Original Article

The Novel Measurements and Correlations for Pulmonary Function Tests (TNMC-PFT) in interstitial lung diseases (ILD) - Using technology to simplify patient care

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ABSTRACT

BACKGROUND Interstitial lung disease (ILD) patients often have difficulty in performing spirometry. Simple tests of pulmonary functions like the single breath count (SBC) and breath hold time (BHT) have been studied since years. At our institute (TNMC) we used these tests innovatively with modern technology in cases of ILD. The novel measurements and correlations for pulmonary function tests (TNMC-PFT) were compared with standard measures of PFT. **MATERIAL AND METHODS** A prospective study was conducted in adult ILD patients referred to the PFT laboratory of a tertiary care hospital. The diagnosis of interstitial lung disease was arrived at with multi-disciplinary discussion. Spirometry, SBC and BHT were recorded. SBC was timed to a metronome (downloaded from a free online App) set at 2 counts per second. Six minute walk test was done. The average of SBC and BHT were labelled as TNMC-PFT. Spearmen's Rho calculator was used to study correlation of TNMC-PFT with spirometry and six- minute walk distance (6MWD). **RESULTS** The study included 18 men and 47 women. They consisted of 21 hypersensitivity pneumonitis, 17 CTD-ILD, 7 sarcoidosis, 11 idiopathic pulmonary fibrosis, 5 idiopathic non-specific interstitial pneumonia, and 4 other ILD cases. Mean Age, FVC and 6MWD were 51.1 (14.9) years, 1.3 (0.5) L and 266.2 (75.5) m. SBC, BHT and their average (TNMC-PFT) correlated moderately with FVC ($r=0.5$, $p<0.05$) and 6MWD ($r=0.5$, $p<0.05$). **CONCLUSION** TNMC–PFT correlated well with FVC and six minute walk distance. TNMC-PFT can be a potential alternative to spirometry in ILD in severe disease and resource limited settings.
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INTRODUCTION

Interstitial lung disease are a group of heterogenous disorders affecting the alveolo-capillary membrane.[1,2] Pulmonary function tests (PFT) have a role in the management of these patients.[3,4] However, ILD patients often have difficulty in performing simple spirometry and are often unable to perform other complex PFTs. Simple tests of pulmonary functions like the single breath count (SBC)[5] and breath hold time (BHT)[6] have been studied since years. At our institute (TNMC) we used these tests innovatively in cases of interstitial lung diseases (ILD). The novel measurements and correlations for pulmonary function tests (TNMC-PFT) were compared with standard measures of PFT like spirometry and six minute walk distance (6MWD).

METHODOLOGY

A prospective observational study was conducted in adult ILD patients referred to the PFT laboratory of a tertiary care hospital with ethics committee permission from May 2018 to October 2018. The study was an independent analysis of ILD patients enrolled in a study on profile of ILD at our center. Consequent patients were enrolled in the study. As follow-up was not the objective of the study; the chronologically first PFT was only included in case of repeated follow-up of the same patient within the six-month study period. The diagnosis of ILD was arrived at with multi-disciplinary discussion and clinico-radiological correlation. Clinical history and examination were noted from patient's clinic database. The radiographic features on chest X-Ray and high resolution computed tomography of thorax were documented. Spirometry was performed on an ATS/ERS 2005 compliant pulmonary function test machine (KOKO spirometer) first by a PFT technician. The variables of forced vital capacity (FVC), forced expiratory volume in first second (FEV1), the FEV1/FVC ratio and the peak expiratory flow (PEF) were measured. The SBC was recorded after 10 minutes of completion of spirometry. The patients were asked to take a deep breath and count as far as possible in their normal speaking voice without taking another breath. SBC was measured in cadence to a metronome (downloaded from a free online application) set at 2 counts per second. Figure 1 is the schematic representation of the metronome used in the study with arrow pointing to selection frequency of 120 beats per minute corresponding to 2 beats per second. Best of three attempts was noted. BHT was recorded after 10 minutes of SBC testing. The patients were asked to hold

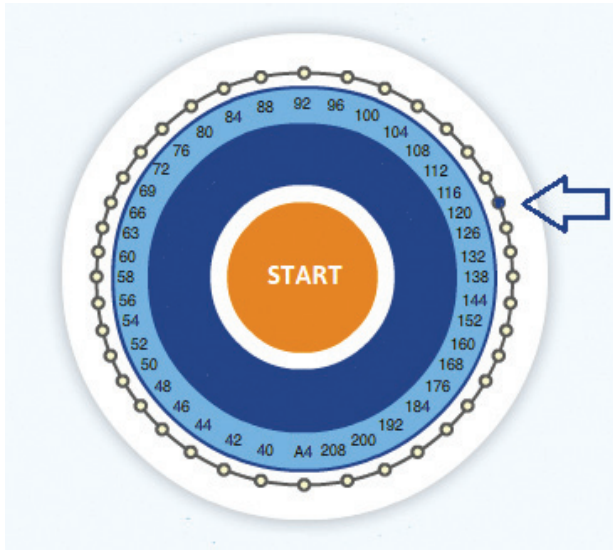

FIGURE 1. Schematic representation of the metronome used with arrow depicting the selection frequency of 120 beats per minute i.e 2 beats per second.

their breath after an effort inhalation until the breaking point and time duration was recorded in seconds. The best of three attempts was noted. Six minute walk test was done under supervision of a doctor as per ATS/ERS recommendation 10 minutes after BHT measurement. The 6MWD was recorded. All patients were offered bronchoscopy and transbronchial lung biopsy (TBLB).

Qualitative data was analysed with percentages and mean. The patients performed variably on the SBC and BHT manoeuvres, hence their average value was calculated. This parameter, "The Novel Measurement and Correlation of Pulmonary Function Test" was labelled as TNMC-PFT as it represented the abbreviated name for the purpose of the test as well as our institute too. Spearmen's Rho calculator was used to study correlation of SBC, BHT and TNMC-PFT with FVC and six minute walk distance. P value of less than 0.05 was considered to be significant.

RESULTS

Total 81 patients of ILD presented to the PFT lab during the study period. Of them, 16 patients came for a repeat PFT. Their first PFT was only included. Thus the study included 65 patients finally. They consisted of 18 (27.7%) men and 47 (72.3%) women. The ILD subtype distribution was 21 (32.3%) hypersensitivity pneumonitis (HP), 17 (26.2%) connective tissue diseases associated ILD

(CTD-ILD), 7 (10.8%) sarcoidosis, 11 (16.9%) idiopathic pulmonary fibrosis (IPF), 5 (7.7%) idiopathic non-specific interstitial pneumonia (iNSIP) and 4 (6.1%) others ILD (one cryptogenic organising pneumonia, one drug induced ILD, one Hermansky-Pudlak syndrome associated ILD & one Neurofibromatosis associated ILD). Mean age of the patients was 51.1 (14.9) years. The mean height and weight were 151.3 (9.7) cm and 55.4 (15.5) kg respectively. Seventeen of the eighteen men were smokers. None of the women smoked. All patients complained of cough and breathlessness. The severity varied. Thirty eight had comorbidities. Forty-three had Vitamin D deficiency. The clinical examination revealed crackles in all patients. The chest X-ray showed bilateral reticulonodular changes in all. HRCT thorax was consistent with changes of ILD and helped in the MDD.

The mean FVC was 1.3 (0.5) litres. The mean 6MWD was 266.2 (75.5) meters. The mean SBC was 20.5 (5.6) ranging from minimum count of 10 to maximum of 35. The mean BHT was 18.1 (5.5) ranging from 8 to 35 seconds. The mean TNMC-PFT was 19.1 (5.4) ranging from 9 to 32.5. The SBC correlated strongly with FVC ($r = 0.46$, $p<0.05$) and 6MWD ($r = 0.48$, $p<0.05$). The BHT correlated strongly with FVC ($r = 0.54$, $p<0.05$) and 6MWD ($r = 0.48$, $p<0.05$). The TNMC-PFT correlated strongly with FVC ($r = 0.51$, $p<0.05$) and 6MWD ($r = 0.49$, $p<0.05$). Fifty-seven patients had an FVC of more than one litre and 61 patients had a BHT of more than 10 seconds. Table 1 summarises the clinical characteristics of the various ILD.

In nine of total patients, bronchoscopy and TBLB was not done due to various reasons (unwillingness on part of patient-6, baseline desaturation - 2, resolution of ILD - 1). In the rest 56 patients; 29 (52%) had a positive yield, 17 (30%) had negative yield and in 10 (18%) records were not available for TBLB. Amongst the 21 HP patients; TBLB was consistent with diagnosis in 12 (57%), inconclusive in 5 (24%), records not available in 3 (14%) and not done in 1 (5%). Amongst the 17 CTD-ILD; TBLB was consistent with diagnosis in 8 (47%), inconclusive in 4 (23%), records not available in 2 (12%) and not done in 3 (18%). In Sarcoidosis, TBLB was consistent with diagnosis in 6 (86%), inconclusive in none and records not available in 1 (14%). In IPF, TBLB was consistent with diagnosis in 1 (9%), inconclusive in 5 (46%), records not available in 1 (9%) and not done in 4 (36%). Amongst the iNSIP, TBLB was consistent in 1(20%), inconclusive in 2 (40%) and records not available in 2(40%). TBLB was not done in COP (as disease had resolved), conclusive in HPS-ILD & NF-ILD and inconclusive in Drug induced ILD.

DISCUSSION

ILD is a heterogenous disease with ongoing research in its multitude aspects.[1,2] While the investigation aspect focuses on newer invasive procedures to prove the type of ILD; modification/simplification of the common PFTs

TABLE 1. Clinical characteristics of various Interstitial lung diseases (ILD)

Type of ILD	N	M/F	Mean Age	Mean Height	Mean Weight	Mean FVC	Mean 6MWD	Mean SBC	Mean BHT	Mean TNMC -PFT
HP	21	6/15	54.4 (12.1)	151.3 (10.1)	62.5 (16)	1.2 (0.5)	268.1 (64.5)	19.9 (4.3)	17.7 (3.9)	18.8 (3.7)
CTD-ILD	17	4/13	43.7 (13.8)	151.8 (10.8)	50.6 (14.5)	1.3 (0.6)	258.8 (80.8)	21.8 (6.5)	19.3 (6.3)	20.3 (6.5)
Sarcoidosis	7	1/6	42.9 (17.1)	151.9 (4.7)	52.7 (14.3)	1.6 (0.6)	314.3 (86.6)	21.4 (3)	17.9 (2.9)	19 (3.9)
IPF	11	5/6	63.3 (14.5)	152.6 (9.1)	50.4 (12.7)	1 (0.5)	246.4 (46.5)	15.7 (5.3)	14.7 (5.5)	15.2 (5)
iNSIP	5	2/ 3	49.8 (12.7)	150.4 (9.4)	57 (15.6)	1.4 (0.4)	274 (111.7)	26.4 (3.5)	24 (6.5)	25 (4.4)
COP	1	0/ 1	51	146	63	1.8	310	25	22	23.5
D-ILD	1	0/ 1	62	150	58	1.2	210	19	15	17
NF-ILD	1	0/ 1	42	158	75	1.8	360	28	23	25.5
HPS-ILD	1	0/ 1	35	126	26	0.5	110	15	10	12.5
Total	65	18/ 47	51.1 (14.9)	151.3 (9.7)	55.4 (15.5)	1.3 (0.5)	266.2 (75.5)	20.5 (5.6)	18.1 (5.5)	19.1 (5.4)

ILD: Interstitial lung disease, HP: hypersensitivity pneumonitits, CTD-ILD: connective tissue disease associated ILD, IPF: idiopathic pulmonary fibrosis, iNSIP: idiopathic non-specific interstial pneumonias, COP: cryptogenic organising pneumonia, D-ILD: drug induced ILD, NF-ILD: neurofibromatosis associated ILD, HPS-ILD: Hermansky-Pudlack syndrome associated ILD, N: number, M: male, F: female, FVC: forced vital capacity, 6MWD: six minute walk distance, SBC: single breath count, BHT: breath hold time.

has failed to gain attention. FVC and diffusion capacity of lung for carbon monoxide (DLCO) are major determinants to the disease monitoring, progression and aid the diagnosis. 6MWD is a prognostic marker. However, the pulmonologist do see a considerable number of patients with advanced disease wherein they are often not able to perform these tests or report extreme exhaustion. Hence there is an urgent need to simplify PFT.

The SBC and BHT were traditionally studied in healthy population. Ours's is a novel, first of its kind study wherein simple PFTs were studied in ILD. We observed the variation in SBC and BHT measurement and hence hypothesised on their average the "TNMC-PFT". The SBC manoeuvre requires maintenance of tempo and rhythm while performing the test on part of the patient. The previous studies used a metronome for the same. Metronome is a device that produces an audible click or other sound at a regular interval that can be set by the user, typically in beats per minute (BPM). The word metronome is derived from ancient Greek where in métron means "measure" and némo means "I manage", "I lead". The metronome is used by musicians to practice playing to a regular pulse. Musicians practice with metronomes to improve their timing, especially the ability to stick to a tempo. Composers use a metronome as a standard tempo reference. The various kinds of metronome are mechanical, electronic, software and apps. A mechanical metronome uses an adjustable weight on the end of an inverted pendulum rod to control tempo. The weight slides up the pendulum rod to decrease tempo, or down to increase tempo. The pendulum swings back and forth in tempo, while a mechanism inside the metronome produces a clicking sound with each oscillation. Mechanical metronomes don't need a battery, but run from a spring-wound clockwork escapement. Most modern metronomes are electronic and use a quartz crystal to maintain accuracy, comparable to those used in wristwatches. The simplest electronic metronomes have a dial or buttons to control the tempo. Many electronic musical keyboards have built-in metronome functions. Software metronomes run either as stand-alone applications on computers and smart phones, or in music sequencing and audio multitrack software packages. In recording studio applications, such as film scoring, a software metronome may provide a click track to synchronize musicians. Smart phones can install a wide range of metronome apps which obviates the need to carry a physical metronome along. We used the smartphone downloadable free metronome app for this study.

In our study the SBC, BHT and their average TNMC-PFT correlated strongly with FVC and 6MWD. There are no previous documentation of the TNMC-PFT. We found that ILD patients performed variably with the SBC and BHT irrespective of the spirometry readings. Hence we took an average of both the readings to explore unventured details. The SBC and BHT have correlated with lung functions like PEF in healthy adults[5,6]. The BHT was found to be gender independant[7]. The SBC measurement with an mobile app has been documented once in literature in healthy individuals[8]. As far as disease states were concerned, the SBC correlated with FEV1 and PEF in adult patients with obstructive airway diseases[9]. The SBC correlated with lung functions both PEF and FVC in situations wherein spirometry is difficult to perform like children[10] and neurological diseases[11]. There is no mention of SBC or BHT in ILD as a large patient series. In a case study, SBC correlated with lung function post single lung transplant in an ILD patient[12].

As a by-product of this study also we discovered few new details. The change in the spectrum of ILD as compared to that reported earlier 13 at our center was consistent with the changing trends as reported by the ILD India registry[14,15]. We reported a predominant IPF disease earlier, now the cases of HP seemed to form the major group. This could be due to newer insight into the disease diagnostics and an slight investigator bias at the physician and radiology end post publication of the registry data. To avoid the bias we offered TBLB to all our patients. The yield of bronchoscopy guided TBLB in ILD was also studied. The good TBLB yield of 57% in HP was an interesting finding further reiterating the need for use of simpler invasive established procedures like TBLB in this disease which is an airway centred ILD. The poor yield in IPF is known, but with the MDD criteria in place 16 there remains no need for any biopsy diagnosis in IPF. The small sub-groups of iNSIP and the HP-inconclusive on TBLB could benefit from biopsies obtaining larger lung tissue for analysis like surgical lung biopsy or cryobiopsy. Analysis of a larger database would provide further validity to these.

Limitations of study- Our study was disease centred and not population centred like most studies on PFT. As our focus was ILD patients we focused on the disease. The site of study being a tertiary care center, the selection bias and referral bias were unavoidable. We did not include a control arm as we wanted to set a background for future elaborate studies. We studied only the correlation aspect. Severity classification of the disease on lines with the FVC and six minute walk test criteria was not attempted. While

most patients could have performed DLCO manoeuvre as per ATS/ERS criteria, DLCO was not a part of the study protocol due to erratic gas supply.

To conclude, we used technology to simplify patient care. TNMC–PFT correlated well with FVC and six minute walk distance. In ILD patients unable to perform spirometry, TNMC- PFT can be a reasonable alternative to spirometry.

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