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Clinical Investigation

# Long-Term Effect of Bosentan Therapy on Cardiac Function and Symptomatic Benefits in Adult Patients With Eisenmenger Syndrome

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## ABSTRACT

**Background:** Bosentan improves symptoms in patients with Eisenmenger syndrome (ES). This study evaluated the effect of long-term bosentan therapy on cardiac function and its relation to symptomatic benefits in ES patients.

**Methods and Results:** Twenty-three consecutive adult ES patients (15 with ventricular septal defect, 6 with atrial septal defect, and 2 with patent ductus arteriosus) underwent standard and tissue Doppler echocardiography before and 24 ± 9 months after bosentan therapy. Echocardiographic measurements included pulmonary arterial systolic pressure (PASP), myocardial performance index (MPI), tricuspid and lateral mitral annular pulsed-wave tissue Doppler systolic (Sa) and early diastolic (Ea) long-axis motions. Patients' World Health Organization (WHO) functional class, 6-minute walk distance (6MWD), and systemic arterial oxygen saturations ($SaO_2$) were also recorded. The PASP, WHO functional class, 6MWD, and $SaO_2$ all improved (118 ± 22 to 111 ± 19 mm Hg, 3.2 ± 0.4 to 2.4 ± 0.5, 286 ± 129 m to 395 ± 120 m, and 84.6 ± 6.5% to 88.8 ± 3.9%, respectively; all $P < .01$) after therapy. There was also significant improvement in right ventricular (RV) MPI (by 23.9%: 0.46 ± 0.15 to 0.35 ± 0.09) and biventricular long-axis function (tricuspid Sa and Ea: 6.7 ± 1.5 to 8.8 ± 1.7 cm/s and 5.7 ± 1.3 to 7.0 ± 1.2 cm/s, respectively; lateral Sa and Ea: 6.8 ± 1.3 to 8.4 ± 1.5 cm/s and 7.6 ± 2.0 to 8.5 ± 2.1 cm/s, respectively; all $P < .05$). Posttherapy RV MPI was moderately correlated with PASP and 6MWD.

**Conclusions:** Sustained improvement of pulmonary arterial hypertension and RV function in ES patients was evident 2 years after bosentan therapy, and this may provide insights on the symptomatic benefits gained in these patients. (*J Cardiac Fail 2012;■:1–6*)

**Key Words:** Bosentan, Eisenmenger syndrome, myocardial performance index, long-axis function.

Eisenmenger syndrome (ES) refers to the reversal of the left-to-right shunt in patients with intracardiac systemic-to-pulmonary communications as a result of severe pulmonary vascular disease.[1] In the past, treatment options for ES patients were mainly supportive, and heart-lung transplantation or lung transplantation with corrective cardiac surgery is usually not feasible, owing to the lack of potential organ donors. Bosentan is a safe and effective oral endothelin dual-receptor antagonist for treating patients with pulmonary arterial hypertension associated with congenital heart disease,[2–6] mainly by improving short-term exercise capacity in patients.[5–8] Recent (2010) European Society of Cardiology guidelines for the management of grown-up congenital heart

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disease also recommends bosentan therapy in World Health Organization (WHO) functional class III patients based on those short-term studies.[9] However, there is a lack of long-term echocardiographic studies to address the underlying mechanisms for the observed clinical improvement.

ES patients have increased pulmonary vascular resistance, leading to chronic pressure overload on the right ventricle (RV) with subsequent dilatation and failure.[10] Assessment of global RV systolic function by the biplane Simpson method is often inaccurate owing to complex RV geometry.[11] RV diastology studied by transtricuspid pulsed-wave Doppler filling indices (peak E- and A-wave velocities, E-wave deceleration time, and isovolumic relaxation time) have the drawbacks of heart rate and load dependency as well as the lack of generally acceptable reference values, particularly for different age groups.[12] On the other hand, myocardial performance index (MPI), initially described by Tei et al as a surrogate of combined left ventricular (LV) systolic and diastolic function,[13] has been widely applied to congenital heart diseases predominately affecting the RV. Moreover, Gatzoulis et al showed an improvement in RV long-axis function 3 months after bosentan therapy in 10 ES patients.[6] Their findings are in agreement with our observation that ventricular long-axis function is more sensitive than global LV or RV ejection fraction in unveiling cardiac dysfunction in other congenital conditions.[12,14]

The aims of the present study were therefore: 1) to assess the long-term clinical benefits of bosentan therapy in ES patients; and 2) to prospectively characterize the change in cardiac long-axis function after therapy and its relation to clinical benefits.

## Methods

### Population

We prospectively studied 23 consecutive ES patients who were followed in an adult congenital heart disease clinic and received transthoracic echocardiography in 2005−2008. Enrolled patients were in WHO functional class III and IV and free from decompensated heart failure, severe arrhythmias causing hemodynamic compromise, and hemoptysis for ≥3 months before study entry. ES was defined as all of the following: 1) known intracardiac or great artery shunt; 2) comparable pulmonary arterial systolic pressure to systemic pressure; and 3) reversed or bidirectional shunt resulting in hypoxemia (systemic arterial oxygen saturation [$SaO_2$] <92% at rest or <87% with exercise).[10] Patients with suboptimal echocardiographic windows, more-than-mild valvular heart disease, coronary artery disease, or significant hepatic and renal dysfunction and those with contraindication to bosentan therapy were excluded from the study. Informed consent was obtained from each of the studied patients, and the study was approved by the local ethics committee.

Transthoracic echocardiography was performed at baseline and 1 month, 3 months, and every 3 months after starting bosentan therapy according to the study protocol. Clinical information collected at baseline and during scheduled follow-ups included: WHO functional class, systemic blood pressure, $SaO_2$ in room air, and 6-minute walk distance (6MWD). Patients' right arm systolic and diastolic blood pressures were measured with the use of a sphygmomanometer with the patient lying supine. $SaO_2$ was measured by resting finger pulse oximetry. Exercise capacity was evaluated by 6MWD.[15]

### Medications

Baseline medications, including angiotensin-converting enzyme inhibitors, digoxin, diuretics, and antithrombotic agents, were continued during follow-up. Bosentan (Tracleer; Actelion Pharmaceuticals, Allschwil, Switzerland) was started at a dose of 62.5 mg twice per day and was subsequently titrated to the target dose of 125 mg twice per day after 4 weeks. It was initiated in the hospital setting with close monitoring of $SaO_2$ and blood pressure. Physical examinations and laboratory tests, particularly hemoglobin and hepatic transaminase levels, were performed monthly or as clinically indicated. Derangement of liver function was defined as an elevation of hepatic transaminase level >3 times the upper limit of normal.

### Echocardiographic Examination

Echocardiograms were recorded according to the guidelines of the American Society of Echocardiography[16] by using a Vivid 7 (GE-Vingmed Ultrasound, Horten, Norway). At least 3 consecutive beats in sinus rhythm were recorded, and the average values were taken for analysis. The LV end-diastolic and end-systolic dimensions (LVEDD and LVESD, respectively) and RV end-diastolic dimension (RVEDD) were measured from M-mode recordings in the parasternal long-axis view. LV ejection fraction was calculated by biplane Simpson estimates. Right and left atrial dimensions were measured in the apical 4-chamber view. The LV mass was calculated with the Devereux formula.

LV filling velocities were obtained by placing a 2-mm pulsed-wave Doppler sample volume at the tips of mitral valve leaflets from the apical 4-chamber view. Peak early LV filling velocity (E-wave), peak atrial filling velocity (A-wave), E/A ratio, and E-wave deceleration time were all measured. The LV filling pattern was characterized as a normal pattern, an abnormal relaxation pattern (ARP), a pseudonormal pattern, or a restrictive filling pattern as previously described.[17]

LV and RV MPI were calculated from pulsed-wave Doppler recordings of LV and RV inflows and outflows as previously described.[13,18] Segmental myocardial long-axis function was assessed by recording longitudinal motions at tricuspid and lateral mitral annular sites with pulsed-wave tissue Doppler imaging technique.[19] Long-axis peak systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities were measured. E/Ea ratios were then calculated. Tricuspid regurgitation (TR) was assessed by color-flow and continuous-wave Doppler from the apical 4-chamber view. Pulmonary artery systolic pressure (PASP) was estimated from RV systolic pressure (peak retrograde) as TR pressure drop + right atrial pressure (RAP). The RAP was assessed at subcostal view by inferior vena caval (IVC) size and collapsibility as recommended by American Society of Echocardiography. An IVC diameter of ≤2.1 cm that collapsed >50% with a sniff suggested a normal RAP of 3 mm Hg, whereas an IVC diameter of >2.1 cm that collapsed <50% with a sniff suggested a high RAP of 15 mm Hg. In indeterminate cases in which the IVC diameter and collapse did not fit this paradigm, an intermediate value of 8 mm Hg was used. The pulmonary acceleration time and ejection time were calculated from pulsed-wave Doppler recordings at pulmonary valve level. All echocardiographic

measurements were carried out by 2 experienced observers who were unaware of the clinical data.

### Reproducibility of the Measurements

Intraobserver and interobserver variability of the echocardiographic measurements were assessed in 10 randomly chosen patients by 2 independent observers on 2 separate occasions. Variability was calculated as the percentage error, derived as the absolute difference between 2 sets of measurements, divided by the mean of the observations. Both investigators were blinded to the patients' diagnoses.

### Statistics

All of the data are expressed as mean ± SD unless otherwise stated. Comparisons of variables before and after treatment were made using 2-tail paired Student *t* test. Mann Whitney *U* test was used for comparison of variables between RV MPI ≤12% and >12% groups. Categoric variables were presented as absolute values and percentages, and comparisons were tested by the chi-square test. Correlations were tested with Pearson coefficients. A significant difference was defined as $P < .05$ (2 tailed). All statistical analyses were performed using software (SPSS statistical package for Windows, cersion 13.0; SPSS, Chicago, Illinois).

## Results

### Demographics

A consecutive sample of 26 patients with ES were identified during the study period. Two patients with more-than-mild valvular heart diseases and 1 patient with significant hepatic and renal dysfunction were excluded from the study. The remaining 23 (13 female) patients, with a mean age of 31 ± 12 years, were included. Their underlying diagnoses were: unrestrictive ventricular septal defect (n = 15), large atrial septal defect (n = 6), and patent ductus arteriosus (n = 2). The mean follow-up duration was 24 ± 9 months (range 12−36 months). All of the patients received 125 mg bosentan twice daily after the initial up titration period. They tolerated the therapy well, and no dropout was reported during the study period. Regarding other medications, 3(13%), 10 (43%), 16 (70%), and 21 (91%) of patients were prescribed with angiotensin-converting enzyme inhibitors, digoxin, diuretics, and antithrombotic agents, respectively, during follow-up.

### Clinical Benefits

No significant changes in heart rate, systemic blood pressure, and liver enzymes were observed during follow-up. Pulmonary arterial systolic pressure dropped (118 ± 22 to 111 ± 19; $P = .044$), WHO functional class, 6MWD, and $SaO_2$ all improved (3.2 ± 0.4 to 2.4 ± 0.5, 286 ± 129 m to 395 ± 120 m, and 84.6 ± 6.5% to 88.8 ± 3.9%, respectively; all $P < .01$) after therapy (Table 1).

### Cardiac Structure and Function

Echocardiographic data are presented in Table 2. No significant cardiac structural remodeling was observed. A nonsignificant decrease in RVEDD and reduction in biatrial sizes were also noted. LV global diastolic function improvement also was not evident. There was significant improvement in RV MPI (by 23.9%: 0.46 ± 0.15 to 0.35 ± 0.09; Figure 1), which was partly accountable by a prolonged pulmonary ejection time. Moreover, biventricular long-axis function was improved (tricuspid Sa and Ea: 6.7 ± 1.5 to 8.8 ± 1.7 cm/s and 5.7 ± 1.3 to 7.0 ± 1.2 cm/s, respectively; lateral Sa and Ea: 6.8 ± 1.3 to 8.4 ± 1.5 cm/s and 7.6 ± 2.0 to 8.5 ± 2.1 cm/s, respectively; Table 2).

**Table 1.** Clinical Variables Before and After Bosentan Treatment

| | Before Therapy | After Therapy | *P* Value |
|---|---|---|---|
| Heart rate, beats/min | 78 ± 8 | 80 ± 9 | .744 |
| Blood pressure, mm Hg | | | |
| Systolic | 109 ± 12 | 108 ± 8 | .577 |
| Diastolic | 66 ± 8 | 64 ± 9 | .460 |
| PASP, mm Hg | 118 ± 22 | 111 ± 19 | .044 |
| WHO functional class | 3.2 ± 0.4 | 2.4 ± 0.5 | .001 |
| II | 0 | 17 | |
| III | 20 | 6 | |
| IV | 3 | 0 | |
| 6MWD, m | 286 ± 129 | 395 ± 120 | .001 |
| $SaO_2$, % | 84.6 ± 6.5 | 88.8 ± 3.9 | .006 |
| Liver function tests, IU/L | | | |
| ALT | 31 ± 6 | 34 ± 7 | .168 |
| AST | 28 ± 7 | 30 ± 8 | .213 |

WHO, World Health Organization; 6MWD, 6-minute walk distance; $SaO_2$, systemic arterial oxygen saturation; PASP, pulmonary artery systolic pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Table 2.** Ventricular Structure, Function and Long-Axis Function After Bosentan Therapy

| | Before Therapy | After Therapy | *P* Value |
|---|---|---|---|
| Left atrial and ventricular variables | | | |
| LV end-diastolic diameter, mm | 41.1 ± 4.9 | 42.3 ± 5.2 | .142 |
| LV end-systolic diameter, mm | 27.4 ± 4.5 | 26.2 ± 4.7 | .139 |
| LV ejection fraction, % | 60 ± 7 | 63 ± 9 | .057 |
| LA size, mm | 33.3 ± 4.9 | 31.1 ± 6.2 | .063 |
| LV mass, g | 147.9 ± 40.9 | 148.1 ± 40.3 | .975 |
| Right atrial and ventricular variables | | | |
| RV end-diastolic diameter, mm | 35.3 ± 10.5 | 31.8 ± 10.3 | .066 |
| RA size, mm | 40.5 ± 4.5 | 35.4 ± 5.2 | .140 |
| LV global diastolic function | | | .604 |
| Normal pattern | 11 | 14 | |
| Abnormal relaxation pattern | 9 | 6 | |
| Pseudonormalization pattern | 3 | 2 | |
| Restrictive filling pattern | 0 | 1 | |
| Pulmonary variables | | | |
| Pulmonary valve acceleration time, ms | 74.5 ± 21.6 | 84.2 ± 21.3 | .157 |
| Pulmonary ejection time, ms | 283.7 ± 24.5 | 287.5 ± 48.5 | .074 |
| Lateral mitral annular site | | | |
| Sa, cm/s | 6.8 ± 1.3 | 8.4 ± 1.5 | .001 |
| Ea, cm/s | 7.6 ± 2.0 | 8.5 ± 2.1 | .010 |
| Aa, cm/s | 7.7 ± 1.3 | 8.5 ± 2.8 | .325 |
| E/Ea | 7.5 ± 3.0 | 8.6 ± 4.3 | .128 |
| Tricuspid site | | | |
| Sa, cm/s | 6.7 ± 1.5 | 8.8 ± 1.7 | .003 |
| Ea, cm/s | 5.7 ± 1.3 | 7.0 ± 1.2 | .001 |
| Aa, cm/s | 10.4 ± 2.3 | 10.2 ± 3.0 | .753 |
| E/Ea | 10.0 ± 4.5 | 8.6 ± 3.9 | .004 |

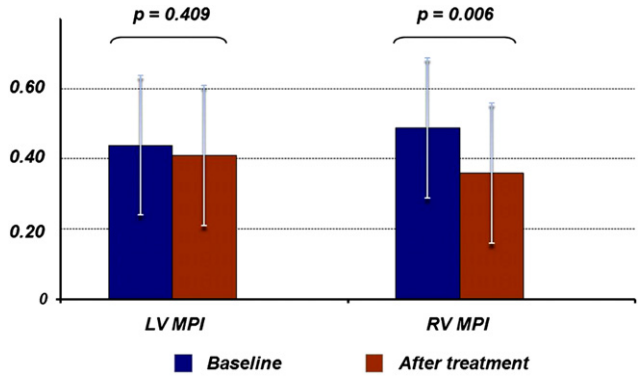


**Fig. 1.** Change of the myocardial performance indices before and after bosentan treatment. MPI, myocardial performance index.

### Relationship Between PASP, RV MPI, and Clinical Benefits

Post-therapy change in RV MPI was moderately correlated with changes in PASP and 6MWD (ΔRV MPI vs ΔPASP: $r = 0.523$; ΔRV MPI vs Δ6MWD: $r = -0.549$; all $P < .05$; Figure 2). A greater degree of clinical benefits gained (6MWD and WHO functional class) was observed in ES patients with RV MPI improvement $>12\%$ than $\leq 12\%$ (Table 3).

### Intraobserver and Interobserver Variability

Intraobserver and interobserver variability for conventional Doppler and tissue Doppler–derived variables (LVEDD, Sa, Ea, Aa, and MPI) ranged from 2% to 7%. Reproducibility of long-axis measurements has been published previously.[14,19]

## Discussion

### Main Findings

To our knowledge, this is the first study that examined in depth the effect of bosentan therapy on long-term change in cardiac function and its relation to symptomatic benefits in ES. We demonstrated a sustained clinical benefit (WHO functional class, $SaO_2$, and 6MWD) of bosentan therapy without serious adverse events during long-term follow-up. Such clinical benefit was accompanied by a drop of PASP and an improvement in RV MPI and biventricular long-axis function. Furthermore, the extent of RV functional improvement was seemingly related to the degree of symptomatic benefits gained in 6MWD and WHO functional class in these patients.

### Sustained Clinical Benefits of Bosentan Therapy in ES Patients

Endothelin-1 plays a major role in structural and functional abnormalities found in pulmonary vasculature in ES patients. Early small-scaled nonrandomized studies demonstrated that bosentan therapy has a positive impact on functional class, oxygenation, and pulmonary hemodynamics in ES patients.[3,5–8] BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy for Pulmonary Hypertension 5) was the first randomized controlled trial including 54 ES patients, and that study showed reduced pulmonary vascular resistance and improved 6MWD (by 53 m) in ES patients after 4 months' bosentan therapy compared with placebo.[2] The present study recorded an average 109-m 6MWD improvement at 24 ± 9 months' follow-up. Seventy-four percent of our studied patients had an increase in 6MWD of >54 m. Recent data suggested that an improvement of such magnitude is associated with a perceivable improvement in exercise capacity for the patients.[20] The improvement in exercise capacity was likely attributed to the increased tissue oxygen delivery secondary to reduced right-to-left shunting and augmented pulmonary blood flow, as suggested by the increased $SaO_2$ and prolonged pulmonary ejection time noted in our patients. In fact, most of our studied patients felt better, as evidenced by improved WHO functional class without experiencing major drug-related sided effects. Our findings

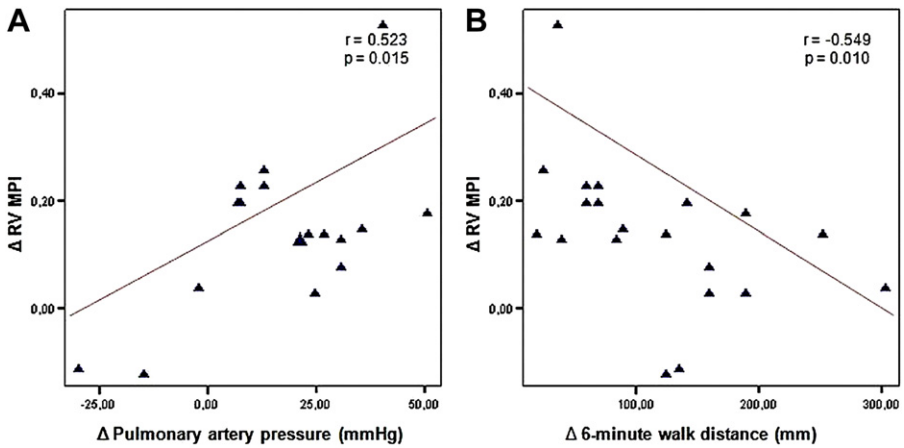


**Fig. 2.** Correlation results between RV MPI and (left) change in change in PASP and (right) 6-minute walk distance.

**Table 3.** Relationship of Changes in RV MPI to 6MWD, WHO Functional Class, and $SaO_2$ After Bosentan Therapy

| | All Patients (n = 23) | RV MPI >12% Improvement (n = 12) | RV MPI ≤ 12% Improvement (n = 11) | *P* Value |
|---|---|---|---|---|
| Change in 6MWT, m | 108 ± 85 | 126 ± 72 | 64 ± 76 | .009 |
| Improvement in WHO functional class | 0.76 ± 0.43 | 0.96 ± 0.44 | 0.42 ± 0.54 | .001 |
| Change in $SaO_2$, % | 4.2 ± 5.1 | 5.0 ± 4.9 | 3.2 ± 3.6 | .112 |

thus add to the current literature that bosentan therapy should be offered to ES patients at a longer duration, given their sustained clinical benefits.

### Evaluation Treatment Effect With RV MPI and Long-Axis Function in ES Patients Receiving Bosentan

There is a pressing need for developing a sensitive echocardiographic marker for monitoring treatment progress in ES patients for 2 main reasons. Adverse cardiac remodeling with biventricular hypertrophy is a fairly established process, given the longstanding nature of the disease. Conventional parameters for assessment of global ventricular structures and functions are often insensitive to pick up the changes after bosentan therapy. Moreover, demonstrating prognostic benefit with bosentan therapy is ES patients is often challenging because patients with ES often exhibit a more favorable hemodynamics profile than those with idiopathic pulmonary hypertension and thereby have better survival. Outcome measures in contemporary studies that are largely based on symptoms and semiquantitative clinical parameters are also inadequate.

The present data confirmed the selective sensitivity of RV MPI and long-axis function in revealing the changes of myocardial function after treatment over conventional parameters (cardiac dimensions, LV ejection fraction, and global diastolic function) that are often equivocal. Both RV MPI and long-axis velocities have been validated as surrogates for ventricular function, which would make them ideal tools for assessing treatment effect and predicting prognosis in ES patients. Earlier data showed an average value for RV MPI in normal population ranging from 0.26 to 0.28.[21] The present population had an abnormally high pretreatment RV MPI of 0.46 ± 0.15, indicating significant baseline global RV dysfunction. Bosentan therapy resulted in a 23.9% improvement in RV MPI to 0.35 ± 0.09, which was still abnormal compared with normal population. Furthermore, we demonstrated not only RV but also LV functional improvement by long-axis measurements by ≥6.8%. One potential explanation for the improvement in LV long-axis function is likely the influence of interventricular dependence. We think that the change in RV MPI and long-axis function are real, given their relatively low interobserver and intraobserver variability.

Post-therapy RV function (MPI) was related to a drop of PASP and an improvement in 6MWD (Figs. 2 & 3). A greater degree of clinical improvement (6MWD and WHO functional class) also occurred in ES patients with RV MPI improvement >12%. Further studies are welcomed to confirm the results of our studies. These data seemingly suggested that the degree of RV functional improvement might determine the symptomatic benefits observed in ES patients. Further large-scaled prospective studies are welcomed to test this hypothesis.

### Clinical Implications

Bosentan therapy should be prescribed to adults ES patients in long-term given its sustained clinical benefits and excellent safety profile. Physicians should include assessment of RV MPI and long-axis function in future studies (bosentan or other selective pulmonary vasodilators) as they are the sensitive markers for evaluating treatment effect and more importantly they may shed light on the mechanism of clinical improvement as well as predicting prognosis in ES patients.

### Study Limitations

Most limitations were inherent to the small sample size. However, this study already included a respectable contemporary cohort of ES patients, given it was a rare disorder. Furthermore, invasive data was not available, particularly on absolute pulmonary arterial pressure, which might have explained some other contributing factors. Some of the studied patients had atrial septal defect (n = 6) and may not develop significant pulmonary vascular disease until young adulthood, meaning that the RV is not conditioned to pressure overloading in the same way as other ES patients with posttricuspid shunts. Finally, the current state-of-art echocardiographic machine with myocardial tissue Doppler imaging and speckle tracking techniques may provide in-depth regional quantitative assessment of RV dysfunction.

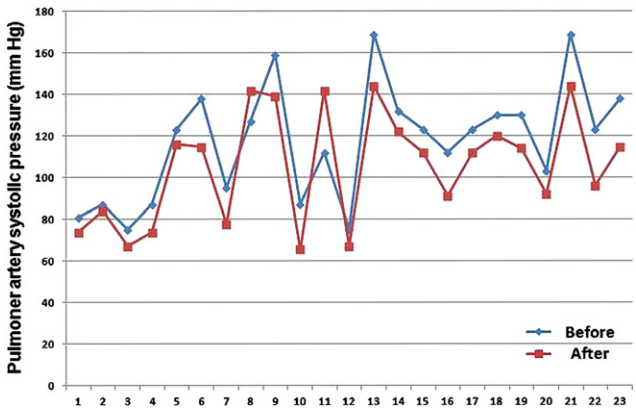


**Fig. 3.** Individual changes in PASP before and after bosentan treatment.

## Conclusion

Sustained improvement of pulmonary arterial hypertension and RV function in ES patients was evident 2 years after starting bosentan therapy. These hemodynamic improvements should provide insights on the symptomatic benefits gained in these patients.

## Disclosures

None.

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