Plethysmography and its relationship with biochemical parameters in the Maltese population

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Abstract

Plethysmography is an ever increasing test being performed at Mater Dei Hospital. The aim of the study was to obtain descriptive data regarding plethysmography in the Maltese population as well as to investigate the association of these lung function tests to various biochemical parameters.

282 patients who had plethysmography between June 2015 and March 2016 at Mater Dei Hospital were enrolled in the study. The indications for referral, demographic data, lung function parameters, white cell count (WCC), urea, potassium and fasting blood glucose were noted. The mean BMI of the population cohort was 29.06 (SD +/- 6.16). BMI was found to be negatively correlated to serum potassium levels (r=-0.14) and residual volume (r=-0.2). Diffuse lung capcicity of Oxygen (DLCO), total lung capacity and forced expiratory flow in one second were negatively correlated to the WCC (r=-0.2, r=-0.17 and r=-0.12 respectively) in the population. The current study confirms a significant association between lung function testing, diabetes, BMI and total serum white cell count after correcting for confounding factors. This highlights the need for clinicians to be more aware of the possibility of underlying lung disease in these patients. A good clinical evaluation using history and examination of such patients is essential so as to identify which patients should be referred for lung function testing. Such early referrals could potentially avoid progression of undiagnosed lung disease thus reducing the burden on the health care service with particular emphasis on acute hospital admissions and respiratory outpatient clinics.

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Introduction

Whole body plethysmography is the test of choice whenever information regards absolute lung volumes is required in addition to the spirometry results. Plethysmography should be performed on patients with suspected restrictive lung diseases where the measured lung volumes can help to differentiate between an obstructive and a restrictive pattern. Plethysmography is also useful

in the evaluation of obstructive lung diseases such as cystic fibrosis and bullous emphysema as well as to assess the resistance to airflow. Moreover, it can be used during the course of the disease where it aids in assessing the response to treatment.[1]

Due to the challenges associated with performing and interpreting plethysmographies and the ever increasing amount of referrals for plethysmography at Mater Dei Hospital this study primarily aims to obtain descriptive statistics associated with plethysmography for the first time in Malta including appropriateness of referral. The secondary aim of the study was to investigate the association between lung function testing and various biochemical parameters thus helping clinicians during the overall evaluation of patients.

Materials and Method:

Patients

A total of 282 patients who had a plethysmography at the Mater Dei Pulmonary Function laboratory were included in this retrospective study. All patients who had plethysmography between June 2015 and March 2016 were included in the study, after permission to collect patient data was obtained from the hospital and data protection. Data collection included indications for referral, demographic data including age, gender, height and weight, total lung capacity (TLC), residual volume (RV), diffusion lung capacity for carbon monoxide (DLCO), forced expiratory volume in the 1st second (FEV_1), forced vital capacity (FVC) and the FEV_1 and FVC ratio.

Blood investigations including urea and creatinine, potassium, sodium, calcium, phosphate, magnesium, haemoglobin, white cell count, platelets, as well as fasting blood glucose and glycated haemoglobin taken within 2 months from the plethysmography study date were reviewed and documented for each patient. Data from the plethysmography test of patients who did not have any blood results were still collected for the purposes of studying the demographics of patients referred for plethysmogtaphy yet were then excluded in studying the associations of lung volumes to biochemical parameters. Previous chest X rays, Thoracic CT Scans and High resolution CT scans were reviewed in order to confirm underlying diagnosis.

Statistic

Patients were then subdivided according to the indication for which they were referred for plethysmography and the average age, weight, height and BMI for the male and female participants of each population were worked out together with standard deviation of the respective parameters. Weight, height and BMI are mandatory parameters for performing lung function testing and therefore all lung function tests reviewed had these patient parameters included.

The mean values were used for all parameters included in the study since normality testing showed a normal distribution of data. The Pearson correlation was performed to investigate (i) the linear correlation of age, height, weight and BMI with renal profile, electrolytes, CBC and plethysmography parameters and (ii) the linear correlation of DLCO, TLC, RV, FEV_1 and FVC with renal profile, electrolytes, CBC and plethysmography parameters. Double sided P-values were worked out.

Multiple regression analysis was carried out to investigate any interdependencies between the variables studied and to further evaluate the association between DLCO and weight, height, BMI, urea, creatinine, potassium, sodium, haemoglobin, platelets and WCC.

Analysis was performed using EXCEL13 and p-values of less than 0.05 were considered to be statistically significant.

Results

Demographic information of the patient cohort are as presented in Table 1.

Demographic data

A total of 153 males and 129 females participated in this study. A total of 43 patients were referred in view of diagnosis other than chronic obstructive pulmonary disease (COPD) or fibrosis (shown in Table 2 and Table 3) and these included asthma, bronchiectasis, pleural plaques, sarcoidosis, systemic sclerosis or neuromuscular disorders. In 54 of patients, no indication was documented on the referral ticket for plethysmography.

***Table 1**: Demographics of the cohort population: Means, standard deviation and 95% CI for the demographic, biochemical and lung function parameters*

Parameter	Mean	Standard Deviation	95% Confidence Interval (Mean)
Age	66	12.45	1.47
Weight	75.77	18.83	2.22
Height	161.13	9.65	1.14
BMI	29.06	6.16	0.72
Urea	6.96	4.97	0.59
Creatinine	87.49	43.35	5.14
Potassium	4.78	0.03	0.07
Sodium	141.03	4.12	0.49
Phosphate	1.11	0.23	0.04
Magnesium	0.83	0.13	0.06
Fasting Blood Glucose	6.08	1.87	0.26
HbA1c	45.9%	12.12	1.94
White cell count (WCC)	8.66	2.96	0.35
Haemoglobin	13.81	1.57	0.18
Platelets	268.24	104.97	12.46
Total Lung capacity (TLC)	103.9%	40.35	4.82
Residual volume (RV)	133.6%	98.50	11.80
Forced Expiratory Volume in 1s (FEV_1)	72.3%	49.47	6.07
Forced vital capacity (FVC)	67.9%	29.07	3.49
FEV_1/FVC	75.4%	17.28	2.12
Diffuse lung capacity (DLCO)	70.7%	32.33	4.11

***Table 2**: **Indication for referral for body plethysmography**:*
The greatest indication was in patients with lung fibrosis. Gender distribution is also shown. (COPD – chronic obstructive pulmonary disease)

Disease	Total number of patient referred (%)	Male (%)	Female (%)
Fibrosis	42.6%	49.2%	50.8%
COPD	18.4%	86.5%	13.5%
Hypersensitivity pneumonitis	4.6%	30.7%	69.2%
Other diagnosis incl. asthma, bronchiectasis, pleural plaques	15.3%		
No diagnosis found	19.1%		

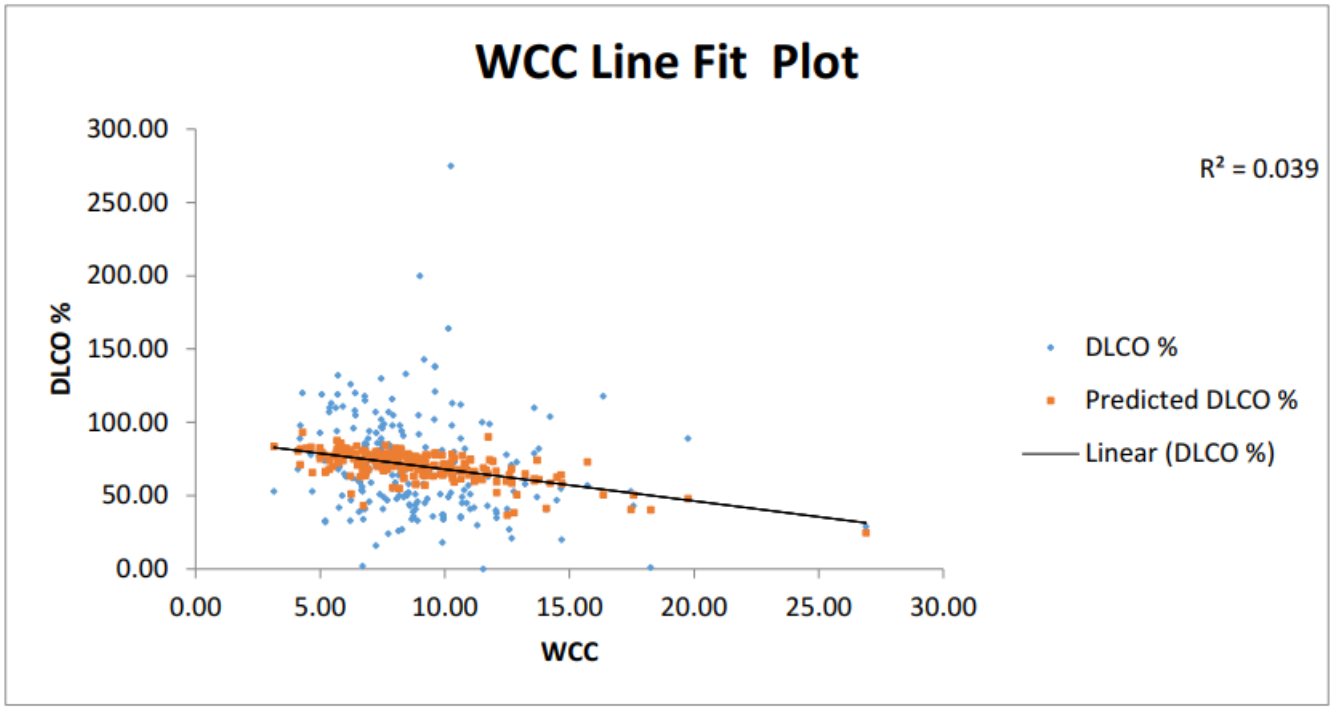
Table 3: Age, BMI and DLCO in the commonest presenting pathologies
Obesity has been noted across all the different groups as shown above.

	Mean Age		Mean BMI		Mean DLCO %	
Disease	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
COPD	70.16	72.14	26.93	26.23	74	47
Fibrosis	68.23	67.93	29.42	28.64	64	62
Hypersensitivity pneumonitis	52.50	65.89	34.49	35.79	54	69

Table 4: Pearson Correlate between the variables studied
A statistically significant negative correlation was noted between the HbA1c and RV and FVC. There is also a negative correlation between FVC and urea. A clinically significant positive correlation between FVC and sodium was also noted.
(RV: residual volume, FVC: forced vital capacity, HbA1c (glycated haemoglobin)

Parameters	**R value**	**P value**
RV to Hba1c	-0.27	0.00077
FVC to Urea	-0.13	0.02
FVC to Sodium	0.13	0.04
FVC to Hba1c	-0.166	0.04

Figure 1: Multiple regression analysis showing the relationship of white cell count (WCC) and diffuse lung capacity of CO (DLCO)*: A statistically significant negative correlation was found showing that with impaired lung function patients are more likely to have raised WCC.*



The mean BMI of the population cohort studied was 29.06 (SD +/- 6.15). BMI was negatively correlated with serum potassium levels (r=-0.14, p=0.02) and positively correlated with calcium levels (r=0.21, p=0.02) after correcting for any confounding factors. Both TLC (r=-0.19, p=0.002) and RV (r=-0.2, p=0.001) were negatively correlated to BMI.

Plethysmography

The total mean white cell count of the studied population, was negatively correlated with the mean DLCO levels (r=-0.2 and p=0.002).

A similar association was also noted between the TLC and WCC (r=-0.17, p=0.006) and between FEV_1 and WCC (r=-0.12, p=0.05). Other associations between different parameters were also noted as documented in Table 4. No significant association was noted between DLCO and HbA1c (r=-0.06, p=0.52) or haemoglobin (r=0.06, p=0.32).

Multiple Regression Analysis

The association found between the DLCO and the WCC was confirmed when controlling for other factors including the weight, height, BMI, urea, creatinine, potassium, sodium, haemoglobin and platelets as shown in Figure 1. An R^2 value of 0.84 and a p value of 0.0004.

Discussion

In this first retrospective study targeting patients referred to Mater Dei Hospital for plethysmography, a total of 282 patients with respiratory disease, were investigated.

The study is the first large cohort, population based study relating the plethysmography results to the metabolic profile. One of the benefits of Malta being a small island, with one general hospital, is that all patients requiring plethysmography were referred to the same medical center. Moreover, the service is not provided in private hospitals and thus all patients requiring the test are referred to Mater Dei. This provided both lab and operator standardization hence, eliminating inter-operational and calibration errors.

All the patients referred for this investigation in the current study were suffering from chronic respiratory diseases such as pulmonary fibrosis, chronic obstructive pulmonary disease and asthma. These results highlight the need to better understand the indications of when a plethysmography study is needed during the clinical work up of patients since nearly 20% of referred patients were suffering from obstructive airway diseases only. This highlights the importance of not using this type of investigation in the management of such patients unless a specific indication such as review of diagnosis or lung transplant work up is being considered. The authors suggest the inclusion of a checklist contain the main indications for plethysmography on the current lung function test referral form. One limitation of this study is that no data regarding justification of referral of such patients for plethysmography was available since patients' clinical files were not accessed.

In Malta, like in many westernized countries, obesity is an increasing problem with an estimated 69.75% of the Maltese population being overweight or obese.[2] Obesity affects lung volumes with a negative correlation observed between increasing BMI and expiratory reserve volume (ERV) and functional residual capacity (FRC).[3] FRC in the obese individual is also linked to airway resistance and airway conductance. Airway resistance increases with an increasing BMI and this might lead to obesity-related problems with breathing. The total lung capacity (TLC), residual volume (RV) and vital capacity (VC) decrease proportionately with an increase in weight while an increase in DLCO is associated with increasing BMI.[3]

The current study demonstrates that the TLC, FEV_1 and DLCO was found to have a significant negative correlation with the total the peripheral white cell count (p=0.002). Multiple studies have also shown that peripheral leucocyte numbers are significantly higher among smokers versus non-/former smokers[4-11] contrary to what other evidence that suggests that the negative association between serum leucocyte count and FEV_1 is independent of smoking status.[4,11-14] Studies have shown that serum leucocyte count is also significantly inversely correlated with FVC.[4, 12] This trend was also noted in our study, however the results were not found to be statistically significant. One potential limitation of the current study is that the differential white cell count was not investigated since serum neutrophil counts have been associated with a decrease in DLCO.[15]

Results from two longitudinal studies over a period of years affirm that raised serum leucocytes are not only related to poor initial pulmonary function, but are moreover a predictor of follow up

decline in lung function[12-13] and a significant predictor for respiratory symptoms both among smokers and non-smokers. [16] A low FEV_1 and a raised WCC have both been shown to be independent predictors of increased all cause mortality rate. [11] Our findings are thus in keeping with those of previous studies suggesting that the serum leucocyte count is an important independent determinant of lung function, irrespective of smoking status.[4, 15]

Since the prevalence of diabetes in the Maltese population is 10.39% [1] the current study has focused on the association between lung function tests and diabetes. Results showed that worsening glucose control, as measured by glycated haemoglobin level, was significantly associated with a low RV and low FVC. Two studies reported a similar relationship between Hba1c and FVC [17] while multiple studies have shown that pulmonary function is indeed reduced in patients with both type 1 and type 2 diabetes mellitus.[17-20] Patients with a decreased RV have restrictive lung disease for which long-term steroids are prescribed. Steroids are known to have a profound effect on glucose metabolism and hence, it is essential that patients receiving therapy have their Hba1c monitored regularly.

There is however conflicting evidence regarding the relationship between Hba1c and lung function tests. In fact, some evidence suggests that duration of diabetes is a more significant factor for poor respiratory function.[18,20-22] Conversely, research also shows that lung function is inversely related to the risk of future diabetes.[23–27] Of note is that diabetes is a significant influencer for low DLCO.[19-22] This trend has been observed in our study but was not found to be statistically significant.

The lack of data regarding the smoking status of patients participating in the study as well as the presence of multiple comorbidities that might be affecting the results are potential limitations of the study.

The current study confirms a significant association between lung function testing, diabetes, BMI and total serum white cell count after correcting for confounding factors. This is of particular relevance in the Maltese population which has a high prevalence of obesity and diabetes when compared to other European countries. Since most of the patients recruited in the study were of Maltese background (as stipulated from their ID numbers), the authors propose that there might be an underlying genetic, environmental and geographical predisposition to pulmonary pathology in this cohort of patients. This highlights the need for clinicians to be more aware of the possibility of underlying lung disease in these patients. A good clinical evaluation using history and examination of such patients is essential so as to identify which patients should be referred for lung function testing. Such early referrals could potentially avoid progression of undiagnosed lung disease thus reducing the burden on the health care service with particular emphasis on acute hospital admissions and respiratory outpatient clinics.

References

1. Townsend Rocchiccioli J, O'Donoghue CR, Buttigieg S. Diabetes in Malta: Current findings and future trends. *Malta Medical Journal*. 2005; 17(1): 16-19
2. Cuschieri S, Vassallo J, Calleja N, Camilleri R, Borg A, Bonnici G, et al. Prevalence of obesity in Malta. Obesity science and practice. 2016; 2(4): 466-470
3. Jones R, Nzekwu MM. The effects of body mass index of lung volumes. Chest. 2006; Sep 130(3): 827-33
4. Chan-Yeung M, Dy Buncio A. Leukocyte count, smoking, and lung function. Am J Med 1984; 76: 31-7.
5. Corre F, Lellouch J, Schwartz D. Smoking and leucocyte-counts: Results of an epidemiological survery. Lancet 1971; 298: 632-4.
6. Friedman GD, Siegelaub AB, Seltzer CC, Feldman R, Collen MF. Smoking habits and the leukocyte count. Arch Environ Health 1973; 26: 137-43.
7. Chan-Yeung M, Ferreira P, Frohlich J, Schulzer M, Tan F. The effects of age, smoking and alcohol on routine laboratory tests. Am J Clin Pathol 1981; 75: 320-6.
8. Petitti DB, Kipp H. The leukocyte count: Associations with intensity of smoking and persistence of effect after quitting. Am J Epidemiol 1986; 123: 89-95.
9. Jensen EJ, Pedersen B, Frederiksen R, Dahl R. Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. Thorax 1998; 53: 784-9.
10. Noble RC, Penny BB. Comparison of leukocyte count and function in smoking and non-smoking young men. Infect Immun 1975; 12: 550-5.
11. James AL, Knuiman MW, Divitini ML, Musk AW, Ryan G, Bartholomew HC. Associations between white blood cell count, lung function, respiratory illness and mortality: the Busselton Health Study. Our Respir J 1999; 13: 1115-9.
12. Sparrow D, Glynn RJ, Cohen M, Weiss ST. The relationship of the peripheral leukocyte count and cigarette smoking to pulmonary function among adult men. Chest 1984; 86: 383-6.

13. Chan-Yeung M, Abboud R, Dy Buncio A, Vedel S. Peripheral leucocyte count and longitudinal decline in lung function. Thorax 1988; 43: 462-6.
14. Gillum RF. Peripheral leucocyte count and pulmonary function in a national sample of women and men. Ann Epidemiol 1991; 1: 525-31.
15. Neas LM, Schwartz J. The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. AM J Respire Crit Care Med 1996; 153: 656-64.
16. Schwartz J, Weiss ST. Peripheral blood leucocyte count and respiratory symptoms. Ann Epidemiol 1993; 3: 57-63.
17. Schnack Ch, Festa A, Schwarzmaier-D'Assie A, Haber P, Schernthaner G. Pulmonary dysfunction in type 1 diabetes in relation to metabolic long-term control and to incipient diabetic nephropathy. Nephron 1996; 74: 395-400.
18. Davis TM, Knuiman M, Kendall P, Vu H, Davis WA. Reduced pulmonary function and its associations in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Res Clin Pract 2000; 50: 153-9.
19. Sinha S, Guleria R, Misra A, Pandey RM, Yadav R, Tiwari S. Pulmonary function in patients with type 2 diabetes mellitus & correlation with anthropometry & microvascular complications. Indian J Med Res 2004; 119: 66-71.
20. Sandler M, Bunn AE, Stewart RI. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. Am Rev Respir Dis 1987; 135: 223-9.
21. Ljubic S, Metelko Z, Car N, Roglic G, Drazic Z. Reduction of diffusion capacity for carbon monoxide in diabetic patients. Chest 1998; 114: 1033-5.
22. Asanuma Y, Fujiya S, Ide H, Agishi Y. Characteristics of pulmonary function in patients with diabetes mellitus. Diabetes Res Clin Pract 1985; 1: 95-101.
23. Shah SH, Sonawane P, Nahar P, Vaidya S, Salvi S. Pulmonary function tests in type 2 diabetes mellitus and their association with glycemic control and duration of the disease. Lung India 2013; 30: 108-12.
24. Borst BB, Gosker HR, Zeegers MP, Schols AM. Pulmonary function in diabetes: A metaanalysis. Chest 2002; 138: 393-406.
25. Engstrom G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population-based cohort study. Diabetic Med 2002; 19: 167-70.
26. Lawlor DA, Ebrahim S, Davey Smith G. Associations of measures of lung function with insulin resistance and type 2 diabetes: findings from the British Women's Heart and Health Study. Diabetologia 2004; 47: 195-203.
27. Lange P, Parner J, Schnohr P, Jensen G. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and non diabetic adults. Eur Respir J 2002; 20: 1406-12.