Research Article

6 Minute walk test and idiopathic pulmonary fibrosis: distance or desaturation? A prospective observational study

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Abstract

Background: 6MWT is simple, easy to perform, highly reproducible test. Its precise indication is to assess the response to therapy in various chronic lung disorders. High cost and inaccessibility of diffusion measurements in most of the clinical settings brings the utility of this test in top priority in routine follow-up of patients suffering from ILDs. However, results in various studies are not the same.

Material and Methods: 17 patients with Idiopathic Pulmonary Fibrosis were included in the study. They were assessed clinically, radiologically and by complete pulmonary function tests at initial presentation. They were all treated with same protocol with standard doses of pirfenidone, low dose corticosteroid and N-Acetyl Cysteine. A six-month follow-up study with same protocol was performed. The parameters of clinical importance were NYHA Dyspnea grading, 6MWT, FVC and DL_{CO}. The statistical analysis was performed to assess the clinical significance.

Results: In contrast to some of the quoted studies, we found that 6MWD is not the sole parameter to be relied upon in patients with IPF treated with pirfenidone containing regimes as it did not change significantly over 6 months' follow-up. Rather it was the baseline oxygen saturation and desaturation after 6MWT that carries a prognostic significance in this group of patients. Furthermore, its trend during 6 months closely followed the trends in change in grade of dyspnea, FVC and DL_{CO}.

Conclusion: Inclusion of oxygen saturation studies in 6MWT carries a prognostic significance and must be an integral part of physiological parameters to be followed in patients with IPF.

Abbreviations

6MWT: Six Minute Walk Test; 6MWD: Six Minute Walk Distance; IPF: Idiopathic Pulmonary Fibrosis; ILD: Interstitial Lung Diseases; FVC: Forced Vital Capacity; DL_{CO}: Diffusion Capacity of Lungs; NYHA: New York Heart Association

Introduction

6 MWT is a simple test, easy to perform, better tolerated and more reflective of day to day activities than other walk tests [1]. Since more of the activities of daily living are performed at sub-maximal levels of exertion, the 6MWD may better reflect the functional exercise levels for daily physical activities and formal measures of quality of life [2]. The strongest indication for 6MWT is for measuring the response to medical intervention in patients with moderate to severe heart or lung disease. Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea [3,4]. The test has a better reproducibility and lesser short term variability.

A diagnosis of IPF is associated with a median mortality of approximately 3 years. According to ATS/ERS Guidelines (2013), every 6-12 months follow up is necessary in case of ILD patients. It includes a full work up of PFTs including spirometry, diffusion capacity and 6MWT apart from HRCT chest and clinical evaluation. Small changes in FVC and DL_{CO} within first 6 to 12 months of observation may translate into major survival differences during long term follow-up [5].

We performed 6MWT in all of our patients of IPF-

1. As a protocol at the time of diagnosis and 6 monthly follow-up along with other clinical, radiological and functional parameters.

2. Because the original ATS Statement [6] does not include ILD as an indication for 6MWT, only isolated studies are available in the literature.

3. Pulse oximetry is considered as an optional parameter in 6MWT, distance being the primary outcome measure. We did pulse oximetry based on the concept that improvement in SpO_2 (peripheral capillary oxygen saturation) during serial evaluation may be manifested either by an increased distance or reduced symptoms with same distance walked [3].

While going through various studies done in the past using 6MWT in patients with IPF, we found that some of them did not observe any significant change in 6MWD over the time in these patients while few others opined that a fall in 6MWD was associated with increased mortality (discussed later). Such a difference in opinion in these studies and our observations in patients with IPF prompted us to share our results and views.

Material and methods

The study was carried out in the Department of Respiratory Medicine, Jawahar Lal Nehru Medical College, Ajmer. 17 consecutive cases of IPF consistent with diagnosis of UIP on HRCT (high resolution

computerised tomography) Chest were included in the study after informed consent. After detailed clinical history including NYHA grading of dyspnea [7] and physical examination, all these patients were subjected to complete pulmonary function tests including spirometry, DL_{CO} and 6MWT as per standard protocol. Oxygen saturation was recorded in all the patients during 6MWT along with 6MWD. Desaturation during 6MWT was also observed.

All these patients were treated with standard doses of Pirfenidone (200mg tablets, 1 tablet thrice a day for one week followed by 2 tablets thrice a day for 2nd week and 3 tablets thrice a day from 3rd week onwards), low dose corticosteroids (10mg prednisolone daily) and N-Acetyl Cysteine (600 mg thrice a day). All these patients were under regular follow-up and were re-evaluated at the end of 6 months with the same protocol. No significant dose limiting side effects were observed. The results were recorded, tabulated and statistically analysed.

Results

Our study included 17 cases of IPF, out of which 14 completed the study while 3 patients died. All the three patients who died during the study had a baseline 6MWD of less than 126 meters and DL_{CO} of less than 35% at the time of initial presentation. The overall results are depicted in tables 1 to 4. The data are clearly evident and reveal that although there was an increase in mean 6MWD in the study population (144 meters at initial presentation and 151.79 meters at the end of 6 months), it was statistically insignificant, p value was 0.967. In other words, it was interpreted that although mean distance walked in 6 minutes by the subjects did not changed significantly but the FVC, DL_{CO}, grading of dyspnea and Desaturation during 6MWT consistently fell which were statistically significant.

Table 1 shows demographic characteristics of 17 patients. Mean age of the study population was 63 years with male to female ratio of 2.4:1. Mean total duration of illness was 9 months and almost half of the subjects were smokers. All the patients had HRCT pattern consistent with diagnosis of IPF and none of them had any co-morbid illnesses in the form of emphysema, Tuberculosis, malignancies, cardiac, renal, hepatic disorders and were negative for relevant collagen profile.

Details of physiological parameters are depicted in Table 2 which includes 6MWD, Desaturation during 6MWT, FVC, DL_{CO} and grading of dyspnea at the time of presentation and at the end of 6 months of standard regimen. All the patients except one (case no 15) had mild to moderately advanced disease in terms of FVC and were thus eligible candidates for pirfenidone therapy. 6 patients had an increase in 6MWD (ranging from 12 to 100 meters). 8 patients recorded fall in 6MWD (ranging from 8 to 52 meters). Irrespective of these figures, none of our patients recorded an improved FVC, DL_{CO} or grading of dyspnea at the end of 6 months. Except one patient (case no 12), all others also recorded an increase in desaturation during 6MWT at the end of 6 months (Table3 and Figure 1).

Table 1. Demographic profile of patients with IPF

Total number of patients	17
Patients completed study	14
Mortality	03
Male(12):Female(5)	2.4:1
Mean age	63 years
Mean total duration of illness	9 months
Smoker	9/17 (53%)
Co morbidities	None
Collagen profile	All negative

Importantly Table 4 and Figure 2 shows that 13 out of 14 patients had grade II dyspnea at the time of initial presentation which progressed to grade III or IV at the end of 6 months.

Of note, an observation of immense importance is that all the three patients who died had 10% or more fall in saturation during 6MWT at the time of initial presentation. These patients also had the lowest FVC and lowest 6MWD. Mean DL_{CO} of these patients was also the lowest i.e. 30.75%. Although very early to comment on outcome and not an intend of this study, at the end of 6 months, we observed that 7 patients (41%) were stable, another 7 patients (41%) progressively deteriorated and 3 patients (18%) died.

Discussion

It is important to learn from various studies that long term survival was not linked to the underlying histological pattern of the disease (i.e. NSIP or UIP) but was solely dependent on the changes of lung physiology [8,9]. The ATS guidelines 2013[5] also suggests that in subjects with ILD, a reduction in FVC of at least 10% or DL_{CO} of at least 15% over a period of 6-12 months is associated with reduced survival. Therefore, it is important to realize that a 6 monthly follow up of these patients with complete pulmonary function testing is of paramount importance. While plenty of literature is available on ILD and its co-relation to FVC and DL_{CO} [10-15], 6MWT has not much been studied with special reference to oxygen saturation and desaturation during the test. The CAPACITY and ASCEND Trials assessed the efficacy of pirfenidone in varying doses and compared with placebo. These studies revealed a reduced rate of decline in lung function with use of pirfenidone which was also associated with reduction in risk of death and disease progression [16,17]. A reduced decline in 6MWD was also noted. Similar results were also reported by Jeffery J Swigris et al. [18] and Essam et al. [19].

Our findings are similar to previous studies, where we found that overall mean distance walked by the patients during 6MWT did not change significantly (5.41 meters; p value 0.967). However, in our study all three patients who died had a 6MWD of 126 meters or less suggesting that baseline low 6MWD might also have prognostic implications.

In contrast, a study by Roland M du Bois et al. [20] have clearly demonstrated that a decline of greater than 50 meters (6MWD) over 24 weeks had a fourfold increase in the risk of death at 1 year, suggesting that 6MWT is an important measure of prognosis and might be used as a key physiological outcome parameter. According to them, 6MWT might provide important incremental prognostic information, in addition to change in FVC which is considered a strong independent predictor of mortality in patients with IPF.

Therefore, from varying opinion in different studies, it can be concluded that 6MWD cannot be a sole parameter to explain prognosis of patients with UIP pattern specially when they are on pirfenidone therapy.

In our opinion, recording of O_2 saturation at the beginning and degree of desaturation during 6MWT in follow up should be the other vital parameters to be monitored apart from 6MWD. We observed that the mean desaturation after 6MWT at time of presentation was 6.35% and it increased to 9.64% at the end of 6 months. The difference between the mean was 4.64% and p value was 0.001 which was statistically significant. Similar results were reported by Caminati et al. [21] in their patients of UIP which were followed for 12 months. They concluded that fall of saturation is the best predictor of prognosis. Liela et al. [22] also reported that O_2 desaturation during 6MWT may be another

**Table 2.** 6MWT and Physiologic profile of patients studied

S. No.	Distance covered		Desaturation (%)		FVC (%)		DLco (%)		Grading of dyspnea	
	0months	6months	0months	6months	0months	6months	0months	6months	0 months	6months
1	126	142	8	12	64	60	37	31	3	3
2	147	110	8	12	72	67	42	30	2	4
3	136	152	2	2	93	90	60	44	2	3
4	105	-	10	-	42	-	35	-	3	-
5	147	112	4	12	71	50	42	30	2	4
6	147	132	5	10	97	84	52	41	2	4
7	146	126	0	7	69	54	50	38	2	2
8	122	147	7	20	60	48	35	16	2	4
9	210	158	5	12	57	48	38	25	2	3
10	126	-	13	-	53	-	31	-	3	-
11	148	172	4	8	60	52	58	45	2	3
12	170	270	3	0	91	83	37	30	2	3
13	160	152	5	10	80	74	48	40	2	3
14	168	160	7	10	93	88	33	23	2	3
15	86	-	15	-	38	-	25	-	2	-
16	158	134	9	12	59	53	46	28	2	3
17	146	158	3	5	66	65	53	53	2	3

Table 3. Mean, Percentage of difference and p value of various functional parameters at 0 and 6 months. Mean DLco in patients who died was 30.75%
Mean desaturation in patients who died was 12.66%

	Mean±SD		Mean Difference (0-6months)	P value
	0 months	6 months		
DLco	42.47±9.900	33.86±10.007	11.214	<0.001
FVC	68.53±17.565	65.43±15.649	8.286	<0.001
Desaturation	6.35±3.904	9.43±4.941	-4.429	0.001
Distance	144.00±27.604	151.79±38.579	0.429	0.967

Table 4. NYHA grading of study population

NYHA Grading	0 months	6 months	P value
1	-	-	
2	13(45%)	1(3%)	0.001
3	1(3%)	9(31%)	
4	-	4(14%)	
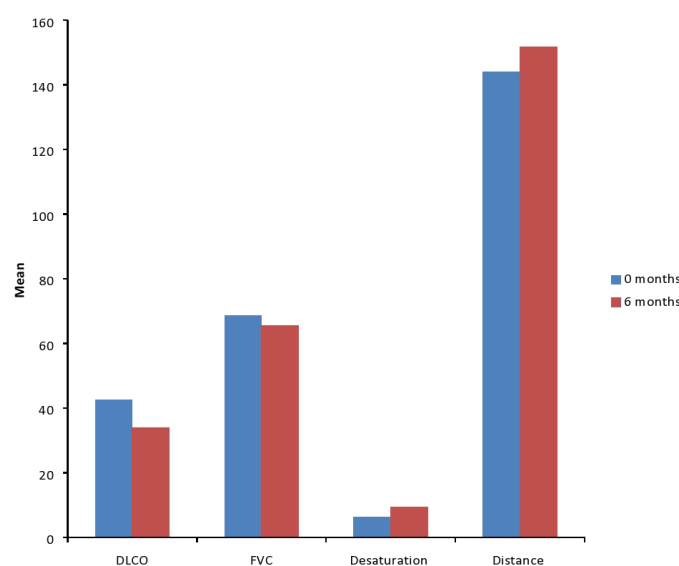
Figure 1. Graphical Observation of all the parameters studied at 0 month and end of 6th month

significant prognostic marker in patients with IPF. According to them, patients with oxygen saturation lower than 88% during the test have a higher mortality rate, a fourfold increase of mortality is probable in these patients during 3 years follow up. Lance *et al.* [11] demonstrated a strong correlation of measures of fall in saturation on 6MWT and survival, independent of the format used to define desaturation. Patients who desaturate had a higher mortality than patient who did not desaturate.

Antonella Caminati [23] stated that desaturation during 6MWT was not predictive of mortality in multivariate analysis. However, they observed that the only physiologic parameter that was predictive of survival over time was basal oxygen saturation suggesting that stability of PFTs might not reflect period of disease quiescence. One cannot deny that all 3 patients who died during follow up in our study had a significant fall in oxygen saturation during baseline 6MWT (>10%).

This statistically significant increase in value of desaturation during 6MWT closely followed the statistically significant decline in FVC, DLco and grading of dyspnea in our patients (Table 3).

NYHA grading of dyspnea may be another important clinical parameter to be observed in these patients. Our observation with NYHA grading reconfirm that 6MWD did not have any impact on subject's perception of breathlessness. In most of our patients (12 out of 14), we observed a down grading (deterioration) of breathlessness scale despite the fact that the mean distance covered did not change significantly (Figure 2). We observed a statistically significant progression of dyspnea scale in our patients (p value 0.001). To the best of our knowledge, there are no similar observations in the literature till now with new NYHA classification of dyspnea.

The fall in FVC, increased desaturation, reduction in diffusion capacity are ultimately reflected clinically by downgrading of NYHA dyspnea scale. Why these parameters did not correlate with 6MWD is not clear. A possible explanation given by Essam H Alhamad [19] sounds scientifically relevant. He hypothesised that skeletal muscle weakness (i.e acquired myopathy), which is frequently observed in IPF patients due to hypoxia, stress, malnutrition, corticosteroid therapy and other factors, is associated with increased activity of transforming
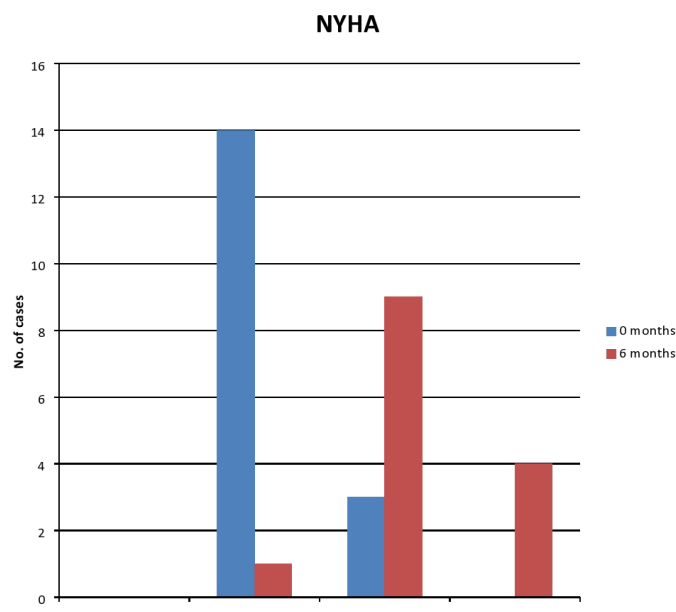
Figure 2. Graph showing pattern of NYHA grading at 0 and 6 months

growth factor beta (TGF-β). Because the anti-fibrotic properties of pirfenidone are mediated by the inhibition of TGF-β expression, as observed in many models of fibrosis, including in the lung, heart, liver and kidney, such actions may also occur in skeletal muscles, resulting in improved functional capacity and exercise tolerance in patients with IPF. However, this hypothesis is only speculative, and future studies are needed to address the precise role of pirfenidone on TGF-β signaling in skeletal muscles and possible subsequent effect on 6MWD.

The main constraint in our study was smaller sample size of population studied but we could not resist ourselves to share our observations which posed very indispensable to us. The study is still ongoing and we will like to update it in future with a bigger sample size and more promising and well-founded results.

Conclusion

Our observations and correlating them with previous studies, we are of the opinion that-

I.   NYHA dyspnea grading must be a part of clinical examination in patients of IPF. It closely correlates with other pulmonary function parameters.

II. 6MWT is still a very helpful, simple, noninvasive test to evaluate exercise capacity of patients with IPF. However, 6MWD cannot be solely relied upon as a prognostic factor but measurement of baseline oxygen saturation and desaturation during 6MWT and follow up studies must be incorporated in evaluation of these patients.

III. Facilities of spirometry and diffusion capacity may not be universally available, in that case NYHA grading and 6MWT must suffice to prognosticate the patient.

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