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ORIGINAL PAPER

Effect of bosentan therapy on ventricular and atrial function in adults with Eisenmenger syndrome. A prospective, multicenter study using conventional and Speckle tracking echocardiography

Mohamed Y. Abd El Rahman · Axel Rentzsch · Philipp Scherber · Siegrun Mebus · Oliver Miera · Günther Balling · Petra Böttler · Karl-Otto Dubowy · Birgit Farahwaschy · Alfred Hager · Joachim Kreuder · Brigitte Peters · Felix Berger · Ingram Schulze-Neick · Hashim Abdul-Khaliq

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Abstract
Background The effect of bosentan on the ventricular and atrial performance in patients with Eisenmenger syndrome is unclear. In adult patients with Eisenmenger syndrome, we aimed to evaluate the midterm effect of bosentan on physical exercise, ventricular and atrial function, and pulmonary hemodynamics.
Methods Forty adult patients before and after 24 weeks bosentan therapy underwent 6 min walk test, two-dimensional speckle tracking echocardiography, plasma NT-proBNP measurement and cardiac catheterization.
Results After 24 weeks, bosentan therapy an improvement was observed regarding the 6 min walk distance from a median (quartile 1–quartile 3) of 382.5 (312–430) to 450 (390–510) m ($p = 0.0001$), NT-proBNP from 527.5 (201–1,691.25) to 369 (179–1,246) pg/ml ($p = 0.021$), right ventricular mean longitudinal systolic strain from 18 (13–22) to 19 (14.5–25) % ($p = 0.004$), left ventricular mean longitudinal systolic strain from 16 (12–21) to 17 (16–22) % ($p = 0.001$), right atrial mean peak longitudinal strain from 26 (18–34) to 28 (22–34) % ($p = 0.01$) and right atrial mean peak contraction strain from 11 (8–16) to 13 (11–16) % ($p = 0.005$). The invasively obtained Qp:Qs and Rp:Rs did not significantly change under bosentan therapy.
Conclusions In adult patients with Eisenmenger syndrome, bosentan therapy improves ventricular and atrial functions resulting in enhancement of physical exercise and reduction in the NT-proBNP level, while the pulmonary vascular resistance does not change substantially.

Keywords Pulmonary arterial hypertension, echocardiography · Myocardial contraction · Remodeling

M. Y. Abd El Rahman · A. Rentzsch · P. Scherber · H. Abdul-Khaliq (✉)
Department of Pediatric Cardiology, Saarland University Hospital, Kirrberger Straße, 66421 Homburg/Saar, Germany
e-mail: hashim.abdul-khaliq@uniklinikum-saarland.de; abdul-khaliq@uks.eu

M. Y. Abd El Rahman
Department of Pediatrics and Pediatric Cardiology, Cairo University, Cairo, Egypt

S. Mebus · O. Miera · B. Farahwaschy · F. Berger · I. Schulze-Neick
Department of Congenital Heart Disease/Pediatric Cardiology, Deutsches Herzzentrum, Berlin, Germany

S. Mebus · G. Balling · A. Hager
Department of Pediatric Cardiology and Congenital Heart Defects, German Heart Centre Munich, Technische Universitaet Muenchen, Munich, Germany

P. Böttler
Department of Congenital Heart Defects/Pediatric Cardiology, University Hospital Freiburg, Freiburg, Germany

K.-O. Dubowy
Center for Congenital Heart Defects, Heart and Diabetes Center NRW, Bad Oeynhausen, Germany

J. Kreuder
Pediatric Heart Center, Justus-Liebig University Giessen, Giessen, Germany

B. Peters
Department of Biometry and Medical Informatics, Otto von Guericke Universitaet Magdeburg, Magdeburg, Germany

I. Schulze-Neick
UK Service for Pulmonary Hypertension in Children, Cardiac Unit, Great Ormond Street Hospital, London, UK

Abbreviations

2-D STE	Two-dimensional speckle tracking echocardiography
6MWT	Six-minute walk test
CHD	Congenital heart defect
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PACS	Peak atrial contraction strain
PAH	Pulmonary arterial hypertension
PALS	Peak atrial longitudinal strain
Qp:Qs	Pulmonary blood flow:systemic blood flow
ROI	Region of interest
Rp:Rs	Pulmonary resistance:systemic resistance
TAPSE	Tricuspid annular plane systolic excursion

Introduction

Congenital heart diseases (CHD) are the most common congenital malformations in newborns, accounting for about 8–10 cases per 1,000 births [1]. A large proportion of patients with congenital disease with relevant systemic to pulmonary shunt will develop pulmonary arterial hypertension (PAH), if their condition is left untreated. Eisenmenger syndrome is an advanced form of secondary PAH due to untreated systemic to pulmonary shunts. It is characterized by increased a pulmonary vascular resistance that exceeds the systemic vascular resistance resulting in reversal of the direction of the shunt and development of central cyanosis [2].

Bosentan, a dual endothelin receptor antagonist, is now approved for treatment of PAH associated with congenital heart disease and Eisenmenger syndrome [3, 4]. The data regarding the effect of bosentan on ventricular and atrial performance in patients with Eisenmenger syndrome, in particular concerning the left side of the heart is sparse or even lacking.

Speckle tracking derived strain is a reproducible method that has been used in the assessment of ventricular and recently of atrial performance [5]. In addition, this method may be able to detect latent changes in myocardial dysfunction and possible improvement, which not detectable using the conventional echocardiography methods.

The purpose of this study performed on a cohort of adult Eisenmenger syndrome patients with various congenital heart defect (CHD) was, to evaluate the midterm effect of bosentan on physical exercise, ventricular and atrial function, and pulmonary hemodynamics.

Methods

Study design and patients

The present study was a part of an open-label, uncontrolled, nonrandomized, prospective, multicenter study with 24 weeks of bosentan treatment in Eisenmenger patients, sponsored by the German Competence Network for Congenital Heart Defects (Clinical Trials.gov.ID NCT00266162). The study protocol was approved by the local ethics committees, and informed written consent was obtained from the patients.

Sixty patients fulfilled the inclusion and exclusion criteria of the Clinical Trials.gov. ID NCT00266162. The inclusion criteria were age at least 18 years, presence of cyanosis with $<$93 % arterial oxygen saturation (measured by transcutaneous pulse oximetry), PAH as diagnosed by invasive methods with Rp:Rs $>$0.75 measured at rest, before testing of pulmonary vasodilatory reserve and presence of PAH due to noncorrected large congenital shunting defect at atrial, ventricular or arterial level. The exclusion criteria were pulmonary hypertension of any etiology other than those specified in the inclusion criteria, acute decompensated heart failure within 7 days before the invasive procedure, left ventricular diseases, significant valvular diseases other than tricuspid or pulmonary regurgitation, bronchopulmonary dysplasia or other chronic lung diseases and trisomy 21.

Additional echocardiographic exclusion criteria were poor echocardiographic window to scan the ventricular or atrial walls adequately, greyscale image with a frame rate $<$than 40 frames/s, presence of stationary reverberations or dropouts and presence of atrial fibrillation. Accordingly, 40 out of 60 included Eisenmenger syndrome patients (24 females and 16 males) were included in this study to analyze the myocardial function after therapy by the novel echocardiography method. Thirty patients had nonoperated ventricular level (VSD), three patients had nonoperated atrial septal defect (ASD), three patients had nonoperated patent ductus arteriosus (PDA) and four patients had nonoperated truncus arteriosus. Patients' median (quartiles 1–3) age at baseline was 35.5 (22.25–41) years. Baseline medications, including digoxin, diuretics and antithrombotic agents, were continued unchanged during the bosentan therapy. None of the included patients received β-blocker or angiotensin converting enzyme (ACE) inhibitor.

Protocol for bosentan therapy

Bosentan (Tracleer®, Actelion Pharmaceuticals, Allschwil, Switzerland) was started at a dose of 62.5 mg/bid while and was subsequently titrated to the target dose of 125 mg/bid after 4 weeks.

Study assessment

Clinical and laboratory assessment

Physical examinations and laboratory tests, particularly hemoglobin and hepatic transaminase levels were

performed monthly. The six-min walk test (6MWT) was conducted at baseline and during each visit according to the guidelines of the American Thoracic Society [6].

N-terminal pro-B-type natriuretic peptide (NT-proBNP) was determined in the local laboratories with commercially available kit (Roche, Elecsys™). All laboratories were collected on the same day of the hemodynamic study. Responders with a reduction of NT-proBNP more than 20 % were identified.

Echocardiography

All patients were examined by echocardiography 24 h before the hemodynamic study using a 2.5–3.5 MHz phased-array transducer with a Vingmed Vivid 7 ultrasound system (General Electrics, Fairfield, Connecticut, USA). All echocardiographic measurements were done offline by three investigators blinded from the laboratory, 6MWT and cardiac catheterization results.

Echocardiography derived longitudinal M-mode

Tricuspid annular plane systolic excursion (TAPSE) was measured using two-dimensional echocardiographically guided M-mode recordings from the apical four-chamber view with the cursor placed at the free lateral wall of the tricuspid annulus [7].

Two-dimensional echocardiography

The cardiac chambers were scanned using a conventional four-chamber view in left lateral decubitus position. The gain was set to achieve optimal differentiation of myocardium and endocardium. Then, a loop of three cardiac cycles was recorded and stored for offline analysis. The atrial areas in end-systolic and end-diastolic phases were outlined along the endocardium. The atrial area filling fraction [(area at end-systole − area at end-diastole)/area at end-systole × 100 %] was calculated).

Doppler echocardiography

The inflow and outflow from each ventricle were assessed to measure the Tei index of both ventricles as previously described [8].

Two-dimensional speckle tracking echocardiography (2-D STE)

Standardized 2-D echocardiography views from the ventricles and atria in four-chamber view were acquired and digitally stored as cine loops and transferred to an image database via a web-data program for further 2-D STE analysis. All images were recorded at a frame rate of 50–80 frames/s to allow reliable operation of the 2-D STE software (Echo Pac, GE, USA). For the ventricular 2-D STE analysis, regions of interest (ROIs) were placed in the apical four-chamber view of a 2-D image in the free lateral wall of the right ventricle and lateral wall of the left ventricle. 2-D STE derived longitudinal mean deformation (strain) was calculated from the basal, middle and apical region of each ventricular free wall [9]. The interventricular septum (IVS) was not assessed since the majority of patients had VSD making its assessment unreliable.

For atrial speckle tracking (Fig. 1), the atrial endocardial surface is manually traced. Care was taken to extrapolate the pulmonary veins and coronary sinus from the tracking.

The beginning of the QRS was set as the reference from which the software starts to calculate atrial deformation. The software generates the longitudinal strain curves for each segment and a mean curve of all segments (Fig. 1). The peak atrial longitudinal strain (PALS), measured at the end of the reservoir phase (i.e. end of atrial filling), and peak atrial contraction strain (PACS), measured just before the start of active contractile phase, are calculated by averaging values observed in all atrial segments [5].

Cardiac catheterization

Cardiac catheterization was performed at baseline and after 24 weeks of bosentan therapy. Cardiac catheterization was performed on the day following echocardiographic examination. The pulmonary to systemic flow ratio was calculated as previously described [10]. The relative pulmonary (Rp) to systemic resistance (Rs) was calculated.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Data are shown as median (quartiles 1–3). The nonparametric Wilcoxon's and Mann–Whitney tests were used to assess the differences between two paired and unpaired groups, respectively.

A $p < 0.05$ was considered statistically significant. Correlations were evaluated using the nonparametric Spearman's rank correlation. Interobserver variability was calculated according to Bland–Altman [11].

Results

Clinical and laboratory assessment

The clinical characteristics and laboratory data before and after bosentan therapy are given in Table 1. Thirty-five

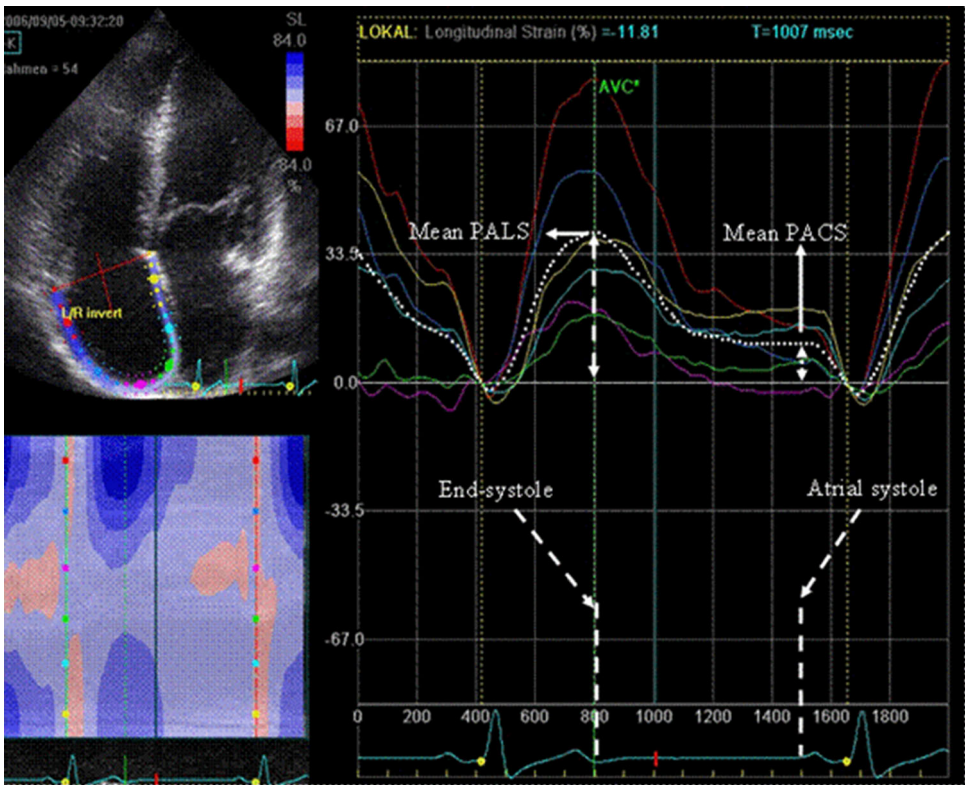

Fig. 1 Peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS) derived from atrial speckle tracking echocardiography in a patient with Eisenmenger syndrome

patients showed an improvement in the 6MWT distance, five patients showed deterioration. After 24 weeks of bosentan therapy, 13 patients showed a reduction >200 pg/ml in their NT-proBNP level, 3 patients showed an elevation >200 pg/dl in their NT-proBNP level and in the remaining 24 patients the change observed in NT-proBNP level was <200 pg/dl.

The right ventricle (RV) performance

The interobserver variability for the RV systolic strain was 4.68 % (95 % confidence interval −1.69 to 1.68). At baseline, the NT-proBNP correlated significantly with TAPSE ($r = -0.49$, $p = 0.001$), pulmonary pre-ejection time ($r = 0.57$, $p = 0.0001$) and RV free wall longitudinal strain ($r = -0.5$, $p = 0.001$). After 24 weeks of bosentan therapy, the RV Tei index decreased significantly ($p = 0.043$), RV free wall longitudinal mean strain increased significantly ($p = 0.004$, Table 2).

The left ventricle (LV) performance

The interobserver variability for LV systolic strain was 6.15 % (95 % confidence interval −1.95 to 2.01). At baseline, NT-proBNP correlated significantly with LV lateral wall longitudinal mean strain ($r = -0.32$, $p = 0.039$) and LV Tei index ($r = 0.45$, $p = 0.004$). After 24 weeks of bosentan therapy, LV lateral wall mean longitudinal strain ($p = 0.001$) and LV Tei index ($p = 0.001$) showed a significant improvement (Table 2).

The atrial performance

The interobserver variability for the RA PALS was 3.01 % (95 % confidence interval −1.43 to 1.76), while that for the LA PALS was 6.76 % (95 % confidence interval −3.66 to 4.68). The NT-proBNP at baseline correlated significantly with RA end-systolic area ($r = 0.7$, $p = 0.001$), RA end-diastolic area ($r = 0.73$, $p = 0.001$) and RA atrial filling fraction ($r = -0.5$, $p = 0.001$) and RA PALS ($r = -0.82$, $p = 0.001$, Fig. 2).

At baseline, the RA PALS correlates significantly with TAPSE ($r = 0.55$, $p = 0.001$) and RV free wall mean longitudinal strain ($r = 0.6$, $p = 0.001$).

After 24 weeks of bosentan therapy, the RA PALS ($p = 0.01$, Fig. 3) and RA PACS ($p = 0.005$) and the RA atrial filling fraction ($p = 0.039$) increased significantly in comparison with baseline values (Table 3).

No significant differences were observed in LA PALS and LA PACS LA end-systolic area and LA end-diastolic area as compared to baseline (Table 3).

Table 1 Effect of bosentan on clinical and laboratory performance

Variable	Before treatment	After treatment	*p* value
Type of lesion			
ASD ($n = 3$)			
VSD ($n = 30$)			
PDA (n = 3)			
TA ($n = 4$)			
Age (years)	35.5 (22.25–41)		
Body weight (kg)	56.9 (50.3–63.3)	57.7 (50–64.2)	0.18
Height (cm)	168 (160–174)	167.5 (160-174)	0.593
SatartO2 (%)	86 ± 7	88 ± 7	0.87
NYHA class	3.1 ± 0.4	2.62 ± 0.6	0.0001
6MWD (m)	382.5 (312–430)	450 (390–510)	0.0001
RR interval (ms)	794.6 (707–902.3)	820 (724–964)	0.051
QRS duration (ms)	100 (82–140)	108 (80–140)	0.246
NT-proBNP (pg/ml)	527.5 (201–1,691.3)	369 (179–1,246)	0.021
Hb (g/dl)	19.1 (17.6–21.9)	18.5 (16.6–20.2)	0.0001
Aspartate aminotransferase (U/L)	26 (20–32)	25.5 (21–30.2)	0.51
Alaninine aminotransferase (U/L)	18 (14.1–26.8)	20 (15–29.5)	0.17

ASD atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *TA* truncus arteriosus, *Satart02 %* transcutaneous oxygen saturation in percent, *NYHA* New York Heart Association, *6MWD* Six-minute walking distance, *R–R* R–R interval on the surface electrocardiogram, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *QRS* duration of the QRS complex on the surface electrocardiogram

Table 2 Effect of bosentan on ventricular performance

Variable	Before treatment	After treatment	p-value
TAPSE (mm)	19 (15–21)	20 (16–22)	0.01
RV Tei index	0.55 (0.45–0.65)	0.48 (0.41–0.63)	0.043
LV Tei index	0.46 (0.35–0.6)	0.37 (0.28–0.52)	0.001
RV diastolic time (ms)	343 (285–439)	363 (308–448)	0.21
LV diastolic time (ms)	336 (294–446)	386 (319–466)	0.021
RV systolic/diastolic time	1.32 (1.03–1.59)	1.25 (0.97–1.46)	0.26
LV systolic/diastolic time	1.20 (1–1.52)	1.14 (0.91–1.32)	0.033
RV pre-ejection time (ms)	91 (80–109)	89 (77–102)	0.285
LV pre-ejection time	92 (77–125)	92 (78–115)	0.844
RV E/A	1.18 (0.76–1.48)	1.09 (0.89–1.45)	0.61
LV E/A	0.86 (0.74–1.27)	0.90 (0.78–1.31)	0.34
RV mean strain (%)	18 (13–22)	19 (15–25)	0.004
LV mean strain (%)	16 (12–21)	17 (16–22)	0.0001

A late diastolic peak velocity, *E* early diastolic peak velocity, *LV* left ventricle, *RV* right ventricle, *TAPSE* tricuspid annular peak systolic excursion

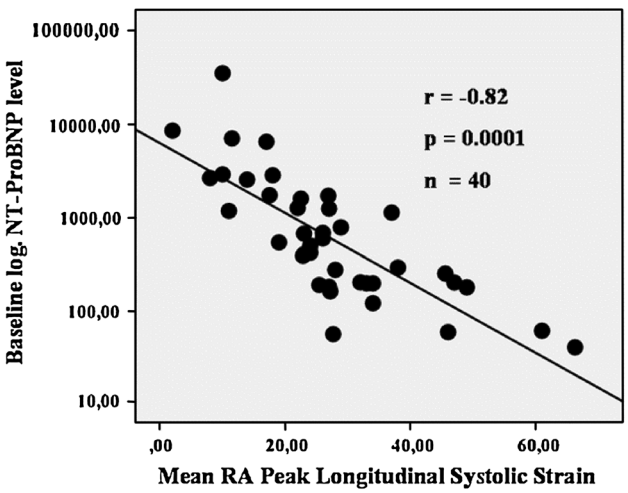

Fig. 2 Correlation among Eisenmenger patients before initiation of bosentan therapy between mean RA peak longitudinal strain assessed by STE and serum level of N-terminal pro-b-type natriuretic peptide (NT-proBNP). The scale of NT-proBNP values were transformed logarithmic

Invasive hemodynamic assessment through cardiac catheterization

At baseline, the mean RA pressure correlates significantly with RA PALS ($r = -0.54$, $p = 0.001$), RA PACS ($r = -0.43$, $p = 0.005$) and NT-proBNP ($r = 0.53$, $p = 0.001$).

The Qp:Qs ratio increased under bosentan therapy; however, this increase did not reach a statistically significant level ($p = 0.066$, Table 4). The Rp:Rs ratio shows a trend to decrease under bosentan therapy ($p = 0.08$, Table 4).

Response to therapy according to change in the NT-proBNP level

Responders with a reduction in the pro-BNP level of more than 20 % were identified. According to this definition, 20 patients were considered responders and 20 patients were considered nonresponders. At baseline, the responders had a significantly lower LA filling fraction (41.9 ± 17.5 vs. 27.3 ± 12.2 %, $p = 0.008$), invasively measured arterial aortic saturation (84.7 ± 8.8 vs. 76.3 ± 8.8 %, $p = 0.007$)

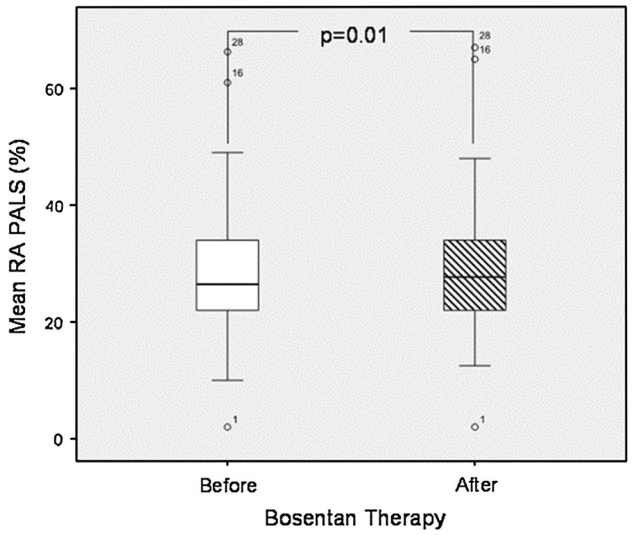

Fig. 3 Box plot comparing mean right atrial peak atrial longitudinal strain (RA PALS) before and after bosentan therapy. The mean RA PALS was significantly increased after bosentan therapy, reflecting improved right atrial reservoir function

Table 3 Effect of bosentan on atrial performance

Variable	Before treatment	After treatment	*p* value
RA end-diastolic area (cm^2)	11.1 (9.5–17.5)	11.6 (9–15.2)	0.84
RA end-systolic area (cm^2)	16.2 (13.6–21.9)	16.7 (13.8–21.5)	0.15
RA filling fraction (%)	26 (18–33)	33 (20–43)	0.016
RA PALS (%)	26 (18–34)	28 (22–34)	0.01
RA PACS (%)	11 (8–16)	13 (11–16)	0.005
LA end-diastolic area (cm^2)	6.9 (4.8–9)	6.3 (5.2–7.8)	0.42
LA end-systolic area (cm^2)	10.2 (9–12)	11.2 (8.4–12.9)	0.67
LA filling fraction (%)	34 (24–49)	40 (32–50)	0.058
LA PALS (%)	31 (20–36)	31 (26–37)	0.36
LA PACS (%)	12 (7–19)	13 (10–18)	0.48

LA left atrium, *PALS* peak atrial longitudinal strain, *PACS* peak atrial contraction strain, *RA* right atrium

and significantly reduced RA PALS (31.3 ± 14.8 vs. 23.7 ± 9.5 %, $p = 0.038$) than nonresponders. The other investigated variables did not differ significantly between the two groups. For prediction of responders, the area under the ROC curve was 0.78 for LA filling fraction, 0.77 for invasively measured arterial aortic saturation and 0.7 for RA PALS. For identification of responders, a LA filling fraction of <38.93 % had 93 % sensitivity and 52 % specificity, an arterial aortic saturation <79.5 had sensitivity of 64 and 86 % specificity and a RA PALS of <27 % had 80 % sensitivity and 57 % specificity (Fig. 4). For good prediction, it is generally accepted that the area under the ROC curve should be more than 0.9. Therefore, we considered the predictive value of the above parameters for prediction of responders to be rather weak.

Table 4 Effect of bosentan on the pulmonary hemodynamics as assessed invasively by cardiac catheterization

Variable	Before treatment ($n = 40$)	After treatment ($n = 40$)	*p* value
Qp:Qs	0.73 (0.51–0.91)	0.84 (0.62–1.02)	0.066
Mean PAP (mmHg)	80 (71–91)	78 (70–94)	0.26
Mean RAP (mmHg)	5 (1–7)	4 (3–6)	0.83
Mean LAP (mmHg)	6 (3–8)	4 (2–8)	0.94
Mean SAP (mmHg)	80 (74–92)	81 (76–90)	0.86
Mean aortic saturation (%)	82 (73–88)	84 (78–87)	0.86
Rp:Rs	1.24 (0.98–1.88)	1.21 (0.84–1.61)	0.08

LAP left atrial pressure, *PAP* pulmonary artery pressure, *Qp:Qs* pulmonary blood flow:systemic blood flow, *RAP* right atrial pressure, *Rp:Rs* pulmonary resistance:systemic resistance, *SAP* systemic artery pressure

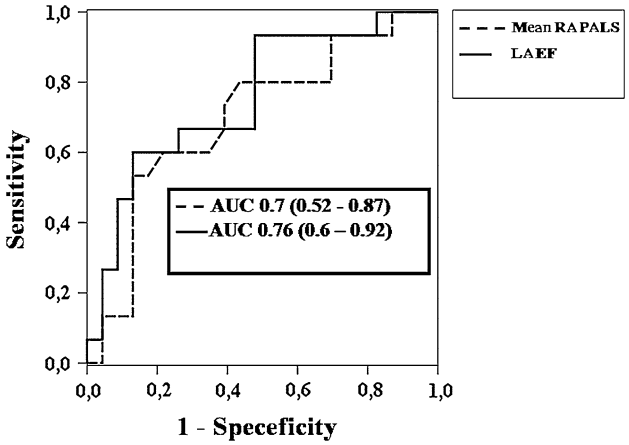

Fig. 4 Receiver-operating characteristic (ROC) curve of the mean right atrial peak longitudinal strain (RA PALS *dotted line*) and left atrial filling fraction (LAFF *line*) for prediction of responders in Eisenmenger patients after Bosentan therapy. *AUC* area under the curve

Discussion

The present study confirms the previously reported beneficial effect of bosentan in Eisenmenger patients on the 6MWD [12, 13], representing the daily needs for exercise

performance, and NT-proBNP as surrogate variable for survival [14, 15]. In addition, it showed that in these patients bosentan treatment may exert a significant beneficial effect not only on the right ventricular, but also on the left ventricular systolic function. Moreover, after a period of 24 weeks bosentan therapy, Eisenmenger patients showed an improved diastolic reservoir and pump function of the right atrium independently of significant changes in pulmonary vascular resistance and pulmonary arterial pressure.

Effect of bosentan on ventricular performance

The geometry of the ventricles in Eisenmenger patients is frequently altered. Consequently, the assessment of the ventricular function using conventional echocardiography is challenging, because most of the volumetric measurements are based on geometrical assumptions [16]. The Doppler-derived Tei index as well as 2-D STE and TAPSE do not need geometrical assumptions and might, therefore, be useful in this clinical setting to reflect the global and regional ventricular function.

Before the initiation of bosentan therapy, the RV function was significantly reduced as compared to published normal values [8]. Altered regional and global RV function in Eisenmenger patients is not surprising and can be explained by the chronic long-term pressure overload, leading to RV hypertrophy and maladaptive RV response with extracellular matrix accumulation, activation of apoptotic pathways and pro-inflammatory cytokines [17].

After a 24 weeks of bosentan therapy, improvement of the longitudinal function of the right ventricle can be concluded from our data, supported by the marginal improvement of the TAPSE, the mean longitudinal strain of the lateral wall of the right ventricle and reduction in the RV Tei index (Table 2). Data regarding effect of bosentan on the RV longitudinal function in Eisenmenger syndrome patients varies considerably in the literature. Kaya et al. [18] reported improvement of RV function under bosentan therapy. In contrast, Serino et al. [19] recently demonstrated that the longitudinal RV function assessed by TAPSE among patients with Down and Eisenmenger syndrome has not significantly changed under bosentan therapy although that the exercise capacity has been greatly improved. One has to consider that bosentan therapy is indicated among Eisenmenger syndrome patients with NYHA functional class III–IV. These patients suffered from chronic ventricular pressure overload which leads to myocardial fibrosis [16]. Accordingly, the capacity of the reverse remodeling of the myocardium among such cohort is limited. This would explain the minimal improvement of RV deformation seen among our patients under bosentan therapy. Nevertheless, these minimal changes were reflected greatly on their exercise performance and NT-proBNP level.

Data regarding the effect of bosentan on left ventricular function are sparse. Schulze-Neick et al. [20] reported an improvement in the systolic LV ejection fraction, which did not reach statistical significance. Kaya et.al [18] reported among 23 patients a slight improvement in the longitudinal LV ejection fraction. The present study with a larger number of patients with Eisenmenger syndrome confirms the trend in LV systolic function improvement previously noticed by others [18, 20], since LV mean strain was significantly increased under bosentan therapy (Table 2). Moreover, the filling period (diastolic time) was significantly prolonged under bosentan therapy (Table 2), reflecting additional improvement of LV diastolic function and such significant improvement of LV systolic and diastolic functions was reflected on the Tei index which showed a highly significant reduction under bosentan therapy (Table 2).

The observed exercise performance in the present study is not surprising and might reflect the improved ventricular performance. The observed improvement in the exercise performance was even more than that reported by Galie et al. [3]. Such difference might be related to the relatively younger age of the patients included in the present study. In addition, the majority of the studied patients had Eisenmenger syndrome secondary to a post-tricuspid valve defect. In such clinical setting the right ventricular function remains initially preserved due to the persistent "training effect" from fetal life on, when equality in systemic and pulmonary pressure exists and consequently the right and left ventricular thickness, muscle mass and force development are similar [17]. Interestingly, the present study observed a drop in the hemoglobin level under bosentan therapy. Reductions in blood viscosity have been demonstrated to improve ventricular–vascular interaction by enhanced ventricular systolic function determining a significant increase in ventricular strain and marked improvement in exercise performance [21].

Data regarding the effect of bosentan on the pulmonary hemodynamics are contradictive [3, 4, 20]. In the present study, the Rp:Rs drops only marginally under bosentan therapy but the decrease did not reach significance (Table 4). A borderline improvement of the pulmonary vascular resistance cannot be the only cause of the obvious clinical, echocardiographic and laboratory improvement observed in the present study, as well as in other studies [3, 4, 20]. Accumulating evidence indicates that elevated endothelin levels induce adverse remodelling and cause progressive aggravation of congestive heart failure by reducing coronary flow, direct chronotropism, growth effects on cardiac myocytes and interaction with other neurohormonal systems [22–24]. Bosentan can improve the cardiac reverse remodeling by blocking the action of

endothelin [25–28]. In contrast to these promising studies, the endothelin antagonisim with bosentan and lowering of events (ENABL) study was prematurely stopped, due to unexpected increases of adverse events, without improvements in clinical status [29]. We attribute the differences in our results from ENABL study to the different underlying mechanism of heart failure. Patients included in the present study initially suffered from systemic to pulmonary shunt which consequently leads to variable degree of ventricular volume and pressure overload and eventually to myocardial hypertrophy and fibrosis [17]. In addition, none of our patients received ACE inhibitors and β-blockers, accordingly we may assume that the neurohormonal systems were not already blocked in our patients, making the blocking effect of bosentan most likely more obvious to translate the reverse remodeling into clinical and functional improvement. A clear benefit of treatment with bosentan might have also emerged in the ENABL study [29] if congestive heart failure patients with raised pulmonary arterial pressures were only included.

Effect of bosentan on atrial performance

Before initiation of bosentan therapy, a highly significant negative correlation was observed between the NT-proBNP and the right atrial PALS (Fig. 2) and to a lesser extent with RV systolic mean strain. This can be explained by the data reported from previous studies on molecular level demonstrating that endothelin-1 participates in the mechanical stretch-induced expression of BNP and directly stimulates the release of BNP by the atrial myocytes [30, 31]. In favor of this hypothesis, the correlation obtained in the present study between the invasively measured RAP at baseline and NT-proBNP. Accordingly, we conclude that NT-proBNP is a good biological marker that reflects the right atrial reservoir function which is mainly determined by the RV longitudinal systolic function.

Under bosentan therapy, the RA PALS and PACS (Table 3) were significantly improved, indicating that patients with bosentan therapy may exert an improvement in the RA reservoir and pump function (Table 3). In contrast, unexpectedly the LA PALS was not significantly increased although the systolic function of the LV had improved (Table 3). This might be explained by an interatrial interaction, that is, the distended RA hampers adequate filling and pumping of the LA. Further comparative studies using magnetic resonance imaging (MRI) are needed to support this hypothesis.

Prediction of best responders to bosentan therapy

In the present study NT-proBNP was used to determine best responders. N-terminal pro-B-type natriuretic peptide (NT pro-BNP) is a relatively new, but well-established biological marker in assessing heart failure [32] and can reflect an improvement in the severity of PHT in Eisenmenger syndrome patients [33]. Moceri et al. [15] demonstrated that NT-proBNP can be applied to predict clinical outcome in Eisenmenger syndrome when combined with echocardiographic parameters. Interestingly, our echocardiography derived data showed that the evaluation of atrial rather than ventricular performance is more promising in predicting laboratory responders. Initially, this might sound paradoxical and unexpected; however, the close correlation between NT pro-BNP and atrial performance on the clinical and molecular level, as mentioned and discussed above might be a possible explanation. In addition, in this group of patients with limited window scanning, functional assessment of the hypertrophied, but in shape less altered atria is much easier than scanning and assessment of much altered ventricles, making the data derived from atria more robust. We, therefore, suggest that scanning and interpretation of the atria might be a good alternative to obtain more reliable information about patients' overall condition.

Limitations

The number of patients with pre-tricuspid valve lesions was small (3/40); accordingly we could not compare patients who have a right ventricle not conditioned to chronic pressure overload to those with post-tricuspid valve lesions and conditioned RV.

STE derived strain is still considered a new parameter and certainly not used routinely in the clinical praxis. However, an increasing number of studies have confirmed its diagnostic and prognostic value, particularly in characterizing latent myocardial changes, which cannot be detected by conventional methods [9, 18]. Comparative studies using the gold standard MRI are warranted in the future to confirm the improvement on ventricular level under bosentan therapy.

For evaluation of atrial function, we used the novel speckle derived strain. Tracking the thin walled atria requires reduction of the width of the ROI, which may result in reduction in the lateral resolution of the technique and convert it into an angle dependent one. In pulmonary hypertension, the atrial wall is hypertrophied; accordingly not much reduction of the ROI width is required, which will consequently improve the speckle tracking technique.

Conclusion

In adult patients with Eisenmenger syndrome and chronic myocardial hypertrophy, bosentan therapy improves

ventricular and atrial functions resulting in enhancement of physical exercise and reduction of the NT-proBNP level while the pulmonary vascular resistance does not change substantially.

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Conflict of interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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