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Effects of Pirfenidone on Echocardiographic Parameters of Left Ventricular Structure and Function in Patients with Idiopathic Pulmonary Fibrosis

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ABSTRACT

Aim: Pirfenidone is a novel anti-fibrotic agent utilized in the treatment of idiopathic pulmonary fibrosis (IPF). It has been implicated in mitigating myocardial fibrosis and left ventricular (LV) systolic and diastolic dysfunction in animal models. However, its impact on LV mechanics in humans remains unknown. The aim of this study was to retrospectively evaluate the effects of pirfenidone on echocardiographic parameters of LV function and structure in patients with IPF. **Methods:** A total of 124 patients with IPF were included in this study: 64 patients treated with pirfenidone (treatment group) and 60 patients not taking pirfenidone (control group), who had serial pretreatment/baseline and posttreatment/follow-up echocardiograms done within a time frame of four years. Changes in the means of parameters of LV function (systolic, diastolic, and global longitudinal strain) and LV structure (mass and volume indices) were compared between the treatment and control groups. This was followed by a subgroup analysis that included only 88 patients (47 treated, 41 controls) with echocardiographic evidence of myocardial dysfunction at baseline (defined as an ejection fraction of ≤45, or diastolic dysfunction stage 1 or more) in addition to a known clinical diagnosis of congestive heart failure. To account for potential confounders, a secondary adjusted analysis by way of 1:1 propensity score matching (PSM) was carried out. This yielded a sample consisting of 62 patients with 56 patients in the subgroup cohort. **Results:** Patients in the treatment group were significantly younger (69.4 vs. 77 years, $p<0.001$) and had relatively lower forced vital capacity (69.9% vs. 80.6%, $p = 0.005$) in comparison to the control group. However, after PSM, the age demographics were comparable between both groups (72.18 vs. 72.15, $p = 0.9$). In the primary unadjusted analysis, there was no statistically significant change in any of the mean parameters of LV function and structure after pirfenidone administration when compared to the control group. Furthermore, no significant differences were noted in the subgroup cohort. Such findings were re-demonstrated after a secondary analysis with PSM. **Conclusion:** From an echocardiographic perspective, pirfenidone had no significant effects on LV structure and function in patients with IPF, even in patients with more overt cardiac dysfunction.

Keywords: pirfenidone, idiopathic pulmonary fibrosis, heart failure, myocardial dysfunction

INTRODUCTION

Pirfenidone, a novel anti-fibrotic agent, has been shown to reduce the rate of pulmonary function decline and improve disease-free progression in patients with idiopathic pulmonary fibrosis (IPF).[1] Although its precise mechanism of action remains to be deciphered, pirfenidone inhibits transforming growth factor-beta (TGF-β)-mediated fibroblast activation and collagen synthesis,[2] one of the key pathways in the pathogenesis of myocardial fibrosis.[3] Myocardial fibrosis is known to occur in both subtypes of heart failure, being more pronounced in heart failure with reduced (HFrEF) rather than preserved ejection fraction (HFpEF).[4] However, in patients with HFpEF, the degree of myocardial fibrosis is significantly correlated to the severity of diastolic dysfunction.[4]

In pre-clinical studies, pirfenidone was found to mitigate myocardial fibrosis and attenuate left ventricular (LV) remodeling and diastolic and systolic dysfunction in animal models,[5–9] suggesting the possibility of a mechanistic overlap between cardiac and pulmonary fibrosis. This may prove beneficial in the treatment of congestive heart failure (CHF), and in particular HFpEF, where disease-specific therapy is lacking and thus carries a poor prognosis.[10]

To date, the effects of pirfenidone on LV mechanics in humans remains unknown. We therefore sought to investigate this further by retrospectively examining the effects of pirfenidone on echocardiographic parameters of LV structure and function in patients with IPF. This was followed by a subgroup analysis to only include patients with more overt cardiac dysfunction. We hypothesize that patients taking pirfenidone will have more favorable changes in markers of LV function and structure compared to the control group.

Such a hypothesis-generating study from an already existing patient cohort could elucidate the implications of pirfenidone on human myocardial mechanics and potentially lead to newer indications.

MATERIALS AND METHODS

Patient selection

In this single-center retrospective study, 900 consecutive patients with an International Classification of Diseases (ICD)-10 diagnosis code of IPF were initially identified between June 1, 2014 and June 1, 2018. Electronic medical records were then reviewed for clinical and echocardiographic data. Patients were included if they had a confirmed radiological or histological diagnosis of IPF in addition to serial baseline and follow-up echocardiograms, both done after the diagnosis was established. In patients who were on pirfenidone (treatment group) we defined baseline/pretreatment echocardiograms as those done within two years before treatment and follow-up/posttreatment echocardiograms as those done within two years after treatment. Only patients taking pirfenidone continuously throughout the defined time interval were included. The control group consisted of patients with IPF not taking pirfenidone or any other pulmonary disease modifying medications and who had two serial echocardiograms done within four years of each other. Patients with mitral stenosis or mitral valve surgery, severe mitral regurgitation, severe aortic stenosis or regurgitation, and atrial fibrillation at the time of echocardiographic analysis were excluded. Of note, patients who had a history of atrial fibrillation were only included if they were in normal sinus rhythm during echocardiographic analysis, to allow for detailed diastolic assessment.

Sequentially, a total of 124 patients with IPF were included in the primary analysis, 64 treated with pirfenidone and 60 controls not on pirfenidone. This was followed by a subgroup analysis that included only 88 patients (47 treated, 41 controls) with echocardiographic evidence of myocardial dysfunction at baseline (defined as either EF of ≤45% or grade 1 or more diastolic dysfunction) in addition to a known clinical diagnosis of CHF. In this study, the clinical diagnosis of CHF was established if a patient fulfilled the well-validated Framingham criteria.[11] Clinical data pertaining to the diagnosis was obtained from electronic medical records of patient encounters with internists or cardiologists within our institution.

Institutional Review Board approval was granted for retrospective collection of data and informed consent was waived. This study complied with the Declaration of Helsinki.

Statistical considerations

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS v26 for Windows, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation if normally distributed, and as mean (median, interquartile range) if non-normally distributed, as determined by the Shapiro-Wilk W test. Independent t test score and Mann-Whitney U test were utilized to assess for any statistical significance for normal and non-normally distributed variables, respectively. Categorical variables were expressed as a percentage, and the Chi-squared test was used to ascer-

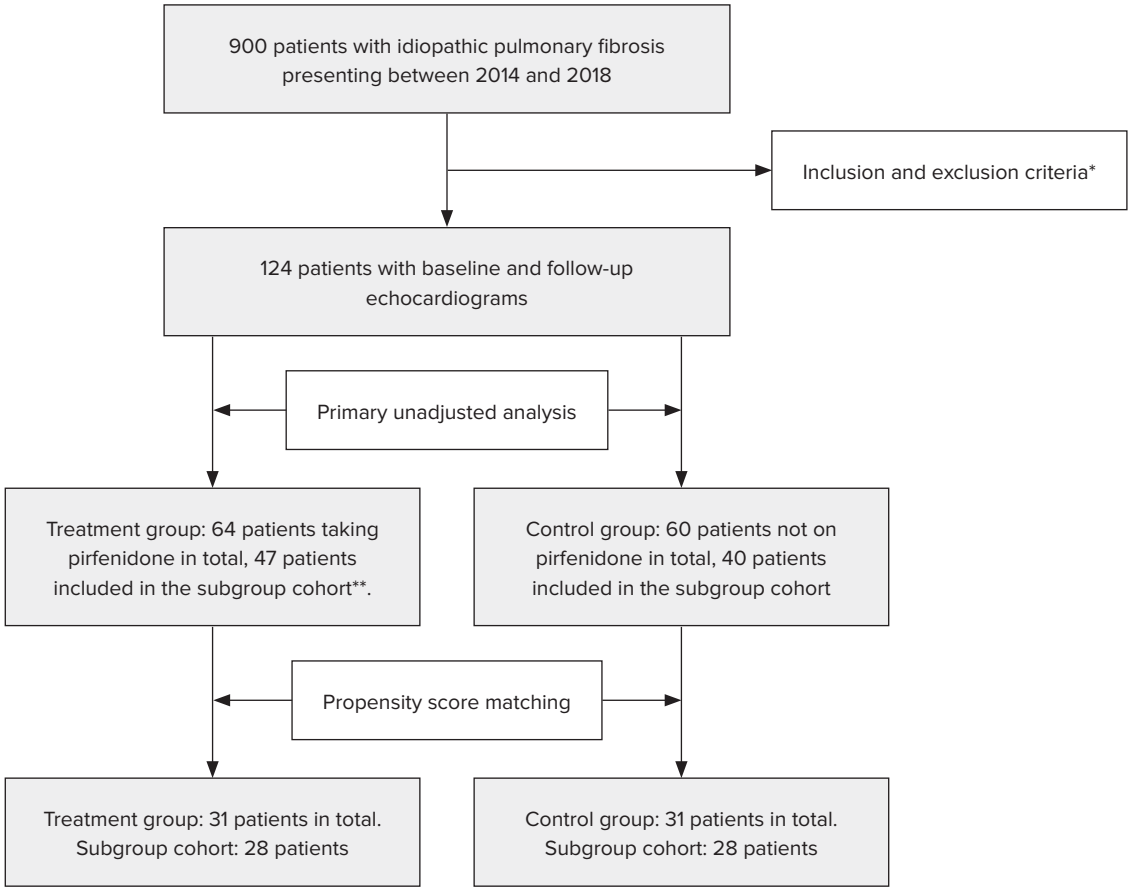

FIGURE 1. Patient selection process and statistical methodology

tain any statistical significance. A two-tailed p value of less than 0.05 was considered significant. In the primary unadjusted analysis, changes in the means of echocardiographic parameters of LV structure and function were compared between the treatment and control groups. This was followed by a subgroup analysis to only include patients with more overt echocardiographic evidence of myocardial dysfunction at baseline in addition to an established clinical diagnosis of heart failure.

To account for confounding variables that can potentially impact changes in parameters of LV function and structure, an adjusted secondary analysis was carried out by way of 1:1 propensity score matching (PSM). To estimate the propensity score, a set of variables (including

TABLE 1. Baseline demographic and clinical characteristics

	Treatment group (n = 64)	Control group (n = 60)	p value
Age (years)	69.4 ± 7	77 ± 8.8	<0.001
Male % (n)	71.9 (46)**	65 (39)	0.4
Body surface area (m^2)	2 ± 0.2	1.9 ± 0.3	0.1
Body mass index (kg/m^2)	30.1 ± 4.8	28.2 ± 6	0.1
Systolic blood pressure (mmHg)	122.6 ± 14.9	127.9 ± 16.5	0.2
Diastolic blood pressure (mmHg)	73 ± 7.3	76 ± 6.2	0.2
Cardiac risk factors and co-morbidities % (n)			
Hypertension	68.7 (44)	56.6 (34)	0.2
Diabetes	21.9 (14)	15 (9)	0.5
Hyperlipidemia	67.2 (43)	51.2 (31)	0.08
Chronic kidney disease	31.3 (20)	45 (27)	0.07
Atrial fibrillation	17.2 (11)	30 (18)	0.09
Coronary artery disease	42.2 (27)	41.7 (25)	0.6
Cardiac medications % (n)			
Beta-blockers	43.8 (26)	35 (21)	0.6
Diuretics	34.3 (22)	33.3 (20)	0.9
Renin-angiotensin-aldosterone inhibitors	39.1 (25)	35 (21)	0.5
Pulmonary function testing			
Baseline predicted forced vital capacity (%)	69.9 ± 18.2	80.6 ± 42.8	0.005
Laboratory testing			
Serum creatinine (mg/dL)	1.1 ± 0.4	1.2 ± 0.7	0.2
Time interval between baseline and follow-up echocardiogram (years)	1.7 ± 1.3	1.5 ± 1.1	0.2

n, number of patients; **numbers within the brackets represent absolute figures

age, gender, body mass index, history of coronary artery disease, chronic kidney disease, diabetes, hypertension, atrial fibrillation, use of beta blockers, and use of renin-angiotensin-aldosterone inhibitors) that could potentially impact the degree of myocardial fibrosis and thus LV function and structure were selected. Such variables were then included in a multi-variable logistic regression model which produced a propensity score for each of the 124 patients included in the primary analysis. Taking the estimated propensity score of each patient, a 1:1 match analysis without replacement was carried out using the nearest-neighbor matching technique, with a match tolerance of 0.2 of the pooled standard deviation of the logit of the propensity score, as previously described in the literature.[12] This yielded a sample consisting of 62 patients with IPF in total (31 treated, 31 controls), all of which were included in the secondary adjusted analysis. Finally, the process was repeated once more to only include the matched subgroup cohort, which resulted in 56 patients with relatively more severe cardiac dysfunction (28 treated, 28 controls). The C-statistic of the propensity score models was approximately 0.8, which is considered an adequate model fit.[12]

Figure 1 summarizes the patient selection process according to the aforementioned inclusion criteria, exclusion criteria, and statistical methodology.

Echocardiographic analysis

Comprehensive echocardiographic data extracted from a total of 248 echocardiograms (two echocardiograms per patient) were reviewed for parameters of LV structure, systolic function and diastolic function. Missing data, including detailed diastology analysis and global longitudinal strain, were obtained by directly performing measurements on stored images offline. This was performed by an experienced research sonographer in a blinded manner, using commercially available software from Siemens Healthcare (Syngo Dynamics 9.0). LV ejection fraction (EF) and cardiac volumes (indexed LV end-systolic volume, LV end-diastolic volume, and left atrial volume) were calculated using the modified Simpson bi-plane method in the apical 2- and 4-chamber views. In the parasternal short axis view, LV mass was estimated utilizing the Devereux formula after measuring the LV end-diastolic dimension, interventricular septal thickness, and posterior wall thick-

TABLE 2. Baseline echocardiographic characteristics

Baseline echocardiographic parameter	Treatment group (n = 64)	Control group (n = 60)	p value
LV structure			
Indexed LV mass (gm^2)	91.6 ± 31.2	94.1 ± 30.1	0.7
LV diastolic internal dimension (cm)	4.5 ± 0.7	4.4 ± 0.8	0.6
LV systolic internal dimension (cm)	3.3 ± 1.9	3.12 ± 0.7	0.6
Intraventricular septal wall thickness (cm)	1.12 ± 0.1	1.19 ± 0.2	0.2
Posterior wall thickness (cm)	1.03 ± 0.1	1.11 ± 0.2	0.1
Indexed LV end-systolic volume (mL/m^2)	17.8 ± 9.5	20.4 ± 9.6	0.2
Indexed LV end-diastolic volume (mL/m^2)	44.5 ± 20	45.6 ± 12.9	0.8
LV systolic function			
EF (%)	60.1 ± 6.2	60.2 ± 10.4	0.7
Patients with EF ≤45% (n)	9.4% (6)	15% (9)	0.5
LV diastolic function			
Indexed left atrial volume (mL/m^2)	27.3 ± 10	31.2 ± 13.3	0.1
Mitral valve E wave	67 (73, 37.5)	76 (65, 19)	0.1
Mitral valve A wave	81 ± 9.6	88 ± 21.1	0.1
Mitral valve E/A ratio	0.89/0.4	0.88/0.4	0.1
Mitral valve deceleration time (ms)	43 (226, 72)	38 (203, 74)	0.1
Septal e´ (cm/s)	6.3 ± 1.3	5.8 ± 1.6	0.1
Septal E/e´	11.8 ± 4.4	13.1 ± 4.7	0.1
Lateral e´ (cm/s)	8.2 ± 2.1	8.1 ± 2.9	0.8
Lateral E/e´	8.9 ± 3.2	9.94 ± .1	0.1
Pulmonary vein systolic wave (cm/s)	52 ± 15.1	56 ± 15.3	0.3
Pulmonary vein diastolic wave (cm/s)	40.3 (40, 12.5)	42.7 (38, 13.5)	0.8
Pulmonary vein systolic wave to diastolic wave ratio	1.4 (1.5, 0.4)	1.4 (1.5, 0.4)	0.9
Diastolic stage % (n)			
0	26.5% (17)	33.3% (20)	0.9
1	67.2% (43)	51.7% (31)	0.1
2	6.3% (4)	15% (9)	0.2
3	0	0	1
LV global longitudinal strain (%)	–16.5 (–16.5, 1.09)	–15.6 (16, 2.8)	0.1

n, number of patients; LV, left ventricle; EF, ejection fraction

ness. In this study, several parameters of diastolic function measured in the apical 4-chamber view were obtained by placing the sample volume at the mitral annulus as well as the tip of the mitral valve leaflets; peak mitral inflow velocities during early and late atrial filling (E and A waves), mitral valve deceleration time and peak early velocity (e´) measured at both septal and lateral locations. Subsequently, pulmonary vein systolic wave and diastolic wave were measured by placing the sample volume at the right upper or lower pulmonary vein, and the systolic to diastolic wave ratio was then calculated.

The severity of diastolic dysfunction was graded in accordance to the American Society of Echocardiography/European Association of Cardiovascular Imaging.[13] Global longitudinal strain was assessed using velocity vector imaging; strain contours were drawn from the apical 4-chamber, 2-chamber, and the apical long axis view in those with adequate frame-rate capture, respectively. Endocardial borders were automatically generated by the software and were manually adjusted as needed.

RESULTS

As illustrated in Table 1, patients in the treatment group were significantly younger (69.4 vs. 77 years, p <0.001) and had relatively lower forced vital capacity (69.9% vs. 80.6%, p = 0.005) in comparison to the control group. Other baseline clinical and echocardiographic variables were statistically comparable between the two groups (p >0.05). Moreover, after PSM, the age demographics of both groups were comparable as well (72.18 vs. 72.15 years, p = 0.9).

TABLE 3. Mean change in echocardiographic parameters

Mean change in echocardiographic parameter	Treatment group (n = 64)	Control group (n = 60)	p value
LV structure			
Indexed LV mass (gm^2)	–4.1 ± 30.3	–8.2 ± 50	0.1
LV diastolic internal dimension (cm)	-0.1 ± 0.6	+0.3 ± 0.2	0.1
LV systolic internal dimension (cm)	-0.1 ± 0.8	+0.1 ± 1.4	0.4
Intraventricular septal wall thickness (cm)	0 ± 0.3	+0.3 ± 1.3	0.3
Posterior wall thickness (cm)	0 ± 0.2	–0.1 ± 0.3	0.4
Indexed LV end-systolic volume (mL/m^2)	–1.4 (0.1, 9.8)	–1.6 (0, 15)	0.8
Indexed LV end-diastolic volume (mL/m^2)	–0.3 ± 19	+2.7 ± 20.8	0.5
LV systolic function			
EF (%)	+7 (3, 10.75)	+4 (3.5, 9.75)	0.3
LV diastolic function			
Indexed left atrial volume (mL/m^2)	+3 (4, 11.6)	+6 (4, 18.6)	0.5
Mitral valve E wave	–3.3 (2, 19.5)	–0.1 (–2.5, 33.2)	0.4
Mitral valve A wave	–0.12 (–2, 22)	–0.3 (–2, 24)	0.8
Mitral valve E/A ratio	0 ± 0.3	–0.1 ± 1	0.3
Mitral valve deceleration time (ms)	–11.6 ± 58	–12.6 ± 133.1	0.1
Septal e´ (cm/s)	–0.1 (0, 2)	–2 (0, 3)	0.3
Septal E/e´	–0.6 (0.6, 4.5)	–0.6 (–0.4, 6.2)	0.9
Lateral e´ (cm/s)	–0.3 ± 2.8	–0.4 ± 3.3	0.2
Lateral E/e´	–0.5 ± 4.9	–0.4 ± 5.3	0.9
Pulmonary vein systolic wave (cm/s)	–3.1 ± 11.1	–6.8 ± 34.5	0.6
Pulmonary vein diastolic wave (cm/s)	–0.9 ± 14.2	–2.8 ± 29	0.8
Pulmonary vein systolic wave to diastolic wave ratio	–0.7 ± 0.7	–0.5 ± 0.7	0.3
LV global longitudinal strain (%)	+0.5 ± 3.1	–0.2 ± 1.7	0.2

n, number of patients; LV, left ventricle; EF, ejection fraction

Of note, baseline and follow-up echocardiograms were done at similar time intervals in treatment and control groups, respectively: 1.7 vs. 1.5 years (p >0.05).

Table 2 summarizes the various baseline echocardiographic parameters measured in this study, all of which were comparable between the treatment and the control group, respectively (p >0.05): mean baseline LVEF was 61% vs. 62%, 9.4% vs. 15% of patients had an impaired LVEF ≤45%, 51.7% vs. 67.2% of the patients had grade 1 diastolic dysfunction, 6.3% vs. 15% grade 2 and 0% grade 3. Global longitudinal strain was –16.5% vs. –15.6%, mean indexed end-diastolic volume was 44.5 mL/m^2 vs. 45.6 mL/m^2, and mean indexed end-systolic volume was 17.8 mL/m^2 vs. 20.4 mL/m^2.

As shown in Table 3, in the primary unadjusted analysis, there was no statistically significant change in the means of any of the echocardiographic parameters of LV structure, diastolic function, systolic function, and global longitudinal strain post pirfenidone administration when compared to the control group.

In addition, we observed no significant difference in the mean change of any of the echocardiographic parameters between the treatment and control groups included in the subgroup cohort (Table 4).

After accounting for confounding variables by means of PSM, the aforementioned findings were re-demonstrated in the secondary adjusted analysis (please refer to Table S1 and Table S2 in the supplemental section).

DISCUSSION

The key finding of our study is that pirfenidone did not significantly impact echocardiographic parameters of left ventricular structure, diastolic function, systolic function, and global longitudinal strain in patients with IPF when compared to a control group of patients not on any disease-modifying medications. Furthermore, there were no significant changes in any of the echocardiographic parameters, not even in patients who had more overt echocardiographic evidence of myocardial dysfunction in addition to a clinical diagnosis of CHF. Contrary to our hypothesis, from an echocardiographic perspective, pirfenidone did not seem to improve LV function or attenuate the degree of myocardial dysfunction in patients with IPF.

TABLE 4. Mean change in echocardiographic parameters of patients in the subgroup cohort

Mean change in echocardiographic parameter	Treatment group (n = 47)	Control group (n = 41)	p value
LV structure			
Indexed LV mass (gm^2)	–8.5 ± 30.3	+7.7 ± 53.5	0.1
LV diastolic internal dimension (cm)	–0.9 ± 5.8	–0 ± 1.5	0.3
LV systolic internal dimension (cm)	–0.2 ± 0.9	–0.1 ± 1.2	0.7
Intraventricular septal wall thickness (cm)	+0.1 ± 0.3	–0.1 ± 0.5	0.5
Posterior wall thickness (cm)	0 ± 0.2	0 ± 0.4	0.6
Indexed LV end-systolic volume (mL/m^2)	+0.6 ± 12.9	+0.7 ± 11.3	0.9
Indexed LV end-diastolic volume (mL/m^2)	+3.4 ± 22.7	–2.1 ± 21.6	0.3
LV systolic function			
EF (%)	+4.5 (5, 10.5)	+2.7 (4, 13)	0.5
LV diastolic function			
Indexed left atrial volume (mL/m^2)	+3 ± 9.6	+6.9 ± 21.7	0.3
Mitral valve E wave	+6.3 (3, 22.5)	+0.4 (–3, 35)	0.2
Mitral valve A wave	–2 (–2, 20)	–7.3 (–6, 23)	0.6
Mitral valve E/A ratio	+0.1 (0, 0.31)	+0.1 (0, 0.5)	0.5
Mitral valve deceleration time (ms)	–6.3 ± 66.2	–34.9 ± 129.2	0.4
Septal e´ (cm/s)	+0.1 ± 1.8	+0.4 ± 2.8	0.5
Septal E/e´	+0.8 ± 5.1	+0.1 ± 5.8	0.6
Lateral e´ (cm/s)	+0.5 ± 2.6	–0.7 ± 2.7	0.1
Lateral E/e´	+0.9 (0.2, 3.2)	–0.5 (–0.3, 3.3)	0.6
Pulmonary vein systolic wave (cm/s)	–2.9 (–2, 14.5)	–5.9 (0, 62)	0.8
Pulmonary vein diastolic wave (cm/s)	+2.1 (–0.5, 21.2)	+0.7 (0, 56)	0.9
Pulmonary vein systolic wave to diastolic wave ratio	0 ± 0.5	–0.3 ± 0.7	0.2
LV global longitudinal strain (%)	+0.7 (0.3, 3.9)	+0.7 (0, 1.7)	0.7

n, number of patients; LV, left ventricle; EF, ejection fraction

Several factors may have contributed to our findings. First, the study design was retrospective in nature, with a small sample size and inherited selection bias based on availability of echocardiograms and pirfenidone. Although PSM did statistically adjust for potential confounders (such as age, gender, history of coronary artery disease etc., mentioned previously), there are unmeasurable confounding factors that could not have been accounted for. Second, approximately 60% of the entire study sample had grade 1 dysfunction, and only 9.4% of the patients in the treatment group vs. 15% of patients in the control group had LVEF ≤45%, suggesting that most patients included in the study did not have echocardiographic evidence of severe cardiac dysfunction. Third, the pathophysiology of heart failure is complex, multi-modal, and unique; myocardial fibrosis represents one component only, and we do not have direct assessments to quantify fibrosis.[14] Changes in echocardiographic parameters of LV structure and function serve as indirect markers of myocardial fibrosis. It is possible that some patients may have subclinical evidence of myocardial fibrosis that could not have been detected on serial echocardiography. Finally, there is evidence suggesting that some patients with heart failure may not have myocardial fibrosis, thus an anti-fibrotic is not applicable in this context.[10]

Larger prospective studies and randomized control trials (such as the ongoing PIROUETTE study[15]) in patients with known heart failure are therefore needed to assess the impact of this novel agent on myocardial fibrosis, utilizing cardiac magnetic resonance imaging. Findings should then be correlated to clinical outcomes to ascertain any benefit this anti-fibrotic agent may have in the context of heart failure. It would also be interesting to examine the effects of this novel agent on right-sided cardio-mechanics.

CONCLUSION

In conclusion, in our retrospective single-center study of idiopathic pulmonary fibrosis patients, treatment with pirfenidone was not associated with any significant changes in echocardiographic parameters of left ventricular structure and function. Our findings therefore caution the implications that pirfenidone may have anti-fibrotic properties that extend beyond its pulmonary indications. To our

knowledge, this is the first study in humans reviewing the implications of this novel agent outside the field of pulmonary medicine.

CONFLICT OF INTEREST

Nothing to declare.

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