Transcatheter closure for patent ductus arteriosus in patients with Eisenmenger syndrome: to do or not?

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Research article

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Abstract

Background: Patent ductus arteriosus (PDA) complicated by Eisenmenger syndrome (ES) remains to be a major cause of morbidity and mortality worldwide. Giving increasing evidence of benefit from targeted therapies, ES patients once thought to be inoperable may have increasing options for management. This study aims to explore whether the PDA in patients with ES can be treated with transcatheter closure (TCC).

Methods: Between August 2014 and July 2016, four out of fifteen PDA-ES patients whose Qp/Qs improved significantly and Qp/Qs>1.5 after acute vasodilator testing with 100% oxygen were selected to receive TCC and pulmonary vasodilator therapy. PAH-targeted drugs were prescribed before and after occlusion for all patients. Trial occlusion was performed before permanent closure.

Results: The first TCC failed after the initiation of PAH-targeted drugs for 6 months in four patients. After the medication was adjusted and extended to 12 months, TCC was performed for all without hemodynamic intolerances during perioperative period. Pulmonary artery systolic pressure (PASP) was significantly decreased (≥ 40%) immediately after TCC. During a mean 52-month follow-up, there was a further decrease of PASP in two patients, the other two showed improved pulmonary vascular resistance (PVR), WHO functional class and six-minute walking distance although PASP was deteriorated again.

Conclusion: Some selected PDA-ES patients with PVR<15Wood U and Qp/Qs>1.5 at baseline might benefit from TCC and PAH-targeted drugs pre- and post-occlusion play a crucial role.

Background

Patent ductus arteriosus (PDA) is one of the most common congenital heart defects (CHDs). Without timely correction, vasomotor dysfunction of endothelial cells and vascular remodeling will develop gradually in pulmonary arteries, leading to increased pulmonary vascular resistance (PVR), severe pulmonary arterial hypertension (PAH) and eventually Eisenmenger syndrome (ES) which remains to be a major cause of morbidity and mortality worldwide [1,2]. Additionally, in developing countries such as China, PDA associated with ES is common because CHDs are not detectable until adulthood and ES has developed. This situation is now becoming a frontier issue.

Transcatheter closure (TCC) for PDA has been established as a safe and effective alternative to surgical closure with the advancement and improvement of techniques and materials [3]. However, TCC is generally considered as contraindicated for ES patients due to irreversible obstructive lesions of the pulmonary vasculature in the past clinical practice.

Recently, giving increasing evidence of benefit from targeted therapies[4], ES patients once thought to be inoperable may have increasing options for management[5,6]. Patients with severe PAH are amenable to surgery or TCC after successful treatment with targeted drugs[7,8,9]. However, there is not much information regarding the immediate and long-term prognosis with such patients.

In this study, we aim to study the change of pulmonary artery systolic pressure (PASP), cardiac function and hemodynamic variables of four PDA-ES patients who underwent TCC and pulmonary vasodilator therapy by diagnostic treatment and repair strategy with long-term follow-up, in order to identify whether PDA-ES patients can benefit from TCC.

Methods

Patients

The records of fifteen patients with clinical and echocardiographic findings of PDA and ES were retrospectively reviewed from August 2014 to July 2016. The inclusion criteria for ES is based on European guidelines[10]. Each patient underwent blood gas analysis, six-minute walking distance (6MWD), World Health Organization functional class (WHO FC), echocardiography and right heart catheterization (RHC). This study was conducted in accordance with the amended Declaration of Helsinki. Written informed consents were obtained from all the patients.

Hemodynamic measurement

RHC was performed with Swan-Ganz catheter (Edwards 774,7.5F) and monitoring system (Edwards Lifesciences LLC, Vigilance II). All measurements were performed with the patients in supine position. Hemodynamic parameters included right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP). Cardiac output (CO) was assessed using the Fick's method before TCC or continuous thermodilution method during follow-up. Arterial blood gases and mixed venous oxygen generation (SvO_2) were measured. Pulmonary to systemic flow ratio (Qp/Qs), PVR and systemic vascular resistance (SVR) were calculated using standard formulas. All measurements were made in a stable baseline period without oxygen for at least 2 hours.

Acute vasodilator testing was then performed with oxygen. Standardized oxygen was given via standard commercial equipment at a flow rate of 8 L/min to achieve an oxygen saturation of 100% in every patient. Oxygen was applied for at least 10 min. Hemodynamic parameters, particularly Qp/Qs, were again recorded. Qp/Qs>1.5 after inhalation of 100% oxygen was defined as an absolute cutoff value to screen the candidates for our study.

After diagnosis by initial RHC and acute vasodilator testing, four PDA-ES patients (3 female and 1 male) were selected to be treated with PAH-targeted drugs (Fig.1).

Intervention procedure

Under local anesthesia and transthoracic echocardiographic guidance, interventional procedure was performed after percutaneous puncture of the femoral artery and vein. Orphology of PDA was demonstrated with 6F pigtail in descending thoracic aorta by angiography and the narrowest diameter of PDA was measured meanwhile. Trial occlusion using PDA occluder(Shanghai Shape Memory Alloy Ltd,

China) was performed for 30 minutes to record the change in hemodynamic data which were obtained from RHC. Then the occluder was released when all the following criteria were satisfied after trial occlusion: 1) a decrease in PASP≥ 40%; 2) no decrease in the aortic pressure (AOP); 3) an increase in systemic arterial oxygen saturation (SaO_2).

Follow-up

The patients were followed up in out-patient clinic every 6 months after discharge with the last follow-up in August 2020. 6MWD, transthoracic echocardiography and blood gas analysis were routinely carried out. The hemodynamic evaluations by RHC were assessed in case 2,3,4 at 72,48,36 months follow-up, respectively.

Results

Study patients

The mean age of the selected four PDA-ES patients were 28.5 years (ranging from 19 to 34 years) with WHO FC□-□. Baseline demographic characteristics and echocardiography parameters were shown in Table 1.

The mean PVR was 22.19 Wood U (ranging from 14.70 to 36.91 Wood U). The mean PASP and AOP were 126 mmHg (ranging from 105 to 145 mmHg) and 129 mmHg (ranging from 113 to 144 mmHg), respectively. Baseline hemodynamic parameters obtained by RHC and the changes of Qp/Qs after 100% oxygen inhalation were shown in Table 2.

Diagnostic treatment and repair strategy

After initiation of PAH-targeted therapy for 6 months, the first attempt of TCC failed because PASP measured by RHC did not decrease or the reduction was less than 20%. After targeted therapy was adjusted and extended to 12 months, all the criteria were met and the PDA occluder was released following trial occlusion. There was no residual shunt for all and none had a complication or adverse event during or after TCC. All patients were discharged 1-2 days after TCC with PAH-targeted drugs. Initial and adjusted PAH-targeted drugs were shown in Table 3. The PDA diameter,changes of PASP, AOP and SaO_2 before and after trial occlusion were shown in Table 4.

Follow-up

At 12-month follow-up, Cases 1 and 2 discontinued targeted therapy because PASP decreased to near normal. Case 2 was treated with ambrisentan again at 60-month follow-up as PASP rose to 72 mmHg. At 72-month follow-up, the PASP fall to 58mmHg.PASP of Case 3 decreased to 98mmHg at 12-month follow-up but rose to 140mmHg at 24-month after she stopped targeted drug without doctor consultant, therefore she was prescribed with bosentan and sildenafil again and the PASP was 111mmHg at 48-month follow-up. PASP of Case 4 decreased to 70mmHg at 12-month but rose again to 87mmHg at 24-

month. She was prescribed with macitentan instead of ambrisentan at 29-month while the PASP increased to 131mmHg at 36-month. The data of PASP during follow-ups were shown in Table 5.

All the four patients showed improved 6MWD, WHO FC and SaO_2 without enlarged RV diameter during a mean 52-month (range 32-72) follow-up. Hemodynamic assessment by RHC showed there was a significant fall in PVR of 3.83Wood U in case 2. Case 3 and 4 also displayed improved PVR of 12.68Wood U,12.54 Wood U and PVR/SVR of 0.88,0.80, respectively (Table 6). RV diameter, WHO FC, 6MWD and PAH-targeted drugs were shown in Tables 7.

Discussion

CHDs patients with ES were previously considered to have irreversible pulmonary hypertension. Isolated correction of the cardiac defect in patients with ES has typically been considered a contraindication[11]. Historically, management options for patients with ES have been limited to palliative measures or heart-lung transplantation. The recent introduction of targeted therapies in PAH has led to a renewed insight in the pathophysiology and treatment of ES [11,12]. Considering ES patients maintain some degree of pulmonary vasoreactivity despite the presence of obstructive pulmonary hypertension[13],patients with ES using a diagnostic treatment and repair strategy are amenable to surgery or TCC after successful treatment with advanced therapy, but no proof of its efficacy has really been shown in large-scale studies[14,15,16]. Our study indicated that some selected PDA-ES patients might be amenable to and benefit from TCC over a long follow-up period. Uninterrupted combination of PAH-targeted drugs before and after occlusion play a crucial role especially for the high-risk PDA-ES patients.

Treatment with advanced therapies[17,18,19] for a sufficient period to assess the hemodynamic and symptomatic response is strongly recommended before closure[13,14].Supomo et al[20] described a atrial septal defect(ASD)-ES female with highly symptomatic PAH(NYHA class III, mean PAP 77 mmHg, PVR 4 Wood U) underwent occlusion successfully after oral beraprost for two years. After surgery her mean PAP decrease to 38 mmHg with PVR of 2.52 Wood U. Hu et al[21] reported a ventricular septal defect (VSD)-ES patient with initial PVR of 18.84 Wood U underwent a successful operation after oral bosentan for 12 weeks, as a result of which her PVR decreased to 9.63 Wood U. Our four PDA patients were all ES with a higher PASP and PVR compared to the reports above. Our findings indicated that initial combination of PAH-targeted drugs for one year at least may provide ES patients with better occlusion opportunity. Especially for the ES patients as case 3 and 4 with baseline PVR>15Wood U and Qp/Qs<1.5, initial dual or triple combination of PAH-target drugs for a longer period before occlusion are needed to be taken into account.

Selecting ES patients who can be treated with TCC is an important issue that needs to be addressed. The indications for PDA with severe PAH patients to be considered for correction are not uniformly defined and may include pulmonary artery vasoreactivity and/or the presence of Qp/Qs at least 1.5 to 1.0[2,10]. A strength of the this study is that all of our patients was classified as ES according to a recent

definition[10], the Qp/Qs of our four patients improved significantly and Qp/Qs >1.5 following pulmonary vasoreactivity testing was identified with preserved pulmonary vasodilation, which may be deemed candidates for pulmonary vasodilator therapy and subsequent TCC .Of note, after PAH-targeted therapy, significant fall of PASP during trial occlusion indicates a likelihood for final TCC [22,23] . Yan et al [24] reported successful occlusion in twenty PDA patients with mean PASP 104 mmHg, PVR 9.1 Wood U and Qp/Qs 2.1. A decrease of >25% in PASP following trial occlusion was used as the criterion for occlusion. Thanopoulos et al[25] reported a decrease of >30% in PASP as occlusion criterion in seven PDA patients with Qp/Qs≥2.0. Considering our four patients were all ES patients with higher PASP and lower Qp/Qs, our occlusion criteria is more stricter than the above studies. TCC was performed if all the following criteria were met: 1) A drop of ≥40% in PASP; 2) no decrease in AOP; 3) an increase in SaO_2. During the follow-up period, PASP of case 1,2 decreased further while the other two rose again, therefore the optimal occlusion criteria were still needed further explored in more PDA-ES patients.

During the long-term follow-up, our four PDA-ES patients displayed improved WHO FC and 6MWD. The PASP of Case 2 deteriorated after interruption of targeted therapy whereas improved gradually following the drug was administered again, indicating the PAH of Case 2 was partially reversible thus targeted therapy could not be discontinued after TCC. Monotherapy would be adoptable needing to be maintained for a long even life-long period. The PVR of Cases 3 and 4 decreased suggesting improvement of right cardiac function after TCC and pulmonary vasodilator therapy. Nevertheless, the deteriorate PASP indicated the two patients might had structurally irreversible PAH or inadequate PAH-targeted therapy. Our result further suggested after TCC, uninterrupted dual or triple combination of targeted drugs including oral even intravenous or subcutaneous prostacyclin analogues are also considered for these high-risk PDA-ES patients. In general, in spite of initial positive pulmonary vasoreactivity testing and improved hemodynamic status after PAH-targeted therapy, TCC should be performed with caution for such special individuals.

Conclusion

PDA-ES patients whose PVR<15Wood U and Qp/Qs>1.5 at baseline might be amenable to and benefit from TCC. Uninterrupted dual or triple combination of PAH-targeted drugs pre- and post-occlusion play a crucial role especially for the high-risk PDA-ES patients.

Study limitations

There are three main limitations in our study. First, the major limitation of the study was the small sample which limited its power. Second, PASP was evaluated by transthoracic echocardiography rather than RHC in most follow-up time. Third, standard pulmonary vasoreactivity testing should include inhaled nitric oxide in addition to 100% oxygen whereas nitric oxide was not used in our study.

List Of Abbreviations

PDA: patent ductus arteriosus; ES: Eisenmenger syndrome; TCC: transcatheter closure; PASP: pulmonary artery systolic pressure; CHDs: congenital heart defects; PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension; 6MWD:six-minute walking distance ; WHO FC: World Health Organization functional class; RHC : right heart catheterization; RAP: right atrial pressure ; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; SvO_2:mixed venous oxygen generation; Qp/Qs: pulmonary to systemic flow ratio; PVR: pulmonary vascular resistance ;SVR: systemic vascular resistance ; AOP: aortic pressure; SaO_2:systemic arterial oxygen saturation; O_2:Oxygen.

Declarations

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Not applicable.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JX, LW, LG and YLS. The first draft of the manuscript was written by JX, LW. FDC was responsible for the revision of the manuscript for important intellectual content. All authors commented on previous versions of the manuscript and approved the final manuscript.

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Availability of data and materials

The datasets used in the case are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Shanghai east hospital affiliated to Tongji University. Written informed consent was obtained from individual participant.

Consent for publication

Written informed consents were obtained from the patients for publication of this study. The copy of the written consents was available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Baseline demographic characteristics and echocardiography parameters of all patients

Patient (No.)	Sex	Age (years)	WHO FC	6MWD (m)	LVEF (%)	RV diameter (mm)	PASP (mmHg)
1	M	29		440	53	69*42	115
2	F	19		400	67	57*29	120
3	F	32	-	170	72	68*40	144
4	F	34		450	67	75*35	104

Abbreviation: WHO FC, WHO functional class; 6MWD, six-minute walking distances; PASP, pulmonary artery systolic pressure; LVEF, left ventricular ejection fraction; RV, right ventricle.

Table 2. Baseline hemodynamics parameters measured by right heart catheterization

Patient (No.)	RAP (mm Hg)	PASP (mm Hg)	TPR (Wood U)	PVR (Wood U)	SVR (Wood U)	PVR/SVR	AOP (mmHg)	SaO_2(%)	Qp/Qs	
									Baseline	O_2 test
1	13/6/9	105/73/81	18.95	16.14	28.29	0.57	114/69/79	91.8	1.73	2.92
2	5/0/2	105/65/85	15.82	14.70	40.34	0.36	115/65/80	95	2.13	2.46
3	9/2/5	143/63/95	40.31	36.91	36.07	1.02	142/62/95	88.9	1.00	1.72
4	11/3/7	134/72/98	23.13	21.01	24.50	0.86	130/70/90	89.7	1.10	2.60

Abbreviation: RAP, right atrium pressure; PASP, pulmonary artery systolic pressure; TPR, total pulmonary resistance; PVR, pulmonary vascular resistance. Qp/Qs, pulmonary-systemic blood flow ratio; SVR, systemic vascular resistance; AOP, aortic pressure; SaO_2, systemic arterial oxygen saturation.

Table 3. Initial and adjusted PAH-targeted drugs before TCC

Paitent (No.)	intial	adjusted
1	vardenafil 5mg bid	vardenafil 5mg bid bosentan 125mg bid
2	tadanafil 20mg qd	tadalafil 20mg qd bosentan 125mg bid
3	bosentan 125mg bid tadanafil 20mg qd	bosentan 125mg bid tadanafil 20mg qd
4	ambrisentan 5mg qd tadalafil 20mg qd	ambrisentan 5mg qd tadalafil 20mg qd

Table 4. Comparisons between pre-occlusion and post-occlusion parameters

Patient (No.)	PDA diameter (mm)	PASP (mmHg)		AOP (mmHg)		SaO_2 (%)	
		Before occlusion	After occlusion	Before occlusion	After occlusion	Before occlusion	After occlusion
1	10	105	66	113	124	96	98
2	9	116	68	122	127	97	100
3	9	138	74	137	150	92.3	100
4	11	145	72	144	153	97.2	100

Abbreviation: PDA, patent ductus arteriosus; PASP, pulmonary artery systolic pressure; AOP, aorta pressure; SaO_2, systemic arterial oxygen saturation.

Table 5. PASP changes during follow up by echocardiography

Patient (No.)	PASP (mmHg)					
	12m	24m	36m	48m	60m	72m
1	31	28	27	/	/	/
2	58	57	55	53	72	58
3	98	140	140	111	/	/
4	70	87	131	/	/	/

Abbreviation: PASP, pulmonary artery systolic pressure.

Table 6. Hemodynamics parameters measured by right heart catheterization at follow-up

Paitent (No.)	RAP (mmHg)	PASP (mmHg)	CO (L/min)	SaO_2(%)	PVR (Wood U)	SVR (Wood U)	PVR/SVR
2	11/6/9	55/18/36	6.0	98	3.83	13.33	0.29
3	15/8/11	139/47/82	5.6	94.3	12.68	14.29	0.88
4	12/1/6	136/54/86	5.9	92.2	12.54	15.67	0.80

Abbreviations: RAP, right atrium pressure; PASP, pulmonary artery systolic pressure; CO, cardiac output; SaO_2, systemic arterial oxygen saturation; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Table 7.RV diameter, WHO FC ,6MWD and PAH-targeted drugs at the last follow-up

Paitent (No.)	RV diameter(mm)	WHO FC	6MWD (m)	PAH-targeted drugs
1	50*25	Ⅱ	550	/
2	55*28	Ⅱ	500	ambrisentan
3	65*40	Ⅲ	440	bosentan,sildenafil
4	59*39	Ⅲ	490	macitentan,tadalafil

Abbreviations: RV, right ventricle; WHO FC, WHO functional class; 6MWD, six-minute walking distances.

Figures

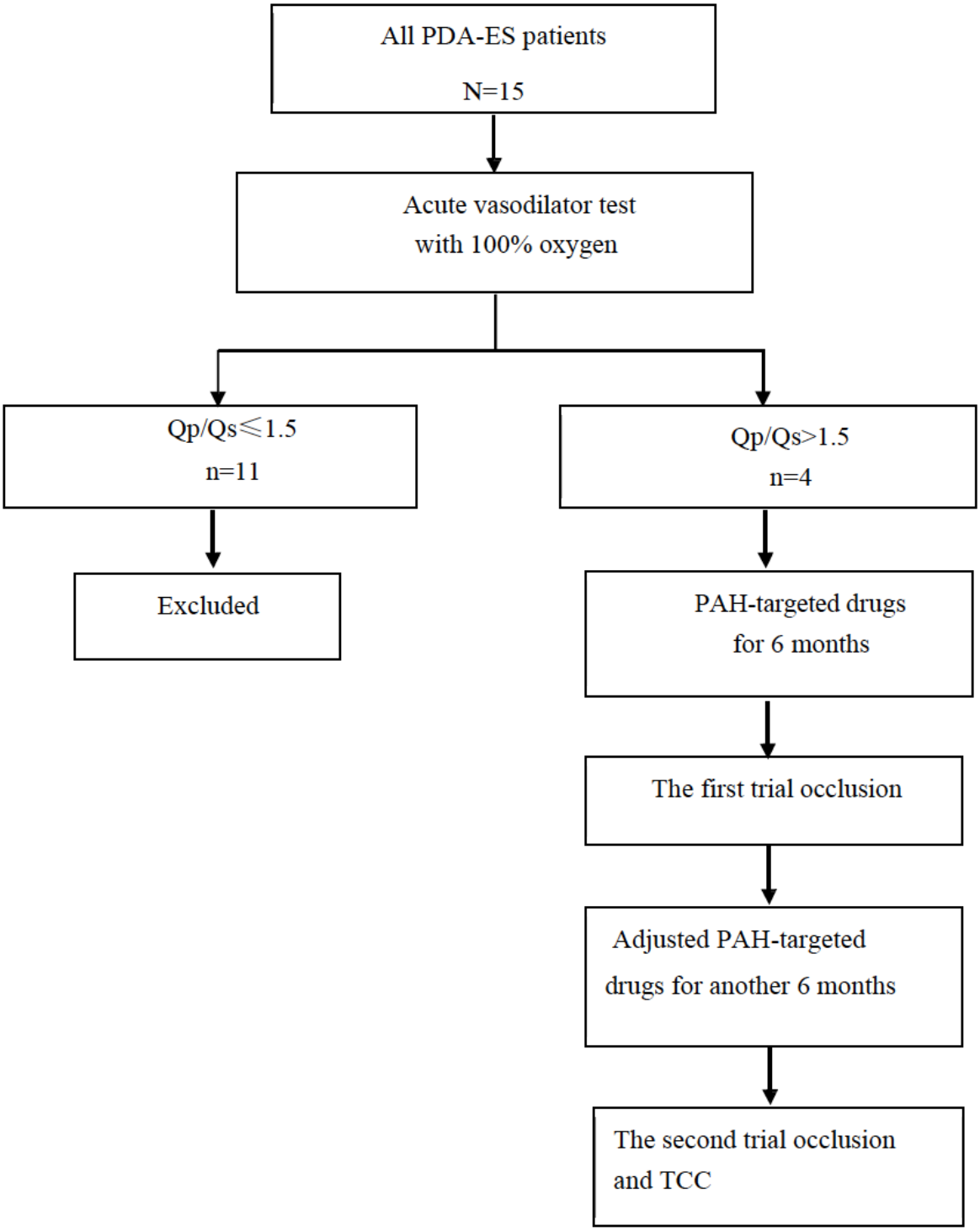

Figure 1

Study flow chart Abbreviation: PDA, patent ductus arteriosus; ES, Eisenmenger syndrome; Qp/Qs, pulmonary-systemic blood flow ratio; PAH, pulmonary arterial hypertension; TCC, transcatheter closure.