A Comparison of Echocardiographic Variables of Right Ventricular Function with Exercise Capacity After Bosentan Treatment in Patients with Pulmonary Arterial Hypertension: Results from a Multicenter, Prospective, Cohort Study

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ABSTRACT: *Purpose.* Bosentan reduces pulmonary arterial pressure and improves exercise capacity in patients with pulmonary arterial hypertension (PAH). However, there are limited data regarding the extent to which the changes in echocardiographic variables reflect improvements in exercise capacity. We aimed to assess the improvement of echocardiographic variables and exercise capacity after 6 months of bosentan treatment for PAH.

Methods. We performed a prospective study from June 2012 to June 2015 in seven participating medical centers. Echocardiography, including tissue Doppler imaging (TDI) and the 6-minute walk test distance (6MWD), was performed at baseline and after 6 months of bosentan treatment.

Results. We analyzed 19 patients with PAH: seven with congenital shunt, six with collagen vascular disease, and six with idiopathic PAH. After bosentan treatment, mean 6MWD increased by 50 meters. Right ventricle (RV) systolic pressure, tricuspid annular plane systolic excursion, myocardial performance index (MPI) derived from TDI (MPI-TDI) of RV and left ventricle (LV), RV fractional area change, and RV ejection fraction were significantly improved. In particular, the magnitude of RV and LV MPI-TDI showed good correlation with changes in the 6MWD.

Conclusions. The magnitude of RV and LV MPI-TDI was strongly associated with improvements in exercise capacity. © 2016 Wiley Periodicals, Inc. *J Clin Ultrasound* **00**:000–000, 2016; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22396

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease of increased pulmonary

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arterial resistance resulting from heterogeneous etiologies. Increased pulmonary arterial resistance reduces the left ventricular (LV) preload leading to reduced cardiac output and dyspnea on exertion (DOE) and prevents systemic venous flow from returning to the right ventricle (RV). These changes can deteriorate exercise tolerance and accelerate the downhill course of PAH.[1,2]

Bosentan treatment typically improves exercise capacity and RV function by reducing pulmonary arterial pressure. This action is mediated by inhibition of endothelin receptors present within the pulmonary artery.[3–5] Improvement in exercise capacity is a primary goal of bosentan treatment for PAH, and it is usually measured by the 6-minute walk test distance (6MWD). The effects of bosentan on cardiac function are also evaluated based on exercise capacity by using the 6MWD as well as echocardiography.

Echocardiography is believed to have advantages in evaluating dyspnea, and RV echocardiographic variables, including RV fractional area change (FAC), the tricuspid annular plane systolic excursion (TAPSE), and RV systolic pressure (RVSP), are thought to predict RV function and the prognosis of PAH.[6,7] The myocardial performance index (MPI), although less commonly used, offers the advantage of measuring combined ventricular systolic and diastolic function.[8,9] The MPI can be obtained using conventional spectral Doppler or tissue Doppler imaging (TDI), without regard to geometric assumptions.

However, the magnitude of exercise capacity improvement is not easy to predict, and there are limited data regarding the extent to which the changes in echocardiographic variables reflect the improvement of exercise capacity. We aimed to assess improvements in echocardiographic variables and exercise capacity and explore the correlations between these variables at baseline and after 6 months of bosentan treatment in patients with PAH.

MATERIALS AND METHODS

Study Protocol and Patients

We performed a multicenter, prospective, observational study with a dose titration to evaluate the efficacy of bosentan treatment for the treatment of PAH. Patients were recruited at seven participating medical centers from June 2012 to June 2015. Our inclusion criteria (based on the fourth World Symposium on Pulmonary Hypertension) were the following: (1) age more than 18 years old; (2) World Health Organization (WHO) functional class III or IV; and (3) PAH with mean pulmonary artery pressure greater than 25 mmHg or tricuspid insufficiency peak gradient greater than 31 mmHg (or tricuspid regurgitation jet velocity greater than 2.8 m/s) diagnosed by either invasive right heart catheterization or noninvasive echocardiography.[1]

All patients provided signed informed consent, and approval was obtained from each regional institutional review board. Whereas all PAH-target or specific medications (endothelial receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin analogs) were not allowed at least 6 weeks before enrollment, the concomitant use or change of nonspecific supportive medications (antiplatelets, anticoagulants, digoxin, diuretics, beta-blockers, calcium-channel blockers, and angiotensin converting enzyme inhibitors, or receptor blockers) was permitted to relieve dyspnea or reduce cardiovascular outcomes. Treatment was initiated with 62.5 mg bosentan twice daily for 4 weeks, and then the dose was increased up to 125 mg twice daily. Patients were monitored for side effects and adverse events through monthly outpatient clinic visits. Serologic studies were performed at baseline and monthly thereafter. The decision to discontinue or taper the dosage of bosentan was left to the physician's discretion in cases where side effects or adverse events occurred. Six-minute walk test and echocardiography were performed at baseline and after 6 months of bosentan treatment.

Echocardiography

Conventional echocardiography according to the American Society of Echocardiography was performed at baseline and after 6 months of bosentan treatment. RV function was evaluated with measurements of RVSP, TAPSE, FAC, and RV ejection fraction (EF). RVSP was measured in an echo-window showing maximal tricuspid regurgitation Doppler velocity. A standard apical four-chamber (RV focused) view was used to measure TAPSE and FAC; an M-mode cursor was positioned at the level of the tricuspid annulus to obtain TAPSE, and the RV endocardium was traced in end-diastole and end-systole to calculate FAC. Two-dimensional RVEF was obtained in an apical four-chamber view by using a disk summation method. TDI was used to measure systolic and diastolic tissue velocities at the septal mitral annulus and the lateral tricuspid annulus. The MPI-TDI was calculated for both ventricles as follows: MPI-TDI = (isovolumic contraction time [ICT] + isovolumic relaxation time [IRT])/ejection

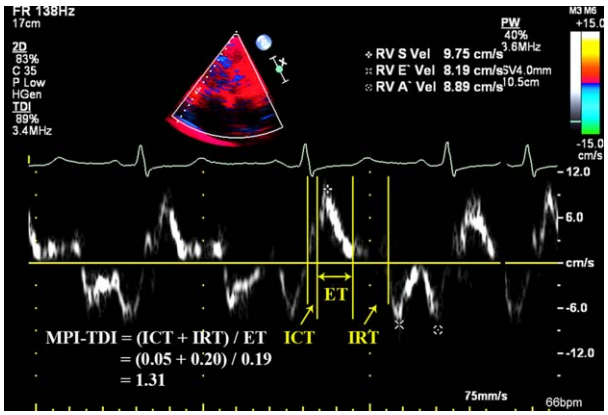

FIGURE 1. Myocardial performance index (MPI) derived from tricuspid annular tissue Doppler imaging (TDI). ET, ejection time; ICT, isovolumic contraction time; IRT, isovolumic relaxation time.

time (ET) (Figure 1). Furthermore, to evaluate precapillary PAH, the echocardiographic pulmonary to left atrial ratio (ePLAR) was calculated as follows: peak tricuspid regurgitation velocity (m/s) divided by the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/e′ ratio).[10]

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS for Windows, Version 13.0, SPSS, Inc., Chicago, IL). The data are presented as the mean ± SD for continuous variables, as frequencies for discrete variables, and as numbers or percentages for categorical variables. The data were tested for normal distribution by using the Kolmogorov-Smirnov test. We analyzed study variables from baseline and follow-up tests after 6 months of bosentan treatment and determined significant differences using a paired-samples t test for normally distributed data, or the nonparametric Wilcoxon signed-rank test for nonnormally distributed data. The degree of correlation between the improvement in the 6MWD and the echocardiographic variables was calculated using either the Pearson or the Spearman's correlation coefficient. Receiver operator characteristic curve was constructed to evaluate the discriminating power of MPI-TDI. We used two-sided p values, and $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of Study Patients

We recruited 30 patients. However, 11 patients were not included in the final analysis: one patient withdrew informed consent during the study period; seven were lost to follow-up, and three could not tolerate the side effects of bosentan. A total of 19 patients (mean age of 58 years, 16 women) were analyzed: seven patients (36.8%) had PAH associated with a congenital shunt; six (31.6%) had PAH associated with collagen vascular disease, and six (31.6%) had idiopathic PAH (Table 1). Most of the study patients had symptoms consistent with WHO functional class III, an increased level of N-terminal pro-B-type natriuretic peptide, and a normal liver function test. There were no changes in the use of nonspecific supportive medications between baseline and follow-up.

TABLE 1
Baseline Characteristics and 6-minute Walk Test Distances of All Subjects

	Mean ± SD or Number (%)
Age, years	58.3 ± 14.7
Female sex, n (%)	16 (84.2)
Height, cm	156.4 ± 7.1
Weight, kg	55.1 ± 7.4
Systolic BP, mmHg	120.2 ± 20.3
Diastolic BP, mmHg	71.4 ± 14.3
Heart rate, bpm	76.2 ± 13.2
Etiology of PAH	
Idiopathic, n (%)	6 (31.6)
Collagen vascular disease, n (%)	6 (31.6)
Congenital shunt disease, n (%)	7 (36.8)
WHO functional class	
III, n (%)	17 (89.4)
IV, n (%)	2 (10.6)
Medications	
Diuretics, n (%)	12 (63.2)
Calcium blockers, n (%)	12 (63.2)
Beta blockers, n (%)	4 (21.1)
ACEi/ARBs, n (%)	3 (15.8)
Antiplatelets, n (%)	9 (47.4)
Anticoagulants, n (%)	2 (10.5)
Serologic laboratory test	
Hemoglobin, mg/dl	14.4 ± 3.1
Blood urea nitrogen, mg/dl	18.1 ± 6.0
Creatinine, mg/dl	0.8 ± 0.2
Aspartate aminotransferase, IU/l	24.1 ± 7.0
Alanine aminotransferase, IU/l	24.1 ± 10.1
Alkaline phosphatase, IU/l	180.4 ± 160.8
Total bilirubin, mg/dl	0.85 ± 0.50
NT-proBNP, pg/ml	2,003.9 ± 1,297.9
6-minute walk test distances, m	308 ± 115

Abbreviations: BP, blood pressure; PAH, pulmonary arterial hypertension; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Baseline Echocardiography and 6MWD

Baseline echocardiographic characteristics are shown in Table 2. All patients had normal LV chamber size and EF. The E/e′ ratio was 11.3 ± 6.2 (mean) and ePLAR was 0.42 ± 0.21 m/s. Echocardiographic RV function variables

TABLE 2
Baseline Echocardiographic Characteristics and After Bosentan Treatment

Variables	Baseline	After 6 months	*p* Value
Left ventricle parameters			
LVEDd, cm	4.5 ± 0.9	4.6 ± 0.5	0.786
LVESd, cm	2.9 ± 0.7	2.8 ± 0.6	0.942
LVEF, %	67.8 ± 7.2	68.3 ± 6.0	0.894
Mitral E velocity, m/s	0.67 ± 0.26	0.66 ± 0.22	0.624
Mitral A velocity, m/s	0.67 ± 0.25	0.72 ± 0.20	0.303
Isovolumic relaxation time, ms	86.7 ± 28	108 ± 35	0.342
Deceleration time, ms	199 ± 44	248 ± 26	0.260
Septal s′, cm/s	7.2 ± 1.5	7.5 ± 1.8	0.547
Septal e′, cm/s	8.6 ± 1.6	7.4 ± 2.3	0.553
Septal a′, cm/s	9.1 ± 2.8	8.8 ± 2.2	0.735
E/e′ ratio	11.3 ± 6.2	9.2 ± 2.4	0.095
LV MPI-TDI	0.52 ± 0.20	0.44 ± 0.15	0.030
Right ventricle parameters			
TAPSE, mm	16.9 ± 4.1	21.6 ± 5.5	0.004
RVSP, mmHg	67.4 ± 30.1	56.1 ± 29.8	< 0.001
RVEF, %	37.8 ± 12.7	47.8 ± 12.6	< 0.001
RV-FAC, %	33.1 ± 11.9	37.7 ± 12.2	0.030
RV MPI-TDI	0.58 ± 0.27	0.45 ± 0.28	0.012
ePLAR, m/s	0.42 ± 0.21	0.41 ± 0.14	0.920

Data are expressed as mean ± SD.

Abbreviations: LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; s′, systolic tissue Doppler imaging of septal mitral annulus; e′, early diastolic tissue Doppler imaging of septal mitral annulus; a′, late diastolic tissue Doppler imaging of septal mitral annulus; E/e′ ratio, the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity; MPI-TDI, myocardial performance index derived from tissue Doppler imaging; TAPSE, tricuspid annular plane systolic excursion; RVSP, right ventricular systolic pressure; RVEF, right ventricular ejection fraction; RV-FAC, right ventricular fractional area change; ePLAR, echocardiographic pulmonary to left atrial ratio.

showed values consistent with RV dysfunction; TAPSE, RV-EF, and RV-FAC were decreased, and RVSP was increased. Furthermore, both the RV and the LV showed an increased MPI-TDI. The 6MWD was 308 ± 115 meters (Table 1).

Follow-up 6MWD and Echocardiography After Bosentan Treatment

After bosentan treatment, the mean 6MWD increased by 50 meters (from 308 ± 115 to 358 ± 85 meters, $p = 0.027$), and the WHO functional class improved from 3.1 ± 0.3 to 2.4 ± 0.5 ($p < 0.001$) (Figure 2). RVSP decreased from 67.4 ± 30.1 to 56.1 ± 29.8 mmHg ($p < 0.001$), LV MPI-TDI decreased from 0.52 ± 0.20 to 0.44 ± 0.15 ($p = 0.030$); RV MPI-TDI decreased from 0.58 ± 0.27 to 0.45 ± 0.28 ($p = 0.012$), and RV-FAC increased from 33.1 ± 11.9 to 37.7 ± 12.2% ($p = 0.030$). RVEF improved from 37.8 ± 12.7 to 47.8 ± 12.6% ($p < 0.001$), and TAPSE improved from 16.9 ± 4.1 to 21.6 ± 5.5 mm ($p = 0.004$) (Table 2). The RV and LV MPI-TDIs

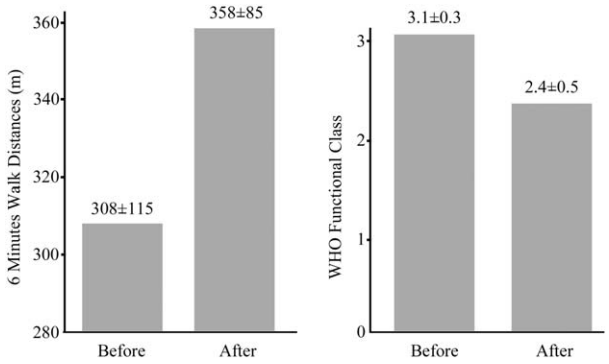

FIGURE 2. Comparison of baseline and follow-up WHO class and 6-minute walk test distance after 6 months of bosentan treatment.

showed a strong correlation with the improvement in 6MWD ($r = 0.701$; $p = 0.001$ and $r = 0.562$; $p = 0.014$, respectively) (Figure 3). The RV MPI-TDI receiver operator characteristic curve analysis resulted in an area under the curve of 0.893 ($p < 0.001$), indicating a high discriminating power for prediction of improvement in 6MWD (Figure 4). Although LV MPI-TDI and septal s′ showed some correlation, there was no significant correlation between RV MPI-TDI changes and conventional RV function variables (Table 3).

Safety

The mean dosage of bosentan was 177.6 ± 63.4 mg a day. Adverse events occurred in 6 of the 30 patients we recruited for this study: three patients experienced hepatotoxicity and discontinued the medication, and the remaining three patients reduced the dosage, continued the medication, and completed the study.

DISCUSSION

Our findings demonstrate that bosentan treatment improved patient exercise capacity, as shown by an improvement in the 6MWD and WHO functional class. However, it is not clear whether an increase in 6MWD correlates with an improvement in clinical outcomes such as mortality. Medications that reduce pulmonary arterial pressure may result in improved 6MWD, and values greater than 300 meters are associated with a favorable prognosis.[11–13] The mechanism by which reduced pulmonary arterial pressure results in increased exercise tolerance is complex and not perfectly understood. From the standpoint of cardiac function, LV end-diastolic pressure is regarded as a key parameter to explain DOE; elevated LV end-

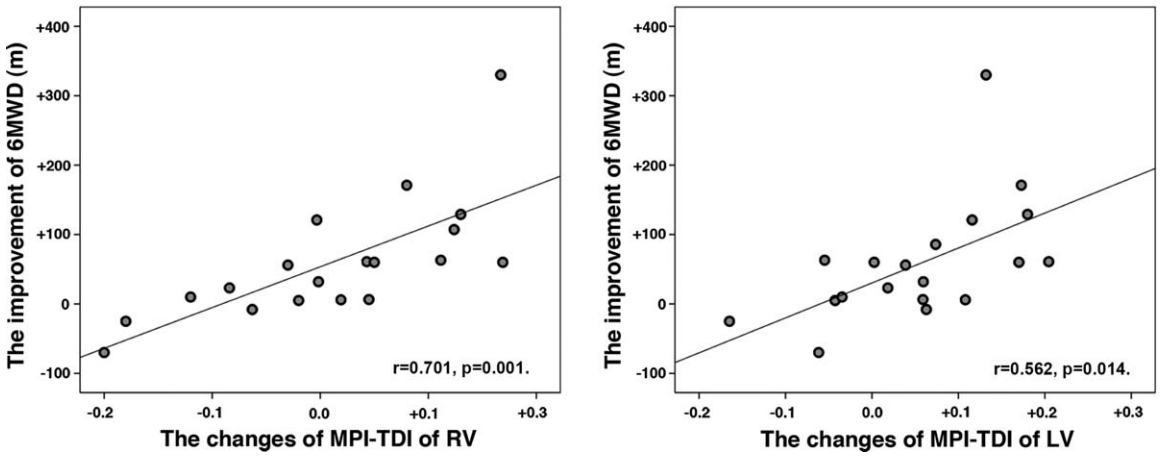

FIGURE 3. Correlation of the changes of myocardial performance index (MPI) derived from tricuspid annular tissue Doppler imaging (TDI) of the right and left ventricles with the improvement in the 6-minute walk test distance at baseline and after bosentan treatment. LV, left ventricle; RV, right ventricle.

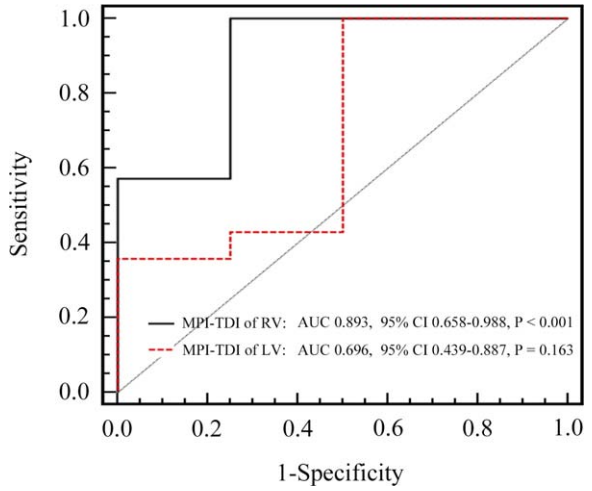

FIGURE 4. Receiver operating characteristic curve to evaluate the discrimination power of myocardial performance index (MPI) derived from tricuspid annular tissue Doppler imaging (TDI) of the right and left ventricles for the improvement of 6-minute walk test distance after bosentan treatment. AUC, area under the curve; CI, confidence interval.

TABLE 3
Correlation Between Changes of Myocardial Performance Index Derived from Tissue Doppler Imaging of Right Ventricle and Other Echo Parameters

Variables	Correlation Coefficient, *r*	*p* Value
TAPSE	−0.150	0.661
RVSP	0.195	0.438
RV-FAC	−0.178	0.525
RVEF	0.054	0.831
Septal s′	0.717	0.009
Septal e′	−1.03	0.382
Septal a′	0.113	0.371
E/e′ ratio	0.039	0.454
LVEF	−0.262	0.218
LV MPI-TDI	0.594	0.007

Abbreviations: TAPSE, tricuspid annular plane systolic excursion; RVSP, right ventricular systolic pressure; RV-FAC, right ventricular fractional area change; RVEF, right ventricular ejection fraction; s′, systolic tissue Doppler imaging of septal mitral annulus; e′, early diastolic tissue Doppler imaging of septal mitral annulus; a′, late diastolic tissue Doppler imaging of septal mitral annulus; E/e′ ratio, the ratio of early transmittal velocity to tissue Doppler mitral annular early diastolic velocity; LVEF, left ventricular ejection fraction; MPI-TDI, myocardial performance index derived from tissue Doppler imaging.

diastolic pressure generally reflects high left atrial pressure or pulmonary capillary wedge pressure. In addition, PAH could impair or reduce LV preload, and the resultant decrease in cardiac output could contribute to DOE. Therefore, both LV and RV functions should be considered when treating patients with PAH, and a thorough workup necessitates evaluation of global cardiac function.

Patients responded to bosentan treatment with remarkable improvements in RVSP, RV-FAC, TAPSE, and RVEF, all of which are considered indicators of RV, but not LV function.[6] Unfortunately, these echocardiographic changes were not significantly correlated with the improvement in 6MWD after 6 months of bosentan treatment. This could be attributed to the heterogeneous mechanism of 6MWD, not just to RV function, although we acknowledge that there may be a certain degree of lag between clinical and laboratory improvement. Alternatively, the lack of correlation could be explained by the fact that FAC and RVEF are not sensitive enough to reflect ventricular functional changes because of irregular cardiac geometry. Exercise usually causes changes in loading conditions, and, thus, measures that are less dependent on hemodynamic loading, including the MPI-TDI method, should be considered in

the workup of patients with PAH.[14–16] This is particularly true because measurements of single-chamber parameters, such as LVEF or RVEF, usually correlate poorly with exercise capacity.

In contrast to conventional echocardiographic variables, TDI is a straightforward and feasible technique; it provides useful information about cardiac function, particularly for LV diastolic function, such as E/e′ ratio.[17] Considering that the conventional echocardiographic assessment of ventricular function requires geometric assumptions, ventricular interdependence in PAH may mean that MPI-TDI provides a better global assessment of cardiac function than single-ventricle parameters can offer.[18,19]

Recently, studies of atrial fibrillation and right-sided heart diseases have shown that MPI based on TDI has great advantages over MPI derived from color Doppler.[20,21] MPI derived by conventional Doppler has an important limitation in the fact that IRT, ICT, and ET cannot be measured simultaneously during the same cardiac cycle. However, MPI-TDI has the advantage of simultaneous measurement of IRT, ICT, and ET. In addition, MPI-TDI is thought to be relatively unaffected by volume overloading conditions that are frequently encountered in congenital heart diseases, such as right-sided volume loading in atrial or ventricular septal defects.[22,23] These advantages could render MPI-TDI helpful for predicting the exercise capacity in response to bosentan. Furthermore, even in healthy athletes, RV MPI has been shown to be a good estimate of exercise capacity and closely correlated with maximal oxygen consumption.[14]

Unfortunately, few studies have evaluated the usefulness of MPI-TDI in assessing global cardiac function or exercise capacity. In the present study, changes in RV MPI-TDI were not well correlated with conventional RV variables, but were correlated with changes in systolic TDI of the septal mitral annulus ($r = 0.717$, $p = 0.009$) and LV MPI-TDI ($r = 0.594$, $p = 0.007$). Therefore, RV MPI-TDI reflected the response of LV function to bosentan therapy, and this correlation might imply that both RV and LV function would be impaired together because of interventricular dependency in PAH.[16]

Limitations

This study has several limitations that should be noted. First, we analyzed data from only 19 of the initial 30 patients recruited for the study. Second, right heart catheterization is required to confirm a diagnosis of PAH, but some patients in this study did not undergo cardiac catheterization. To overcome this limitation, we calculated the noninvasive echocardiographic index (ePLAR), and values compatible with precapillary PAH were obtained (an optimal cutoff value for ePLAR of >0.28 m/s is proposed to differentiate precapillary PAH from postcapillary PAH).[10] Furthermore, considering that the main purpose of our study was to determine the echocardiographic predictors of response to bosentan, as indicated by increased exercise capacity, the current data could be sufficient to provide clinical information for the treatment of PAH diagnosed without catheterization.

CONCLUSION

In patients with PAH, bosentan treatment enhanced exercise capacity through improvement in RV function primarily through a reduction in pulmonary arterial pressure. Changes in LV or RV function measured by MPI-TDI correlated well with exercise improvement.

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