Treatment in patient with severe PAH-ASD -Set a treatment plan after hemodynamic evaluation following advanced Med.

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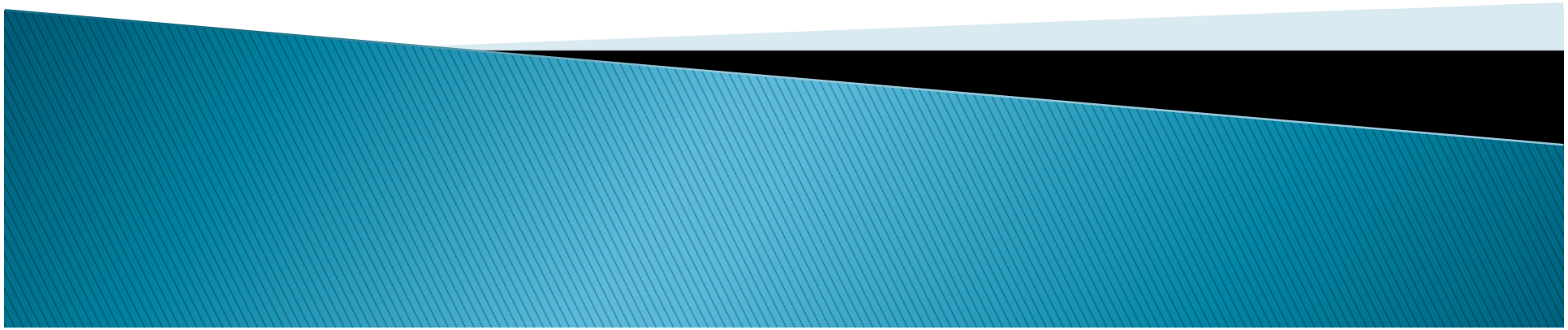

32yr/Male, ASD 2nd Large(28mm)

- Severe PAH

  Aortic Pressure 120/70(90)mmHg

  MPA pressure 95/50(70)mmHg

  Pressure Ratio of PA/Ao: 0.79(0.77)

  Rp 8.2 Wood unit/m^2 , Rp/Rs 0.33

- Normal sinus rhythm

Long term survival in PAH-ASD

Isolated atrial septal defect with pulmonary vascular obstructive disease — long-term follow-up and prediction of outcome after surgical correction

PETER M. STEELE, M.B.B.S. (HONS), VALENTIN FUSTER, M.D., MARC COHEN, M.D., DONALD G. RITTER, M.D., AND DWIGHT C. MCGOON, M.D.

ASD-PAH 40(6%) of 702 from 1953-78 at cardiac cath.

- PVR > 7U/m²
- 26 surgical closure(age 47yr)
- 14 medical treatment(44 year)
- F-U, median 12year

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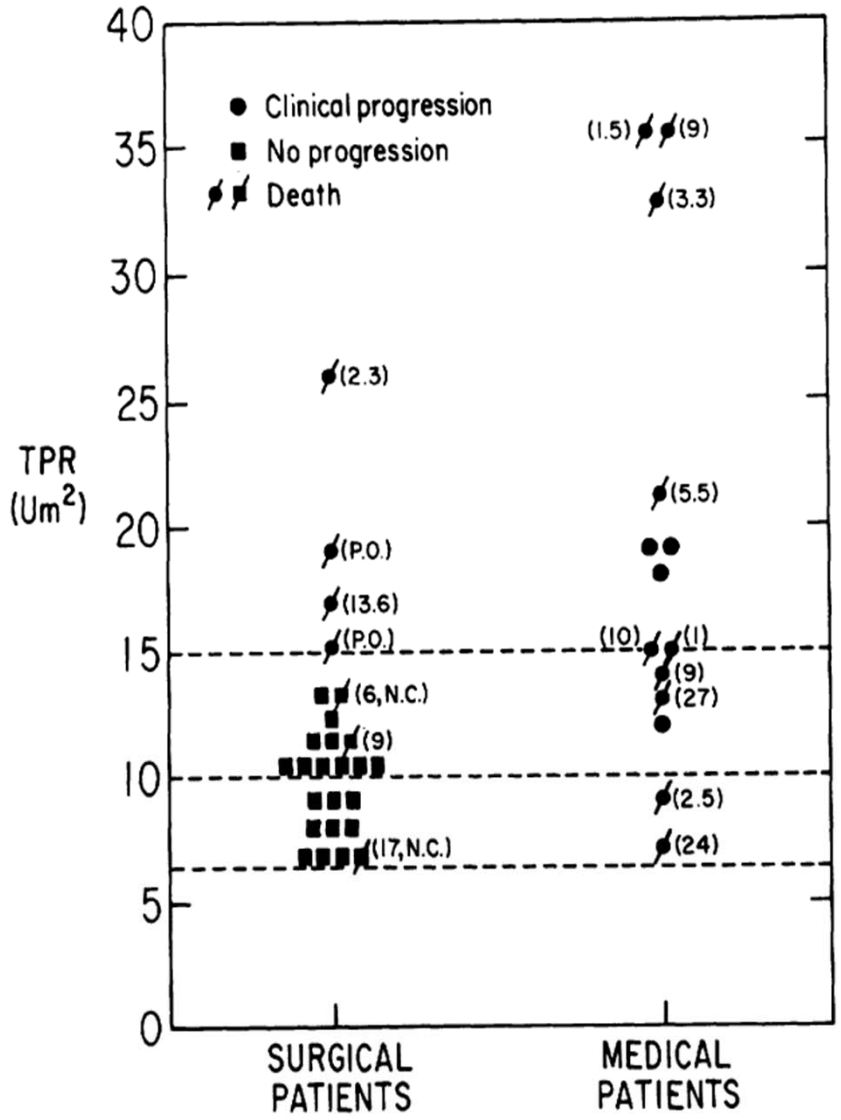
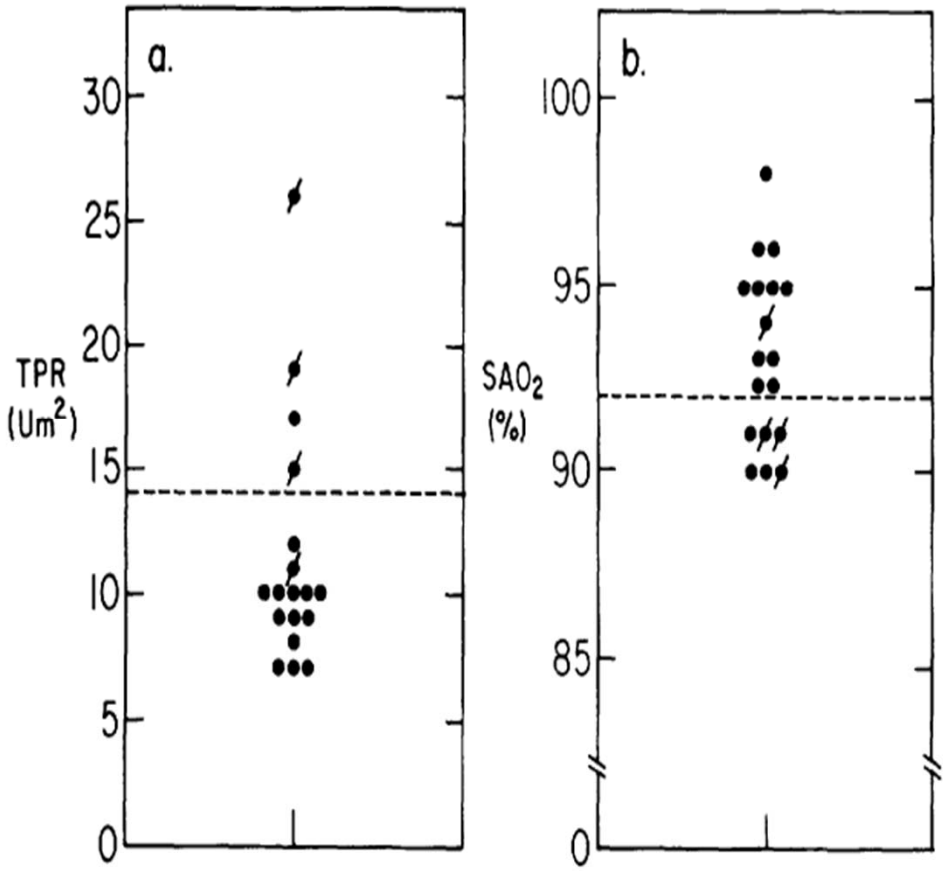
Circulation 76, No. 5, 1037–1042, 1987.

Cardiac catheterization data

	Medically treated patients (n = 14)		Surgically treated patients (n = 26)	
	Mean	Range	Mean	Range
Pulmonary arterial pressure (mm Hg)				
Peak	87	46–122	74	35–120
Mean	52	27–80	44	25–67
Total pulmonary resistance (U/m^2)	20	7–42	11	7–26
Pulmonary arteriolar resistance (U/m^2)	17	5–38	9	4–24
Ratio of pulmonary to systemic resistance	0.6	0.2–1.3	0.3	0.1–0.6
Ratio of pulmonary to systemic flow	1.2	0.5–1.8	1.8	1.1–2.8
Pulmonary arterial oxygen saturation (%)	73	61–81	82	70–88
Systemic arterial oxygen saturation (%)	88	76–95	93	90–98



Outcome of surgically treated patients



Univariate analysis of prognostic variables in surgically treated patients (n=26)

Factor	p value
Total pulmonary resistance	.0001
Pulmonary arteriolar resistance	.0001
Ratio of pulmonary to systemic resistance	.004
Systemic arterial oxygen saturation	.005
Pulmonary arterial oxygen saturation	.007
Ratio of pulmonary to systemic flow	.16
Mean pulmonary arterial pressure	.17
Age	.53

Approach to management according to PVR in ASD-PAH with predominant L to R shunt

- <10 U/m^2

  Should proceed to operation

- >15 U/m^2

  Operation is not advised

- 10-14 U/m^2

  Operation should probably be performed

Result of Surgical closure in 9 patients with ASD and PAH.

- Mean F-U 13.3 (4-25) year
- PVR before surgery 9 (3-12.7) U/m^2
- 2 death
- 1 deteriorated clinically with worsening FC await for transplantation
- 6 remained the same or improvement in symptoms or PAP

The Natural & modified history of CHD, Hospital for Sick Children Hospital, Toronto, Canada, 2004

Outcome of pecutaneous ASD closure in patients with PAH-ASD

Table 1 Baseline characteristics

Characteristics	Value
Total patients (n)	54
Age at time of device closure (years), mean (SD)	59 (15)
Female	41 (76)
History of left ventricular dysfunction	2 (4)
History of systemic hypertension*	14 (26)
History of atrial arrhythmia	12 (22)
Contributory causes of PAH†	10 (19)
NYHA functional class ⩾II	32 (59)
Echocardiographic data	
ASD diameter (mm), mean (SD)	18 (7)
ASD >2 cm	19 (35)
PAH according with RVSP	
Moderate PAH (50–59 mm Hg)	34 (63)
Severe PAH (⩾60 mm Hg)	20 (37)
Associated anomalies (VSD, severe PR)	2 (4)

Table 2 Echocardiographic changes during early and late follow-up

	Baseline (n = 54)	Early follow-up (n = 54)	p Value	Baseline (n = 39)	Late follow-up (n = 39)	p Value*
RVSP (mm Hg), mean (SD)	57 (11)	51 (17)	0.003	58 (10)	44 (16)	0.004
RV dilatation	52 (96)	50 (93)	0.84	38 (97)	14 (36)	<0.001
RV dysfunction†	22 (41)	17 (31)	0.015	26 (67)	9 (23)	<0.001
Residual shunt		7 (13)			4 (10)	

- Early F-U, 2.3± 1.2 month
- Late F-U, 31 ± 15month (2 patient died)

Balint et al. Heart 2008 (Canada)

Indication for intervention in ASD

for management of adults with CHD

Indications	Class[a]	Level[b]
Patients with significant shunt (signs of RV volume overload) and PVR <5 WU should undergo ASD closure regardless of symptoms	I	B[26]
Device closure is the method of choice for secundum ASD closure when applicable	I	C
All ASDs regardless of size in patients with suspicion of paradoxical embolism (exclusion of other causes) should be considered for intervention	IIa	C
Patients with PVR ≥5 WU but <2/3 SVR or PAP <2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy) and evidence of net L–R shunt (Qp:Qs >1.5) may be considered for intervention	IIb	C
ASD closure must be avoided in patients with Eisenmenger physiology	III	C

2010 ESC guideline

- May be considered in presence of net L-R shunting, PAP <2/3 systemic pressure, PVR <2/3 SVR, or when responsive to either pulmonary vasodilater therapy or test occlusion of defect.
- Class IIb, Level C

2008 AHA/ACC guideline

32yr/Male, ASD 2nd Large(28mm)

- PVR >5 Wood unit/m^2 (8.2) but PVR <2/3 SVR(0.33) or PAP <2/3 systemic pressure (0.79/0.77)
- And evidence of L-R shunt(Qp :Qs>1.5) ??

2010 ESC guideline(IIb, C)

- PVR >5 Wood unit/m^2 (8.2) but PVR <2/3 SVR(0.33)

Or PAP <2/3 systemic pressure (0.79/0.77)

Or evidence of L-R shunt(Qp :Qs>1.5) ??

Or Responsiveness to vasodilator or test occlusion??

2008 AHA guideline(IIb,C)

Introduction of targeted therapy in PAH

- Growing interest in pre-Eisenmenger syndrome
- inoperable based in order to remodel the pulmonary vascular bed and perform interventional or surgical correction

Primary vs. Advanced medical therapy for PAH-CHD

- Primary therapy

  Targeted of PAH symptoms

- Advanced therapy

  Directed PAH itself, at its underlying mechanism

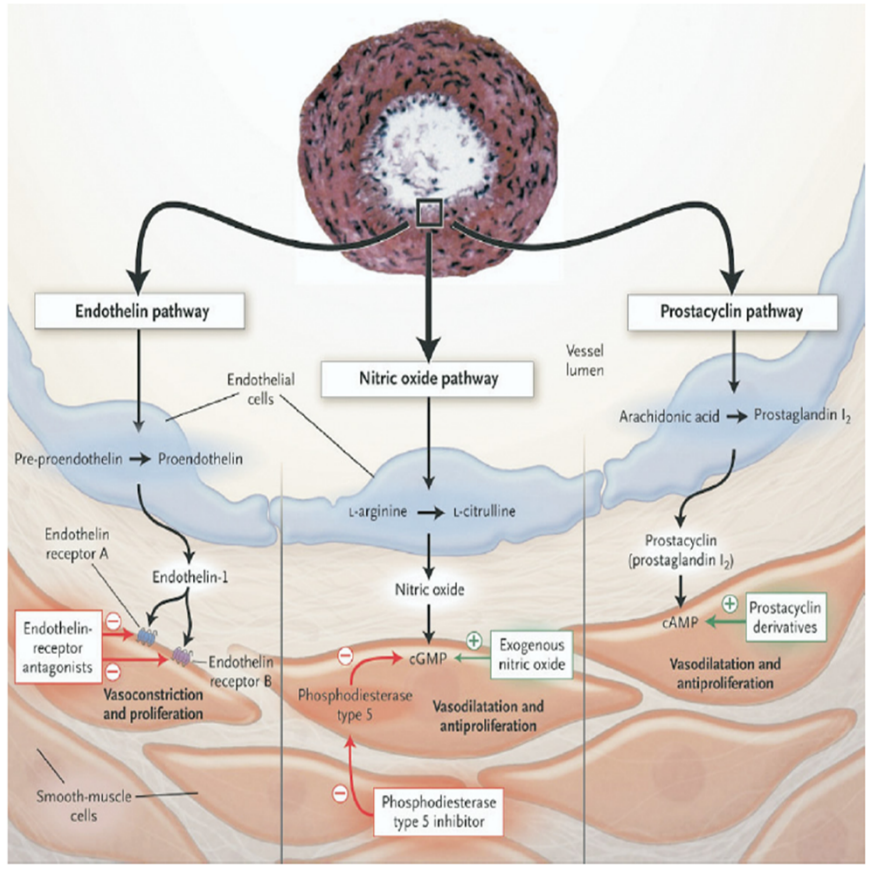


Figure 2 The 3 Pathophysiological Pathways in Pulmonary Arterial Hypertension

PAH studies reporting effect of bosentan in patients with PAH-CHD

First author	Design	Year	n	F/U (months)	Endpoint	Adverse effect
Galiè (BREATHE-5)	RCT	2006	54	4	Functional class; catheterization	LE; headache; dizziness; palpitations
Apostolopoulou	Prospective cohort	2007	21	28	Treadmill	Dizziness; flushing; hemoptysis
D'Alto	Prospective cohort	2007	22	12	6MWD; catheterization	Leg edema, LFT > 3UNL
Diller	Retrospective cohort	2007	18	24	6MWD	Death
Galiè (EARLY)	RCT	2008	32	6.5	6MWD; catheterization	Anemia, cardiac failure
Gatzoulis	Prospective cohort	2008	37	10	6MWD	LE; diarrhea; headache; AP; abortion
Berger	Post-hoc	2009	54	4	Catheterization	Angina pectoris
Diaz (BREATHE-5)	Prospective cohort	2009	10	25	6MWD	None
Duffels	Retrospective cohort	2009	58	22	Laboratory tests; 6MWD; MRI	Throat pain; LFT > 3UNL; death
Dimopoulos	Retrospective cohort	2010	50	48	Survival	–
Jing	Multicenter open-label trial	2010	34	6	6MWD; catheterization	–

Abbreviations: F/U, follow-up; PAH, pulmonary arterial hypertension; RCT, randomized controlled trials; 6MWD, 6 minute walking distance; MRI, magnetic resonance imaging; GI, gastrointestinal; LE, leg edema; AP, angina pectoris; LFT, liver function test; UNL, upper normal limits.

Vascula

Bosentan Therapy in Patien

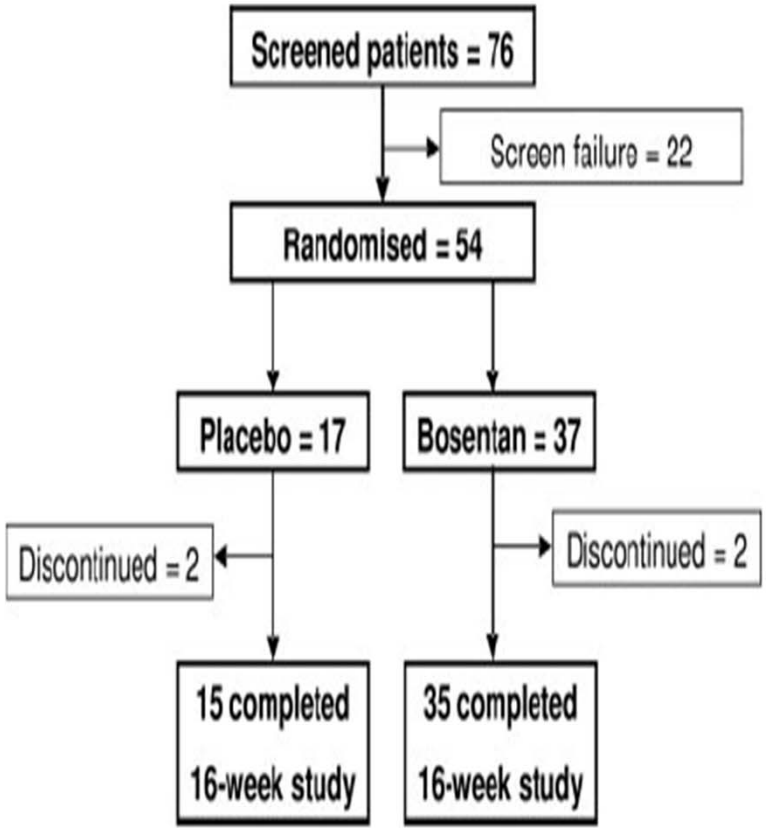


Figure 1. Disposition of the patients.

TABLE 1. Baseline Clinical, Functional, and Hemodynamic Characteristics of the Patients

Characteristic	Placebo (n=17)	Bosentan (n=37)
Female, n (%)	10 (59)	23 (62)
Age, y	44.2±8.5	37.2±12.0
Time from Eisenmenger syndrome diagnosis, y	20.5±13.0	23.7±13.6
Race, n (%)		
White	14 (82)	34 (92)
Asian	2 (12)	2 (5)
Other	1 (6)	1 (3)
Weight, kg	63±18	64±14
Type of congenital heart defect, n (%)		
Ventricular septal defects	12 (71)	24 (65)
Atrial septal defects	5 (29)	8 (22)
Ventricular+atrial septal defects	...	5 (14)
Previous or concomitant treatments, n (%)		
Antithrombotic agents	11 (65)	25 (68)
Diuretics	10 (53)	13 (35)
Calcium channel blockers	4 (24)	3 (8)
6-min walk distance, m	366.4±67.5	331.9±82.8
Systemic pulse oximetry, %	83.6±5.1	82.4±5.3
Hemodynamic variables*		
Heart rate, bpm	77.8±12.8	76.3±16.7
Mean pulmonary arterial pressure, mm Hg	72.1±19.4	77.8±15.2
Mean left atrial pressure,† mm Hg	6.5±3.6	8.1±3.5
Pulmonary flow index, $L \cdot min^{-1} \cdot m^{-2}$	2.0±0.5	1.9±1.1
Pulmonary vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	2870.0±1209.3	3425.1±1410.5
Mean systemic arterial pressure, mm Hg	93.9±17.3	90.7±14.6
Mean right atrial pressure, mm Hg	5.0±3.7	6.1±3.4
Systemic flow index, $L \cdot min^{-1} \cdot m^{-2}$	2.1±0.7	2.7±2.3
Systemic vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	3658.1±1428.8	3244.2±1447.0

TABLE 2. Hemodynamic Effects of Placebo and Bosentan at Week 16

Parameter	Change From Baseline		Treatment Effect	
	Placebo (n=17)*	Bosentan (n=37)*	(Bosentan−Placebo)	*P*
Heart rate, bpm	−0.8 (2.7)	−2.0 (1.9)	−1.2 (3.4)	0.7329
Mean pulmonary arterial pressure, mm Hg	0.5 (1.4)	−5.0 (1.6)	−5.5 (2.5)	0.0363
Mean left atrial pressure,† mm Hg	0.5 (1.2)	0.4 (0.6)	−0.2 (1.3)	0.8862
Pulmonary flow index, $L \cdot min^{-1} \cdot m^{-2}$	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.4675
Pulmonary vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	155.1 (134.0)	−316.9 (138.3)	−472.0 (221.9)	0.0383
Mean systemic arterial pressure, mm Hg	2.5 (2.2)	−3.8 (1.6)	−6.3 (2.8)	0.0282
Mean right atrial pressure, mm Hg	0.4 (0.9)	0.3 (0.5)	−0.1 (1.0)	0.9448
Systemic flow index, $L \cdot min^{-1} \cdot m^{-2}$	−0.2 (0.1)	0.9 (0.8)	1.1 (1.1)	0.2981
Systemic vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	378.9 (246.8)	−372.9 (244.6)	−751.8 (388.4)	0.0595

Atrial septal defects versus ventricular septal defects in BREATHE-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: A subgroup analysis ☆

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ABSTRACT

Background: Eisenmenger's syndrome (ES) is the most advanced form of pulmonary arterial hypertension related to congenital heart disease. Evolution of pulmonary vascular disease differs markedly between patients with atrial septal defects (ASD) versus ventricular septal defects (VSD), potentially affecting response to treatment. We compared the effects of bosentan and placebo in patients with isolated ASD (ASD subgroup) versus patients with isolated VSD or both defects (VSD subgroup).
Methods: Post-hoc analysis of a 16-week, multicenter, randomized, double-blind, placebo-controlled trial was performed. Fifty-four patients (13: ASDs, 36: VSDs, 5: VSD + ASD) were randomized to bosentan 62.5 mg bid for four weeks (uptitrated to 125 mg bid thereafter) or placebo. Main outcome measures were: indexed pulmonary vascular resistance (PVRi), exercise capacity, mean pulmonary artery pressure (mPAP), pulmonary blood flow index (Qpi), and changes in oxygen saturation (SpO_2).
Results: Placebo-corrected median (95% CI) treatment effects on PVRi were -544.0 dyn·s·cm^{-5} (-1593.8, 344.7) and -436.4 dyn·s·cm^{-5} (-960.0, 167.0) in the ASD and VSD subgroups, respectively. Effects of bosentan on exercise capacity and mPAP were similar in both subgroups. No changes in SpO_2 or Qpi were observed in either bosentan or placebo subgroups.
Conclusions: Improvements in exercise capacity and cardiopulmonary hemodynamics, without desaturation, were observed in ES patients with both ASDs and VSDs. Although not reaching statistical significance, improvements were similar to those in the BREATHE-5 analyses, suggesting that the location of septal defects is not a key determinant of treatment response. These data further support the use of bosentan for the treatment of ES, independent of shunt location.

Baseline clinical, functional and hemodynamic characteristics of the patients.

Congenital heart defect	ASD ($n=13$)	
Treatment	Bosentan	Placebo
Patients, n	8	5
Females, n (%)	8 (100.0)	4 (80.0)
Age, years (mean ± SD)	39.9 ± 16.9	49.4 ± 6.9
Weight, kg (mean ± SD)	57.0 ± 14.8	69.9 ± 25.4
Race, n (%)		
White	7 (87.5)	5 (100.0)
Asian	1 (12.5)	–
Hispanic	–	–
Other	–	–
SpO_2, % (mean ± SD)*	84.1 ± 6.0 ($n=7$)	83.0 ± 3.7 ($n=5$)
6MWD, m (mean ± SD)*	341.3 ± 55.2 ($n=8$)	380.6 ± 72.7 ($n=5$)
PVRi, $dyn \cdot s \cdot cm^{-5}$ (mean ± SD)*	2327.5 ± 827.7 ($n=8$)	2470.9 ± 692.3 ($n=5$)
mPAP, mm Hg (mean ± SD)*	62.1 ± 12.2 ($n=7$)	58.5 ± 12.1 ($n=4$)
Qpi, $L \cdot min^{-1} \cdot m^{-2}$ (mean ± SD)*	2.3 ± 1.3 ($n=7$)	1.6 ± 0.3 ($n=4$)
Patients receiving ≥1 previous /concomitant medication, n (%)	8 (100.0)	5 (100.0)
Calcium channel blockers	1 (12.5)	3 (60.0)
Cardiac glycosides	2 (25.0)	2 (40.0)
Diuretics		
High ceiling	3 (37.5)	3 (60.0)
Low ceiling	0 (0.0)	1 (20.0)
Antithrombotics	8 (100.0)	5 (100.0)
Oxygen	1 (12.5)	1 (20.0)

Table 2
Change from baseline to week 16 and placebo-corrected treatment effects within each treatment a

	ASD		
	Change from baseline		
	Bosentan	Placebo	Treatment effect
SpO_2, %	$n=7$	$n=5$	$n=12$
Median*	3.0 (0.0, 4.0)	2.0 (1.0, 3.0)	1.0 (−2.4, 10.6)
Mean†	2.7 ± 0.7	0.4 ± 2.4	2.3 (−2.6, 7.2)
PVRi, $dyn \cdot s \cdot cm^{-5}$	$n=8$	$n=5$	$n=13$
Median*	−38.6 (−662.1, 298.2)	502.9 (396.7, 700.7)	−544.0 (−1593.8, 344.7)
Mean†	−83.1 ± 297.5	458.9 ± 174.0	−542.0 (−1434.4, 350.3)
6MWD, m	$n=8$	$n=5$	$n=13$
Median*	26.0 (−6.3, 33.8)	−5.5 (−9.5, 2.5)	32.5 (−16.3, 325.5)
Mean†	24.9 ± 15.8	−64.8 ± 67.1	89.7 (−32.3, 211.8)
mPAP, mm Hg	$n=7$	$n=4$	$n=11$
Median*	−5.0 (−19.0, 2.0)	6.5 (2.0, 7.0)	−9.0 (−26.6, 1.1)
Mean†	−6.7 ± 4.0	4.5 ± 2.2	−11.2 (−24.0, 1.6)
$Qpi, L \cdot min^{-1} \cdot m^{-2}$	$n=7$	$n=4$	$n=11$
Median*	0.0 (−0.5, 0.5)	−0.0 (−0.2, 0.1)	0.0 (−0.6, 0.8)
Mean†	0.0 ± 0.2	−0.1 ± 0.1	0.1 (−0.6, 0.7)

PULMONARY HYPERTENSION

Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect

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Background: Oral bosentan is an established treatment for pulmonary arterial hypertension (PAH).
Objective: To evaluate safety, tolerability, and clinical and haemodynamic effects of bosentan in patients with PAH related to congenital heart disease (CHD).
Patients: 22 patients with CHD related PAH (8 men, 14 women, mean (SD) age 38 (10) years) were treated with oral bosentan (62.5 mg×2/day for the first 4 weeks and then 125 mg×2/day).
Main outcome measures: Clinical status, liver enzymes, World Health Organisation (WHO) functional class, resting oxygen saturations and 6-min walk test (6MWT) were assessed at baseline and at 1, 3, 6, and 12 months. Haemodynamic evaluation with cardiac catheterisation was performed at baseline and at 12 month follow-up.
Results: 12 patients had ventricular septal defect, 5 atrioventricular canal, 4 single ventricle, and 1 atrial septal defect. All patients tolerated bosentan well. No major side effects were seen. After a year of treatment, an improvement was seen in WHO functional class (2.5 (0.7) *v* 3.1 (0.7); $p<0.05$), oxygen saturation at rest (87 (6%) *v* 81 (9); $p<0.001$), heart rate at rest (81 (10) *v* 87 (14) bpm; $p<0.05$), distance travelled in the 6MWT (394 (73) *v* 320 (108) m; $p<0.001$), oxygen saturation at the end of the 6MWT (71 (14) *v* 63 (17%); $p<0.05$), Borg index (5.3 (1.8) *v* 6.5 (1.3); $p<0.001$), pulmonary vascular resistances index (14 (9) *v* 22 (12) WU m^2; $p<0.001$), systemic vascular resistances index (23 (11) *v* 27 (10) WU.m^2; $p<0.01$), pulmonary vascular resistances index/systemic vascular resistances index (0.6 (0.5) *v* 0.9 (0.6); $p<0.05$); pulmonary (4.0 (1.3) *v* 2.8 (0.9) l/min/m2; $p<0.001$) and systemic cardiac output (4.2 (1.4) *v* 3.4 (1.1) l/min/m2; $p<0.05$).
Conclusions: Bosentan was safe and well tolerated in adults with CHD related PAH during 12 months of treatment. Clinical status, exercise tolerance, and pulmonary haemodynamics improved considerably.

See end of article for authors' affiliations

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Table 2 Demography and diagnosis in adult patients with CHD

Patients	22
Men:women	8:14
Age (years)	38 (10)
Follow-up (months)	12 (3)
Diagnosis:	
VSD	12
AVC	5
ASD	1
Single ventricle (complex)	4

ASD, atrial septal defect ; AVC, atrioventricular canal; VSD, ventricular septal defect.

Table 3 Clinical, haematological, and haemodynamic variables before and after oral bosentan treatment

	Basal	End of observation	p Value
Clinical status			
Sat art O_2 (%)	81 (9)	87 (6)	<0.001
HR (bpm)	87 (14)	81 (10)	<0.05
WHO functional class	3.1 (0.7)	2.5 (0.7)	<0.05
Exercise tolerance: 6MWT			
Travelled distance (m)	320 (108)	394 (73)	<0.001
HR at the end (bpm)	119 (17)	112 (24)	NS
Sat art O_2 at the end (%)	63 (17)	71 (14)	<0.05
Borg index	6.5 (1.3)	5.3 (1.8)	<0.001
Heart catheterisation pressure			
RA (mm Hg)	12 (4)	11 (3)	NS
sPAP (mm Hg)	106 (28)	105 (37)	NS
dPAP (mm Hg)	52 (8)	49 (16)	NS
mPAP (mm Hg)	73 (18)	71 (22)	NS
mCWP (mm Hg)	12 (3)	12 (4)	NS
mSAP (mm Hg)	84 (14)	83 (18)	NS
Blood flow			
QP ($l/m/m^2$)	2.8 (0.9)	4.0 (1.3)	<0.001
QS ($l/m/m^2$)	3.4 (1.1)	4.2 (1.4)	<0.05
QP/QS	0.9 (0.3)	1.0 (0.3)	NS
Vascular resistances			
PVRi ($WU.m^2$)	22 (12)	14 (9)	<0.001
SVRi ($WU.m^2$)	27 (10)	23 (11)	<0.01
PVRi/SVRi	0.9 (0.6)	0.6 (0.5)	<0.05

Reversal of Pulmonary Hypertension and Subsequent Repair of Atrial Septal Defect After Treatment With Continuous Intravenous Epoprostenol

Atrial septal defect closure in a patient with "irreversible" pulmonary hypertensive arteriopathy

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Abstract

The presence of irreversible pulmonary hypertension in patients with atrial septal defect (ASD) is thought to preclude shunt closure. We report the case of a woman with plexiform pulmonary arteriopathy secondary to an ostium secundum ASD who was able to successfully undergo percutaneous shunt closure following therapy with chronic intravenous prostacyclin (Flolan). One year after closure, the patient was weaned off Flolan over a period of 7 months following the institution of oral Bosentan therapy. Our case illustrates how aggressive vasodilator therapy with prostaglandins may be capable of reducing pulmonary artery pressure and permitting shunt closure in a patient once considered to have "inoperable" pulmonary arteriopathy.

Conclusion

- Some potential risk factor for intervention
- Usefulness/efficacy of intervention is less well established by evidence/opinion(IIb) and level of evidence C
- Advanced therapy and new drugs affecting pulmonary arteriolar matrix composition and smooth muscle tone are likely to play an important role in the treatment of this patients with PAH- ASD
- Set a Treatment Plan after hemodynamic evaluation following Advanced medical therapy(Treat and Intervention)