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Original Article

The effect of bosentan in patients with a failing Fontan circulation

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Abstract *Objectives:* To investigate the effect of bosentan in patients with a failing Fontan circulation. *Design:* A multicentric open label, non-controlled study. *Setting:* 5 tertiary care centres for congenital cardiology. *Patients:* We included 10 patients with a failing Fontan circulation. Their median age at inclusion was 12.12 years, with a range from 4.41 to 33,41 years. The median interval between the Fontan operation and inclusion was 7.84 years, with a range from 1.96 to 12,18 years. Participants received half the usual dose of bosentan for 4 weeks, and then the full dose for a further 12 weeks. *Main measures of outcomes:* We assessed saturations of oxygen at rest and during exercise, using a 6 minutes walk test, at baseline, and during and after 16 weeks of treatment. At each visit, we assessed blood chemistry and hepatic function, and asked the patients to complete a questionnaire concerning quality of life. All medical events and possible side effects were recorded. *Results:* Of the cohort, 1 patient withdrew. The changes in saturations of oxygen, exercise performance, and scores for the questionnaire did not reach statistical significance for the whole group. We noted, nonetheless, that saturations of oxygen and/or exercise capacity improved in 5 of the patients. This was further confirmed when those patients deteriorated again when the drug was discontinued. *Conclusions:* Our study failed to show significant improvement after 3 months of treatment with bosentan in a small group of patients with failing Fontan circulations. Some individuals, nonetheless, did improve. When planning larger trials, it would be better to identify those patients who might potentially benefit from the treatment prior to commencing the trial.

Keywords: Congenital heart defect; functionally single ventricle; endothelin receptor antagonist; pulmonary vascular resistance

For several decades now, the Fontan operation has been successfully used to palliate patients with functionally univentricular hearts. It is based on the principle that the systemic venous return can pass directly through the lungs without right ventricular contraction. Normalisation of arterial oxygen saturation can thus be achieved, albeit at the expense of increased systemic venous pressure and decreased cardiac output, especially during exercise. As the systemic venous blood flows passively through the lungs, the functionality of the Fontan circulation depends critically on three factors. The first is the presence of a well-developed pulmonary arterial system, with low pulmonary arterial resistance and no significant stenosis in the pulmonary arteries. The second is

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low atrial pressures, in the absence of significant atrioventricular valvar regurgitation and normal diastolic function. The third feature is good systolic function of the dominant ventricle.[1]

At the present time, the early mortality for completion of the Fontan circulation is low, at about 2%, and the survival at 10 years is expected for 85 to 90% of the patients.[2] Early failure of the Fontan operation is associated with higher pre-operative pulmonary arterial mean pressures, higher post-operative systemic venous pressures, longer periods of aortic cross-clamping, the presence of isomerism of the left atrial appendages, and a dominant ventricle of right morphology.[3–7] Post-operative problems include thrombo-embolic complications, atrial arrhythmias, and protein-losing enteropathy. Late failure is described in up to one-twentieth of all patients, and is characterized by low cardiac output, elevated systemic venous pressures and, less frequently, by protein-losing enteropathy.[8] Ventricular failure, atrioventricular valvar incompetence, and/or disorders of rhythm may be responsible for such failure in up to half of all patients.[1,9] For the other half, the aetiology of progressive failure remains poorly understood. Some recent data suggests that it might be related to an increase in pulmonary vascular resistance, due either to micro-embolisation or pulmonary endothelial dysfunction.[10,11]

Bosentan is a dual endothelin receptor antagonist that competes with the binding of endothelin to both ET_A and ET_B receptors, with slightly higher affinity for the ET_A receptors. Concentrations of endothelin-1 are increased in both the tissues and plasma in several cardiovascular disorders, including acute and chronic heart failure, pulmonary arterial hypertension, and in patients with failing Fontan circulations.[12,13] By inhibiting the binding of endothelin to its receptors, bosentan can reduce or attenuate the deleterious consequences of over-expressed endothelin in pathological states.[14] In adults and adolescents with pulmonary hypertension, the agent has been shown to improve quality of life, exercise capacity, haemodynamics and clinical outcomes in patients graded in the third or fourth functional classes of the system devised by the World Health Organisation.[15,16] In this study, therefore, we sought to evaluate the effect of treatment with bosentan of patients with a failing Fontan circulation.

Methods

Design

We performed a multicentric trial of oral bosentan in an open-label, single-drug, non-controlled, pilot study, recruiting patients in 4 Belgian centres (University Hospitals Leuven; Cliniques Universitaires Saint-Luc, Brussels; Universitair Ziekenhuis Gent; Hôpital Universitaire des Enfants Reine Fabiola, Brussels) and one Dutch centre for paediatric cardiology (University Medical Centre, Leiden). The study protocol was approved by all local research and ethics review boards. Before inclusion in the project, informed consent was obtained from all patients or parents. This project was financially supported by Actelion Pharmaceuticals Belgium, who provided the medication for the trial and logistic support.

Protocol

We included all patients 2 years of age or more, with a functionally univentricular heart and failure occurring at least 6 months after the Fontan operation. Patients were considered as having a failing Fontan circulation in presence of 1 or more of marked cyanosis, with saturations of oxygen below 90% at rest or at exercise, a chronic state of low output with elevated systemic venous pressure reflected by hepatomegaly and elevated jugular central venous pressure with or without pleural effusions or ascites, documented protein-losing enteropathy, and marked symptoms consistent with grading in the second, third or fourth functional classes established by the World Health Organisation.

We excluded patients we found with any potentially treatable cause of failure, such as stenosis of a conduit or the pulmonary arteries, significant systemic-pulmonary collateral arteries, important atrioventricular valvar regurgitation with elevated atrial pressures, severe ventricular dysfunction with elevated ventricular end-diastolic pressures, atrial arrhythmias, or the presence of thrombus in a conduit or the pulmonary arteries. We also excluded patients if they were aged less than 2 years, pregnant, had systolic blood pressure below 80% of lower limit of normal range, had levels of aspartate aminotransferease and/or alanine aminotransferase values above 3 times the upper limit of normal, showed moderate to severe hepatic impairment, had levels of haemoglobin and/or the haematocrit below 75% of lower limit of normal, or if they were using other pulmonary vasodilators, such as sildenafil or prostacyclin.

After inclusion, we made baseline assessments of their functional class in the system of the World Health Organisation, their physical examination with vital signs, saturations of oxygen at rest, the 6 minutes walk test with measurement of saturations, and exercise testing with measurement of gas exchange and maximum consumption of oxygen. If cardiac catheterization had been performed recently, we obtained the haemodynamic data. Samples were also taken for haematology and blood chemistry tests, especially hepatic function. A questionnaire assessing quality of life was completed by the parents of patients. The version of the instrument

depended on the age of the patient.[17] A higher score on the total scale, or the subscales for physical, emotional, social, and educational functioning, represent a better quality of life. Parents/patients also completed the index of global impression, which rates severity of illness with respect to other similar patients, global improvement with respect to baseline measurements, and efficacy. The maximum score is 18. The use of concomitant medications was recorded. Initially, bosentan was given at half the full dose adjusted for age and weight, and was increased to full dose after 4 weeks in the absence of elevations of aminotransferase, according to the European labelling for patients with pulmonary hypertension.

We re-evaluated the patients after 1, 4, 6, 8 and 16 weeks of treatment. All medical events and possible side effects were recorded. Full clinical examination, oxygen saturation at rest, and blood analysis were performed at each visit. Quality of life was reassessed 4, 8 and 16 weeks of the initiation of bosentan. In addition, we calculated the score for the global impression index. At 16 weeks, the evaluation was completed with an echocardiogram, a 6 minutes walk test, and an exercise test with measurement of maximal consumption of oxygen. The participating centres collected data by means of forms specially designed for this project. A qualified monitor verified the forms and the origin of the data.

Outcome parameters

The primary parameters analyzed were the effect on clinical state, the baseline saturation of oxygen at rest and during exercise, and the effect on plasma albumin for patients with protein-losing enteropathy.

Follow-up

At the end of the period of study, the medication was stopped in most of the patients, and follow-up was performed by assessing the effect of withdrawal of the drug. In selected patients in whom there was a clear negative effect of withdrawal, treatment was restarted, and its effect evaluated.

Statistics

Descriptive statistics were used to describe the baseline characteristics of the patient population. The results are presented as median and range. With respect to the questionnaire, we calculated a mean score for each subscale and for the total instrument. The Friedman test was used for non-parametric analyses of repeated measures. For comparison of saturation and exercise data, a paired t-test was used. Statistical significance level was considered if p was below 0.05.

Results

Population and criterions for inclusion

Between January and June 2006, we enrolled 10 patients in the study. Of these, 1 patient discontinued treatment at an early stage, but all others completed 16 weeks of therapy. All patients had functionally univentricular physiology, with dominant left ventricles in 80%. The demographics are summarized in Table 1.

The main signs of Fontan failure and, hence, indications for inclusion were cyanosis with poor exercise tolerance in 4 patients, venous congestion with poor exercise tolerance in 2 patients, isolated poor exercise tolerance in 1 patient, cyanosis and venous congestion in another, and protein-losing enteropathy with cyanosis in the final 2 patients.

All patients were being treated with antiplatelet and/or anticoagulant agents. Inhibitors of angiotensin converting enzyme were prescribed for 2 patients, diuretics for 5, and digoxin for 2. Methylprednisone was given to 1 patient with protein-losing enteropathy.

Baseline parameters

Of the patients, 5 were in the second functional class, and 4 in the third class of the gradings developed by the World Health Organisation. Data was missing for 1 patient. Median saturations of oxygen at rest were 85.5%, with a range from 66 to 95%. The median was 85% for those patients with an open fenestration, and 94% for those with a closed fenestration. The 6 minutes walk test was performed in 8 patients. The median distance achieved, in 7 patients, was 445 metres, with a range from 170 to 520 metres. Normal values were recently reported for children.[18] Saturations dropped during the test from a starting median of 84%, with a range from 81 to 97%, to a median of 78.5%, and a range from 70 to 92% after 6 minutes. Surprisingly, the median drop, at 3%, was the same for patients with or without fenestrations. Maximal consumption could only reliably be measured during exercise testing in 3 patients, with values of 25.14, 35.2, and 25.8 ml/min/kg respectively, as opposed to normal levels of between 30 and 50 ml/min/kg.

Table 1. Patient demographics.

Sex ratio	7 male/3 female
Median age (range) at Fontan	3.65 years (2.19–23.60)
Type Fontan (extracardiac/intracardiac)	3/7
Median interval (range) Fontan – inclusion	7.84 years (1.96–12.18)
Median age (range) at inclusion	12.12 years (4.41–33.41)
Median weight (range) at inclusion	32 kg (14.5–72.6)
Fenestration at time of study (open/closed)	7/3

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Table 2. Mean cardiac parameters at baseline and week 16.

	Baseline (range)	Week 16 (range)	Mean change versus baseline
Weight, kg (n = 9)	28.5 (14.5–62.4)	30.4 (14.2–65.6)	+1.9 (P = NS)
Baseline O_2 saturation, % (n = 9)	86 (66–95)	89 (87–95)	+3 (P = NS)
Baseline O_2 saturation, % increase		2.25 (–1.1–25) (n = 9)	N/a
WHO FC (n = 8)	2.5 (2–3)	2 (2–3)	−0.5 (P = NS)
6MWT saturation T_0, % (n = 7)	84 (81–97)	87 (80–96)	+3 (P = NS)
6MWT saturation T_6, % (n = 7)	79 (70–92)	82 (74–95)	+3 (P = NS)
6MWT % saturation drop, T_0 to T_6 (n = 7)	6 (2–11)	4 (1–7)	N/a
6MWT saturation post-test, % (n = 4)	82 (75–92)	85.5 (79–91)	+3.5 (P = NS)
6MWT distance, metres (n = 6)	442.5 (170–520)	407 (285–562)	−35.5 (P = NS)
VO_2max, ml/min/kg (n = 4)	25.6 (17.9–35.2)	25.55 (24.25–29.8)	−0.05 (P = NS)
Total PedsQL score (n = 9)	67 (44–72)	57 (43–74)	−10 (P = NS)

WHO FC = World Health Organisation functional Class, 6MWT = 6 minutes walk test, VO_2max = maximum oxygen consumption, N/a = not applicable; NS = not statistically significant.

Haemodynamic assessment by cardiac catheterisation had been performed in 9 patients. All procedures had been performed under general anaesthesia at a median of 7.43 years, and a range from 1.12 to 11.78 years, after the Fontan procedure, and a median of 4.6 months, with a range from 0.03 to 10.93 years, before inclusion in the study. Data was insufficient reliably to calculate pulmonary resistance values due to differences in the protocols between the different participating centres. The median pressure in the conduit, available for 7 of the 9 patients, was 11 mmHg, with a range from 7 to 17 mmHg. The median pressure was similar in those with and without fenestrations. The median ventricular end diastolic pressure, also available for 7 patients, was 6 mmHg, with the range from 3 to 12 mmHg. The median venous mixed saturation in the superior caval vein, again measured in 7 patients, was 55%, with a range from 47 to 74%, in room air. Test occlusion of the fenestration had been performed in one patient, with a drop in venous saturation down to 35%, precluding closure of the fenestration.

Tolerance

Treatment with bosentan was initiated at half the usual dose adapted for weight, and was increased to the full dose after 4 weeks in 9 patients. An adult patient, with controlled protein-losing enteropathy and a history of psychological problems, complained of a gain in weight and oedema during the early part of the trial, and elected to withdraw from the study after 2 weeks of treatment. The symptoms could not be linked clinically with the treatment, and levels of protein also remained stable.

An additional 2 patients complained of mild transient fatigue, occurring 1 day and 2 weeks after starting the drug. No other side effects were recorded. Mild infection of the upper airways was noted in 2 patients during the study, and 1 of these received

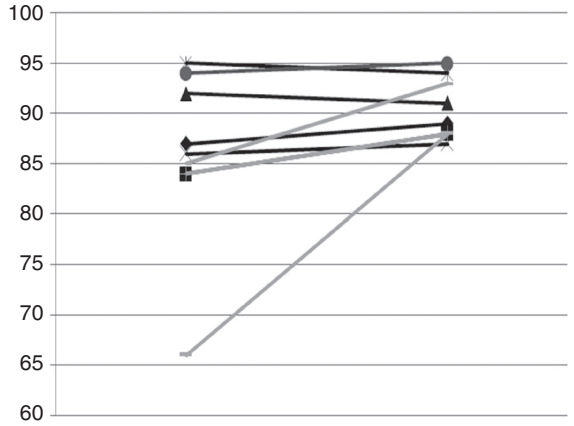

Figure 1.
Oxygen saturations (%) at rest, at baseline (left) and at the 16th week (right).

treatment with amoxicillin. Another patient experienced an episode of fever, with reactivation of labial herpes, and was treated with acyclovir. Assessments of hepatic and haematological parameters remained normal in all patients.

Cardiac parameters and general state

Measurements of cardiac parameters at baseline and after 16 weeks of treatment are shown in Table 2. Although not reaching statistical significance, saturations of oxygen at rest (Fig. 1), and during the 6 minutes walk test (Fig. 2), improved for most patients, with less desaturation at the end of the test. The total distance achieved did not statistically significantly increase for the whole group. There was no statistically significant improvement in the other parameters. For some individual patients, there were significant improvements in exercise capacity and or saturations. Table 3 shows the results for these individuals. We considered 5 of the 9 patients to be responding positively to the treatment based on

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the 6 minutes walk test, the effect on protein-losing enteropathy, and/or the effect on percutaneous saturations.

In Table 4, we show the mean scores for the subscales and the total scale for the questionnaire. Emotional functioning and school functioning differed significantly over the period of the study. These overall differences were mainly due to a significant increase in emotional functioning (Wilcoxon $Z = -2.132$; $p = 0.033$) and school functioning (Wilcoxon $Z = -2.388$; $p = 0.017$) between baseline and 4 weeks of treatment. After 4 weeks of treatment, these values decreased again, falling to their initial level or lower. No statistically significant differences were observed for physical functioning, social functioning, and total score. The global index depicted the patients as better in 5 cases, and significantly better in 1 case. For 2 patients, there was no change, and the other patient was not available for evaluation.

Of the 2 patients with protein-losing enteropathy who completed the full study, one improved. The patient reported feeling better, and the enteropathy seemed better controlled during treatment, permitting the dose of steroids to be reduced and eventually completely stopped.

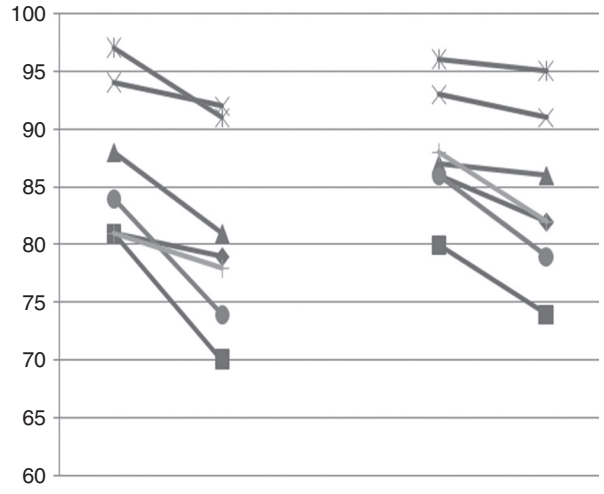

Figure 2.
Oxygen saturations during exercise using the 6 minutes walk test at the beginning and end of the test for the patients at baseline (left) and at the 16th week (right).

Follow-up study

In most patients, bosentan was stopped at the end of the study. This was either due to lack of effect, or due to other reasons, mainly lack of reimbursement in the Belgian Health care system for this indication. In some patients we could continue or restart bosentan.

We followed 1 of the patients (Table 3, patient #3) with protein-losing enteropathy, who has continued to receive bosentan now for two years. During this period, his steroids could progressively be tapered, and were stopped after 1 year on bosentan. The total levels of protein have remained stable 11 months after stopping the steroids. We had tried to wean him off steroids before treatment

Table 3. Individual patient data and follow-up data.

Patient	Sat before	Sat end	Sat after stop (FU)	Sat after restart	6MWT before	6MWT end	6MWT stop	6MWT restart	REMARKS
patient 1	86	87	87	NA	NA	NA	NA	NA	VO_2max did not change on medication
patient 2	**94**	**95**	**94**	**94**	**300**	**400**	**389**	**439**	**effect on 6MWT, restarted on bosentan**
patient 3	**95**	**94**	**Continued**	**Continued**	**445**	**434**	**Continued**	**Continued**	**effect on PLE, weaned from steroids, continued on Bosentan**
patient 4	84	86	87	NA	520	500	NA	NA	no effect
patient 5	87	89	88	NA	370	350	NA	NA	no effect, suboptimal LV function
patient 6	**84**	**88**	**79**	**NA**	**520**	**430**	**NA**	**NA**	**effect on saturation at rest and exercise and VO_2max, bosentan stopped after study**
patient 7	**91**	**91**	**92**	**NA**	**170**	**285**	**NA**	**NA**	**effect on 6MWT, bosentan stopped after study**
patient 8	85	93	NA	NA	474	384	NA	NA	No effect on PLE
patient 9	**66**	**88**	**NA**	**NA**	**3 minutes**	**8 minutes**	**NA**	**NA**	**effect of saturations and 6MWT, continued on sildenafil**

Bold patients are 'responders', sat = saturation in %, 6MWT = 6 minutes walk test results expressed in meters walking distance, NA = not available, VO_2max = maximum oxygen consumption, PLE = protein-losing enteropathy.

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Table 4. Analysis of the scores for the questionnaire.

Median (Q1–Q3)	Baseline	After 4 weeks of treatment	After 8 weeks of treatment	After 16 weeks of treatment	Friedman test (p-value)
Physical functioning	75 (30–77)	75 (31–84)	72 (34–75)	56 (34–77)	$\chi^2 = 2.6$ ($p = 0.457$)
Emotional functioning	65 (58–83)	78 (66–98)	70 (65–88)	65 (55–85)	$\chi^2 = 10.8$ ($p = 0.013$)
Social functioning	75 (45–75)	73 (58–79)	70 (50–84)	55 (43–83)	$\chi^2 = 0.682$ ($p = 0.877$)
School functioning	55 (38–56)	63 (51–69)	55 (45–65)	60 (48–68)	$\chi^2 = 16.1$ ($p = 0.001$)
Total score	67 (44–72)	75 (51–80)	63 (49–76)	57 (43–74)	$\chi^2 = 7.1$ ($p = 0.068$)

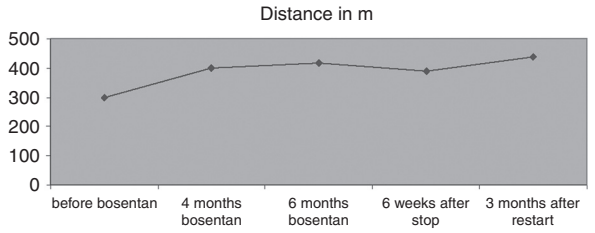

Figure 3.
The evolution of the distance walked by our second patient performing the 6 minutes walk test during follow-up.

with bosentan, but he suffered a recurrence of the enteropathy within 1 month of weaning.

In a second patient (Table 3, patient #2), we noted a significant effect on exercise tolerance, with a significant increase in walking distance and also in subjective well-being of the patient. Before the drug was started, this patient could not finish the 6 minutes walk test. During the first 4 minutes, she reached a distance of 300 metres. After starting the drug, she was capable of finishing the test, and could walk up to 400 metres in 6 minutes after four months of treatment, remaining stable after six months of treatment. After the treatment was stopped, her exercise tolerance decreased again, falling back to 389 metres on the 6 minutes walk test 7 weeks after stopping the treatment. After restarting the treatment, exercise tolerance improved again, and she was capable of walking 439 metres two months after restarting treatment (see Fig. 3). Also subjectively she was feeling better again and did better in daily life activities as reported by the parents.

In a third patient (Table 3, patient #9) who responded very well to vasodilatory treatment, with an increase in saturations from 66% baseline to 88% after 3 months of treatment and an increase in exercise duration from 3 to 8 minutes, bosentan was switched to sildenafil after the trial period. This patient has since remained stable on this treatment for more than 2 years.

Another patient who (Table 3, patient #7) had a significant improvement on exercise performance on the 6 minutes walk test, the medication had to be stopped at the end of the trial because of lack of reimbursement. Unfortunately exercise tests could not be repeated after stopping treatment. Subjectively she felt better on drug treatment.

A final patient (Table 3, patient #6) improved his saturations at rest and at exercise. Maximum consumption of oxygen improved despite no improvement in total distance achieved at the 6 minutes walk test. Medication had to be stopped at the end of the trial for lack of reimbursement, and exercise tests were not repeated. Subjectively, he felt better while receiving treatment.

Discussion

In the absence of ventricular failure, atrioventricular valvar regurgitation, disorders of rhythm, and/or pulmonary arterial stenosis, failure of the Fontan circuit may be associated with a progressive increase in pulmonary vascular resistance due either to micro-embolisation or to pulmonary endothelial dysfunction. In the pulmonary circulation of patients with the Fontan circulation, the normal flow is non-pulsatile, and the associated change in shear stress might affect endothelial function. This is suggested in a recent study, which demonstrated that pulmonary vascular resistance falls after administration of nitric oxide up to 15 years after the Fontan operation.[11] Elevated pulmonary vascular resistance has also been found in 11 of 14 patients with the Fontan circuit who underwent cardiac transplantation.[10] Of the patients with normal pulmonary vascular resistances after transplantation, 3 had undergone the transplantation less than 1 year after the Fontan operation, while those with elevated pulmonary vascular resistances had been transplanted more than 1 year after the Fontan operation.

During the past 20 years, several drugs with potent vasodilatory effects on the pulmonary vasculature have been approved for the treatment of pulmonary hypertension in adults, including intravenous analogues of epoprostenol and prostacyclin, such as inhaled iloprost or subcutaneous treprostinil. The anatogonist of endothelin receptors, bosentan, is also approved for this indication. Bosentan has been studied in patients with a range

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of pulmonary hypertension aetiologies. Emerging results of longer-term studies suggest that, when given as a first line of treatment, bosentan has a positive effect on long term outcomes in patients with idiopathic pulmonary hypertension,[16,19] pulmonary hypertension associated with connective tissue disease,[20,21] and in children, mainly those with idiopathic pulmonary hypertension, pulmonary hypertension related to congenital heart disease[22] and Eisenmenger's syndrome.[23] Other antagonists, such as sitaxsentan and ambrisentan,[24–26] and sildenafil,[27] a phosphodiesterase type 5 inhibitor, are currently in clinical development. Recently published case reports have shown beneficial effects for pulmonary vasodilators in patients with failing Fontan circulations. A beneficial effect was found in a patient with a failing Fontan circuit and poor haemodynamics complicated by plastic bronchitis prior to cardiac transplantation.[28] A beneficial effect of combined nitric oxide and epoprostenol infusion was shown in patients with compromised pulmonary perfusion early after Fontan operation.[29] Sildenafil has also been shown to have a beneficial effect in 2 patients with failing Fontan circulations associated with protein-losing enteropathy and plastic bronchitis.[30,31] Recently, a favourable acute effect of Sildenafil was demonstrated for exercise performance and haemodynamics in stable adults with the Fontan circuit.[32]

No large studies, however, are yet available to prove the efficacy of pulmonary vasodilatory treatment in a larger group of patients with poor haemodynamics in the Fontan circuit. Ours is the first open-label study assessing the effect of this treatment in a larger group of such patients. We analysed the efficacy of bosentan in modifying cardiac parameters over a 3-month period in 10 children and young adults. Only 9 patients finished the study. When looking at the individual results, a favourable effect was achieved in 5 patients, as based on saturations of oxygen, exercise capacity and/or protein-losing enteropathy. Most patients who responded to treatment also reported an improved well-being. While the design of the study does not exclude the possibility of a placebo effect in the self assessment of wellbeing, bosentan has been shown previously to improve quality of life in patients with pulmonary hypertension. We failed to show significant and rapid improvement in cardiac parameters like percutaneous saturations or 6 minutes walk test distance for the whole group treated. This is due to the fact that, in about half of the patients, no significant effect could be noted. Due to the heterogeneous characteristics of the group, it was difficult to assess the effects of treatment, making it also difficult to achieve statistical significant results for the entire group. For individual patients, however, the treatment made a big difference, as shown by our follow-up. Exercise capacity improved significantly in 1 patient during treatment, but her clinical state deteriorated markedly when treatment was stopped. She improved again after restarting the treatment, with a progressive further improvement in exercise capacity. A second patient with protein-losing enteropathy could be entirely weaned from steroids, and has suffered no relapse whilst treated only with bosentan. A third patient had a significant improvement in saturations of oxygen and exercise capacity after starting treatment. She was switched to sildenafil at the end of the trial period, and continues to do well on this treatment. The 2 remaining patients improved in terns of exercise capacity and/or saturations, but deteriorated subjectively after stopping the treatment.

The fact that only half of our patients responded to treatment suggests that we might have selected them inappropriately. Probably only the patients with a mild increase in pulmonary vascular resistance might benefit from pulmonary vasodilation. This was not defined as a criterion for inclusion. We included only those with poor haemodynamics for which no good explanation could be found. None of the patients had an obstructed conduit, significant atrioventricular valvar regurgitation, or obvious ventricular systolic dysfunction based on echocardiographic and recent cardiac catheterisation data. The catheterisation data was obtained retrospectively, and the multicentric nature of the study resulted in different haemodynamic measurements being performed in different centres. This precluded a reliable calculation of pulmonary vascular resistance in most of the patients. Pulmonary vascular reactivity to pulmonary vasodilators like nitric oxide or intravenous sildenafil was also not evaluated acutely.

Some of the patients underwent a repeat cardiac catheterisation during follow-up for different clinical indications. The most common indication was persistent desaturation to rule out abnormal collaterals giving rise to right-to-left shunts. Instead of measuring responsiveness to nitric oxide, which is difficult to assess especially in patients with residual right-to left shunts, we decided to study the effect of volume loading on cardiac pressures in some of the patients. The reasoning behind this is that volume loading helps to distinguish between increased vascular resistance and decreased ventricular compliance. Most of the patients are treated with diuretics to reduce preload. This means that ventricular filling pressures can be reduced irrespective of the underlying mechanism. Using volume loading, we wanted to distinguish between those patients with a reduced ventricular compliance and those with an increased pulmonary vascular resistance. We started giving a volume

load of 10 to 15 ml/kg over 10 minutes during the haemodynamic assessment. Pulmonary arterial pressures, wedge pressures, and left ventricular end-diastolic pressures, were all evaluated. We observed that, in a patient who responded to treatment with bosentan, pressures in the systemic veins and pulmonary arteries increased when we volume loaded the patient, with only a very limited increase in left ventricular end-diastolic pressure. This suggests that the pulmonary vascular bed is restrictive, and has difficulties dealing with the increased volume, probably due to increased resistance, as no stenosis could be detected on the angiography. In a non-responder who underwent a similar volume loading, the systemic venous pressures increased, but left ventricular end-diastolic pressure also increased significantly. The last patient had a poorly compliant left ventricle, with increased left ventricular end-diastolic pressure, which probably explains the failure of his Fontan circuit, and extreme sensitivity to fluids. This patient also had poorly controlled diabetes mellitus, which could explain his diastolic dysfunction. A strategy better to identify patients with failing Fontan circuits, who might benefit from the treatment, is warranted. We suggest that volume loading during the haemodynamic assessment might be a useful tool.

Limitations of the study

Ours was a pilot study with an open label design, and included only a limited number of patients. This is an obvious limitation. Despite this, we think our experience could be important for the design of larger placebo-controlled trials on the same topic. One of the most difficult issues is how to define the criterions for inclusion of patients. It is difficult to define the failing patient. Some patients with the Fontan circuit just do not do very well, albeit without being in overt failure with oedema, pleural fluid, ascites or pericardial fluid. Others are in a chronic state of low output, with limited exercise tolerance, and are again not easy to identify. The small number of patients in our present study reflects the diversity of those with a failing Fontan circuit. Some had protein-losing enteropathy, some were desaturated, and some had poor exercise tolerance. Appropriate selection of patients will be crucial when larger trials are organized. A second problem is how to assess reliably the response to treatment, especially in children. We question the reproducibility of the 6 minutes walk test in children, but further information regarding this issue is needed. Treadmill and bicycle exercise tests are sometimes difficult to perform, particularly in the young patients aged less than 8 or 9 years. This also becomes important for the design of a larger study on this population, and requires further validation of the reproducibility of the tests. A further problem, discussed at length, is the identification of those patients who might benefit most from this treatment. A protocol for catheterisation including study of reversibility to nitric oxide and/or volume loading should be considered. A final issue is how long the treatment should be continued before an effect of endothelin-receptor blockers can be observed in patients after the Fontan operation. In adult patients with primary pulmonary hypertension, the effect is evaluated after three months of treatment. It is still uncertain whether the same interval is reasonable in patients with the Fontan circuit, who have profoundly different haemodynamics. When designing larger trials also this should be taken into account.

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