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

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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 drug 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 by diagnostic treatment and repair strategy. 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 the follow-up period, there was a further decrease of PASP in two patients, the other two showed improved WHO functional class and six-minute walking distance although a worsening PASP.

Conclusion Some selected PDA-ES patients with PVR < 15Wood U and Qp/Qs > 1.5 at baseline might benefit from TCC by diagnostic treatment and repair strategy and uninterrupted combination of 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.

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 drug 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 PASP, cardiac function and hemodynamic variables of four PDA-ES patients who underwent TCC by diagnostic treatment and repair strategy during the long follow-up period, 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. Each patient underwent blood gas analysis, six-minute walking distance (6MWD), World Health Organization functional class (WHO FC), echocardiography and right heart catheterization (RHC). Four PDA-ES patients were selected to receive TCC from August 2014 to July 2016 (Fig.1). 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 using a Swan-Ganz catheter (Edwards 774,7.5F). 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. Arterial blood gases and mixed venous oxygen generation (SvO$_2$) were measured. Pulmonary to systemic flow ratio (Qp/Qs), pulmonary vascular resistance (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.

Intervention procedure

After diagnosis by initial RHC and acute vasodilator testing, 3 female and 1 male PDA-ES patients were selected to be treated with PAH-targeted drugs(Fig.1). Interventional procedure was performed after percutaneous puncture of the femoral artery and vein. Under local anesthesia and transthoracic echocardiographic guidance,trial occlusion was performed for 30 minutes to record the change in hemodynamic data which were obtained from RHC.TCC was performed with the PDA occluder (Shanghai Shape Memory Alloy Ltd, China) when all the following criteria were satisfied: 1) a decrease in pulmonary

artery systolic pressure（PASP）≥ 40%; 2) no decrease in the aortic pressure (AOP); 3) an increase in systemic arterial oxygen saturation (SaO2).

Follow-up

The patients were followed up in out-patient clinic every 6 months after discharge with the last follow-up in January 2020. 6MWD, echocardiography and blood gas analysis were routinely carried out during follow-up. The PASP was estimated by colour Doppler echocardiography.

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 Ⅱ-Ⅲ. The baseline information of demographic characteristics, echocardiographic and hemodynamic parameters were shown in Table 1.

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

Patient No.	Sex	Age (years)	WHO FC	6MWD （m）	LVEF （%）	RV sizes （mm）	PASP (mmHg)	PDA sizes （mm）
1	M	29	Ⅱ	440	53	69*42	115	10
2	F	19	Ⅱ	400	67	57*29	120	9
3	F	32	Ⅱ-Ⅲ	170	72	68*40	144	9
4	F	34	Ⅱ	450	67	75*35	104	11

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

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

Table 2. Baseline hemodynamics parameters measured by the right heart catheterization

Patient No.	RAP (mm Hg)	PAP (mm Hg)	TPR (Wood U)	PVR (Wood U)	Qp/Qs Baseline	Qp/Qs O$_2$ test
1	13/6/9	105/73/81	18.95	16.14	1.73	2.92
2	5/0/2	105/65/85	15.82	14.70	2.13	2.46
3	9/2/5	143/63/95	40.31	36.91	1.00	1.72
4	11/3/7	134/72/98	23.13	21.01	1.10	2.60

Abbreviation: RAP, right atrium pressure; sPAP, systolic pulmonary artery pressure; TPR,total pulmonary resistance; PVR, pulmonary vascular resistance. Qp/Qs, pulmonary-systemic blood flow ratio

Diagnostic treatment and repair strategy

After initiation of PAH-targeted drug 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 drug therapy was adjusted and extended to 12 months,all the criterias were met and the PDA occluder was released following trial occlusion. There was no residual shunt for all 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. Changes of SPAP, AOP and SaO2 before and after trial occlusion were shown in Table 4.

Table 3. Initial and adjusted PAH-targeted drugs regimen 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.	PASP(mmHg)		AOP(mmHg)		SaO$_2$ (%)	
	Before occlusion	After occlusion	Before occlusion	After occlusion	Before occlusion	After occlusion
1	105	66	113	124	96	98
2	116	68	122	127	97	100
3	138	74	137	150	92.3	100
4	145	72	144	153	97.2	100

Abbreviation: PASP, pulmonary artery systolic pressure; AOP, aorta pressure; SaO2,systemic arterial oxygen saturation.

Follow-up

At one-year follow-up, Cases 1 and 2 discontinued targeted-drug therapy because PASP decreased to near normal. Case 2 was treated with ambrisentan again as PASP rose to 72 mmHg at 60-month follow-up. PASP of Case 3 decreased to 98mmHg at 12-month follow-up but rose to 140mmHg at 36-month after she stopped targeted drug therapy without doctor consultant, she was prescribed with bosentan and sildenafil again. PASP of Case 4 decreased to 70mmHg at the first year, but rose again to 87mmHg at the 24-month and 131mmHg at the 36-month. She used macitentan instead of ambrisentan at the 29-month.

All the four patients showed improved 6MWD, WHO FC and SaO2 without enlarged RV size during a mean follow-up of 52.0 months (range 32-72).Relevant PASP, RV size, WHO FC and PAH-targeted drugs regimen during follow-ups were shown in Tables 5 and 6.

Table 5.PASP changes during follow-up

Patient (No.)	PASP (mmHg)					
	12m	24m	36m	48m	60m	72m
1	31	28	27	/	/	/
2	58	57	55	53	72	62
3	98	140	140	/	/	/
4	70	87	131	/	/	/

Abbreviation: PASP, pulmonary artery systolic pressure measured by echocardiography.

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

Paitent (No.)	RV size (mm)	WHO FC	6MWD	drugs
1	50*25	ⅰ	550	/
2	55*28	ⅰ	500	ambrisentan
3	68*46	ⅰ	440	bosentan,sildenafil
4	69*40	ⅰ	490	macitentan,tadalafil

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

Discussion

Our study indicated that some selected PDA-ES patients might be amenable to and benefit from TCC by diagnostic treatment and repair strategy. Uninterrupted combination of PAH-targeted drugs before and after occlusion play a crucial role, especially for the ES patients with partial structurally reversible PAH.

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 [10]. 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[10,11]. Patients with ES using a diagnostic-treatment-and-repair strategy are amenable to surgery after successful treatment with advanced therapy, but no proof of its efficacy has really been shown in large-scale studies[12,13,14].

The indications for ES 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[10]. To our best knowledge, breathing Oxygen (O2) as one of the standard methods for testing pulmonary vasodilation was used for unrepaired CHD to determine surgical operability[15,16]. In this study, the Qp/Qs of our four patients improved significantly and Qp/Qs >1.5 following 100% O2 inhalation test was identified with preserved pulmonary vasodilation, as is shown in Table 2.

Pretreatment 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 ASD-ES female with highly symptomatic PAH(NYHA class III, mPAP 77 mmHg, PVR 4 Wood U) underwent occlusion successfully after oral beraprost for two years. After surgery her mPAP 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 patients had a higher PASP and PVR compared to the reports above. Our findings indicated that initial combination of PAH-targeted drugs therapy for 1 year at least may provide ES patients with better occlusion opportunity.

Recently, significant fall of PASP during trial occlusion indicates a likelihood for TCC after PAH-targeted therapy[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 a 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 criterias were met: 1) A drop of≥40% in PASP ; 2) no decrease in AOP; 3) increase in SaO2. During follow-up period, PASP of case 1,2 decreased further while the other two rose again, thus the optimal occlusion criteria were still needed further exploration in such ES patients.

During the long follow-up period, our four patients displayed improved WHO functional class and six-minute walking distance. Upon 1-year follow-up, targeted drug therapy was discontinued for Cases 1 and 2 as PASP decreased to near-normal. In view of the PASP of Case 2 didn't decrease further, we considered the PAH of Case 2 was partially reversible thus targeted drug therapy could not be discontinued. The PASP of Cases 3 and 4 turned out worse indicating the two patients might had structurally irreversible PAH, positive inhaled oxygen test did not necessarily mean reversibility. Steele et al[11] concluded that the total PVR was highly predictive of outcome after surgery in this patient population and suggested that patients with a PVR of less than 10Wood U should proceed to surgery while those with a PVR of 15Wood U or greater should not undergo surgical correction. The outcome of this study showed that PDA-ES patients with PVR<15Wood U and Qp/Qs>1.5 at baseline might be amenable to and benefit from TCC. Dual or triple combination of drugs therapy for a long period after occlusion are needed for the PDA-ES patients with partial structurally reversible PAH.

Conclusion

In spite of positive inhaled oxygen test and improved hemodynamic status after PAH-targeted therapy, some high risk PDA-ES patients should not undergo TCC yet the selection criteria remains incompletely defined.

PDA-ES patients whose PVR<15Wood U and Qp/Qs>1.5 at baseline might be amenable to and benefit from TCC but need to be further validated in larger clinical trials. Uninterrupted combination of PAH-targeted drugs play a crucial role for these ES patients with partial structurally reversible PAH.

Study limitations

There are two main limitations in our study. First, the major limitation of the study was the small sample which limited its power. Second, during the follow-up, PASP was only evaluated by echocardiography rather than right heart catheterization.

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 :echocardiography and 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; SaO2:systemic arterial oxygen saturation; O2: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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Figures
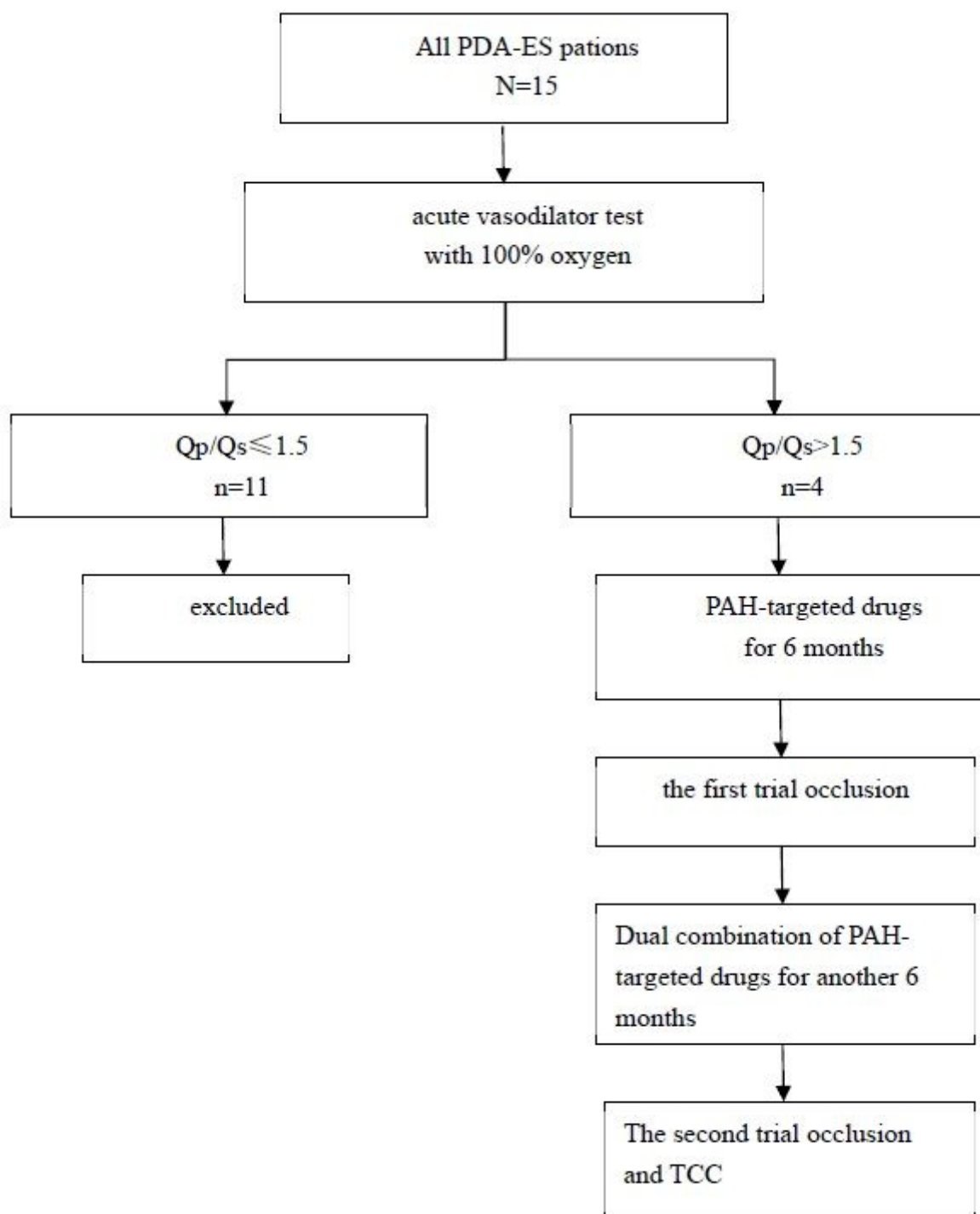
Figure 1

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.