Research Article Open Access

Oral Sildenafil has No Acute Effect on Diffusion Capacity Measurements in Patients with Diffuse Parenchymal Lung Disease and Pulmonary Hypertension

Isabel Mira-Avendano[1]*, Umur Hatipoglu[1], Catherine Sant[1], Daniel Laskowski[1], Ruchi Yadav[2] and Raed Dweik[1]

[1]Respiratory Institute, Cleveland Clinic, Cleveland, Ohio, USA

[2]Imaging Institute, Cleveland Clinic, Cleveland, Ohio, USA

*Corresponding author: Isabel Mira-Avendano, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio, USA, Tel: 904-953-6728; E-mail: mira.isabel@mayo.edu

Abstract

Diffuse parenchymal lung diseases have diverse etiology and treatment often requires individualization taking into consideration comorbidities. Pulmonary hypertension represents one such comorbidity which, when present, worsens prognosis and confounds approach to treatment. Sildenafil is a pulmonary vasodilator, which has recently generated considerable interest for use in patients with diffuse parenchymal lung disease and concomitant pulmonary hypertension.

We wondered whether acute administration of oral sildenafil affects the diffusion capacity measurement, which is a tool for serially monitoring patients with diffuse parenchymal lung diseases.

Methods: 15 patients with diffuse parenchymal lung disease and pulmonary hypertension (WHO Class III) had diffusion capacity measurements and 6 minute walk test performed before and after receiving sildenafil 20 mg orally. CT scans of the chest were scored to determine burden of interstitial lung disease.

Results: The mean change in DLCO after administration of oral sildenafil was -0.26 ± 0.94 ml/min/mmHg (p=0.30) and -0.41 ± 2.84 % predicted (p=0.58). The average 6 minute walk distance at baseline was 363.28 ± 141 meters. After oral administration of sildenafil, 6 minute walk distance was 369 ± 116 meters (p=0.63). No correlation was observed between composite radiology scores and DLCO measurements or change in DLCO and radiology scores (p=0.43 and p=0.17 respectively).

Conclusion: We found no acute change in diffusion capacity after a single dose of oral sildenafil in patients with diffuse parenchymal lung disease and pulmonary hypertension.

Keywords: Pulmonary hypertension; Parenchymal lung disease; Diffusion capacity

Introduction

Diffuse parenchymal lung diseases have diverse etiology and treatment often requires individualization taking into consideration comorbidities. Pulmonary hypertension represents one such comorbidity which, when present, worsens prognosis [1,2] and confounds approach to treatment. Furthermore, with the exception of pulmonary hypertension in the setting of connective tissue disease-related parenchymal lung disease, there is controversy in the utility of treatment of pulmonary hypertension in this group of patients (WHO Group III).

Sildenafil is a cyclic GMP selective phosphodiesterase type 5 inhibitor approved for use in patients with pulmonary arterial hypertension. The drug has recently generated considerable interest for use in patients with diffuse parenchymal lung disease and concomitant pulmonary hypertension. A theoretical concern has been the possible worsening in oxygenation when pulmonary vasodilators are introduced to patients with abnormal ventilation perfusion matching at baseline. In a small, but meticulously conducted physiological studies, sildenafil has shown salutary effects with improvement in pulmonary pressures with negligible impact on oxygenation and ventilation perfusion mismatch [3]. In a post hoc subgroup analysis of 84 patients with pulmonary arterial hypertension and connective tissue disease who had been included in the SUPER-1 trial, Badesch and colleagues demonstrated improvements in exercise capacity, hemodynamic changes and functional class, following 12 weeks of treatment with varying doses of sildenafil [4]. Later, 259 patients from the SUPER-1 trial were enrolled in an open label extension study (SUPER-2) of 3 years duration which demonstrated continued improvement or maintenance of functional status while on sildenafil [5]. Recently, sildenafil was associated with small but statistically significant improvements in diffusion capacity and oxygenation while having no effect on 6 minute walk distance in 180 patients with advanced idiopathic pulmonary fibrosis and pulmonary hypertension [6].

Diffusion capacity of the lung for carbon monoxide (DLCO) measurement is ubiquitously available and is used as a tool for serially monitoring patients with diffuse parenchymal lung diseases. The American Thoracic Society has endorsed its use in the assessment of patients with idiopathic interstitial pneumonias [7]. Diffusion capacity measurements are affected by blood volume and transit time in the capillary bed. Therefore, pulmonary vasodilators can potentially affect measurements by altering pulmonary vascular hemodynamics.

The aim of our study was to determine the acute effect of oral sildenafil on diffusion capacity in patients with diffuse parenchymal lung disease and concomitant pulmonary hypertension. The significance of this information is twofold. First, it would be helpful clinically to determine the contribution of a pulmonary vasodilator to the change in DLCO to separate this effect from a change in the clinical status of parenchymal disease. Second, sildenafil's effect on gas exchange may lead to modifications in therapy such as changes in oxygen flow delivered to patients.

Study Population

Adult patients over age 18 years of age, who were able to consent and had received a diagnosis of diffuse parenchymal lung disease with concomitant pulmonary hypertension, were eligible. The diagnosis of diffuse parenchymal lung disease was made by the primary pulmonologist based on clinical presentation, high resolution chest CT findings and presence of restrictive or mixed pattern in spirometry.

The diagnosis of pulmonary hypertension was based on echocardiographic findings and/or invasive hemodynamic measurement (estimated RVSP 35 mm Hg or more, or mean pulmonary artery pressure over 25 mmHg with pulmonary capillary wedge pressure less than 15 mm Hg, respectively).

Materials and Methods

The study was approved by the Institutional Review Board of the Cleveland Clinic. Informed consent was obtained from each patient. Assuming 15% change in DLCO representing a significant clinical difference and a standard deviation of 17.4% in normal non-smoking individuals [8], 13 subjects needed to be studied to reject the null hypothesis when there is no significant difference between DLCO measurements before and after sildenafil, with power 0.8 and type I error probability 0.05 (SAS 9.2, SAS Institute Inc., Cary, NC)

Methods

Diffusing capacity of the lung for carbon monoxide

Measurement of the diffusing capacity of the lung for carbon monoxide (DLCO) was performed on the Jaeger Master screen Body PFT unit (Care Fusion, Inc., Yorba Linda, CA) in accordance with the 2005 ATS/ERS recommendations for a standard single-breath technique [9]. Measurements were performed in duplicate (or more if expected laboratory standard for DLCO repeatability of <10% or 3 mL/min/mmHg was not met) and the mean value for single-breath DLCO, DLCO/VA and VA were reported.

6 minute walk

Six minute walk was performed in accordance with ATS guidelines [10]. In brief, the patient sat at rest in a chair, located near the starting position, for at least 10 minutes before the test. Time in was started as soon as the patient started to walk. Standard phrases of encouragement were used during the walk. The total distance walked was calculated by counting the laps and rounding to the nearest meter.

High resolution chest tomography

Radiology score Computed tomography (CT) scan of the chest studies which were ordered at the discretion of the treating physician were interpreted when available. Imaging studies which were within 6 months of DLCO measurements were included. A radiological scoring system for idiopathic pulmonary fibrosis [11] was employed for the study protocol. A radiologist with expertise in thoracic radiology (R.Y.), who was blinded to patient history and research protocol, scored all available images. Scores for groundglass opacity (GGO) and fibrosis were obtained. The GGO and fibrosis scores were added to create a composite score that reflected disease burden.

Protocol

Baseline FVC, FEV1, TLC (all within the past 6 months of study recruitment), O2 flow if any, were obtained from patient's medical record. Radiology score was calculated for each patient for whom high resolution CT scan of the chest was available. Then, each patient underwent diffusion capacity measurement, and 6 minute walk. After baseline measurements, 20 mg of oral sildenafil was administered. Following one hour of rest, DLCO measurement and 6 minute walk were repeated.

Analysis

Paired t-test was used to assess the change in DLCO before and after sildenafil. Spearman correlation coefficients and respective p-values were derived to assess the correlation between diffusion capacity measurements, pulmonary function test variables and imaging scores using statistical software (SAS 9.2, SAS Institute Inc., Cary, NC).

Results

Patients

Fifteen (7 female, 8 male) with diffuse parenchymal lung disease and concomitant pulmonary hypertension were enrolled in the study. Average age was 58.6 ± 13 years. Six patients had idiopathic pulmonary fibrosis, four had usual interstitial pneumonia (associated with mixed connective tissue disease, undifferentiated connective tissue disease, systemic sclerosis and rheumatoid arthritis), three had nonspecific interstitial pneumonia (2 associated with systemic sclerosis, and one with mixed connective tissue disease), one had sarcoidosis and one had chronic hypersensitivity pneumonitis. Patient characteristics are summarized in Table 1.

DLCO

The mean DLCO before sildenafil was 9.33 ± 3.72 ml/min/mmHg (35.7% predicted), and post Sildenafil was 9.07 ± 3.77 ml/min/mmHg (35.29% predicted). DLCO before and after sildenafil administration for all patients is shown in Figure 1. The mean change in DLCO after administration of oral sildenafil was -0.26 ± 0.94 ml/min/mmHg (p= 0.30) and -0.41 ± 2.84 % predicted (p=0.58) (Table 2).

6 minute walk distance

The average 6 minute walk distance at baseline was 363.28 ± 141 meters. After oral administration of sildenafil, 6 minute walk distance was 369 ± 116 meters (p=0.63).

None of the patients required adjustment of their oxygen flow during the 6 minute walk after sildenafil administration (data not shown).

Association between DLCO before and after sildenafil and other variables

There was not statistically significant correlation between DLCO before and after sildenafil and radiology scores. The Spearman correlation coefficient between the HRCT ground glass score and DLCO (in ml/min/mmHg and as % predicted) pre sildenafil was -0.42 (p=0.12) and -0.23% (p=0.40), respectively. After sildenafil, the coefficients were -0.38 (DLCO in ml/min/mmHg) (p=0.16) and -0.22% (DLCO as % predicted) (P=0.44). Correlation coefficients between radiologic fibrosis score and DLCO before and after sildenafil were 0.32 (DLCO in ml/min/mmHg) (p=0.24), 0.04 (DLCO as % predicted) (p=0.89) and 0.13 (DLCO in ml/min/mmHg) (p=0.63), -0.07(DLCO as % predicted) (p=0.79). Similarly, no correlation was observed between composite radiology scores and DLCO measurements or change in DLCO and radiology scores (Table 3).

Patient	Age	Gender	Diagnosis	Diagnosis test for PH	FVC (L)	FVC (%)	DLCO (ml/mmhg/m)	DLCO (%)	6MWT (meters)
1	48	M	IPF	RHC	1.15	25	5.6	21	47
2	47	F	IPF	RHC	1.31	30	7.7	18	219
3	58	F	HP	TTE	1.32	37	5.2	20	404
4	43	F	MCTD/UIP	RHC	1.38	40	6.6	29	471
5	63	F	UCT/UIP	RHC	1.94	67	8.2	38	369
6	60	M	SS/UIP	RHC	2.19	44	12.9	44	413
7	74	M	IPF	RHC	2.24	67	8.5	37	268
8	49	F	SS/NSIP	RHC	2.78	85	10.3	46	549
9	47	F	MCT/NSIP	RHC	2.81	82	6.9	30	380
10	81	M	RA/UIP	TTE	2.95	66	7.5	33	310
11	48	F	SS/NSIP	TTE	3.01	75	11.5	47	504
12	70	M	IPF	RHC	3.03	64	10.9	41	447
13	83	M	IPF	TTE	3.73	93	8.5	34	327
14	61	M	SAR	RHC	4.63	97	20.3	64	410
15	63	M	IPF	RHC	2.37	48	9.4	33	331

Table 1: Patient Characteristics (P: patient l IPF: Idiopathic Pulmonary Fibrosis/ MCTD: Mixed connective tissue disease I UDCT: undifferentiated connective tissue disease I ILD Dx: diagnosis of Interstitial lung disease I PH Dx: method used to diagnose Pulmonary Hypertension / SS: Systemic Scleroderma I UIP: Usual interstitial Pneumonia / SAR: Sarcoidosis / HRCT: High resolution CT / GGO: Ground Glass opacity I HRCT Total: combined radiologic score (GGO + Fibrosis) / 6MWT: 6 minutes walking test l RHC: Right Heart Catheterization / TTE: Transthoracic Echocardiography)All the patients were able to sign a consent form, authorizing publication of all the data presented in this table.

Discussion

In a group of patients with concomitant diffuse parenchymal lung disease and pulmonary hypertension, we found that there was not a significant change in diffusion capacity and 6 minute walk distance after administration of a single dose of sildenafil. Diffusion capacity measured before and after sildenafil, did not correlate with imaging scores that reflect burden of parenchymal disease.

The approach to pulmonary hypertension in patients with diffuse parenchymal lung disease remains controversial. The main theoretical concern for administering pulmonary arterial vasodilator therapy has been worsening of ventilation perfusion matching due to release of hypoxic vasoconstriction. Nevertheless, in the only study which addressed the effect of sildenafil on gas exchange [3], Ghofrani et al observed improvement in ventilation perfusion matching in eight patients with interstitial lung disease using the multiple inert gas elimination technique (MIGET). Correlation between FVC (L and % predicted) and radiologic score was -0.23 (p=0.42) and -0.07 (p=0.8) respectively for GGO, (0.03 (p=0.9) and -0.32 (p=0.25) for fibrosis. Composite radiology scores and DLCO measurements were not significantly correlated, either (Table 4).

	DLCO PRE SILDENAFIL (ml/min/mmHg)	DLCO POST SILDENAFIL (ml/min/mmHg)	DLCO Change	p-value
Total	9.33	9.07	-0.26	0.3
Percentage	35.7	35.29	-0.41	0.58

Table 2: Change in dlco pre and post sildenafil (n=15).

Figure 1: Changes in DLCO (ml/min/mmHg) after sildenafil (n=15)
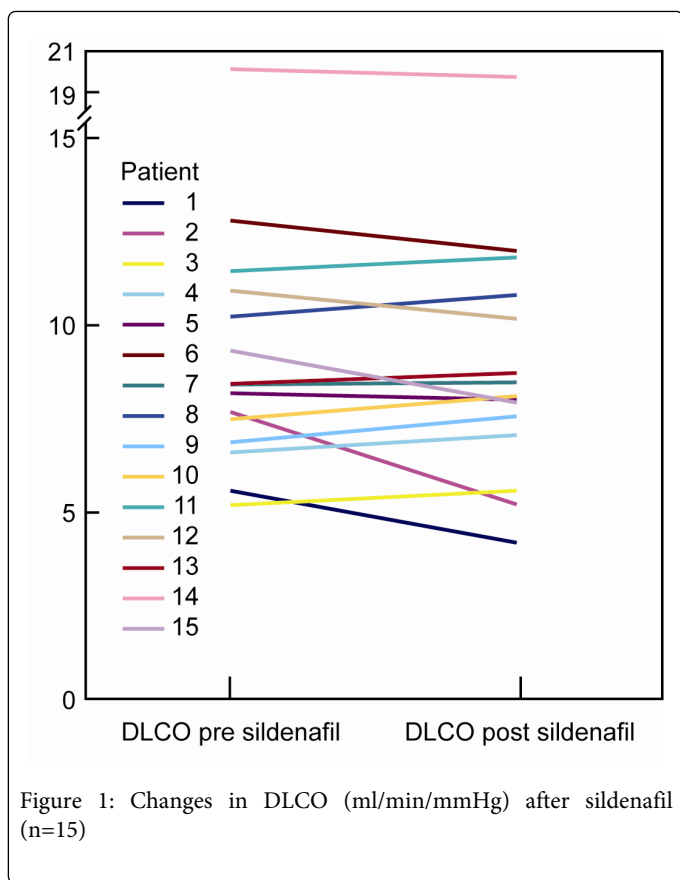
Other small clinical trials have also demonstrated modest hemodynamic and functional improvement in this group of patients [12,13]. More recently, the post hoc analysis of the SUPER Trial [4] and the Step-IPF trial [6], demonstrated that patients with parenchymal lung disease and pulmonary hypertension improved their 6 minute walk distance after twelve weeks of treatment with sildenafil. Furthermore, Step-IPF trial demonstrated significant improvement in diffusion capacity in the group of patients who received sildenafil compared with control. The standard dose of sildenafil used in the Step-IPF trial [14] was 20 mg orally 3 times a day, which formed the basis of our decision to use this dose. Furthermore, response to higher doses was not reported to result in significant clinical outcome differences in the SUPER trial [4]. The mechanism of action for sildenafil in these cases is unclear. Snyder et al. [15], analyzed the effect of this medication on DLCO and its components in healthy subjects. When fourteen subjects were exposed to acute resting and exertional hypoxia, sildenafil improved alveolar-capillary membrane conductance relative to pulmonary capillary volume (DM/Vc) in comparison with placebo suggesting a direct salutary effect on alveolar capillary membrane function. However, overall effect on DLCO was not significant in this study.

When clinicians encounter a decrease in diffusion capacity in patients with diffuse parenchymal lung disease, progression of disease and/or the presence of pulmonary hypertension are primary considerations. Severe decrements in diffusion capacity in the presence of parenchymal lung disease may signify presence of pulmonary hypertension and also provide a means for follow up of these patients. Lettieri et al. [1] reported 10.2 times higher likelihood of pulmonary hypertension among patients with idiopathic pulmonary fibrosis, whose DLCO was less than 40% predicted. In this cohort, diffusion capacity was the only independent variable associated with increased mortality. Similarly, Hamada and colleagues [2] found that decreased DLCO was the only statistically significant parameter related to survival in idiopathic pulmonary fibrosis. In our study, lack of correlation between imaging scores that reflect severity of parenchymal disease and diffusion capacity support the notion that the decrease in DLCO is more closely related to the vascular pathology than the parenchymal disease in these patients with both conditions.

	DLCO pre	p	DLCO post	p	DLCO (% predicted) Pre	P	DLCO (% predicted) Post	p	Change in DLCO	P
HRCT GGO Score	-0.42	0.12	-0.38	0.16	-0.23	0.4	-0.22	00.44	-0.23	0.42
HRCT Fibrosis Score	0.32	0.24	0.13	0.63	0.04	0.89	-0.07	0.79	0.03	0.9
HRCT Combined Score	-0.22	0.43	-0.33	0.22	-0.26	0.35	-0.26	0.35	-0.37	0.17

Table 3: Spearman correlation coeffeicient between DLCO pre and post sildenafil and HRCT radiology score.

A limitation of our study is the lack of right heart catheterization data for confirmation of the diagnosis of pulmonary hypertension in four of the 15 study patients, who also have diffuse parenchymal lung disease of various etiologies. The decision to treat pulmonary hypertension with sildenafil was made by the primary pulmonologist in the interstitial lung disease clinic, which makes this cohort, a reflection of real world practice, where this procedure is sometimes forgone due to various reasons (e.g. lack of patient consent). Rather than evaluating efficacy of sildenafil, our study aimed to investigate the effect of the drug on diffusion capacity in this group of patients. We also recognize that in those patients with highly favorable

	FVC (L)	p	FVC % predicted	p
HRCT GGO Score	-0.23	0.42	-0.07	0.8
HRCT Fibrosis score	0.03	0.9	-0.32	0.25
HRCT Composite score	-0.37	0.17	-0.15	0.58

Table 4: Spearman correlation coefficient between HRCT radiology score and FVC

clinical response to sildenafil, exuberant vasodilator response or in specific disease states e.g. sarcoidosis, a significant effect on diffusion capacity is not excluded on the basis of data from our heterogeneous cohort.

In conclusion, our exploratory study found no acute change in diffusion capacity after a single dose of oral sildenafil. While we would caution clinicians for rare exceptions to these findings, we believe our data exclude a significant confounding effect in interpretation of diffusion capacity in patients with parenchymal lung disease who are treated for pulmonary hypertension with oral sildenafil. Whether this conclusion holds true at higher doses of sildenafil, in patients with vasodilator response or in specific disease states may offer further venues for research.

Authors' Contributions

IM: Participated in the conception and design of the trial, patient recruitment, analysis and interpretation of data and drafted the manuscript.

UH: Participated in the conception and design of the trial and revising the manuscript with important intellectual contribution.

CS: Participated in conception and design of the trial and patient recruitment.

DL: Performed DLCO measurements and contributed to data interpretation.

RY: Interpretation and scoring of Chest CT images and data interpretation.

RD: Participated in the trial design, revised the article and final approval for submission.

Acknowledgments

References

1. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF (2006) Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 129: 746-752.

2. Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, et al. (2007) Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest 131: 650-656.

3. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, et al. (2002) Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 360: 895-900.

4. Badesch DB, Hill NS, Burgess G, Rubin LJ, Barst RJ, et al. (2007) Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. J Rheumatol 34: 2417-2422.

5. Rubin LJ, Badesch DB, Fleming TR, Galiè N, Simonneau G, et al. (2011) Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. Chest 140: 1274-1283.

6. Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, et al. (2010) A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 363: 620-628.

7. American Thoracic Society, European Respiratory Society (2002) American thoracic society/european respiratory society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. this joint statement of the american thoracic society (ATS), and the european respiratory society (ERS) was adopted by the ATS board of directors, june 2001 and by the ERS executive committee, june 2001. Am J Respir Crit Care Med. 165: 277-304.

8. Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, et al. (1983) Single breath diffusing capacity in a representative sample of the population of michigan, a large industrial state. predicted values, lower limits of normal, and frequencies of abnormality by smoking history. Am Rev Respir Dis 127: 270-277.

9. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, et al. (2005) Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26: 720-735.

10. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166: 111-117.

11. Kazerooni EA, Martinez FJ, Flint A, Jamadar DA, Gross BH, et al. (1997) Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: Correlation with pathologic scoring. AJR Am J Roentgeno 169: 977-983.

12. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA (2007) Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 131: 897-899.

13. Madden BP, Allenby M, Loke TK, Sheth A (2006) A potential role for sildenafil in the management of pulmonary hypertension in patients with parenchymal lung disease. Vascul Pharmacol 44: 372-376.

14. Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, et al. (2010) A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 363: 620-628.

15. Snyder EM, Olson TP, Johnson BD, Frantz RP (2008) Influence of sildenafil on lung diffusion during exposure to acute hypoxia at rest and during exercise in healthy humans. Eur J Appl Physiol 103: 421-430.