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The Effect of Phosphodiesterase-5 Inhibitor on Pulmonary Hypertension in Patients with Idiopathic Pulmonary Fibrosis, A Single Centre Study

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Abstract

Background: Pulmonary hypertension (PH), group III of the international aetiological classification, is a frequent and severe complication of interstitial lung diseases (ILDs), especially idiopathic pulmonary fibrosis (IPF), Phosphodiesterase 5 inhibitor (Sildenafil) appears induce vasodilatation in well-ventilated lung tissue. Such vasodilatation could gas exchange in patients with idiopathic pulmonary fibrosis.

Aim of Study: To assess the effect of phosphodiesterase 5 inhibitors (sildenafil) on pulmonary hypertension in patient with IPF after 3 months of treatment.

Patients and Methods: Fifty patients with pulmonary hy pertension secondary to idiopathic pulmonary fibrosis, divided into two groups: The first group (30 patients) received phos phodiesterase 5 inhibitors; the second group (20 patients) didn' receive phosphodiesterase 5 inhibitors; all the patients had follow up visit after 3 months with assessment of high resolu tion CT scan & transthoracic echocardiography.

Results: As regarding the class of dyspnea, there was sta tistically significant difference between the two groups with *p*-value (<0.001) favoring the treatment group. As regarding 6MWD and the change in PO2, there was statistically signifi cant difference with *p*-value (<0.001) favouring the treatmen group. Also, there was statistically significant difference *p*-val ue (0.001) favouring the treatment group regarding the change in FVC%.

Conclusion: This study supports that the patients who re ceived sidinafil had a better outcome as regards class of dysp nea, 6 MWD, PO2, FVC% and PASP.

Key Words: *Phosphodiesterase 5 inhibitor – Pulmonary hyper tension – Idiopathic pulmonary fibrosis.*

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Introduction

PULMONARY hypertension (PH), group III of the international aetiological classification **[1],** is a frequent and severe complication of interstitial lung diseases (ILDs), especially idiopathic pulmonary fibrosis (IPF), ILD associated with connective tissue disease, sarcoidosis, and many other ILDs **[2]** and it impactsdramatically morbidity and survival.

Echocardiography examination gives crucial prognostic data in the evaluation haemodynamics of of pulmonary vessels and right heart load. The important parameters help to estimate the mean pressure in the right ventricle, right atrium, and pulmonary artery. The examination should also include the assessment of RV systolic and diastolic function. Everyday clinical practice indicates that a simple and reproducible TAPSE measurement is most commonly performed in patients with pulmonary hypertension. The application of new measurement issues such as tissue doppler imaging (TDI) and 3D visualization is recommended for this aim. The combined consideration of multible echocardiographic parameters describing RV systolic and diastolic function raises their prognostic value. The assessment of the size of the heart chambers and linear values should include parameters that take into account the RA and RV area **[4].**

PH is associated with increased dyspnoea, decreased exercise capacity as measured by the 6- min walk distance (6MWD) and the peak oxygen uptake at cardiopulmonary exercise testing **[3],** lower diffusing capacity of the lung for carbon monoxide

Abbreviations:

ILD : Interstitial lung diseases.
IPF : Idiopathic pulmonary fibrosis.
PH : Ppulmonary hypertension.
PDE : Phosphodiesterase.

(DLCO), greater oxygen requirements and reduced survival **[5].**

The primary treatment approach is, therefore, to correct hypoxaemia using supplemental oxygen whenever appropriate, and to consider lung transplantation when not contraindicated by age or comorbidities. Despite recent progress with pirfenidone and nintedanib, which reduce the rate of decline in lung function in patients with mild-to-moderate disease **[6],** management of IPF remains largely supportive, with a progression to respiratory failure and death after a median of only 3 years from the time of diagnosis.

The dual endothelin-1 receptor antagonists bosentan and macitentan (NCT00903331) demonstrated acceptable toleranceyet no efficacy in patients with IPF **[7].** Ambrisentan, a selective antagonist for the type-A endothelin receptor, hasproven deleterious in patients with IPF and must be avoided inthis setting **[8]**. Riociguat is a recently developed stimulator of soluble guanylate cyclasethat restores the intracellular levels of the second messengercyclic guanosine monophosphate, thereby inducing vasodilationin both a nitric oxide-dependent and independent manner. Riociguat has a generally favourable safety profile and improvesexercise capacity, symptoms and pulmonary haemodynamics in PAH and chronic thromboembolic PH **[9]**.

Aim of work:

This study was conducted to assess the effect of phosphodiesterase 5 inhibitors (sildenafil) on pulmonary hypertension in patients with idiopathic pulmonary fibrosis after 3 months of treatment as regards as clinical & echocardiography findings.

Patients and Methods

Fifty patients admitted in Chest Department or referred from chest outpatient clinic at Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University with suspected pulmonary hypertension secondary to idiopathic pulmonary fibrosis. Study conducted duringthe period between 2016 and 2018. The patients were divided into two groups: the first group included thirty patients that received phosphodiesterase 5 inhibitors (sildenafil 20mg) t.i.d and the second group included twenty patients that didn't receivesildenafil or any other specific treatment for pulmonary hypertension, they continued on their usual treatment which mainly was cough suppressant and acetylcysteine (no change was done on their current treatment.

Inclusion criteria:

- Patients with IPF with HRCT compatible picture.
- Echocardiography showed pulmonary hypertension which cann't be explained by anything than ILD. eg. We exclude cardiac causes.

Exclusion criteria:

- Patients with ILD other than IPF.
- Patients with HRCT findingnot fully compatible with IPF.
- Patients with IPF and doest have PHT on Echo.
- Patients with IPF and any other comorbidity specially cardiac as AF or IHD.
- Patients with pulmonary hypertension secondary to any other cause than idiopathic pulmonary fibrosis, or receiving any other treatment for pulmonary hypertension or have any contraindication for sildenafil (for example: Patients taking nitrates).

All patients proved to have pulmonary hypertension by echocardiography secondary to idiopathic pulmonary fibrosis as diagnosed by HRCT (UIP pattern) according to ATS/ERS Statement 2011.

HRCT features of UIP pattern: Subpleural, basal predominance, Reticular abnormality, Honeycombing with or without traction bronchiectasis and Absence of features listed as inconsistent with UIP pattern.

Patients were subjected to thorough history taking with particular attentiontohistory of smoking, history of breeding birds, Patient's symptoms especially dyspnea&its grading according to New York Heart Association (NYHA) functional classification system. Followed by Full clinical examination, Full routine labs including: CBC, serum sodium, serum potassium, liver & kidney functions, collagen profile and Full spirometric testing (Flow volume loop) which was done byMaster Screen PFT 2012, CareFusion 234 GmbH, Germany (V-781267-057 version 03.00).

Arterial blood gases on ambient air **[10]** was done. The Six minute walk test (6-MWT) was performed according to the ATS recommendations, **[11]** High resolution CT chest was done and the following technique was used: Spiral high-resolution CT, Slice thickness 1mm, Scan spacing 10mm.

Traditional Transthoracic echocardiography was done using commercially available machines by 2.5 MHz probe. The following measurements were taken according American society of echocardiography guidelines 2015.

Pulmonary artery systolic pressure (PASP) was then calculated by adding the value of right atrial pressure (RAP) (evaluated by inferior vena cava respiratory index) to the systolic transtricuspid gradient PASP = $4V^2$ + RAP, Where V = maximal velocity of tricuspid regurgitation jet), PASP was assumed to equate the right ventricular systolic pressure in the absence of pulmonic stenosis and/or right ventricular outflow tract obstruction. Inferior vena cava size/collapsibility for right atrial pressure as follow: Size ≤2.1cm; collapses >50% during sniff

= RAP 0–5mm Hg. Size >2.1cm; collapses >50% during sniff = RAP 5–10mm Hg. Size >2.1; collapses <50% during sniff = RAP 10–20mm Hg. Right atrial volume with normal range 25±7ml/m^2 in men and 21±6ml/m^2 in women. Coronary sinus diameter which is considered abnormal if >1cm. **[12].**

All the patients had a follow-up visit after 3 months to assess vital signs, grade of dyspnea, arterial blood gases on ambient air, six minute walk test (6 MWT), spirometric testing, transthoracic echocardiographic.

Statistical analysis:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test **[13]**. For comparing categorical data; Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 **[14].** *p*-values less than 0.05 were considered as statistically significant.

Results

The study included fifty patients with pulmonary hypertension secondary to idiopathic pulmonary fibrosis.

The patients were divided into two groups: The first group included thirty patients that received phosphodiesterase 5 inhibitors and the second one included twenty patients that didn't receive phosphodiesterase 5 inhibitors.

Among the first group:

There was statistically significant difference between the two groups with *p*-value (<0.001).

There was no statistically significant difference between the two groups except for the FVC%.

By comparing the change in initial & follow-up PASP between the two groups, there was no statistically significant difference.

There was statistically significant difference as regarding change in 6MWD with *p*-value (0.047), change in PO2 with *p*-value (0.009) & change in FVC% with *p*-value (0.001).

There was statistically significant difference as regarding change in 6MWD with *p*-value (0.007)

There was statistically significant difference as regarding the change in PO2 with *p*-value (0.002) & change in FVC% with *p*-value (0.019).

There was statistically significant difference as regarding change in 6MWD with *p*-value (0.006) & change in FVC% with *p*-value (0.041).

There was statistically significant difference as regarding change in PO2 with *p*-value (0.006).

There was statistically significant difference as regarding change in 6MWD with *p*-value (0.002) & change in FVC% with *p*-value (<0.001).

Table (1): Classes of Dyspnea in the patients according to NYHA classification.

	Group			
	Received treatment		Without treatment	
	Count	Column N %	Count	Column N %
Initial grade of dyspnea:				
II	4	13.3%	10	50.0%
III	20	66.7%	8	40.0%
IV	6	20.0%	2	10.0%
Follow-up grade of dyspnea:				
II	8	26.7%	0	0.0%
III	22	73.3%	14	70.0%
IV	0	0.0%	6	30.0%

Table (2): The change in Classes of Dyspnea between both groups.

	Group				*p*-value
	Received treatment		Without treatment		
	Count	Column N %	Count	Column N %	
Change in dyspnea:					
Deteriorated	2	6.7%	12	60.0%	<0.001
Improved	12	40.0%	0	0.0%	
Same	16	53.3%	8	40.0%	

Table (3): Initial Functional affection of the both groups.

	Received treatment					Without treatment					*p*-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Initial PO2	57.87	9.16	60.00	43.00	70.00	60.70	8.96	62.50	43.00	75.00	0.427
Initial SO2	88.60	3.50	89.00	82.00	94.00	90.10	3.16	90.50	84.00	96.00	0.111
Initial 6MWD	184.00	56.57	180.00	105.00	340.00	191.10	63.04	190.00	95.00	280.00	0.551
Initial FVC	47.87	14.09	48.00	25.00	76.00	55.80	9.32	59.00	44.00	69.00	0.032

Table (4): Comparison of functional affection before & after treatment.

	Initial					Follow-up					*p*-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
PO2	57.87	9.16	60.00	43.00	70.00	58.67	8.65	58.00	40.00	70.00	0.819
SO2	88.60	3.50	89.00	82.00	94.00	89.00	3.38	89.00	80.00	94.00	0.279
6MWD	184.00	56.57	180.00	105.00	340.00	178.80	55.39	174.00	100.00	310.00	0.251
FVC	47.87	14.09	48.00	25.00	76.00	46.60	14.78	50.00	25.00	74.00	0.645

Table (5): Comparison between functional affection initially & follow-up without treatment.

	Initial					Follow-up					*p*-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
PO2	60.70	8.96	62.50	43.00	75.00	58.20	8.50	58.50	44.00	75.00	0.014
SO2	90.10	3.16	90.50	84.00	96.00	88.30	4.00	88.00	82.00	97.00	0.001
6MWD	191.10	63.04	190.00	95.00	280.00	162.00	56.53	150.00	80.00	265.00	<0.001
FVC	55.80	9.32	59.00	44.00	69.00	49.80	11.12	50.00	34.00	70.00	<0.001

Table (6): Comparing the change of functional affection between both groups.

	Group										*p*-value
	Received treatment					Without treatment					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
6MWD change	–5.20	17.99	–6.00	–40.00	20.00	–29.10	21.23	–25.00	–76.00	.00	<0.001
PO2 change	.80	4.51	.00	–5.00	14.00	–2.50	4.01	–2.50	–10.00	5.00	.011
FVC change	–1.27	4.98	.00	–10.00	4.00	–6.00	5.09	–4.50	–18.00	1.00	.001

Table (7): Comparison of echocardiography findings before & after treatment.

	Initial					Follow-up					*p*-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
RV basal diameter	40.80	8.30	40.00	23.00	58.00	39.80	7.01	38.00	27.00	57.00	0.079
RV mid diameter	37.73	10.94	36.00	19.00	68.00	36.27	8.08	34.00	23.00	55.00	0.162
RV long. diameter	60.67	19.08	59.00	7.00	90.00	67.27	10.75	69.00	49.00	86.00	0.138
RV outflow	27.53	5.98	27.00	16.00	38.00	27.80	4.80	29.00	20.00	34.00	0.671
RV wall thickness	5.63	1.37	5.50	4.00	8.00	5.97	1.56	6.00	4.00	9.00	0.01
TAPSE	20.47	5.08	20.00	13.00	34.00	19.40	4.67	18.00	12.00	29.00	0.022
RV FAC	36.00	7.04	37.00	22.00	48.00	37.13	5.02	38.00	28.00	46.00	0.326
PASP	61.13	12.92	59.00	39.00	85.00	63.47	11.30	64.00	49.00	89.00	0.184
IVC diameter	1.86	.31	1.80	1.40	2.40	1.91	.29	2.00	1.30	2.30	0.739
CS	.85	.18	.80	.60	1.20	.79	.15	.80	.60	1.10	<0.001
RA volume	59.80	53.73	41.00	20.40	202.00	53.26	40.15	38.00	16.70	145.00	0.122

Table (8): Difference in the change of PASP between both groups.

	Received ttt					Without treatment					P-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
PASP change	2.33	6.83	1.00	−7.00	15.00	3.30	8.04	6.00	−18.00	10.00	0.104

Table (9): Comparing the change of functional affection between both groups in patients with RV dilatation.

	Group										P-value
	Received ttt					Without treatment					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
6MWD change	–1.67	17.15	–5.00	–30.00	20.00	–26.50	31.25	–15.00	–76.00	.00	.047
PO2 change	1.89	5.37	1.00	–5.00	14.00	–4.00	4.34	–3.50	–10.00	1.00	.009
FVC change	–.56	4.23	.00	–10.00	4.00	–8.25	6.56	–6.00	–18.00	–3.00	.001

Table (10): Comparing the change of functional affection between both groups in patients without RV dilatation.

	Group										P-value
	Received ttt					Without treatment					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
6MWD change	–10.50	18.64	–11.00	–40.00	20.00	–30.83	12.22	–30.00	–50.00	–15.00	.007
PO2 change	–.83	2.04	–1.00	–3.00	2.00	–1.50	3.61	–2.00	–5.00	5.00	.319
FVC change	–2.33	5.96	.00	–10.00	4.00	–4.50	3.34	–4.50	–10.00	1.00	.178

Table (11): Comparing the change of functional affection between both groups in patients with RV hypertrophy.

	Group										P-value
	Received ttt					Without treatment					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
6MWD change	–7.75	17.63	–13.00	–30.00	20.00	–36.50	26.71	–27.50	–76.00	–15.00	.052
PO2 change	–.75	3.26	–1.50	–5.00	6.00	–5.50	3.07	–5.00	–10.00	–2.00	.002
FVC change	–.38	4.50	1.00	–10.00	4.00	–7.25	7.65	–6.00	–18.00	1.00	.019

Table (12): Comparing the change of functional affection between both groups in patients without RV hypertrophy.

	Group										P-value
	Received ttt					Without treatment					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
6MWD change	–2.29	18.60	–5.00	–40.00	20.00	–24.17	16.07	–25.00	–50.00	.00	.006
PO2 change	2.57	5.17	1.00	–3.00	14.00	–.50	3.29	–.50	–5.00	5.00	.067
FVC change	–2.29	5.46	–2.00	–10.00	3.00	–5.17	2.37	–4.50	–10.00	–3.00	.041

Table (13): Comparing the change of functional affection between both groups in patients with RV dysfunction.

	Group										P-value
	Received ttt					Without treatment					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
6MWD change	–7.29	16.68	–10.00	–30.00	20.00	–23.33	12.91	–15.00	–40.00	–15.00	.153
PO2 change	2.14	6.01	1.00	–5.00	14.00	–4.00	1.55	–5.00	–5.00	–2.00	.006
FVC change	–2.71	5.28	–2.00	–10.00	4.00	–8.67	8.50	–9.00	–18.00	1.00	.274

Table (14): Comparing the change of functional affection between both groups in patients without RV dysfunction.

	Group										*p*-value
	Received ttt					Without treatment					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
6MWD change	–3.38	19.41	–5.50	-40.00	20.00	–31.57	23.93	–30.00	–76.00	.00	.002
PO2 change	–.38	2.19	–.50	–3.00	3.00	–1.86	4.59	–1.00	–10.00	5.00	.377
FVC change	.00	4.47	2.00	–10.00	4.00	–4.86	2.32	–4.00	–10.00	–3.00	<0.001

Discussion

By comparing the change in classes of dyspnea between both groups, it is noticed that following treatment, two patients deteriorated (6.7%), twelve patients improved (40%) & sixteen patients remained with the same class of dyspnea (53.3%), while without treatment; twelve patients deteriorated (60%) & eight patients remained with the same class of dyspnea (40%).

There was statistically significant difference between the two groups as shown inwith *p*-value (<0.001).

The improvement in dyspnea with phosphodiesterase-5 inhibitor (Sildenafil) is consistent with the largest study of sildenafil in patients with IPF; STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) 2010. In this study, 180 patients with IPF were randomized to either sildenafil (n = 89) or placebo (n = 91) for 12 weeks of treatment without any assessment for the presence or severity of PH, it concluded that patients taking sildenafil had improved dyspnea measured with the use of Borg Dyspnea Index & quality of lifemeasured with the use of St. George's Respiratory Questionnaire. At the other side, Jackson et al 2010 **[15]** assignedtwenty nine patients with IPF in a pilot study to a double-blind, placebo-controlled, randomized control trial for 6 months, In this trial, sildenafil did not decrease the Borg dyspnea index in patients with clinically typical IPF.

As regard Functional affection of the studied patients, the following was noticed:

Among the group that received treatment; Mean of 6MWD decreased from 184 meters (±56.57) to 178.8 meters (±55.39) with no statistically significant difference.

Among the group that didn't receive treatment; mean of 6MWD decreased from 191.1 meters (±63.04) to 162 meters (±56.53) with statistically significant difference of *p*-value (<0.001).

The 6-minute-walk test is a widely used measure of exercise tolerance that has been validated in a variety of cardiac and pulmonary diseases. Du Bois et al., **[16]** stated thatthe 6-minute-walk test is a reliable, valid, and responsive measure of exercise tolerance in patients with idiopathic pulmonary fibrosis. Swigris et al., **[17]** noted that shorter walk distance and delayed heart-rate recovery after walk testing have been associated with an increased risk of subsequent mortality.

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. A mean 6MWD of 630m for 51 healthy adults was reported by Troosterset al., **[18]**.

According to ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension 2015, 6MWD is one of the variables need to be obtained forrisk assessment in pulmonary hypertension, where patients with 6MWD >440m are categorized as low risk with an estimated 1-year mortality <5% & patients with a 6MWD <165m are categorized as high risk with an estimated 1-year mortality >10%.

It was noticed in this study that patients of both groups experienced a decline in their 6MWD but, by comparing the decline in 6MWD between both groups, there was statistically significant difference with *p*-value (<0.001), favouring the treatment group.

This is partially consistent with STEP-IPF 2010, in which the use of sildenafil did not cause a significant difference in the proportion of patients with an improvement of 20% or more in the 6-minute walk distance at 12 weeks (the primary outcome), Jackson et al. **[15]**, alsodemonstrated clearly that the 6MWT distance can vary significantly during 3 months, but it appears to reflect overall clinical decline during 6 months but they found no significant difference between the placebo and sildenafil groups regarding the 6 MWT distance after 3 or 6 months of treatment.

As such, these data differ from the results reported by Ghofrani et al. **[19]**, those investigators assessed the acute effects of high-dose sildenafil (50mg orally) on pulmonary vascular resistance and gas exchange which led to improvement in 6MWD, therefore, their study design and methods were not comparable to ours.

Another study by Collard et al. **[20]** in which Fourteen patients were enrolled in the open-label study, onlyeleven patients successfully complet-

ed both the baseline and follow-up 6MWTs, they demonstrated significant improvement in 6MWD after treatment with sildenafil in patients with IPF and PAH. More than half of patients (57%) improved their 6MWD by >20% at 3 months. A report by Madden et al., *[21]* of three patients with IPF and PAH treated with 8 weeks of sildenafil therapy showed a significant increase in mean 6MWD.

Among the group that didn't receive sildinafil, mean of PO2 decreased from 60.7mmHg (±8.96) to 58.2mmHg (±8.5) with statistically significant difference of *p*-value (0.014) & mean of SO2 decreased from 90.1 (±3.16) 88.3 (±4) with statistically significant difference of *p*-value (0.001).

Comparing the change in PO2 between the two groups, there was statistically significant difference *p*-value (0.011) favouring the treatment group.

Meanwhile, among the group that didn't receive treatment, mean of FVC% decreased from 55.8 (±9.32) to 49.8 (±11.12) with statistically significant difference of *p*-value (<0.001).

These results are comparable with STEP-IPF 2010, in which Sildenafil-treated patients had significant physiological stabilization, as documented by measurements of arterial blood gas and carbon monoxide diffusion capacity, as compared with non-treated patients.

Also, these findings can be explained with previously published databyGhofrani et al. *[19]* that sildenafil improved ventilation-perfusion matching in patients with pulmonary fibrosis.

As regard echocardiography findings of the studied patients, the following was noticed:

With treatment, regarding RV dimensions mean of RV basal diameter & mid diameter decreased from 40.8mm (±8.3) to 39.8mm (±7.01) & from 37.73mm (±10.94) to 36.27mm (±8.08) respectively with no statistical significance. While the mean of RV longitudinal diameter & RV outflow diameter increased from 60.67mm (±19.08) to 67.27mm (±10.75) & from 27.53mm (±5.98) to 27.8mm (±4.8) respectively with no statistical significance, regarding RV hypertrophy the mean of RV wall thickness increased from 5.63mm (±1.37) to 5.97mm (±1.56) with statistically significant difference of *p*-value (0.01), regarding RV dysfunction the mean of TAPSE decreased from 20.47mm (±5.08) to 19.4mm (±4.67) with statistically significant difference of P value (0.022). While the mean of RV FAC increased from 36% (±7.04) to 37.13% (±5.02) with no statistical significance & regarding PASP the mean increased from 61.13mmHg (±12.92) to 63.47mmHg (±11.3) with no statistical significance.

Without treatment, regarding RV dimensions, the mean of RV basal, mid, longitudinal & RV outflow increased diameter from 37.8mm (±7.58) to 40.1mm (±8.03), from 34.4mm (±7.64) to 36.5 mm (±7.86), from 62.3mm (±11.3) to 63.5mm (±9.92) & from 25.6mm (±4.08) to 27.2mm (±3.64) respectively with statistical significance, regarding RV hypertrophy, the mean of RV wall thickness increased from 5.65mm (±1.66) to 6.2mm (±1.2) with statistically significant difference of *p*-value (0.038), regarding RV dysfunction the mean of TAPSE decreased from 19.1mm (±4.71) to 17.8mm (±3.04) with no statistically significant difference while, the mean of RV FAC decreased from 38.6% (±10.28) to 33.2% (±7.55) with statistical significance difference of *p*-value (0.004) & regarding PASP the mean increased from 58mmHg (±13.27) to 61.30mmHg (±10.45) with statistical significance difference of *p*-value (0.022).

The variability of the change in the echocardiography findings either with treatment or without treatment is consistent with the Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging forCardiac Chamber Quantification by Echocardiography in Adults, 2015 which stated thatthe right ventricle has unique crescent shape, which adds complexity to the quantification of its size and function so thatthe operator should examine the right ventricle using multiple acoustic windows, and the report should present an assessment based on both qualitative and quantitative parameters.

In a study by Arcasoy et al., *[22]* of patients with advanced lung disease, PASP assessed by echocardiography had a modest correlation compared with RHC measurement (r=0.69; p<0.0001). However, in those with interstitial lung disease, estimation of PASP by echocardiography was only possible in 54% of the patients, and when obtained, it was inaccurate in 37% of cases, with a discordance of greater than 10mm Hg. Results were similar in a study by Nathan et al., *[23]* on a group of patients with IPF, showing that measurement of PASP was possible in 54.5% of the echocardiography, with 40% accuracy between estimated PASP by echocardiography and measured PASP by RHC.

In a retrospective review by corte et al., *[24]* of 14 ILD patients with PH, they reported that 6-month oral sildenafil therapy was safe and well tolerated, and was associated with no change in echocardiographic haemodynamic values (RVSP).

On the contrary, the study byZimmermann et al., *[25]* often ILD patients identified a trend towards improved mPAP measured by RHC during treatment with PDE-5 inhibitors, which did not reach statistical significance.

In our study we categorized the patients either who received or who didn't according to the presence or absence of RV dilatation, hypertrophy & dysfunction, in order to detect the patients who get the most benefit from phosphodiesterase 5 inhibitors.

As was noticed before, the patients who received treatment had a better outcome as regards as 6MWD than those who didn't receive, the same statistically significance difference between both groups was present in patients with RV dilatation with *p*-value (0.047) & without RV dilatation with *p*-value (0.007), & patients without RV hypertrophy with *p*-value (0.006) & without RV dysfunction with *p*-value (0.002).

Han et al. *[26]* revised echocardiography of 119 out of 180 patients (sildenafil, n = 56; placebo, n = 63) enrolled in STEP-IPF 2010 to assess for right-sided ventricular (RV) abnormalities and their relationship to changes in exercise performance & quality of life, they demonstrated that While on average, 6MWD declined over the course of 12 weeks for all subjects, those with any evidence of RV dysfunction treated with sildenafil demonstrated a 99.3 m greater 6MWD as compared with those treated with placebo (*p*=.01). Those without RV hypertrophy treated with sildenafil did not demonstrate a significant change in 6MWD as compared with placebo.

According to the Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis, 2015,the committee did not make a recommendation regarding treatment of PH in patients with IPF as they needed further evidence to guide this clinical decision & that future clinical trials in patients with IPF manifesting PH should consider studies with agents indicated for treatment of PH, especially the ones that have demonstrated an acceptable safety profile in patients with IPF (e.g., dual ERAs & phosphodiesterase-5 inhibitor).

According to ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension 2015, the use of drugs approved for PAH is not recommended for patients with PH due to lung disease. Patients with suspected PAH in addition to their lung diseases (characterized by mild lung parenchymal abnormalities, symptoms insufficiently explained by lung mechanical disturbances and a haemodynamic 'PAH phenotype', i.e. severe PH with high PVR and low CO) may be treated according to the recommendations for PAH, keeping in mind the potential implications of the co-existing lung disease on symptoms and response to therapy.

It is unclear at this time whether PAH specific therapies are of any clinical value in interstitial lung disease complicated by PH. It appears, however, that sildenafil has pleiotropic properties beyond its traditional vasodilatory effects that may render it especially attractive as an add-on treatment for IPF *[27]*.

PDE5 is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres) *[28]*.

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تأثير مثبط الفوسفودايستراز ٥ على ضغط الشريان الرئوى المرتفع فى مرضى التليف الرئوى الغير معلوم السبب

يعرف مرض التليف الرئوى غير معلوم السبب بأنه نوع محدد من التهاب الانسجة البينية للرئة غير معلومة السبب. والمرض يصيب الرئة فقط و يكون مصحوباً بمظهر نسيجى للالتهاب الرئوى الاعتيادى.

كثيرا ما يصاحب ارتفاع ضغط الشريان الرئوى الحالات المتقدمة من مرض التليف الرئوى غير معلوم السبب وحدوثه يزيد من شدة المرض. إن مثبط فوسفوديستيراز ٥ (سيلدينافيل) يحفز توسع الأوعية فى أنسجة الرئة جيدة التهوية. ويمكن لهذا التوسيع بالأوعية الدموية أن يحسن التهوية – مطابقة الارواء وبالتالى يحسن تبادل الغازات فى المرضى الذين يعانون من التليف الرئوى غير معلوم السبب.

والهدف من هذه الدراسة هو تقييم تأثير مثبط الفوسفودايستراز ٥ (سيلدينافيل) على مرضى ضغط الشريان الرئوى المرتفع الناتج عن التليف الرئوى الغير معلوم السبب بعد ثلاث أشهر من العلاج.

وقد شملت الدراسة ٥٠ مريضاً يعانون مرض ضغط الشريان الرئوى المرتفع الناتج عن التليف الرئوى الغير معلوم السبب من المرضى المحجوزين بقسم الأمراض الصدرية بمستشفى القصر العينى.

وقد تم تقسيم المرضى إلى مجموعتين: المجموعة الأولى شملت ثلاثين مريضاً تلقوا مثبط الفوسفودايستراز ٥ والمجموعة الثانية شملت عشرين مريضاً لم يتلقوا مثبط الفوسفودايستراز ٥؛ جميع المرضى قاموا بزيارة متابعة بعد ثلاث أشهر. وتم عمل الاتى لجميع المرضى:

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وبناءا على هذه الدراسة فقد لوحظ الآتى:

ان هناك فروق ذات دلالة إحصائية بين المجموعتين فيما يتعلق بفئة ضيق التنفس، اختبار المشى لمدة ٦ دقائق، الضغط الجزئى للأكسجين والقدرة الحيوية القسرية لصالح مجموعة العلاج، ولكن لا يوجد فرق مهم إحصائياً فى تغيير الضغط الانقباضى الرئوى المقاس بالموجات الصوتية على القلب بين المجموعتين.