Treat-and-repair strategy is a feasible therapeutic choice in adult patients with severe pulmonary arterial hypertension associated with a ventricular septal defect: case series

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Received 24 November 2017; accepted 23 February 2018; online publish-ahead-of-print 22 March 2018

Introduction

Recent advances in pulmonary arterial hypertension (PAH)-specific drugs have dramatically changed the therapeutic strategy for PAH. A strategy that includes ‘treatment’ with PAH-specific drugs initially and then ‘repair’ by closure of the cardiac defect (i.e. ‘treat and repair’) was devised, and has been attempted, in patients with PAH associated with a cardiac defect.

Case presentation

We present three cases of severe PAH associated with a ventricular septal defect (VSD) in adult patients who were initially treated with PAH-specific drugs followed by VSD closure. Two of the patients were treated with a combination of an endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor, and intravenous prostacyclin before VSD closure. The third patient was treated with an ERA and pulmonary artery banding before VSD closure. After 12 months of anti-PAH treatment, the pulmonary vascular resistance index and the ratio of the pulmonary vascular index to the systemic vascular resistance index decreased to levels that allowed VSD closure. At the mid- and long-term follow-up measurements after surgical closure of the VSD, the mean pulmonary artery pressure had markedly decreased.

Discussion

Our case series suggests that the treat-and-repair strategy is a promising approach for adult patients with severe PAH associated with VSD.

Keywords

Pulmonary arterial hypertension • Ventricular septal defect • Treat-and-repair strategy • Case series

Learning points

- Treatment of pulmonary arterial hypertension (PAH)-specific drugs in patients with PAH who have an impossible-to-close ventricular septal defect (VSD) can decrease pulmonary vascular resistance and provide vascular reactivity with oxygen, which then enables VSD closure. However, lifelong follow-up is essential, as long-term studies are lacking.
- Although VSD closure was associated with further reduction in pulmonary artery pressure, PAH-specific drugs were still required after the closure.
Introduction

Pulmonary arterial hypertension (PAH) is characterized by vasoconstriction and remodelling of pulmonary arteries, leading to elevated pulmonary artery pressure and right heart failure. Congenital shunt disease is one of the causes of PAH. High flow by systemic-to-pulmonary (S/P) shunting through a cardiac defect increases shear stress of the pulmonary artery wall and can ultimately remodel pulmonary arteries. In an animal study, the disappearance of shunt flow caused pulmonary arterial vasculopathy to regress after flow correction. Regression of shunt flow by cardiac defect closure can stop progression of PAH and might reverse remodelling of pulmonary arteries.

In the 2015 European Society of Cardiology guidelines, PAH associated with congenital heart diseases (CHD) is divided into four clinical groups: (i) Eisenmenger syndrome; (ii) PAH associated with a prevalent S/P shunt; (iii) PAH with small/coincidental defects; and (iv) PAH after defect correction. Defect closure is a contraindication in those with Eisenmenger syndrome or PAH with small/coincidental defects. The feasibility of defect closure based on pulmonary vascular resistance (PVR) was studied in patients with PAH associated with a prevalent S/P shunt. Defect closure is possible in patients with PAH associated with an S/P shunt who have low PVR. Recently, a ‘treat-and-repair’ strategy has been considered in patients who have S/P shunting but high PVR initially. A cardiac defect can be closed in patients whose PVR decreases after treatment with PAH-specific drugs. It remains unknown; however, which patients would benefit from a treat-and-repair strategy, what sort of anti-PAH treatment is effective, and when to perform surgical closure. We report three adult patients with PAH associated with a ventricular septal defect (VSD) in whom a treat-and-repair strategy was used.

Patient 1

A 49-year-old woman was diagnosed with VSD at birth and underwent pulmonary artery banding during infancy. She was recently diagnosed with severe PAH and was referred to our hospital for treatment. The patient had dyspnoea. Her heart rate was 111 b.p.m., blood pressure 126/94 mmHg, and SpO2 92% with oxygen administration at 2 L/min. Cardiovascular examination revealed increased intensity of P2 and pansystolic murmur at the third right intercostal space on auscultation. The lung field was clear. The remainder of the physical examination was unremarkable. Transthoracic echocardiography showed perimembranous-type VSD (34 × 34 mm) with a bidirectional shunt, dilated right ventricle, and estimated right ventricular systolic pressure of 108 mmHg (Figure 1A–C; see also Supplementary material online, Video S1). Right heart catheterization (RHC) revealed a mean pulmonary artery pressure (mPAP) of 76 mmHg, PVR index (PVRi) of 15.8 Wood units/m², pulmonary blood flow-to-systemic blood flow ratio (Qp/Qs) of 1.68, and PVRi systemic vascular resistance index ratio (Rp/Rs) of 0.4 (Table 1). Vasoreactivity testing with the patient breathing 100% oxygen for 10 min showed the following decreases: mPAP 73 mmHg, PVRi 12.5 Wood units/m², Rp/Rs 0.34. There was also an increase in Qp/Qs of 2.34.

Because surgical closure of the VSD would be difficult, we started combination therapy with sildenafil 60 mg/day and ambrisentan 5 mg/day. Right heart catheterization performed 3 months after treatment showed mPAP 68 mmHg, PVRi 11.4 Wood units/m², Qp/Qs 2.13, and Rp/Rs 0.35. We added epoprostenol and gradually increased the dose. Right heart catheterization at 1 year after treatment showed mPAP 58 mmHg, PVRi 8.8 Wood units/m², Qp/Qs 2.2, and Rp/Rs 0.35. Vasoreactivity testing with 100% oxygen for 10 min showed mPAP 72 mmHg, PVRi 7.2 Wood units/m², Qp/Qs 3.26, and Rp/Rs 0.31 (with the patient on sildenafil at 60 mg/day, ambrisentan at 5 mg/day, and epoprostenol at 30 ng/kg/min). The patient underwent surgery for the VSD with a patch and a flap valve. Transthoracic echocardiography 10 months post-operatively showed an estimated right ventricular systolic pressure of 50 mmHg (Figure 1D–F; see also Supplementary material online, Video S2). Right heart catheterization performed 10 months post-operatively showed mPAP 42 mmHg, PVRi 11.5 Wood units/m² (with the patient on sildenafil 60 mg/day, ambrisentan 5 mg/day, epoprostenol 24 ng/kg/min).

Patient 2

A 20-year-old man had been diagnosed with VSD and PAH at birth in another hospital. Treatment with sildenafil 60 mg and ambrisentan 10 mg was started at age 5 years. The patient was referred to our hospital at age 20 years. The patient had slight dyspnoea. His heart rate was 58 b.p.m., blood pressure 97/52 mmHg, and SpO2 94% in room air. Cardiovascular examination revealed increased intensity of P2 and pansystolic murmur at the third right intercostal space on auscultation and parasternal heave. The lung field were clear. The remainder of the physical examination was unremarkable. Transthoracic echocardiography showed perimembranous-type VSD (18 × 18 mm) with left-to-right shunt, dilated right ventricle, and estimated right ventricular systolic pressure of 91 mmHg (Figure 2A–C; see also Supplementary material online, Video S3). Right heart catheterization showed mPAP 71 mmHg, PVRi 9.0 Wood units/m², Qp/Qs 1.59, and Rp/Rs 0.41 (Table 2). Vasoreactivity testing breathing 100% oxygen for 10 min showed no change in mPAP 73 mmHg but decreases in PVRi of 7.8 Wood units/m², Qp/Qs 2.37, and Rp/Rs 0.30. We initiated administration of beraprost and changed sildenafil to tadalafil. Right heart catheterization performed 1 year later showed mPAP 76 mmHg, PVRi 11.8 Wood units/m², Qp/Qs 1.34, and Rp/Rs of 0.61. Vasoreactivity testing breathing 100% oxygen for 10 min showed mPAP 72 mmHg, PVRi 7.7 Wood units/m², Qp/Qs 2.05, and Rp/Rs 0.36 (with the patient on tadalafil at 20 mg/day, ambrisentan at 10 mg/day, and beraprost at 240 μg/day). The patient underwent surgery for patch closure of the VSD and small atrial septal fenestration. Transthoracic echocardiography 2 years later showed estimated right ventricular systolic pressure of 48 mmHg (Figure 2D–F; see also Supplementary material online, Video S4). Right heart catheterization performed 2 years post-operatively showed mPAP 48 mmHg and PVRi 9.1 Wood units/m² (with the patient on riociguat 7.5 mg/day, macitentan 5 mg/day, and treprostil 15 ng/kg/min).
Patient 3

A 49-year-old woman was diagnosed with VSD and PAH at 2 years of age in another hospital. Left pulmonary artery banding was performed at age 4 years. Treatment with ambrisentan and warfarin was started at age 18 years. At age 49 years, the patient was referred to our hospital for possible VSD closure. The patient had slight dyspnoea. Her heart rate was 76 b.p.m., blood pressure 95/46 mmHg, and SpO2 95% breathing room air. Cardiovascular examination revealed pansystolic murmur at the third right intercostal space on auscultation. The lung field were clear. The remainder of the physical examination was unremarkable. Transthoracic echocardiography showed a perimembranous, muscular-type VSD (18 × 19 mm) with a bidirectional shunt, dilated right ventricle, and estimated right ventricular systolic pressure of 56 mmHg (Figure 3A–C; see also Supplementary material online, Video S5). Right heart catheterization showed mPAP 60 mmHg, PVRi 12 Wood units/m², Qp/Qs 2.54, and Rp/Rs 0.29 (Table 3). Vasoreactivity testing with the patient breathing 100% oxygen for 10 min did show decreased mPAP (at 60 mmHg) but was associated with decreased PVRi of 6.0 Wood units/m² and Rp/Rs of 0.2 and increased Qp/Qs of 4.42. The initial strategy was to band the main pulmonary artery. Right heart catheterization performed 1 year after banding showed decreases in mPAP of 38 mmHg, PVRi of 6.5 Wood units/m², and Rp/Rs of 0.21. Qp/Qs was increased by 2.87. Vasoreactivity testing with the patient breathing 100% oxygen for 10 min showed mPAP 43 mmHg, PVRi 5.8 Wood units/m², Qp/Qs 3.72, and Rp/Rs 0.14 (with the patient on ambrisentan 10 mg/day). The patient underwent surgery for patch closure of the VSD and debanding of the main and left pulmonary arteries. Transthoracic echocardiography 6 months later showed an estimated right ventricular systolic pressure of 29 mmHg (Figure 3D–F; see also Supplementary material online, Video S6). Right heart catheterization performed 6 months after surgery showed mPAP 15 mmHg and PVRi 4 Wood units/m² (with the patient on ambrisentan at 10 mg/day).

### Discussion

During the natural history of PAH associated with VSD in adult patients, PAH and right heart failure develop, ultimately leading to a change from left-to-right shunting to right-to-left shunting (i.e. Eisenmenger syndrome). This condition then leads to severe hypoxia, cyanosis, and death. Recent advances in PAH-specific drugs have dramatically changed the treatment for PAH to a treatment-and-repair strategy. Treatment with PAH-specific drugs initially and then repair by cardiac defect closure has thus been attempted in patients with PAH associated with a cardiac defect. Our experience of three cases of PAH associated with VSD revealed three important points: (i) all three patients showed a response to vasoactive testing with oxygen breathing (decreased PVRi and Rp/Rs without reducing the decreased mPAP because of increased Qp/Qs); (ii) reduced PVRi 12 months after starting treatment with a combination of PAH-specific drugs; (iii) VSD closure was associated with further reduction in mPAP, although PAH-specific drugs were still required.

A treat-and-repair strategy has three merits for patients with PAH associated with a cardiac defect. First, closing the defect can prevent the progression of Eisenmenger syndrome. Although the short-term outcome in these patients is good (5-year survival 88%), their survival rate reportedly declined annually after age 40 years.

### Timeline

| Time          | Events                                                                 |
|---------------|------------------------------------------------------------------------|
| Case 1        | Diagnosis of ventricular septal defect (VSD)                           |
| At birth      | Diagnosis of pulmonary arterial hypertension (PAH). Mean pulmonary artery pressure (PAP) of 76 mmHg and indexed pulmonary vascular resistance (PVRi) of 15.8 Wood units/m². Started treatment with sildenafil (60 mg/day) and ambrisentan (5 mg/day) |
| 3 months later| Addition of epoprostenol and titration of the dose                     |
| 12 months later| Mean PAP of 58 mmHg, PVRi of 8.8 Wood units/m². Repair of VSD          |
| 22 months later| Mean PAP of 42 mmHg and PVRi of 11.5 Wood units/m² (sildenafil at 60 mg/day, ambrisentan at 5 mg/day, and epoprostenol at 24 ng/kg/min) |
| Case 2        | Diagnosis of VSD and PAH                                               |
| At birth      | Diagnosis of VSD and PAH                                               |
| 5 years of age| Started treatment with sildenafil (60 mg/day) and ambrisentan (10 mg/day) |
| 20 years of age| Addition of beraprost (240 µg/day) and change from sildenafil to tadarafal (20 mg/day).                                  |
| 12 months later| Mean PAP of 76 mmHg and PVRi of 11.8 Wood units/m². Repair of VSD      |
| 36 months later| Mean PAP of 48 mmHg and PVRi of 9.1 Wood units/m² (riociguat at 7.5 mg/day, macitentan at 5 mg/day, and treprostinil at 15 ng/kg/min) |
| Case 3        | Diagnosis of VSD and PAH                                               |
| 2 years of age| Left pulmonary artery banding                                          |
| 4 years of age| Left pulmonary artery banding                                          |
| 18 years of age| Left pulmonary artery banding                                          |
| 49 years old of age| Mean PAP of 60 mmHg and PVRi of 12 Wood units/m². Addition of main pulmonary artery banding |
| 12 months later| Mean PAP of 38 mmHg and PVRi of 6.5 Wood units/m². Repair of VSD      |
| 18 months later| Mean PAP of 15 mmHg and PVRi of 4 Wood units/m² (ambrisentan at 10 mg/day) |
pulmonary artery remodelling by increasing shear stress under cardiac shunt.

A treat-and-repair strategy is thought to be more difficult in patients with PAH associated with VSD than in those with PAH associated with an atrial septal defect which is a pretricuspid valve cardiac defect associated with volume overload in the right ventricle. In contrast, VSD is a post-tricuspid valve cardiac defect associated with both volume and pressure overload. Therefore, PAH-specific drugs in patients with VSD could easily cause right heart failure. Hence, care must be taken when using PAH-specific drugs in these patients.

The indication for defect closure is important for a successful treat-and-repair strategy. Defect closure in patients with high PVR could cause pulmonary hypertension crisis and death because shunting partially acts as a safety valve in PAH patients with CHD.9 It was reported that defect closure in patients with high PVR associated

**Table 1  Haemodynamic change in Patient 1**

|                      | First evaluation | Post-treatment | Post-operation |
|----------------------|------------------|----------------|----------------|
|                      | Baseline         | Oxygen         | Baseline       | Oxygen         | Baseline       |
| mPAP (mmHg)         | 76               | 73             | 58             | 72             | 42             |
| mSAP (mmHg)         | 94               | 87             | 69             | 70             | 80             |
| PAWP (mmHg)         | 11               | 9              | 9              | 11             | 9              |
| Qp (L/min/m²)       | 4.11             | 5.11           | 5.54           | 8.53           | 2.86           |
| Qs (L/min/m²)       | 2.44             | 2.18           | 2.51           | 2.62           | 2.86           |
| Qp/Qs               | 1.68             | 2.34           | 2.20           | 3.26           | 1              |
| PVRi (WU m²)        | 15.8             | 12.5           | 8.8            | 7.2            | 11.5           |
| PVRi reduction rate (%) | —              | -21            | —              | -18            | —              |
| SVRi (WU m²)        | 39.3             | 37.2           | 25.1           | 23.3           | 26.6           |
| Rp/Rs               | 0.40             | 0.33           | 0.35           | 0.31           | 0.43           |
| Rp/Rs reduction rate (%) | —              | -18            | —              | -11            | —              |
| SaO₂                | 97               | 99             | 92             | 99             | 98             |

mPAP, mean pulmonary artery pressure; mSAP, mean systemic arterial pressure; PAWP, pulmonary artery wedge pressure; Qp, body surface area (BSA) indexed pulmonary blood flow; Qs, BSA indexed systemic blood flow (cardiac index); PVRi, BSA indexed pulmonary vascular resistance; SVRi, BSA indexed systemic vascular resistance; WU, wood unit; SaO₂, arterial oxygen saturation.
with VSD caused immediate post-operative death. Achieving low PVR is therefore desirable before defect closure. Criteria for shunt closure in the 2015 European Society of Cardiology guidelines were based on baseline PVR data from the most recent literature. Shunt closure is contraindicated when the PVRi is >8 Wood units/m². When PVRi is 4–8 Wood units/m², patients should be referred to a centre with expertise in evaluating patients’ operability via vasoreactivity testing.

Vasoreactivity testing is important for evaluating operability because the criteria for shunt closure based on the results of vasoreactivity testing have been proposed. Lopes et al. recommended that a baseline PVRi < 6 Wood units/m² and Rp/Rs < 0.3 be used as favourable criteria for defect closure. Vasoreactivity testing should be performed if the baseline PVRi is 6–9 Wood units/m² and the Rp/Rs is 0.3–0.5. Here, a decrease in PVRi of 20%, a decrease in Rp/Rs of 20%, a final PVRi of <6 Wood units/m², and a final Rp/Rs < 0.3 indicates

### Table 2 Haemodynamic change in Patient 2

|                     | First evaluation | Post-treatment | Post-operation |
|---------------------|------------------|----------------|----------------|
|                      | Baseline | Oxygen | Baseline | Oxygen | Baseline |
| mPAP (mmHg)         | 71       | 73     | 76       | 72     | 48       |
| mSAP (mmHg)         | 92       | 87     | 86       | 84     | 80       |
| PAWP (mmHg)         | 18       | 20     | 12       | 16     | 18       |
| Qp (L/min/m²)       | 5.87     | 6.8    | 5.44     | 7.27   | 4.5      |
| Qs (L/min/m²)       | 3.69     | 2.87   | 4.06     | 3.55   | 3.3      |
| Qp/Qs               | 1.59     | 2.37   | 1.34     | 2.05   | —        |
| PVRi (WU m²)        | 9.0      | 7.8    | 11.8     | 7.7    | 9.1      |
| PVRi reduction rate (%) | —      | -13    | —        | -35    | —        |
| SVRi (WU m²)        | 22.2     | 26.1   | 19.5     | 21.4   | 21.8     |
| Rp/Rs               | 0.41     | 0.30   | 0.61     | 0.36   | 0.42     |
| Rp/Rs reduction rate (%) | —      | -27    | —        | -49    | —        |
| SaO₂                | 94       | 99     | 94       | 99     | 99       |

mPAP, mean pulmonary artery pressure; mSAP, mean systemic arterial pressure; PAWP, pulmonary artery wedge pressure; Qp, body surface area (BSA) indexed pulmonary blood flow; Qs, BSA indexed systemic blood flow (cardiac index); PVRi, BSA indexed pulmonary vascular resistance; SVRi, BSA indexed systemic vascular resistance; WU, wood unit; SaO₂, arterial oxygen saturation.
that it is possible to close the cardiac defect. In our case series, all three patients showed a response to vasoactive testing with oxygen breathing. These criteria were fully met in Patients 2 and 3 and were almost met in patient 1.

None of our three patients had post-operative complications. Hu et al.\textsuperscript{12} reported results of a treat-and-repair strategy for 39 adult patients with PAH associated with VSD and high PVR. Six patients (15\%) experienced pulmonary hypertension crises, and two patients (5\%) died post-operatively. These patients did not meet the aforementioned criteria preoperatively. Sufficient reduction of the PVR or Rp/Rs by PAH-specific drugs could contribute to successful defect closure.

| Table 3 | Haemodynamic change in Patient 3 |
|---------|----------------------------------|
|         | First evaluation | Post-treatment | Post-operation |
|         | Baseline | Oxygen | Baseline | Oxygen | Baseline |
| mPAP (mmHg) | 60 | 60 | 38 | 43 | 15 |
| mSAP (mmHg) | 73 | 62 | 60 | 70 | 52 |
| PAWP (mmHg) | 13 | 14 | 6 | 9 | 7 |
| Qp (L/min/m²) | 3.92 | 7.69 | 4.91 | 5.88 | 2.26 |
| Qs (L/min/m²) | 1.54 | 1.74 | 1.71 | 1.58 | 2.26 |
| Qp/Qs | 2.54 | 4.42 | 2.87 | 3.72 | 1 |
| PVRi (WU m²) | 12.0 | 6 | 6.5 | 5.8 | 4.0 |
| PVRi reduction rate (%) | -50 | -11 | -11 | -11 | -11 |
| SVRi (WU m²) | 41.6 | 30.5 | 32.2 | 40.5 | 21.7 |
| Rp/Rs | 0.29 | 0.20 | 0.21 | 0.14 | 0.18 |
| Rp/Rs reduction rate (%) | -31 | -33 | -33 | -33 | -33 |
| SaO₂ | 96 | 99 | 92 | 99 | 95 |

mPAP, mean pulmonary artery pressure; mSAP, mean systemic arterial pressure; PAWP, pulmonary artery wedge pressure; Qp, body surface area (BSA) indexed pulmonary blood flow; Qs, BSA indexed systemic blood flow (cardiac index); PVRi, BSA indexed pulmonary vascular resistance; SVRi, BSA indexed systemic vascular resistance; WU, wood unit; SaO₂, arterial oxygen saturation.
The anti-PAH treatment chosen is important. We chose anti-PAH treatment according to the baseline PVRi and PVRi and Qp/Qs responses during vasoreactivity testing. If the responses of PVRi and Qp/Qs during vasoreactivity testing were good, regardless of the baseline PVRi, we chose pulmonary artery binding because we thought that high flow was related to this state. If the baseline PVRi was high and the PVRi and/or Qp/Qs response during vasoreactivity testing was weak, we administered PAH-specific drugs. Treatment with an endothelin receptor antagonist (ERA) and phosphodiesterase 5 inhibitor (PDE5i) has been shown to produce favourable functional and haemodynamic results in patients with PAH associated with CHD. Therefore, our first choice of PAH-specific drugs were an ERA and a PDE5i. When the PVRi remained high and the response of the PVRi and/or Qp/Qs during vasoreactivity testing was weak after treatment with the ERA and PDE5i, we chose epoprostenol. If the PVRi remained moderate and the response of the PVRi and/or Qp/Qs during vasoreactivity testing was weak after treatment with the ERA and PDE5i, we changed the drug and/or used triple oral combination therapy. Hence, further accumulation of cases is needed to establish an effective strategy for anti-PAH treatment before VSD closure.

We performed vasoreactivity testing with 100% oxygen breathing to predict operability. This effectiveness of this method, however, is controversial. The use of 100% oxygen may decrease the accuracy of functional assessment in predicting operability. This effectiveness of this method, however, is controversial. The use of 100% oxygen may decrease the accuracy of functional assessment in predicting operability. This effectiveness of this method, however, is controversial. The use of 100% oxygen may decrease the accuracy of functional assessment in predicting operability. This effectiveness of this method, however, is controversial. The use of 100% oxygen may decrease the accuracy of functional assessment in predicting operability. This effectiveness of this method, however, is controversial. The use of 100% oxygen may decrease the accuracy of functional assessment in predicting operability. This effectiveness of this method, however, is controversial. The use of 100% oxygen may decrease the accuracy of functional assessment in predicting operability.

A fenestrated VSD patch was used in Patient 1. A fenestrated VSD patch converts a large VSD into a small VSD. This fenestration allows systemic desaturation and prolonged intubation. The remaining shunting is associated with infective endocarditis and systemic embolism. A pop-off valve in the VSD patch should be used in selected cases.

**Conclusion**

We successfully adopted a treat-and-repair strategy in adult patients with severe PAH associated with VSD. Our case series suggests that this strategy is a promising approach for adult patients with severe PAH-associated with VSD.

**Supplementary material**

**Supplementary material** is available at European Heart Journal - Case Reports online.

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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