R5-R20, showed similar significant correlation with FEV1/FVC, MMEF, and SRAW to endorse the same rational accordance as well.

There is more increased airway resistance through expiration than inspiration almost always in ILD and this is why the current research showed a positive ΔR5 (R5EX-R5IN) occurring also in COPD, exactly emphysema. R5, the indicator of total airway resistance, correlated indirectly with FEV1/FVC and MMEF but directly with SRAW. FEV1/FVC and MMEF are well-known indicators of expiration air flow while SRAW estimates airway resistance. These correlations raises the accordance between the two modules of pulmonary function evaluation namely, body plethysmography and IOS.

The disease makes also an increased reactance (X5) as detected among our participants beside higher absolute values of X5 through inspiration than expiration to be a discrimination factor between ILD and emphysema when both of the conditions present increased AX and reactance (X5) (12). Naglaa et al. show indirect correlations between X5 and FEV1/FVC, also X5 and FEV1although the former was not significant. They also found that ΔX5 significantly correlated with TLC, VC, RV, and FEV1, indirectly (11). Unlikely, Sugiyama et al. detected a reduced X5 in ILD along with unexpectedly higher Fres and AX (10). They also clarified very negative values of expiratory and inspiratory X5 in COPD and ILD, respectively which, in turn, explain obstructive and restrictive characteristics in COPD and ILD, respectively.

AX, the IOS chief indicator of reduced lung compliance and increased tissue resistance, inversely correlated with FVC and DLCO in our ILD subjects. In other words, the increased tissue resistance and decreased lung compliance in IOS accompanied the decreased FVC and DLCO in body box both expected in ILD. There was also a significant direct relationship between X5 and FVC which means that the more negative the values of X5 in IOS the lower the values of FVC in body box. This certifies the fact that IOS is brilliant not only in ILD diagnosis but also in the estimation of the severity of the disease via by FVC and DLCO using X5 changes.

**Study limitations:** The current study was a prospective work on previous definitive ILD patients. So, there was a challenge to find the patients and persuade them to do IOS test although the test was cheaper than other tests to assess lung function which is very important in ILD management and making the best decisions in future treatment.

**Conclusion:** Our body box and IOS findings matched more or less to finally conclude that IOS may compete with body box in diagnosing and severity definition of ILD. Furthermore, the current study showed bigger absolute values of X5 in ILD but a final positive value of ΔX which is explained by higher X5 Inspiratory in ILD unlike emphysema. This discrimination between the named diseases is hopefully another strength point of IOS although the fact that more studies will be needed.

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**Competing Interests**

The authors declare no competing interests.

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**Table 1: The frequency of demographics and basic information**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Mean±SD | Min | Max | Median | Mode |
| Age | 55.54±14.01 | 27 | 82 | 57 | 61 |
| Heigth | 164.98±8.87 | 145 | 182 | 166 | 170 |
| Weight | 74.92±14.04 | 45 | 110 | 73 | 66 |
| BMI | 27.63±5.2 | 15.21 | 39.95 | 27.49 | 38.06 |

**Table 2: The frequencies of IOS parameters**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Mean±SD** | **Min** | **Max** | **Median** | **Mode** |
| **AX** | **Total** | 821.03±973.88 | 62 | 4572.70 | 458.65 | 62 |
| **AX Expiratory** | 9.99±10.09 | 0.23 | 53.45 | 7 | 9.89 |
| **AX Inspiratory** | 9.91±7.28 | 0.53 | 36.38 | 8.22 | 2.26 |
| **ΔAX** | 0.76±5.50 | -7.71 | 25.77 | -1.42 | -1.61 |
| **Fres** | **Total** | 161.24±72.23 | 78.60 | 383.80 | 144.60 | 88.50 |
| **Fres Expiratory** | 17.29±5.56 | 5.72 | 33.09 | 16.60 | 19.71 |
| **Fres Inspiratory** | 16.67±4.52 | 6.97 | 28.76 | 16.34 | 11.10 |
| **ΔFres** | 0.62±3.04 | -4.56 | 9.22 | 0.18 | 0.14 |
| **R5** | **Total** | 109.89±46.71 | 48.60 | 290.60 | 101.80 | 176.80 |
| **R5 Expiratory** | 3.69±1.54 | 1.24 | 9.80 | 3.60 | 3.81 |
| **R5 Inspiratory** | 3.25±1.18 | 1.32 | 6.58 | 3.25 | 4.54 |
| **ΔR5** | 0.44±0.63 | -0.49 | 3.22 | 0.31 | 0.19 |
| **R20** | **Total** | 99.26±41.68 | 40.90 | 251.60 | 88.45 | 163 |
| **R20 Expiratory** | 2.77±1.10 | 1.12 | 6.38 | 2.69 | 4.02 |
| **R20 Inspiratory** | 2.58±0.92 | 1.11 | 4.68 | 2.56 | 3.13 |
| **ΔR20** | 0.195±0.40 | -0.66 | 1.70 | 0.12 | 0.18 |
| **R5-R20** | **Total** | 175.12±91.03 | 32.30 | 495.10 | 159.55 | 129.30 |
| **R5-R20 Expiratory** | 0.91±0.53 | 0.12 | 3.42 | 0.84 | 0.96 |
| **R5-R20 Inspiratory** | 0.67±0.39 | 0.00 | 1.90 | 0.64 | 0.42 |
| **ΔR5-R20** | 0.24±0.32 | -0.23 | 1.52 | 0.18 | -0.15 |
| **X5** | **Total** | 886.30±1282.53 | 109.30 | 6950 | 518.90 | 171.90 |
| **X5 Expiratory** | -1.410±1.46 | -9.24 | -0.06 | -0.995 | -1.67 |
| **X5 Inspiratory** | -1.413±0.8 | -4.17 | -0.16 | -1.28 | -0.5 |
| **ΔX5** | 0.006±0.96 | -5.47 | 0.94 | 0.21 | 0.21 |

\*All the data are listed as the percent of the predicted value for the patients

\*Δ Variable = Variable Expiratory - Inspiratory

**Table 3: The frequencies for body box findings**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Mean±SD** | **Min** | **Max** | **Median** | **Mode** |
| **FEV1** | 69.82±24.77 | 22 | 129 | 71.5 | 45 |
| **FVC** | 64.02±23.16 | 25 | 124 | 63.5 | 49 |
| **FEV1/FVC** | 88.5±6.59 | 66 | 100 | 89 | 91 |
| **TLC** | 69.77±17.15 | 41 | 111 | 67.5 | 64 |
| **RV** | 87.46±47.84 | 29 | 325 | 74.5 | 61 |
| **DLCO** | 52.89±22.16 | 20 | 113 | 47 | 35 |
| **MEEF** | 95.13±46.12 | 21 | 261 | 85 | 52 |
| **sRAW** | 203.16±137.40 | 62 | 739 | 155 | 89 |

\*All the data are listed as the percent of the predicted value for the patients

**Table 4: Correlations between the IOS and some body box parameters**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **FEV1****Sig(R)** | **FEV1/FVC % Sig(R)** | **MEF 25-75****Sig(R)** | **SRAW****Sig(R)** | **RV****Sig(R)** |
| **R5** | **Pre** | -0.089(0.362) | -0.155(0.119) | -0.220(0.025) | 0.233(0.017) | -0.102(0.296) |
| **Pred%** | -0.142(0.145) | -0.206(0.038) | -0.315(0.001) | 0.273(0.005) | -0.044(0.651) |
| **R5-R20** | **Pre** | -0.159(0.109) | -0.246(0.015) | -0.269(0.007) | 0.274(0.006) | 0.041(0.681) |
| **Pred%** | -0.123(0.209) | -0.211(0.034) | -0.186(0.058) | 0.249(0.011) | 0.167(0.088) |
| **|ΔR5|** |  | -0.109(0.266) | -0.007(0.946) | -0.039(0.688) | -0.024(0.808) | -0.101(0.303) |

**Table 5: Correlations between the IOS and some other body box parameters**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **FVC****Sig(R)** | **TLC %****Sig(R)** | **DLCO%****Sig(R)** | **SRAW****Sig(R)** |
| **X5** | **Pre** | 0.247(0.012) | 0.119(0.228) | 0.116(0.238) | -0.168(0.086) |
| **Pred%** | 0.048(0.622) | -0.186(0.058) | 0.132(0.178) | 0.184(0.060) |
| **ΔX5** |  | 0.027(0.782) | -0.129(0.192) | -0.073(0.456) | -0.211(0.032) |
| **AX** | **Pre** | -0.359(<0.001) | -0.137(0.165) | -0.273(0.005) | 0.244(0.012) |
|  | **Pred%** | 0.084(0.389) | -0.183(0.063) | -0.099(0.311) | 0.042(0.670) |
| **ΔAX** |  | -0.036(0.713) | 0.126(0.200) | 0.025(0.802) | 0.242(0.013) |