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Duration of right ventricular contraction predicts the efficacy of bosentan treatment in patients with pulmonary hypertension

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Aims In patients with pulmonary hypertension (PH), elevated endothelin-1 levels are associated with prolonged duration of right ventricular (RV) contraction, which induces leftward ventricular septal bowing with impaired left diastolic filling. We hypothesized that baseline RV contraction duration predicts efficacy of endothelin receptor antagonist, bosentan.

Methods and results Eighteen PH patients (age 57, range 35–79 years, 33% male) received bosentan. Six minute walk distance (6-MWD) and echocardiography were performed at baseline and after 1 year follow-up. After 1 year of treatment, 6-MWD increased (mean 60 ± 41 m) in 67% of patients (responders). Baseline RV contraction duration was longer in responders, compared with non-responders (612 ± 66 vs. 514 ± 23 ms; $P < 0.01$). A baseline RV contraction duration >550 ms was associated with improved 6-MWD (sensitivity 83%, specificity 83%; $P < 0.01$).

Conclusion An improvement of 6-MWD during bosentan treatment was associated with a decrease in RV contraction duration and could be predicted by a baseline RV contraction duration >550 ms.

Introduction

Pulmonary hypertension (PH) is a progressive disease characterized by elevated endothelin-1 levels associated with vasoconstriction and structural changes in the pulmonary vascular bed.[1,2] In addition, it has been demonstrated that in patients with PH, the duration of right ventricular (RV) contraction[3] is prolonged resulting in leftward ventricular septal bowing and impaired left ventricular (LV) early diastolic filling.[4–6] Prolongation of RV contraction duration is associated with elevated endothelin-1 levels.[7–9]

Recently, it has been demonstrated that treatment with an endothelin receptor antagonist (bosentan) results in reverse remodelling of the pulmonary vascular wall leading to a decrease in pulmonary vascular resistance.[10] Moreover, bosentan treatment resulted in a reduction of contraction duration leading to a reduction of leftward ventricular septal bowing and an improvement of LV early diastolic filling.[11] Consequently, bosentan treatment improves haemodynamics, 6 min walk distance (6-MWD), and survival in patients with various forms of PH.[10,12–20] The 6-MWD is frequently used in clinical practice to assess response to therapy in PH. As an intermediate endpoint, the distance walked may translate to the ability to perform activities of daily living, exercise capacity, and quality of life in PH patients.[21] However, not all patients with PH show improvement of 6-MWD during treatment, and predictors for efficacy of bosentan treatment have not yet been identified.[12,16,19,22] Therefore, the present study was designed to test the following hypotheses: (i) RV contraction duration at baseline is a predictor of improvement in exercise

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capacity and (ii) RV contraction duration shortening during treatment is associated with an increase in exercise capacity.

Methods

Patients

In this retrospective open-label study, we analysed adult patients with pulmonary arterial hypertension associated with congenital heart disease ($n = 9$) and patients with chronic thromboembolic PH ($n = 9$). Excluded were patients with Down syndrome, obstruction of the RV outflow tract, pulmonary valve or pulmonary arteries, or patients who were under treatment with prostacyclin, glibenclamide, or cyclosporin. Patients were examined at baseline prior to treatment and re-examined after 1 year follow-up. A 12-lead surface ECG was recorded of all patients. In patients with congenital heart disease, pulmonary arterial hypertension was diagnosed by echocardiography (systolic pulmonary arterial pressure $>$40 mmHg).[23] The diagnosis chronic thromboembolic PH was established with pulmonary angiography and right heart catheterization (mean pulmonary arterial pressure $>$25 mmHg).[24] To compare pulmonary arterial pressure between patients with pulmonary arterial hypertension associated with congenital heart disease and patients with chronic thromboembolic PH, we used systolic pulmonary arterial pressure estimated by echocardiography.

Exercise capacity

The 6-MWD was the primary endpoint and was measured at baseline and after 1 year of bosentan treatment, according to the guidelines of the American Thoracic Society with continuous pulse oximetry.[25] To avoid the effect of a learning curve, the 6-MWD at baseline was measured twice; the second 6-MWD was used as baseline value in the analysis. Patients with an increase in 6-MWD during bosentan treatment were defined as responders.

Echocardiography

All patients underwent an echocardiographic examination at baseline and after 1 year follow-up. All echocardiographic images were acquired and recorded digitally, and analysed offline. Parasternal and apical views were obtained according to the recommendations of the American Society of Echocardiography.[26] Pulsed and colour-coded tissue Doppler imaging recordings were obtained from an apical four-chamber view. All studies were analysed by a single observer who was blinded to clinical information.

From the apical four-chamber view, LV and RV end-diastolic area,[11] tricuspid annular plane systolic excursion, and tricuspid regurgitation jet were analysed. Left ventricular and RV end-diastolic areas were indexed by body surface area. Tricuspid annular plane systolic excursion was measured by M-mode at the junction of the RV free wall and tricuspid valve annular plane in the apical view. The peak velocity of the tricuspid regurgitation jet was used to calculate systolic pulmonary arterial pressure.[11] The RV fractional area change was calculated from the RV end-diastolic and end-systolic areas.[11] Cardiac output was determined from pulsed-wave measurements of the LV outflow tract velocity profile and LV outflow tract diameter. The eccentricity index was obtained to determine the degree of leftward ventricular septal displacement, and was calculated as the perpendicular ratio of two short-axis diameters measured at early diastole.[27] The minimum diameter of the inferior vena cava during respiration was measured from subcostal images.[11]

Tissue Doppler imaging parameters were measured offline. Colour-coded myocardial velocities were recorded with a 5 mm sample volume at the basal level of the RV free wall. TEI index,[28] LV and RV early diastolic relaxation velocities,[11] and LV and RV contraction duration were analysed. Right ventricular contraction duration was measured from the onset of the QRS complex to the onset of early diastolic filling of the RV (*E*), as shown in *Figure 1*. Right ventricular contraction duration was corrected for heart rate.[3]

Treatment

Bosentan was initiated at a dose of 62.5 mg twice daily, which was doubled after 4 weeks unless elevated liver enzymes were observed. Liver enzymes, serum bilirubin, and haemoglobin levels were monitored monthly. According to the bosentan summary of product characteristics, the standard threshold for liver function abnormality of $>$3 times upper limit of normal was applied.

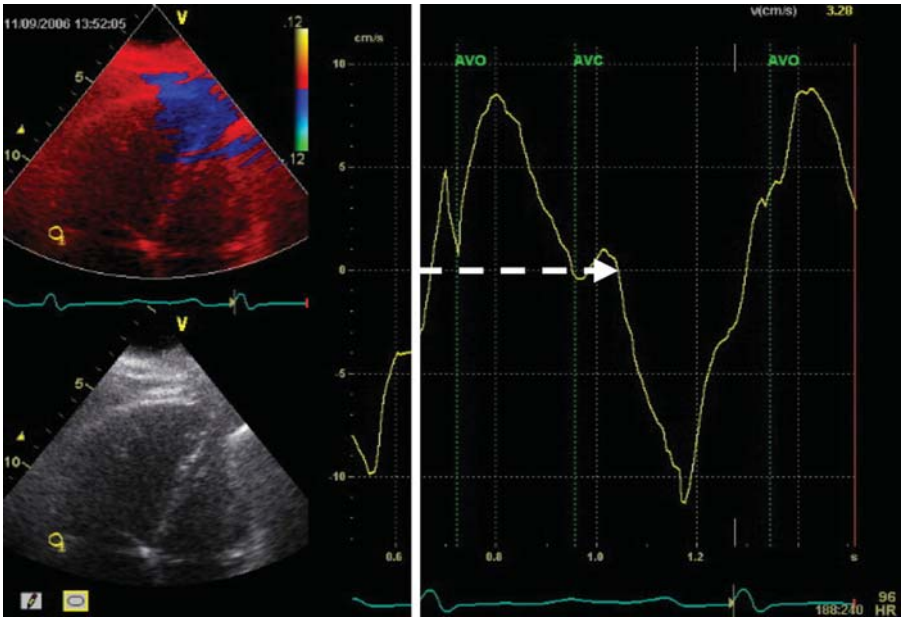

Figure 1 Measurement of right ventricular (RV) contraction duration. Right ventricular contraction duration using tissue Doppler imaging is measured as the time interval between onset of QRS and onset of RV early diastolic relaxation. Dotted arrow represents RV contraction duration.

Statistical analysis

The descriptive data are presented as mean with standard deviation if normally distributed or as median with range as appropriate. Changes from baseline to 1 year were evaluated with a paired *t*-test for continuous variables (and with Wilcoxon's rank-sum test for categorical variables). Comparisons between responders and non-responders were performed by independent samples *t*-testing (two-tailed). Linear regression analysis was used to assess the relation between change in 6-MWD and age and echocardiographically measured parameters. Multivariate analysis of change in 6-MWD, age, and RV contraction duration was used to assess contributing parameters. Receiver operating characteristics were constructed using any increase in 6-MWD as response variable. A value of $P < 0.05$ was considered to be significant.

Results

Baseline characteristics

Eighteen patients (nine patients with pulmonary arterial hypertension associated with congenital heart disease and nine patients with chronic thromboembolic PH) were treated with bosentan for at least 1 year. *Table 1* shows the baseline characteristics of these 18 patients (mean age 57 years, range 35–79 years, 33% males). Underlying diagnoses of the patients with pulmonary arterial hypertension associated with congenital heart disease were ventricular septal defect ($n = 5$), atrial septal defect ($n = 3$), and patent ductus arteriosus ($n = 1$). Of these patients, two patients had persistent pulmonary arterial hypertension after previous device closure of their septal defect (a ventricular septal defect and an atrial septal defect, respectively), and seven patients (78%) had the Eisenmenger syndrome. Among the chronic thromboembolic PH patients, six patients had distal, inoperable chronic thromboembolic PH and three patients had persistent PH, diagnosed 7–12 months after pulmonary endarterectomy.

Effects of treatment

Induction of oral bosentan therapy was well tolerated, without signs of decreasing oxygen saturation. In one patient with pulmonary arterial hypertension associated with congenital heart disease, an asymptomatic increase in liver transaminases (>3 times upper limit of normal) was observed which resolved within 2 weeks after dose reduction, whereupon the 125 mg twice-daily dose was resumed without reoccurrence of the problems.

After 1 year bosentan treatment, 12 patients (67%) showed an improvement in 6-MWD (responders) by a mean of 60 ± 41 m, whereas 6-MWD decreased in six patients (non-responders) by a mean of -24 ± 24 m. Among the responders, seven patients had pulmonary arterial hypertension associated with congenital heart disease (mean increase 44 ± 19 m; $P = 0.001$) and five patients had chronic thromboembolic PH (mean increase 83 ± 54 m; $P = 0.03$). At baseline, responders were younger (mean age 52 ± 11 vs. 68 ± 11 years; $P = 0.01$) (*Table 1*), had a higher mean systolic pulmonary arterial pressure (89 ± 21 vs. 64 ± 19 mmHg; $P = 0.03$), and had a longer RV contraction duration (612 ± 66 vs. 514 ± 23 ms; $P < 0.01$) compared with non-responders, as shown in *Table 2*.

Analyses of the RV tended to demonstrate on average a decrease in RV contraction duration after 1 year bosentan treatment in the responders from 612 ± 66 ms at baseline to 566 ± 77 ms ($P = 0.1$). The minimum diameter of the inferior vena cava decreased significantly ($P = 0.03$). Conversely, other echocardiographic measurements of the RV, e.g. systolic pulmonary arterial pressure, RV fractional area change, tricuspid annular plane systolic excursion, and TEI index, remained unchanged during follow-up in the responders. Analyses of the LV at baseline and after 1 year bosentan treatment showed a significant increase in LV end-diastolic area index in the responders from 11.0 ± 2 to 12.2 ± 2 cm^2/m^2 ($P = 0.04$), together with a significant increase of LV early diastolic relaxation velocity (from 6.7 ± 2 to 8.1 ± 2 cm/s; $P = 0.02$). In *Table 2*, echocardiographic parameters at baseline and after 1 year bosentan treatment are shown for all 18 patients.

Predictors of response

Using linear regression analyses, change in 6-MWD in all 18 PH patients was associated with age ($R = 0.5$, $P = 0.04$) and RV contraction duration at baseline ($R = 0.8$, $P < 0.01$).

Table 1 Baseline characteristics

	Total ($n = 18$)	Responders ($n = 12$)	Non-responders ($n = 6$)	*P*-value
Age (years)	57 (35–79)	52 (35–73)	68 (55–79)	0.01
Gender, male, *n* (%)	6 (33)	3 (25)	3 (50)	0.3
CHD, *n* (%)	9 (50)	7 (78)	2 (22)	0.3
Eisenmenger syndrome, *n* (%)	6 (67)	5 (83)	1 (17)	0.3
CTEPH, *n* (%)	9 (50)	5 (56)	4 (44)	0.3
Six minute walk distance (m)	416 ± 116	430 ± 108	390 ± 136	0.5
Oxygen saturation (%)	89 ± 7	88 ± 9	92 ± 8	0.4
sPAP (mmHg)	81 ± 23	89 ± 21	64 ± 19	0.03
NYHA classification				
NYHA II, *n* (%)	2 (11)	1 (8)	1 (17)	0.6
NYHA III, *n* (%)	16 (89)	11 (92)	5 (83)	0.6
QRS (ms)	111 ± 21	110 ± 20	120 ± 20	0.5
QTc (ms)	404 ± 41	407 ± 40	398 ± 49	0.7

Data are presented as mean with standard deviation if normally distributed or as median with range as appropriate.

Comparisons among the responders and non-responders were performed using an independent *t*-test. CHD, congenital heart defect; CTEPH, chronic thromboembolic pulmonary hypertension; sPAP, systolic pulmonary arterial pressure; QRS, QRS duration; QTc, QTc duration.

Table 2 Echocardiographic parameters pre- and post-bosentan treatment

Parameters	Responders ($n = 12$)			Non-responders ($n = 6$)		
	Pre	Post	*P*-value	Pre	Post	*P*-value
Left ventricle (LV)						
LV ED area index (cm^2/m^2)	11.1 ± 2	12.2 ± 2.1	0.04	13.3 ± 2.3	13.1 ± 3.2	0.8
TVI LVOT index (cm/m^2)	10.6 ± 3.6	11.1 ± 2.7	0.7	11.6 ± 2.1	13.7 ± 3.1	0.1
CI, LV ($L/min/m^2$)	2.8 ± 0.9	3.0 ± 0.6	0.5	3.0 ± 0.8	3.8 ± 1.1	0.06
SV index (mL/m^2)	33 ± 7	38 ± 12	0.2	39 ± 9	41 ± 13	0.6
LV E′ (cm/s)	6.7 ± 2	8.1 ± 2.0	0.02	6.6 ± 4	8.6 ± 3	0.05
LV contraction duration (ms)	571 ± 64	542 ± 45	0.4	503 ± 19	520 ± 60	0.6
Eccentricity index	2.1 ± 0.3	1.8 ± 0.3	0.07	1.6 ± 0.6	1.7 ± 0.7	0.9
Right ventricle (RV)						
RV ED area index (cm^2/m^2)	13.5 ± 5	13.2 ± 4.0	0.6	11.4 ± 2	11.1 ± 3	0.6
TVI RVOT index (cm/m^2)	6 ± 1.3	7.3 ± 1.4	0.001	7.3 ± 2.9	7 ± 1.5	0.6
RV E′ (cm/s)	5.9 ± 2	6.9 ± 2	0.1	4.5 ± 2	5.2 ± 3	0.7
RV contraction duration (ms)	612 ± 66	566 ± 77	0.1	514 ± 23	541 ± 68	0.5
sPAP (mmHg)	89 ± 21	86 ± 23	0.7	64 ± 19	63 ± 22	0.8
TAPSE (mm)	19 ± 6	20 ± 5	0.5	16.9 ± 5	18.1 ± 8	0.6
TEI index	0.5 ± 0.1	0.5 ± 0.1	0.9	0.5 ± 0.1	0.5 ± 0.2	0.9
FAC	31.9 ± 11.4	31.6 ± 11.3	0.9	38 ± 12	38 ± 15.9	0.9
IVC minimum diameter (cm)	1.2 ± 0.5	0.8 ± 0.5	0.03	0.54 ± 0.4	0.8 ± 0.4	0.4

Data are presented as mean with standard deviations; ED, end diastolic; TVI, time velocity integral; LVOT, left ventricular outflow tract; CO, cardiac output; SV, stroke volume; E′, early diastolic filling; RVOT, right ventricular outflow tract; sPAP, systolic pulmonary arterial pressure; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion; FAC, right ventricular fractional area change; IVC, inferior vena cava.

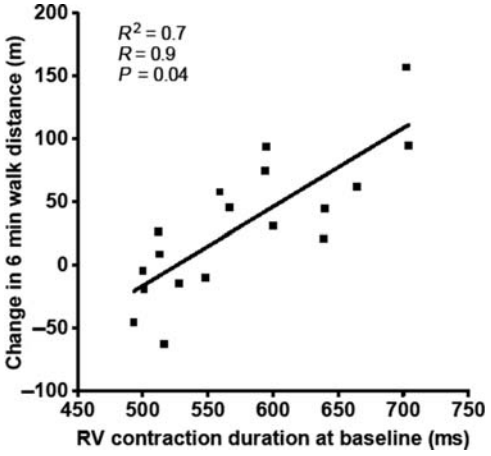

Figure 2 Relation between right ventricular (RV) contraction duration at baseline and change in 6 min walk distance (6-MWD) after 1 year bosentan treatment, adjusted for age, change in RV contraction duration, and change in left ventricular eccentricity index. Right ventricular contraction duration at baseline is positively related with change in 6-MWD ($R = 0.9$; $P = 0.04$). RV, right ventricle.

Moreover, change in 6-MWD was also associated with change in RV contraction duration ($R = -0.6$, $P = 0.02$) and change in LV eccentricity index ($R = -0.7$, $P = 0.003$) after 1 year of bosentan treatment. The other echocardiographically measured parameters at baseline had no contributing effect on change of 6-MWD. In multivariate analysis, RV contraction duration at baseline remained an independent predictor for change in 6-MWD ($\beta = 0.9$; $P = 0.04$) (*Figure 2*).

The optimal cut-off value of RV contraction duration at baseline to predict an increase of 6-MWD was 550 ms. In the receiver operating characteristics, we found an area under the curve of 0.92 ($P = 0.005$) with a sensitivity of 83% and a specificity of 83%.

Discussion

In the present study, we demonstrated that in patients with pulmonary arterial hypertension associated with congenital heart disease and in patients with chronic thromboembolic PH, the beneficial treatment effect of bosentan, i.e. the improvement of 6-MWD, was related with change in RV contraction duration. The main finding of the present study is that RV contraction duration at baseline is an independent predictor for response. A baseline RV contraction duration >550 ms was associated with an improvement of exercise capacity after 1 year bosentan treatment.

In patients with PH, endothelin-1 levels are elevated.[1,2] Bosentan (an endothelin receptor antagonist) has been shown to counteract endothelin-1-induced vasoconstriction, cell proliferation, and migration.[1] Bosentan treatment may result in reverse remodelling of the pulmonary vascular wall leading to a decrease in pulmonary vascular resistance, a decline in RV end-diastolic area index, and an improvement of RV contractility.[1,11,29] In our study, improvement of 6-MWD was present in 67% of the patients. However, treatment resulted neither in a decline of RV end-diastolic area index nor in an improved RV contractility (as assessed by RV fractional area change and tricuspid annular plane systolic excursion) nor in a decrease in systolic pulmonary arterial pressure. These results may suggest that beside a decrease of RV pressure overload, an additional mechanism might be responsible for the increase in exercise capacity during treatment with bosentan.

In this study, we showed that the beneficial treatment effect of bosentan, i.e. the improvement of 6-MWD, was significantly related to RV contraction duration at baseline.

In PH, prolonged RV contraction duration and leftward ventricular septal bowing are associated with LV impaired diastolic filling and reduced stroke volume according to the Frank–Starling mechanism.[4,11,30] In the present study, a RV contraction duration >550 ms was predictive for an increase in 6-MWD after bosentan treatment (sensitivity 83%, specificity 83%).

Elevated endothelin-1 levels, as can be found in PH, are associated with prolongation of action potential duration and RV contraction duration.[7–9] In patients with PH, Marcus *et al*.[4] found an association between prolongation of the RV contraction duration and interventricular dyssynchrony. Similarly, we found that RV contraction duration at baseline was prolonged in all patients. Conversely, endothelin-1 blockade results in normalization of action potential duration.[7,8] Additionally, bosentan treatment improves LV early diastolic filling and stroke volume in patients with PH, as reported by Galie *et al*.[11] Accordingly, we found that improvement in 6-MWD correlated with a reduction of RV contraction duration and leftward ventricular septal bowing (measured by eccentricity index). Consequently, we found a significant improvement of LV early diastolic relaxation and an increase of LV end-diastolic area index after 1 year bosentan treatment.

Our findings support the hypothesis that a positive effect of treatment with bosentan is not only due to a decrease in pulmonary vascular resistance[10] but also results from a decrease in RV contraction duration (*Figure 3*), due in part to a reduction in RV action potential duration.[31] Probably, both mechanisms contribute to the beneficial effect of bosentan and may occur concomitantly. Although treatment effect of bosentan is promising, the usefulness of echocardiography in assessing long-term response to treatment as well as acute changes in the clinical status of patients with PH is unknown.

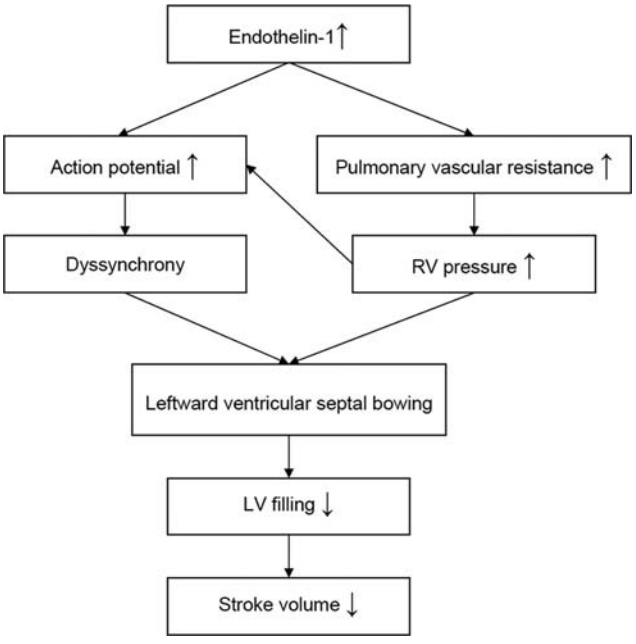

Figure 3 From elevated endothelin-1 levels to reduced stroke volume. Flowchart of the proposed mechanism by which elevated endothelin-1 levels results in leftward ventricular septal bowing, which relates to a decreased left ventricular early diastolic filling and a reduced stroke volume in patients with pulmonary hypertension.

Study limitations

First, patient numbers are limited. Owing to the small sample size, analysis in subpopulations could not be performed. Secondly, invasive measurements of haemodynamic parameters were not performed. However, echocardiography was shown to be a reliable method to non-invasively assess systolic pulmonary arterial pressure, and RV and LV systolic and diastolic functions in patients with PH. Additional studies in larger patient populations are needed to establish whether analysis of RV contraction duration may be used to identify patients who will benefit from bosentan treatment.

Conclusion

One year bosentan treatment resulted in an improved exercise capacity in 67% of the patients with pulmonary arterial hypertension associated with congenital heart disease and chronic thromboembolic PH patients. The improvement in 6-MWD was associated with a reduction of RV contraction duration and leftward ventricular septal bowing. A RV contraction duration >550 ms measured at baseline may be used to identify patients who may benefit from bosentan treatment.

Conflict of interest: none declared.

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