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REVIEW ARTICLE

Berry syndrome—a rare congenital cardiac anomaly

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Abstract
Berry syndrome is a rare congenital cardiac anomaly, characterized by distal aortopulmonary window, hypoplasia or interruption of the aortic arch, intact ventricular septum, and aortic origin of the right pulmonary artery and patent ductus arteriosus. Anatomic depiction of each component is important for the diagnosis. Single-stage surgical repair is challenging but feasible with good survival outcomes. The available literature on this anomaly is limited. Hence, this paper aims at reviewing the literature on Berry syndrome.

Keywords Berry syndrome · Aortopulmonary window · Interrupted aortic arch · Right pulmonary artery

Introduction

Berry et al. first described the association of aortopulmonary septal defect with aortic origin of the right pulmonary artery (AORPA), intact ventricular septum, patent ductus arteriosus, and interruption or coarctation of the aortic isthmus (CoA) in 1982 [1] (Fig. 1). There are fewer than 60 publications on Berry syndrome in the literature [2]. A majority of these patients present in the neonatal period with critical pulmonary hypertension. Anatomic depiction of each component is important for correct preoperative diagnosis.

Embryogenesis

Aortopulmonary window (APW) constitutes 0.1–0.2% of all congenital heart diseases (CHDs). About 30–50% cases of APW have associated cardiac defects, the most common being the interrupted aortic arch (IAA) [3]. The hypothesis proposed for the combination of defects seen in Berry syndrome is impairment in blood flow to the aortic isthmus during the fetal life as a result of a large communication between the aorta and the pulmonary artery [4]. Failure of the septation of common arterial trunk results in an aortopulmonary septal defect ranging from a small communication to complete absence of the septum. The defects can be located in the proximal or distal septum. Failure of septation of primitive arterial trunk posteriorly may disturb the normal flow of events and cause mal-attachment (straddling) of the pulmonary bifurcation to this undivided truncal segment rather than to the main pulmonary arterial trunk. The right pulmonary artery (RPA) thus relates to the aorta and the left pulmonary artery (LPA) to the pulmonary trunk. The right and left pulmonary arterial orifices may be widely separated because the common arterial trunk is dilated or the RPA remained "stranded" because the sixth arches failed to join into a bifurcation.

During normal fetal development, the blood flow in the descending aorta (DA) is supplied through the isthmus (30% of the aortic flow) and through the ductus arteriosus (90% of main pulmonary arterial flow). If the magnitude of blood flow in the ascending aorta (AAo) becomes reduced by such abnormal connections as in aortopulmonary septal defect and aortic origin of the RPA, which can siphon additional highly oxygenated blood from the aortic into the pulmonary arterial circuit, the isthmal flow may become interrupted and consequently that segment of the left dorsal aorta between the left fourth and sixth arches may disappear. In persistent aortopulmonary trunk, the fourth and sixth arches vary inversely in their development and can be applied to the aortopulmonary septal defect. If a large ductus develops in the isthmus, it will likely be interrupted or hypoplastic, and if the ductus is absent or small the arch may be normal. This rule is more likely to apply to a defect located in the distal septum

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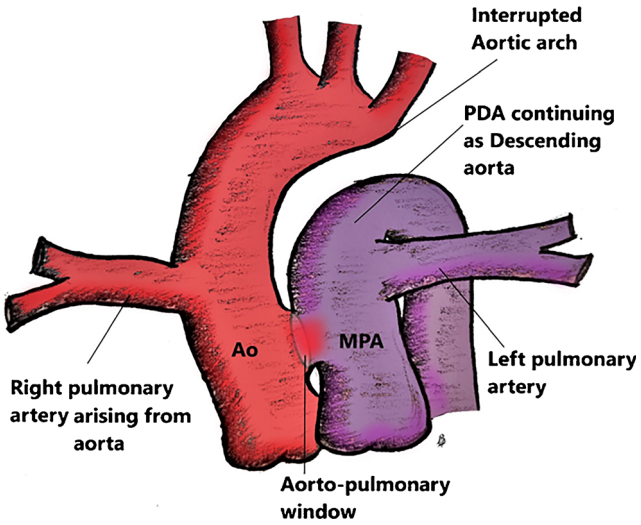

Fig. 1 Diagrammatic illustration of Berry syndrome. Ao, aorta; MPA, main pulmonary artery; PDA, patent ductus arteriosus

near the pulmonary bifurcation and especially when it is associated with aortic displacement of the RPA. The possible embryogenesis of Berry syndrome is illustrated in Fig. 2.

Even though embryologically it shares the same region of origin as the conotruncal anomalies, it is not thought to be the result of an abnormal development involving neural crest cells [5].

Etiology

A majority of the cases are sporadic. Jayaram et al. showed a possible genetic link (102 kb deletion within chromosome band 9p24.2) to Berry syndrome [5]. Higher maternal blood sugar and/or other derangements in the hormonal milieu may result in mutations like 9p24.2 deletion. However, this is less likely since the infant's mother also carries the same genetic mutation without a known cardiac phenotype. The association of trisomy 13 has been reported.

Presentation

Berry syndrome is extremely rare. The estimated incidence within the general population is 0.046% [1]. Neonates born

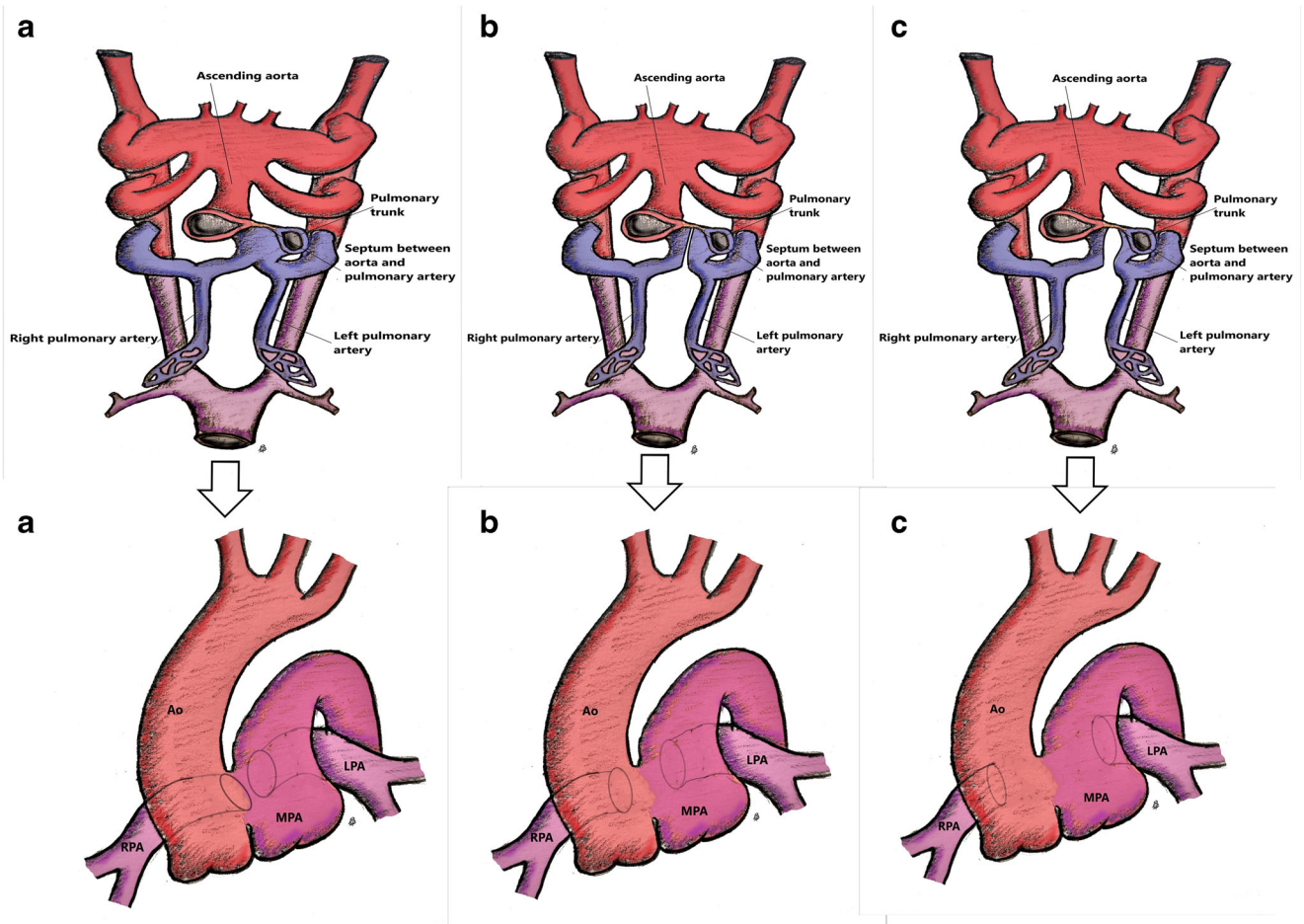

Fig. 2 Embryologenesis of Berry syndrome. Ao, aorta; MPA, main pulmonary artery; LPA, left pulmonary artery; RPA, right pulmonary artery

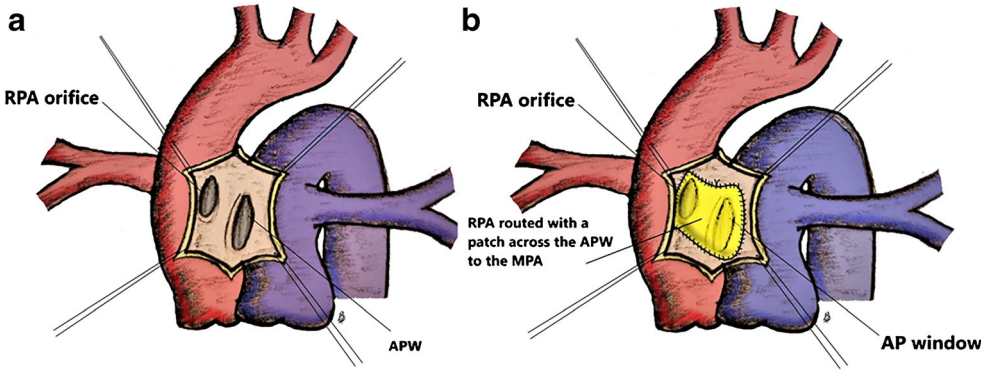

Fig. 3 Intra-aortic baffle. APW, aortopulmonary window; RPA, right pulmonary artery; MPA, main pulmonary artery

with Berry syndrome are sick at birth because of critical pulmonary hypertension. The RPA is dilated due to the consistent left-to-right shunt from the aorta with a tendency to cause airway compression. The perfusion of the lower body is entirely from the ductus arteriosus and depends on the communication between the aorta and pulmonary arteries through the APW. Therefore, early surgical correction in the neonatal period is recommended in these patients to protect the pulmonary vascular bed from irreversible hypertension and to restore normal perfusion of the lower body organs. However, some patients who do not undergo surgery may have a longer survival. Yang et al. reported a case of Berry syndrome in a 12-year-old male who had a thick ductus arteriosus [6]. Therefore, evaluation of the severity of aortic arch dysplasia, shunt flow of the ductus arteriosus, and the collateral vascularity provided are very important information for the patient's prognosis.

Diagnosis

Prenatal diagnosis

Prenatal diagnosis of Berry syndrome has the potential to improve outcomes as early management is possible. Prenatal diagnosis is difficult, but feasible. The difficulty in diagnosis by prenatal fetal echocardiography may be due to the following reasons: (1) These fetuses have a normal four-chamber view and ventricular outflow tract views, and with no associated intracardiac septal defects. (2) The aortic origin of RPA can easily be missed especially if branching of the pulmonary artery is not carefully assessed. (3) In the long-axis view of the aortic arch, the descending aortic arch may be mistaken as the aortic arch; hence, diagnosis of IAA or CoA may be missed. However, the 3-vessel view (3VV) assessment is important in the prenatal diagnosis of Berry syndrome. This view can illustrate the defect between the aorta and the pulmonary trunk, the origin of RPA from the DA, the origin of LPA from the pulmonary trunk, and an abnormal pulmonary artery to aorta (PA-to-AO) ratio. As IAA or CoA can be easily missed, it is important to demonstrate the true cross-sectional and sagittal views by continuously scanning from the 3 vessel-trachea (3VT) view to the long-axis view of the aortic arch. Color and pulsed Doppler echocardiography can be helpful in this regard. Furthermore, the presence of an APW is often the first abnormal sign to be detected by fetal echocardiography in fetuses with Berry syndrome. Therefore, when an APW is detected, it is imperative to define the origin of the RPA and the aortic arch morphology [7]. Given the relatively good survival outcome, an early and accurate prenatal diagnosis would facilitate perinatal management.

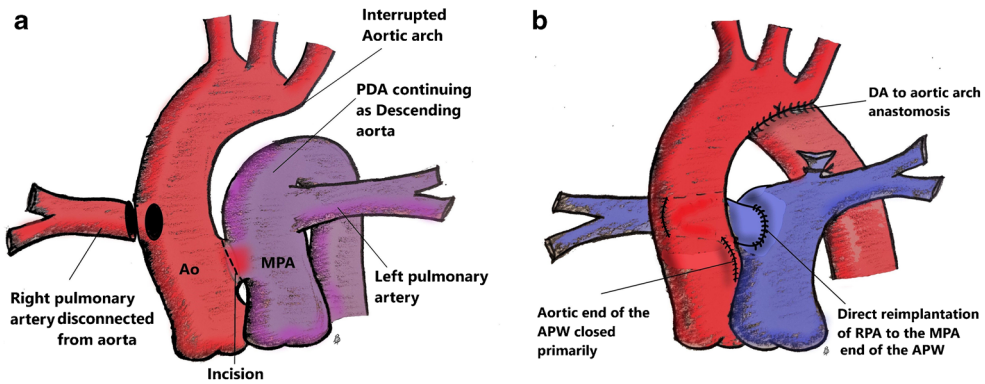

Fig. 4 Right pulmonary artery detachment technique. Ao, aorta; MPA, main pulmonary artery; APW, aortopulmonary window; DA, descending aorta; RPA, right pulmonary artery; PDA, patent ductus arteriosus

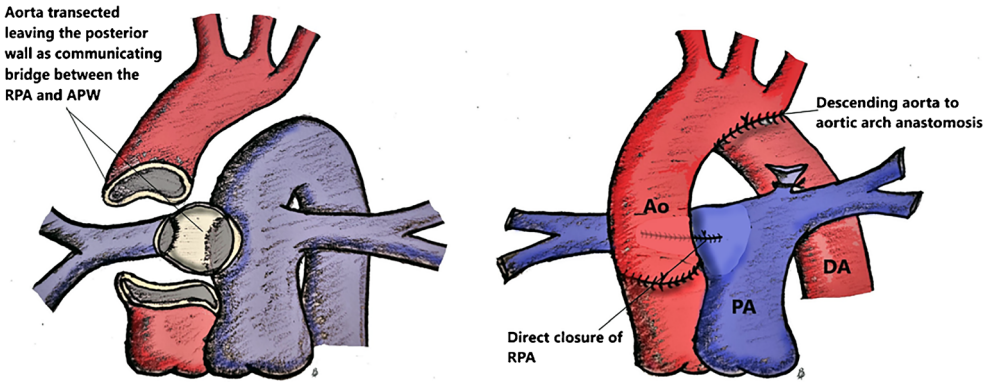

Fig. 5 Right pulmonary artery arterioplasty with an aortic cuff. RPA, right pulmonary artery; Ao, aorta; DA, descending aorta; APW, aortopulmonary window

Postnatal diagnosis

Initially, it was thought that postnatal diagnosis of all the features of Berry syndrome by echocardiography and angiography is a difficult task [5]. Transthoracic echocardiography (TTE) is the initial tool in the postnatal evaluation of Berry syndrome which is a safe and less invasive modality [8]. However, because of limited imaging planes and field of view, further diagnostic evaluations are often needed to confirm the findings. Computerized tomogram angiography (CTA) and three-dimensional (3D) reconstruction, magnetic resonance imaging (MRI) have been used to ascertain the complete anatomical information in patients with Berry syndrome [5, 9].

Management

Berry syndrome is a rare congenital cardiovascular anomaly that is amenable to surgical repair. Usually, neonates presenting with this complex anomaly are critically ill and may need stabilization and urgent surgery. Because of the combination of these two congenital anomalies, surgical treatment seems to be more diverse and difficult when compared with what is typically necessary and used to repair these anomalies, when they occur in isolation. Different surgical techniques have been discussed by different centers. A repair is considered satisfactory only when it results in an unobstructed left ventricular outflow tract, aortic arch, and the RPA. Ideally, the growth potential of the aorta and the pulmonary artery should be maintained. The use of prosthetic material to reconstruct either the aorta or the pulmonary artery impairs the future growth potential of these structures [10–12].

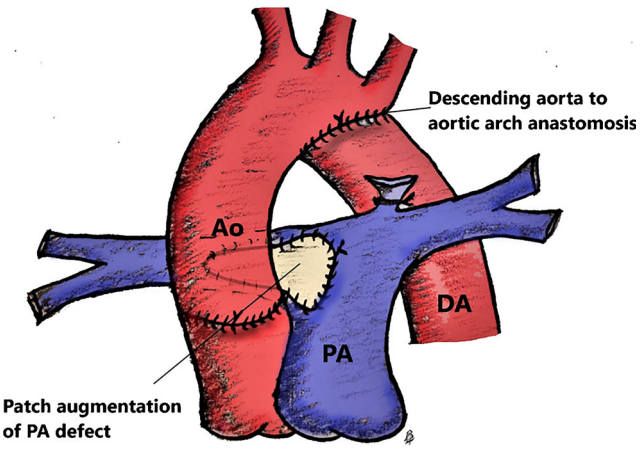

Fig. 6 Anterior patch augmentation of the right pulmonary artery including the main pulmonary artery. Ao, aorta; DA, descending aorta; PA, pulmonary artery

Initially, surgical repair was attempted using the left subclavian artery and a synthetic graft for aortic arch repair [1]. In some patients, surgical correction involved a staged approach, but the results have been unsatisfactory [13, 14]. Most centers advocate one-stage surgery in the neonatal period, although Ghelani and colleagues suggested that a staged repair should be considered in premature infants or small-for-gestational-age infants [15].

There are different techniques described to repair APW and AORPA. Direct implantation of RPA to the main pulmonary artery (MPA) allows native tissue-to-tissue anastomosis with possible growth potential. An anterior patch augmentation will ensure tension-free anastomosis in certain cases. If the distance is of concern, a trap door flap from the anterolateral wall of the MPA allows tissue-to-tissue anastomosis as described by Chang et al. [16]. With the application of this technique, RPA can be translocated anteriorly to prevent compression by the airway which also makes future RPA interventions easy. Burke and Rosenfeld reported a single-stage repair of a 13-day-old neonate with Berry syndrome without homograft tissue or synthetic graft. After the aorta was separated from the pulmonary artery, the DA was anastomosed to the defect in the AAo. The RPA was anastomosed to the defect in the MPA anterior to the aorta. They suggested the shift of the RPA in front of the aorta to avoid compression [17]. Kitagawa et al. used the posterior wall of the AAo to form the posterior portion of the confluence between the RPA and the MPA, and a patch of autologous pericardium to reconstruct the anterior portion [18]. A similar technique was used by Codispoti and Mankad in a 4-month-old infant via the sternotomy-thoracotomy approach [19].

Abbruzzese et al. reported a case of Berry syndrome corrected by direct anastomosis between the ascending and

Table 1 Experiences with Berry syndrome

Author	No. of patients	Age	Gender	Genetic anomaly	Method of RPA reconstruction	Outcome
Sharma et al. [24]	1	Not done	F	Trisomy 13	–	–
Backer et al. [25]	1*	30 days	–	–	RPA detachment	Died
Senzaki et al. [26]	1	6 days	M		Aortic cuff	
Fong et al. [27]	1	3 days	F		Unknown	Residual aortic and RPA stenosis
Konstantinov et al. [22]	5*	8 days Neonatal	F -	- -	Aortic cuff -	Uneventful -
Park et al. [23]	2	4 month	M		Aortic cuff with pericardium	RPA stenosis: balloon dilatation
Konstantinov et al. [28]	1*	3 days	F		Unknown	Uneventful
Mannelli et al. [9]	1	1 month	M		Intra-aortic patch	Uneventful
Morito et al. [29]	1	10 days	F		Intra-aortic patch	Uneventful
Jayaram et al. [5]	1	7 days	F	102-kb deletion within 9p24.2	Intra-aortic patch	–
Ghelani et al. [15]	1	PA banding on 2 days; definitive repair on 13 days	F		Intra-aortic patch with aortic root enlargement	Mild RPA stenosis
Liu et al. [30]	1	13 months	M		Aortic flap and homologous PA patch	Uneventful
Remon et al. [31]	1	Not done		Trisomy 13		
Alsoufi et al. [21]	3*				Aortic cuff	1 patient required reoperation for AAO and branch PA stenosis
Hu et al. [2]	16	8–170 days	F, 04 M, 12		Intra-aortic baffle: 5 (3 bovine pericardium, 2 ePTFE) Aortic cuff: 5 RPA detachment: 6	RPA stenosis in 2 patients with RPA detachment 1—RPA plasty and aortic arch augmentation 2—Balloon dilatation followed by RPA plasty for restenosis

RPA, right pulmonary artery; *PA*. pulmonary artery; *ePTFE*, expanded polytetrafluoroethylene; *AAO*, ascending aorta

*Included in a broad spectrum of patients with disease such as aortopulmonary window

descending aorta, and reconstruction of the pulmonary trunk and RPA using a flap of aortic tissue. A native pericardial patch was used to reconstruct the AAo [20].

Hu et al. conducted a retrospective study of single-stage repair of Berry syndrome in 16 infants using three different techniques namely intra-aortic baffle (Fig. 3), RPA detachment (Fig. 4), and RPA angioplasty with an aortic cuff (Fig. 5). They showed that the single-stage repair of Berry syndrome is possible with acceptable outcomes. Reoperations are mainly related to the aortic or RPA stenosis, and are higher in those having RPA arterioplasty with an aortic cuff. Among the three techniques, intra-aortic baffle yielded the good results in their study [2]. RPA arterioplasty needs aortic transection with a potential risk of posterior aortic wall bleeding which may be difficult to identify sometimes. Direct anastomosis of the aorta may carry a potential risk of RPA and left main bronchus compression which can be mitigated by Lecompte maneuver. Patch augmentation of the posterior aortic wall may be required in certain cases to ensure tension-free anastomosis and to get an adequate aortic length [21, 22]. Studies have reported that this technique is plagued by RPA stenosis requiring re-interventions [21, 23]. Even though anatomy is preserved in intra-aortic baffle technique, the size and growth potential of the baffle patch used are the drawbacks of this procedure considering the growth potential of neonates [17, 19]. Similarly, Mannelli and colleagues also described several cases of intra-aortic patch repair with no complications [9]. RPA detachment is most frequently used in isolated AORPA as long as the adequate mobilization of the RPA is feasible for direct anastomosis. Tension-free anastomosis can be performed either with an anterior patch augmentation or a trapdoor flap from the anterolateral wall of the MPA as described by Chang et al. [16] (Fig. 6). Various surgical experiences with Berry syndrome are summarized in Table 1.

The surgical principles of IAA repair in Berry syndrome are the same as in isolated IAA. However, the surgical outcome of arch reconstruction plays an essential role in Berry syndrome [22, 23]. The distal obstruction of the aortic arch can cause the proximal dilation of the AAo, thus compressing the RPA and the left main bronchus [32]. Under such circumstances, an optimal arch reconstruction method would be patch augmentation to eliminate postoperative arch stenosis [22]. The aortic arch can be reconstructed by anastomosing the DA to the arch and direct end-to-end anastomosis of the AAo [23].

Patients with Berry syndrome are prone to develop pulmonary hypertensive crisis in the perioperative period often requiring inhaled nitric oxide (iNo) besides ventilator and other pharmacological manipulations.

Careful follow-up is mandatory in Berry syndrome patients following the surgery. As shown in the literature, stenosis at the site of aortic reconstruction and the RPA are potential problems. It is possible to treat pulmonary artery stenosis adequately by percutaneous balloon angioplasty or RPA augmentation. Arch stenosis needs redo arch augmentation. One of the complications described is the myocardial ischemia secondary to coronary artery compression following the direct implantation of the RPA to the MPA which was addressed by using an interposition graft between the RPA and the MPA [32].

Berry syndrome is an uncommon and rare congenital cardiac anomaly. It mainly presents as life-threatening critical pulmonary hypertension during the neonatal period. Proper understanding and meticulous anatomical correction determine the surgical outcome. Careful follow-up is necessary to identify the anastomotic stenosis and to treat as necessary.

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Declarations

Ethics committee approval Not required.

Informed consent Not applicable.

Statement of human and animal rights No animals involved.

Conflict of interest The authors declare no competing interests.

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