Journal of the American Heart Association

ORIGINAL RESEARCH

Valsartan to Prevent Acquired Pulmonary Vein Stenosis in Pediatric Patients After Total Anomalous Pulmonary Venous Connection Surgery

Jin Shentu, MD, PhD*; Mingjie Zhang, MD*; Zhuoming Xu, MD, PhD; Chen Wen, MD, PhD; Hao Zhang, MD, PhD; Zhongqun Zhu, MD, PhD; Huiwen Chen, MD, PhD; Guocheng Shi, MD, PhD

BACKGROUND: Recurrent pulmonary vein stenosis (PVS) following surgical repair of total anomalous pulmonary venous connection is associated with poor prognosis. Preclinical studies have shown that use of an angiotensin receptor blocker can attenuate intimal hyperplasia; notwithstanding, its clinical utility is of uncertain benefit.

METHODS: This single-center study included patients undergoing total anomalous pulmonary venous connection repair in 2020 to 2021. Since August 2020, patients have been considered for valsartan therapy early after operation. Contemporaneous participants were subcategorized into study versus control groups based on valsartan exposure. Patients in the control group were treated with the same protocolized algorithm except valsartan administration. The primary end point was postoperative PVS (PPVS) progression.

RESULTS: Overall, 104 patients operated on at a median age of 1.3 months were included (valsartan group: 25 versus control group: 79). The baseline characteristics were similar between the 2 groups. Within a median follow-up of 28.6 months, 27 patients developed PPVS noted by echocardiography and computed tomography angiography, among which 22 with clinical PPVS underwent reoperations. No between-group difference was observed in the incidence of initial PPVS (P=0.80, Cohen's h=0.06 [95% CI, −0.38 to 0.50]) and reoperation (P=0.46, Cohen's h=−0.18[95% CI, −0.65 to 0.29]); however, patients in the valsartan group had a significantly lower risk of PPVS progression (P=0.019, Cohen's h=−1.12 [95% CI, −1.66 to −0.57]) and subsequent PPVS progression after reoperation (P=0.011, Cohen's h=−1.71 [95% CI, −2.61 to −0.82]) compared with the control group. PPVS-related death was observed in 9 cases (11.4%) in the control group versus none (0%) in the valsartan group. No adverse event related to valsartan occurred in this series.

CONCLUSIONS: Early use of valsartan after total anomalous pulmonary venous connection surgery appears to potentially be a feasible and effective adjunct to reoperation in treating pediatric acquired PVS.

Key Words: pulmonary vein stenosis ■ total anomalous pulmonary venous connection ■ transforming growth factor-β ■ valsartan

Pediatric pulmonary vein stenosis (PVS) remains a treatment challenge, with a high recurrence requiring multiple reinterventions (eg, angioplasty/stenting or reoperation), creating a great burden of morbidity and mortality.[1,2] The acquired form of PVS following surgical repair of total anomalous pulmonary venous connection (TAPVC) is a common cause of pediatric PVS.[3,4] Disease in this subgroup of patients

Correspondence to: Guocheng Shi, MD, PhD, Department of Cardio-thoracic Surgery, Congenital Heart Center, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China. Email: shiguocheng@scmc.com.cn

*J. Shentu and M. Zhang contributed equally.

This article was sent to John S. Ikonomidis, MD, PhD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036911

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This prospective cohort study first presented evidence for clinical use of an angiotensin receptor blocker in pediatric pulmonary vein stenosis.
- We evaluated the novel use of valsartan to attenuate the occurrence of and progression of pulmonary vein stenosis following total anomalous pulmonary venous connection surgery.
- Subclinical pulmonary vein stenosis appeared to be well tolerated in the pediatric setting under a structured and close surveillance.

What Are the Clinical Implications?

- Prophylactic administration of valsartan was associated with a significant reduction in progression of acquired form of pulmonary vein stenosis with favorable safety and may represent an additional pharmacotherapeutic agent for modifying disease evolution in this challenging subpopulation.

Nonstandard Abbreviations and Acronyms

EndoMT	endothelial-to-mesenchymal transition
PPVS	postoperative PVS
PV	pulmonary vein
PVS	pulmonary vein stenosis
TAPVC	total anomalous pulmonary venous connection
TGF-β	transforming growth factor-β

is oftentimes progressive within postoperative year 1,[5–7] with the stenosis propagating into intrapulmonary veins, and ultimately leads to pulmonary hypertension and right ventricular failure.[6] Thus, developing therapies to attenuate progression or prevent emergence of the disease is an important unmet need.

Current evidence demonstrates neointimal hyperplasia characterized by myofibroblast deposition in pediatric PVS,[8,9] forming the basis for drug therapies targeted against myofibroblast proliferation. A growing enthusiasm has been generated for the use of antiproliferative chemotherapy directed at the underlying molecular mechanisms. Prior studies have suggested that endothelial-to-mesenchymal transition (EndoMT) with elevated TGF-β (transforming growth factor-β) signaling is a potential pathway related to cellular proliferation in the development of PVS.[10–12] Inhibition of this pathway may hold a promise in modifying disease progression. Accordingly, a pilot study (NCT 02769130) was conducted in the setting of pediatric PVS to evaluate the feasibility and safety of losartan, a drug that can block angiotensin II type 1 receptors and inhibit TGF-β activity; unfortunately, it has been suspended given a recall of losartan.[13] Thereby, existing evidence supporting the use of an angiotensin receptor blocker (ARB) is still derived from the preclinical studies[10,11]; its effectiveness in treating these challenging patients remains unknown and additional clinical data are needed. This study was designed to test a novel strategy of disease modification by early administration of the ARB, valsartan, in pediatric patients following TAPVC surgery, with a specific focus on the efficacy in alleviating progression of postoperative PVS (PPVS).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design, Setting and Participants

This is a single-center, observational, study approved by Shanghai Children's Medical Center Institutional Review Board (SCMCIRB-K2021105-1); all parents gave written informed consent. Since 2016, our center has established a TAPVC program that aims to provide a protocolized management algorithm (Figure S1), including presurgical evaluation/resuscitation, standardized operation and postoperative intensive care, structured follow-up surveillance, and timely reintervention for PPVS. This program includes 2 senior congenital heart surgeons (G.S. and H.C.), 1 senior intensivist (Z.X.), 3 follow-up nurses, and 6 research coordinators (in charge of data collation and input).

Patients diagnosed with isolated TAPVC (TAPVC with no other concomitant cardiac lesion except atrial septal defect or patent ductus arteriosus) who underwent biventricular repair between 2020 and 2021 were included. Our TAPVC program submitted the protocol of the off-label use of valsartan to the ethics committee in January 2020. The committee carefully reviewed the protocol, and several key issues were discussed, including (1) the expected course of disease and preclinical evidence to support the use of valsartan in the PPVS setting; (2) assurance of a full and open discussion regarding the benefits and risks of this therapy between the clinicians and guardians; (3) no nitrosodimethylamine in this brand of commercial valsartan, which is easy to access and commonly used in China (40 mg tablets, Lunan Pharmaceutical Group Corporation, Shandong; Figure S2); (4) detailed documentation of the reason for off-label use in the patient's

record, and (5) the assurance of close surveillance during the valsartan therapy. After a 6-month review, the protocol of valsartan therapy was approved, and we set out to use valsartan as an adjuvant therapy early after TAPVC surgery since August 2020. Accordingly, the data were evaluated retrospectively from January 2020 to July 2020 and prospectively from August 2020 to December 2021. Notably, the initiation of the valsartan therapy was decided upon the parents' agreement after obtainiinformed consent.

The primary objective of this study was to evaluate the efficacy of early administration of an ARB (valsartan) on alleviating PVS progression after surgical repair of TAPVC. Exclusion criteria were (1) patients supported with extracorporeal membrane oxygenation both pre- and postoperatively; (2) patients who lacked follow-up imaging data (echocardiography, computed tomographic angiography [CTA]), which was required to allow PPVS assessment; and (3) patients who underwent TAPVC surgery at outside hospitals.

Data Collection and Quality Control

The electronic database used in our study was established in 2000; this database includes patients' perioperative details during hospitalization as well as outpatient follow-up data after discharge. Since 2016, we have created a single data set for each TAPVC case, and research coordinators of the TAPVC program prospectively and independently registered patient baseline characteristics, procedural and clinical outcomes, echocardiographic and CTA measurements as well as follow-up information. The clinical research center at Shanghai Children's Medical Center monitored enrollment, validated collected data, and performed statistical analyses.

Valsartan Therapy

Evaluation Before Valsartan Administration

Although previous studies have demonstrated generally good safety and tolerability of valsartan in the pediatric population,[14,15] patients with TAPVC, particularly neonates and small infants, are likely vulnerable to hemodynamic instability, and some side effects of valsartan (eg, hypotension) will potentially complicate the postoperative recovery. Hence, within the early postoperative period, careful assessments would be made by the senior cardiac intensivist (Z.X.) before the administration of valsartan, which included (1) milder degree of hemodynamic support (vasoactive-inotropic score <10 points); (2) left ventricular ejection fraction ≥55%; (3) no requirement of peritoneal dialysis; (4) absence of abnormal renal (age-based thresholds of estimated glomerular filtration rate using serum creatinine-based equation[16]) and hepatic function (alanine transferase >31.7 U/L in girls and >38 U/L in boys[17]); (5) no gastrointestinal complications (gastrointestinal bleeding, diarrhea); and (6) a closed sternum.

Dosage

The starting dose of valsartan was 1 mg/kg per day (oral). We chose this dosage given the following reasons: (1) the safety and tolerability of valsartan therapy with a median dose (defined as 1 mg/kg per day) has been confirmed in a previous study[13] that enrolled patients <1 year old; and (2) the preclinical study[11] has demonstrated the beneficial effects on alleviating intimal hyperplasia in PVS with ARB treatment (1 mg/kg per day). Of note, the interval between diuretics therapy and valsartan administration should be more than 2 hours. Doses would be reduced to 0.5 mg/kg per day on confirmation that the serum potassium concentration is >5 mmol/L, or that there was drug-related symptomatic hypotension, or that the estimated glomerular filtration rate using serum creatinine-based equation decreased by 25% or more. Reassessment would be performed within 1 week, and treatment would be stopped if values did not improve.

Duration of Drug Treatment

Patients were treated with valsartan for a planned course of 12 months. We used this cutoff time because, based on the majority of available evidence,[5–7] the highest hazard for acquired PVS is usually within this phase. If the patients did not develop PPVS during the treatment period, valsartan therapy would be stopped thereafter. If the patients developed PPVS, valsartan therapy would be continued until 2 consecutive follow-up assessments demonstrated the absence of PPVS, which was reflected in the change from clinical or subclinical PPVS to no stenosis. We should specifically clarify that reoperations were concurrently performed, if necessary, during the period of valsartan treatment.

Follow-Up and PPVS Assessment

Routine postdischarge follow-up was scheduled at 1, 3, 6, 9, and 12 months and then annually to receive physical examination, transthoracic echocardiograph, and 12-lead ECGs. CTA was further performed for disease assessment if there was a suspicion of PPVS noted by echocardiography in combination with symptoms. The senior doctor (G.S.) and follow-up nurses of the TAPVC program checked on patients' general status, respiratory issues, and feeding intolerance to monitor the occurrence of PPVS after discharge using a mobile phone app (WeChat) or Haodaifu network (a health service platform providing online consultations in China). If there was a suspicion of PPVS, the patients were required to come to our hospital irrespective of the scheduled

follow-up intervals. Patients who received valsartan therapy underwent an additional visit (2 weeks after discharge). Physical examination and collection of blood samples for safety assessment were required in the valsartan group (detailed protocol is shown in Table 1). The final date of follow-up for data collection was September 30, 2023 (the end-of-study date). For the purpose of this study, the image data were reread and reanalyzed by a single cardiologist (M.Z.) in a clinically blinded fashion.

Echocardiographic and CTA Criteria for PVS Diagnosis

Pulmonary venous obstruction (PVO; both pre- and postoperative) was defined on the basis of combined evaluation of echocardiography (nonphasic venous flow velocity >1.8 m/s[18]) and CTA (≥50% luminal narrowing[19]). The velocity of the anastomotic site as well as each PV was assessed. Axial imaging with CTA was used to measure the 2-dimensional cross-sectional diameter of each PV. PPVS was subcategorized into anastomotic restriction, peripheral stenosis, or both. Anastomotic restriction was defined as stenosis at confluence, and peripheral stenosis was further classified into (1) type I: stenosis between PV ostium and the first bifurcation of the PV and (2) type II: stenosis extending from the first PV bifurcation into lung parenchyma.

Clinical Versus Subclinical PPVS

Patients who developed PPVS were subdivided into clinically evident versus subclinical PPVS. Those with clinically evident PPVS had both imaging evidence of restenosis and symptoms, including respiratory issues (recurrent respiratory infection, hemoptysis, dyspnea, cyanosis), which usually required in-hospital treatment and worsening feeding/exercise intolerance. We proposed the term subclinical PPVS to describe those who was asymptomatic, albeit having the evidence of increased PV velocity (>1.8 m/s) noted on echocardiography during follow-up.

PPVS Progression

PPVS was considered to be progressed if (1) new obstruction/atresia was observed in the previously unaffected veins, (2) obstruction extended from proximal site to distal/upstream PVs, or (3) stenotic veins became atresia.

Statistical Analysis

Mean ± SD or median (interquartile range, [IQR]), depending on normality of variables, and count (frequency) are used to show the distribution of the data for continuous and categorical variables. Between-group univariate comparisons were performed using Pearson chi-squared-test or Fisher's exact for categorical variables and Mann–Whitney *U* tests or 2-sided Student's *t* test for continuous data as appropriate. PPVS progression, initial PPVS, and survival were assessed in a time-to-event analysis using unadjusted Kaplan–Meier method and compared with log-rank test. For time-to-event analyses, data were censored at the last available follow-up visit or September 30, 2023. Univariate Cox proportional hazard regression was used to explore the predictors for initial PPVS, and the results were expressed as hazard ratios (HR) with 95% CI. Variables used to generate the univariate Cox proportional hazard regression were the baseline characteristics and predictors regarded as clinically relevant indicated by previous studies.[5,7,18] The Schoenfeld residuals test was used to verify the assumption of proportional hazard assumption, which was satisfied for the outcome of freedom from PPVS progression from the TAPVC operation to the last follow-up.[20] Subgroup analysis was performed by comparing baseline characteristics and outcomes in different group of patients. Only descriptive analysis was conducted in subgroup analysis as the small sample size precluded any adjusted analysis. Considering that there was a nonlinear relationship between the continuous variables (PV velocity and follow-up time), a restricted cubic spline regression analysis (four knots: 5th, 35th, 65th, and 95th percentiles) was used to model the multiple changes in each patient's PV velocities from discharge to the last follow-up within postoperative 1 year, and between-group comparison was further made using structural equation modeling.[21,22] All tests were 2 sided, and a *P* value of <0.05 was considered statistically significant. Difference of proportion between 2 groups was evaluated using Cohen's *h* effect size, and difference in means was evaluated using Cohen's *d* effect size.[23] Analyses were performed using R, version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participants

From January 1, 2020, to December 31, 2021, a total of 104 patients with a median age of 38.7 (IQR, 12.3–93.6) days met the inclusion criteria (Figure 1). Anomalous return was supracardiac in 44.2% (46/104), cardiac in 31.7% (33/104), infracardiac in 18.3% (19/104), and mixed type in 5.8% (6/104). Preoperative PVO was found in 61.5% of the patients; 23% of the patients underwent emergency surgery. Patients were subdivided into 2 groups stratified by the valsartan exposure, and the distribution of demographic and clinical characteristics were similar between the 2 groups (Table 2). None of the patients in the valsartan group had therapy discontinued due to adverse effects.

Table 1. Schedule of Follow-Up Visits and Procedures in the Valsartan Group

Variables	Structured follow-up surveillance								
	At discharge	Postdischarge 2 wks	Postoperative 1 mo	Postoperative 3 mo	Postoperative 6 mo	Postoperative 9 mo	Postoperative 12 mo	Postoperative 2 y	Postoperative 3 y
Adverse events, n									
Hypotension	0	0	1*	0	0	0	0	0	0
Cough	0	0	0	0	0	0	0	0	0
Upper respiratory infection	0	0	0	0	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	0	0	0
Blood for safety, mean±SD									
Serum potassium	3.8±0.5	3.8±0.3	3.9±0.3	3.9±0.3	3.9±0.2	3.9±0.2	3.9±0.3	3.9±0.3	4.0±0.4
Serum creatinine	22.2±7.8	25.4±8.4	26.5±11.6	26.4±9.7	26.3±8.3	26.0±7.7	25.6±6.8	27.7±8.2	29.4±10.5
Estimated glomerular filtration rate using serum creatinine-based equation (mL/min per 1.73 m^2)	96.8±13.1	94.6±14.5	99.4±15.5	96.4±14.2	97.8±16.8	94.7±12.5	98.4±19.4	99.4±17.5	102.4±19.8
Serum alanine aminotransferase (U/L)	25.4±18.7	24.7±19.2	16.1±16.9	28.4±17.5	26.1±9.8	33.2±15.3	39.8±18.9	30.1±12.6	29.5±18.4
Serum aspartate aminotransferase (U/L)	37.8±16.2	35.4±14.5	31.7±13.9	32.4±15.2	33.1±16.6	33.4±15.9	34.4±16.1	35.7±17.1	36.6±16.8

*One patient developed hypotension after 1 mo of valsartan therapy. We adjusted the valsartan dose to 0.5 mg/kg per d, and the hypotension improved. The patient continued medication to 1 postoperative y.

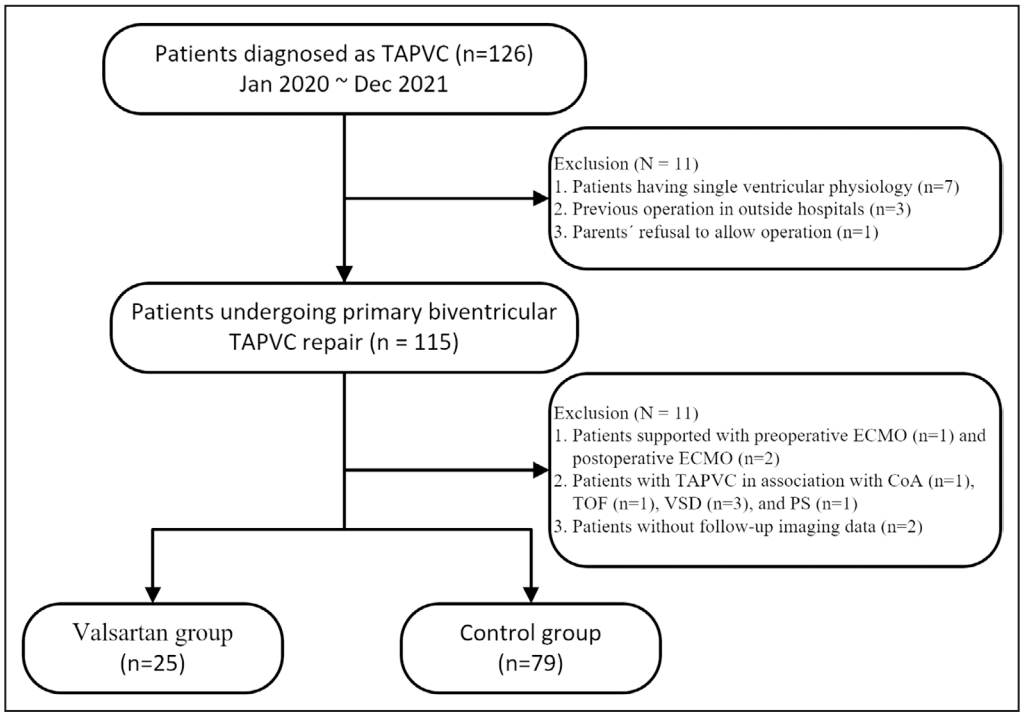

Figure 1. Flow diagram of the study participants.
CoA indicates coarctation of the aorta; ECMO, extracorporeal membrane oxygenation; PS, pulmonary stenosis; TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

PPVS and Mortality

As of September 30, 2023, follow-up was completed in 94% of the participants. The median duration of follow-up was similar between valsartan and the control group (28.4 [IQR, 25.6–32.4] months versus 28.6 [IQR, 18.1–37.0] months; *P*=0.97, Cohen's *d*=−0.28 95% CI, −0.73 to 0.17). All of the patients with PPVS underwent both echocardiographic and CTA (Figure S3).

There were 9 deaths in the control group versus none in the valsartan group (*P*=0.076; Cohen's *h*=1.08 [95% CI, 0.39–1.76]; Figure S4). No difference in the incidence of initial PPVS (*P*=0.82; Cohen's *h*=0.06 [95% CI, −0.38 to 0.50]; Figure 2A) and freedom from reoperation (*P*=0.46; Cohen's *h*=−0.18 [95% CI, −0.65 to 0.29]; Figure 2C) was observed between the valsartan and control groups. Univariable predictors for initial PPVS in the entire cohort (Table S1) included noncardiac type (HR, 2.99 [95% CI, 1.03–8.62]; *P*=0.044); preoperative PVO (HR, 3.12 [95% CI, 1.18–8.23]; *P*=0.02), preoperative CTA evaluation (HR, 0.3 [95% CI, 0.14–0.64]; *P*=0.002), cardiopulmonary bypass time (HR, 1.01 [95% CI, 1.00–1.01]; *P*=0.001), aortic cross-clamping time (HR, 1.02 [95% CI, 1.01–1.03]; *P*=0.001), and delayed sternal closure (HR, 2.39 [95% CI, 1.12–5.10]; *P*=0.024). Initial clinical and subclinical PPVS was observed in 22 and 5 cases, respectively. The anastomotic restriction, peripheral stenosis, and a combination of both types of PPVS, respectively, occurred in 1 (4.0%), 4 (16.0%), and 2 (8.0%) cases in the valsartan group versus 8 (10.1%), 8 (10.1%), and 4 (5.1%) in the control group. Specifically in the valsartan cohort (n=25), patients who developed PPVS were younger (2 [IQR, 1–26] days versus 43 [IQR, 24–63] days; *P*=0.006; Cohen's *d*=0.76 [95% CI, −0.15 to 1.65]), more commonly presented with ex cardiac connection type (supra-, infra- and mixed-form; *P*=0.027; Cohen's *d*=1.57 [95% CI, 0.70–2.44]), and preoperative PVO (7/7, 100% versus 9/18, 50%; *P*=0.027; Cohen's *d*=1.57 [95% CI, 0.70–2.44]) compared with those without PPVS (Table S2). A comparison of patients included before and after August 2020 revealed no observed difference with regard to baseline and perioperative characteristics, except for sex (Table S3).

Reoperations were performed in all of the patients with clinical PPVS, of which a total of 15 cases developed progressive PPVS. These 15 patients developed recurrent stenosis at a median of 3.1 months (IQR, 2.2–5.2) after reoperation. The lesion progression was detected by echocardiography during the subsequent follow-up and then confirmed by CTA examination. Notably, both of the patients with type-II peripheral PPVS were unresponsive to the reoperation. Consistently, a significantly reduced PPVS progression rate was observed in a subgroup analysis excluding the patients with isolated anastomotic restrictions (*P*=0.003; Cohen's *h*=2.37 [95% CI, 1.42–3.31]; Figure S5).

Table 2. Baseline Characteristics and Outcomes

	Valsartan group (N=25)	Control group (N=79)	*P* value
Baseline characteristics			
Male sex, n (%)	19 (76.0%)	44 (55.7%)	0.10
Age at surgery, d, median (IQR)	38.7 (13.5–58.7)	38.6 (11.4–114.4)	0.22
Weight at surgery, median (IQR), kg	3.8 (3.5–4.0)	3.7 (3.2–5.1)	0.75
Prematurity, n (%)	0 (0.0%)	0 (0.0%)	>0.99
Trisomy-21 syndrome, n (%)	0 (0.0%)	0 (0.0%)	>0.99
Subtypes of total anomalous pulmonary venous connection, n (%)			0.35
Supracardiac	8 (32.0%)	38 (48.1%)	
Cardiac	9 (36.0%)	24 (30.4%)	
Infracardiac	7 (28.0%)	12 (15.2%)	
Mixed	1 (4.0%)	5 (6.3%)	
Preoperative pulmonary venous obstruction, n (%)	16 (64.0%)	48 (60.8%)	0.82
Saturation of peripheral oxygen, median (IQR)	85 (78–87)	85 (82–88)	0.44
Computed tomography angiography evaluation, n (%)	22 (88.0%)	64 (81.0%)	0.55
Time of surgery, n (%)			0.40
Emergency	8 (32.0%)	16 (20.3%)	
Urgency	5 (20.0%)	13 (16.5%)	
Elective	12 (48.0%)	50 (63.3%)	
Perioperative characteristics			
Sutureless repair, n (%)	10 (40.0%)	17 (21.5%)	0.11
Cardiopulmonary bypass time, median (IQR), min	105 (87–118)	84 (67–116)	0.10
Aortic cross-clamping time, median (IQR), min	58 (42–71)	45 (29–63)	0.07
Duration of mechanical ventilation, median (IQR), h	100 (47–137)	68 (45–120)	0.19
Delayed closure of sternum, n (%)	10 (40%)	26 (32.9%)	0.63
Cardiac intensive care unit stay, median (IQR), h	180 (112–251)	158 (115–210)	0.45
Hospital stay, median (IQR), d	22.3 (14.5–30.3)	18.0 (13.0–21.9)	0.32
Outcomes			
PPVS, n (%)	7 (28.0%)	20 (25.3%)	0.80
PPVS progression, n (%)	0 (0.0%)	15 (19.0%)	0.019*
Death, n (%)	0 (0.0%)	9 (11.4%)	0.11

IQR indicates interquartile range; and PPVS, postoperative pulmonary vein stenosis.
*Values for statistically significant associations.

For the entire population, there was a significantly lower incidence of PPVS progression in the valsartan group than in the control group (*P*=0.019; Cohen's *h*=–1.12 [95% CI, –1.66 to –0.57]; Figure 2B). A subgroup analysis for those who underwent reoperations revealed a better freedom from PPVS progression in the valsartan group than in the control group (*P*=0.011; Cohen's *h*=1.71 [95% CI, 0.82–2.61]; Figure 2D). Of the 4 patients undergoing reoperation in the valsartan group, 3 had complete relief and 1 had subclinical PPVS at their last follow-ups. By contrast, only 3 of the 18 patients undergoing reoperation in the control group had freedom from PPVS progression (1 had complete relief; 2 switched to the subclinical PPVS). Of the remaining 15 patients, 2 died early after reoperation; the other 13 patients had temporary relief but ultimately developed PPVS progression within a median of 2.7 (IQR, 1.7–4.3) months after reoperation, of which 11 patients' parents refused to consent to any re-reintervention (6 lost to subsequent follow-up, 5 died) and 2 patients died after re-reoperation. Detailed responses and duration for the patients treated with valsartan therapy are shown in Figure 3 and Table S4.

Pulmonary Venous Doppler Velocity Analysis

In the PPVS subcohort (n=27), there was no difference in the distribution of PV velocity at discharge between patients in the valsartan (1.28±0.32 m/s) and control group (1.28±0.28 m/s; *P*=0.99; Cohen's *d*=0.00). However, there was a significant trend in the increase of PV velocity within 12 postoperative months in the control group compared with the valsartan group (*P*=0.014; Figure 4A). Notably, patients' PV velocities in the control group reached a climax with higher thresholds

at around 3 postoperative months than those in the valsartan group (2.25±0.50 versus 1.91±0.11 m/s; P=0.012; Cohen's d=0.78 [95% CI, −0.12 to 1.67]), which was related to more deaths in the control group at this phase (25% [5/20] versus 0% [0/7]). In the subcohort without PPVS (n=77), patients in both groups had relatively low PV velocities at discharge (1.26±0.28 versus 1.05±0.30 m/s; P=0.009; Cohen's d=0.71 [95% CI, 0.17–1.25]), which remained without significant changes during the follow-up (Figure 4B).

Safety, Tolerance, and Duration of Valsartan Therapy

Overall, 18 patients in the valsartan group did not develop PPVS during the follow-up, and they stopped valsartan after postoperative year 1. Of the 7 patients with PPVS, 4 underwent reoperations at 0.9, 1.5, 2.3, and 3.0 postoperative months, respectively, of which 3 had complete relief of stenosis during the subsequent follow-up visits and stopped valsartan after postoperative year 1; the other patient switched to subclinical PPVS and still received valsartan at last follow-up. The remaining 3 patients who developed subclinical PPVS after initial TAPVC surgery were still on valsartan therapy at their last follow-up. During valsartan therapy, no patients had adverse events or side effects. One patient with subclinical PPVS developed drug-related symptomatic hypotension after the first administration of valsartan, and the dose was reduced to 0.5 mg/kg per day, which was well tolerated thereafter. Details of the assessments, including physical examinations and blood sample tests during the follow-up surveillance in the valsartan group, are illustrated in Table 1.

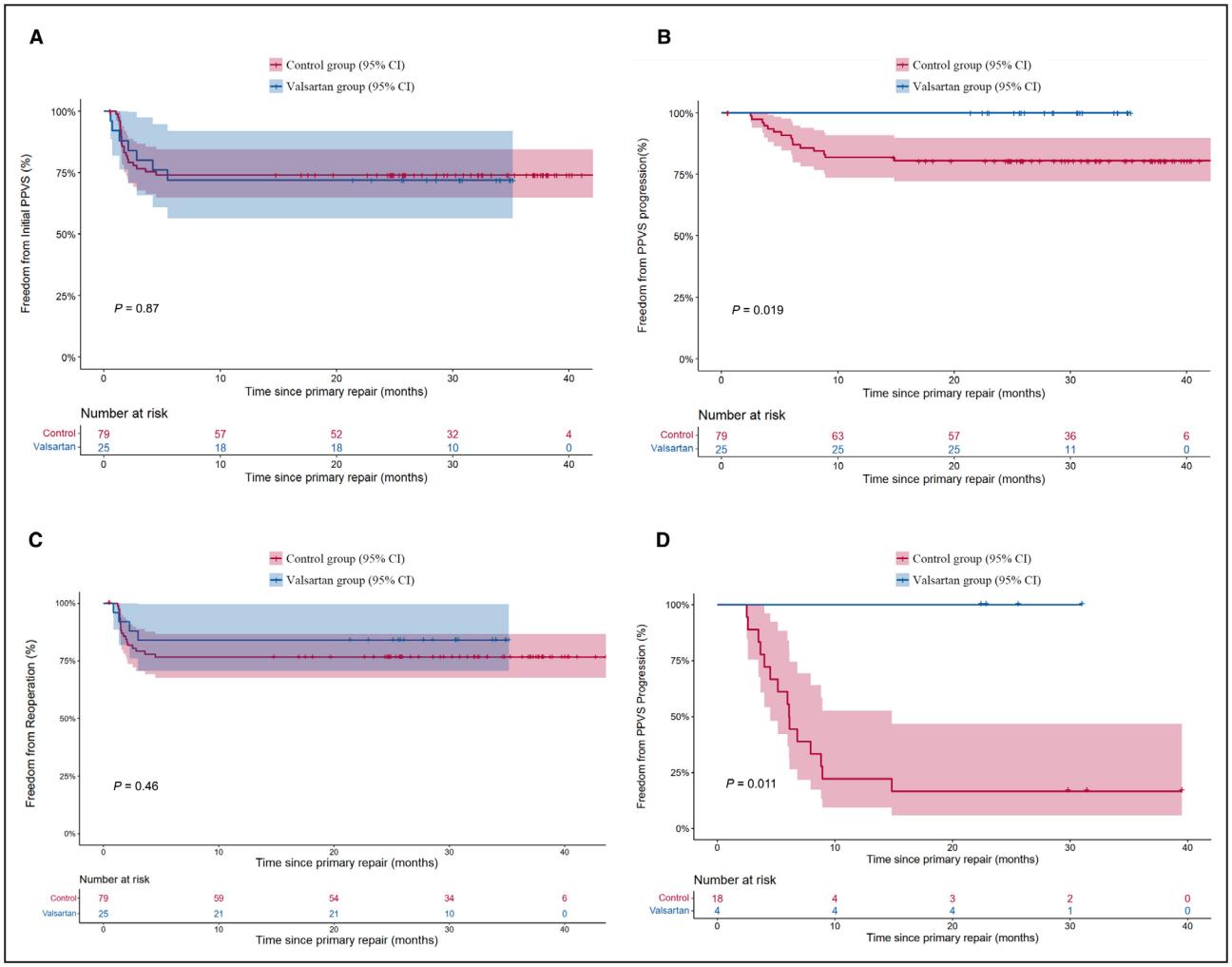

Figure 2. Kaplan–Meier estimates of PPVS incidence and PPVS progression.
A, There was no difference in the PPVS incidence between the valsartan and control group. **B**, Valsartan therapy was associated with a significantly better freedom from PPVS progression. **C**, There was no difference in the freedom from reoperation between the valsartan and control group. **D**, In patients undergoing reoperation, valsartan therapy was associated with a significantly better freedom from PPVS progression. PPVS indicates postoperative pulmonary vein stenosis.

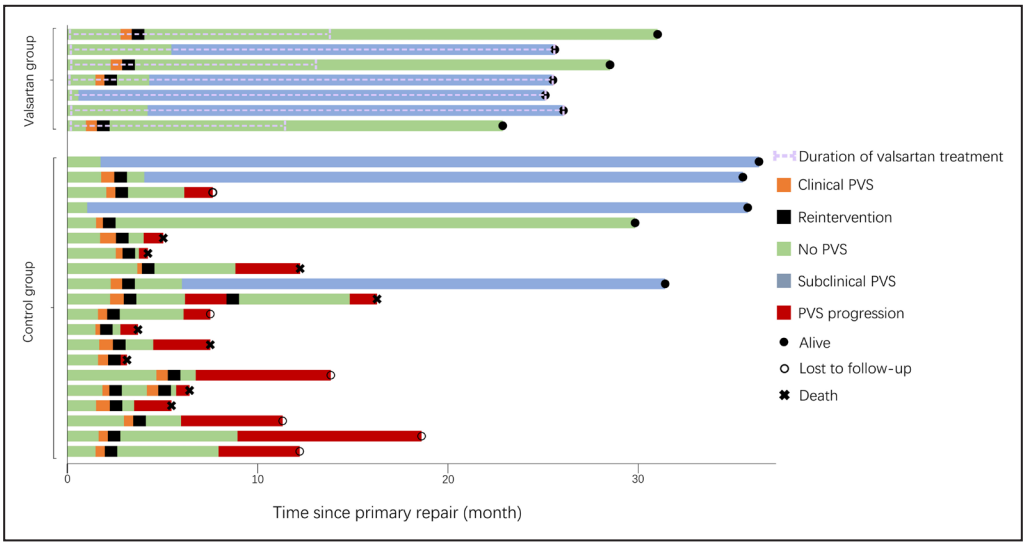

Figure 3. Disease course during the follow-up in patients who developed postoperative PVS (n=27).
PVS indicates pulmonary vein stenosis.

DISCUSSION

In this single-center observational study involving pediatric patients who underwent TAPVC surgery, those receiving valsartan therapy early after operation had a significantly lower risk of PPVS progression within a median follow-up of 28.6 months as compared with the contemporary control group (Figure 5). In the selective cases, multimodal treatment (valsartan plus reoperation), instead of reoperation alone, had a beneficial effect on disease alleviation. A key priority in the contemporary management of pediatric PVS is the exploration of targeted pharmacotherapy. Findings from the present work indicate an opportunity to attenuate disease evolution with an accessible and safe medication.

The rationale for the present work drew from a study of a piglet model of PVS where ARB therapy (losartan) appeared to alleviate disease progression.[11] Although many pathological triggers have been suggested for neointimal proliferation, the underlying mechanism appears to be the stimulation of myofibroblast deposition

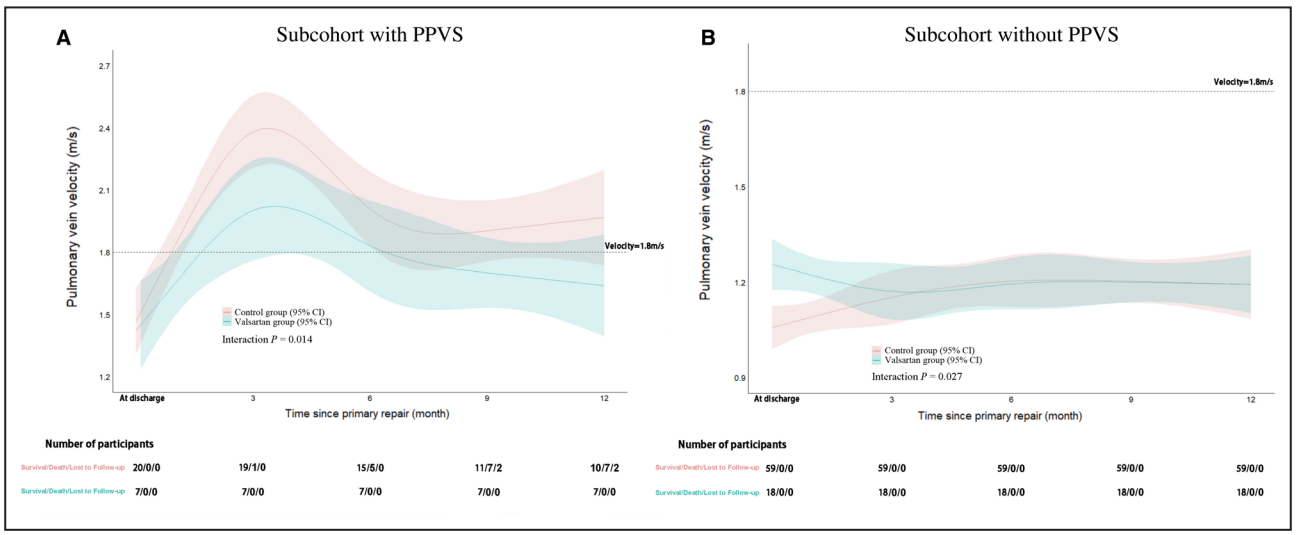

Figure 4. Postoperative changes in PV velocity.
Estimated mean PV velocity with corresponding 95% CI was plotted using restricted cubic spline. **A**, In the subcohort with PPVS, there was a significant trend in the increase of PV velocity within postoperative 12 mo in the control group compared with the valsartan group. **B**, In the subcohort without PPVS, no between-group difference in the trend of PPVS change was observed within postoperative 12 mo. PPVS indicates postoperative pulmonary vein stenosis; and PV, pulmonary vein.

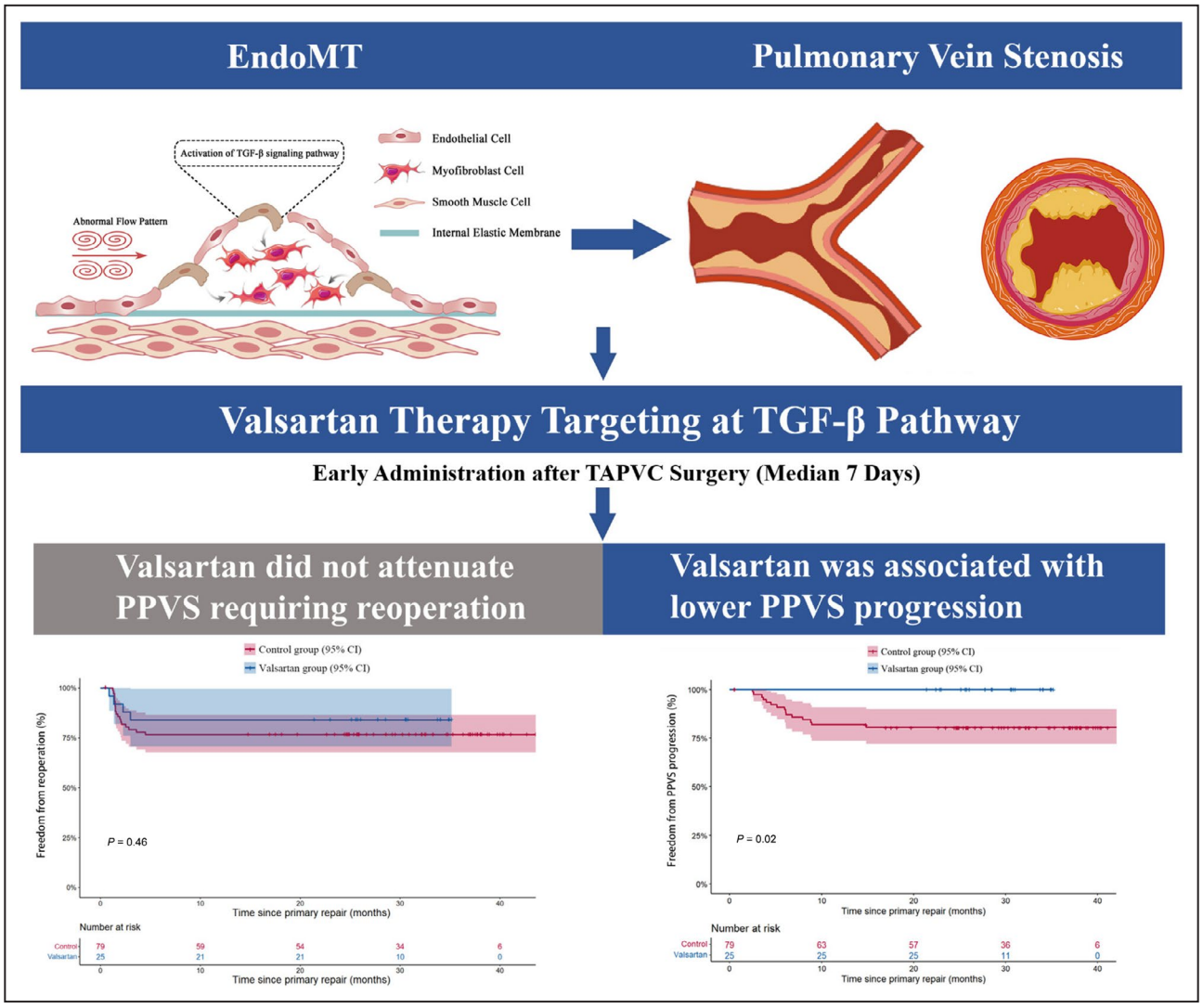

Figure 5. Proposed mechanism of valsartan therapy in attenuating PPVS progression after TAPVC surgery.
EndoMT indicates endothelial-to-mesenchymal transition; PPVS, postoperative pulmonary vein stenosis; TAPVC, total anomalous pulmonary venous connection; and TGF-β, transforming growth factor-β.

as a final common pathway via a complex cascade involving TGF-β.[10,12] Thus, the blockade of TGF-β activation may alter the cellular processes and thereby ameliorate intimal hyperplasia. Notwithstanding, clinical data supporting the use of ARB therapy for pediatric PVS are lacking. To our knowledge, the Atlanta group previously used losartan; however, the early disappointing results led them to switch to systemic sirolimus therapy (inhibition of mammalian target of rapamycin pathway) after 2016, which was largely used in the patients receiving stent therapy with an attempt to prevent in-stent stenosis.[24,25] By contrast, the treatment benefit of valsartan in this series is more encouraging, supporting the notion that ARB therapy might be efficacious in slowing disease progression. This may be related to the fact that the present work specifically focuses on patients with acquired form of PVS secondary to TAPVC repair, whereas the previous studies often included a number of patients with primary PVS wherein the efficacy of ARB therapy would be probably limited because multiple factors (eg, genetic syndrome, prematurity and prematurity-related conditions) besides hemodynamic changes also play a key role in disease development.[26]

Putative explanations for prophylactic use of ARB therapy are as follows. First, myofibroblast cells can come from different sources, that is, EndoMT, dedifferentiation of smooth muscle cells, and transdifferentiation of fibroblasts, and may have temporal contributors over different stages of PVS development.[8,9,27] This partially explains why 2 previous trials targeted myofibroblast proliferation using chemotherapeutic agents with the rationale based on end-stage human PVS samples merely yielded guarded

prognosis.[28,29] In the process of PVS development, the pulmonary venous flow initially exhibits turbulent flow with increased velocity around the narrow site followed by the stretch of upstream PVs in response to the increasing pressures. Mechanotransduction plays a crucial role in vascular remodeling as the endothelial cells can transduce flow signals into intracellular change and modulate endothelium function.[30,31] Presumably, endothelial dysfunction induced by mechanical stimulus is the initiating feature of PVS development, which corresponds to the postulation that flow-induced mechanism plays a trigger role in the disease development and progression.[32] Emerging evidence[33,34] has stressed the importance of mechanical stimulus in potentiating vascular EndoMT via activating the TGF-β pathway. Also, study in porcine model of PVS has suggested that the stenotic pulmonary veins exhibit intimal thickening related to EndoMT with increased TGF-β1 expression.[10] Taken together, it is reasonable to speculate that mechanical stimulus induces EndoMT through modulating the TGF-β pathway, which might play a key role in early-stage PVS, and findings from this study indicate that early therapeutic interventions targeted at this specific pathway may yield treatment benefits. On the other hand, the effect of ARB therapy might be neutralized if administrated at late-stage PVS probably because different subpopulations of myofibroblasts may respond to the flow stimulus in a cell-specific manner driven by different molecular pathways.[8,9] Clearly, however, further studies must be performed to confirm this speculation.

It should be clarified that ARB therapy cannot mitigate the risk of PPVS due to surgical imperfection that results in anastomotic restriction. We included patients with increased PV velocity at confluence given the following reasons. First, the recent study[35] has shown that reduced left atrial strain persists after TAPVC surgery. In addition, Fujimoto et al[36] have found that impaired left atrial contractility could cause decreased diastolic as well as systolic function and is associated with disturbed PV flow and venous remodeling. Second, PVS is progressive and exposure to high flow is an important trigger in the pathogenesis of PVS. Nevertheless, standardization of accelerated pulmonary venous flow is not well established as different cutoff values for pulmonary venous Doppler velocities have been used, varying between 1.2 and 2.0 m/s.[18,37–39] Thus, it is likely that there may be increased flow around the anastomotic site due to suboptimal left atrial function postoperatively, contributing to the disease development.

Although the discrepancy in criteria of PV velocity to define PVS may be due to the angles of interrogation among different observers, it is possible that disease vulnerability can vary among individuals. A previous pathological study[40] has demonstrated preoperative intrinsic hypertrophy and fibrosis of the PVs in patients with TAPVC that varies among disease subtypes and different severity of preoperative PVO. Such patient-specific abnormal changes of the preoperative pulmonary vasculature potentially contribute to the differences in susceptibility of the PV wall in response to flow disturbances. However, it is difficult to know the precise threshold of velocity above which neointimal formation/hyperplasia develops in each patient; moreover, PVS is progressive in nature and the treatment efficacy depends on the extent of upstream vascular remodeling.[8,9,12] Hence, treatment at an early stage to counteract the pathobiology of the disease is an integral component in the optimal therapy to improve the prognosis. In this regard, early administration of valsartan, aiming at inhibiting the flow-activation of TGF-β pathway, appears to play an important role in maintaining endothelial function and protecting against pathophysiological changes of PVS. However, it cannot be excluded that other unmeasured variables and selection bias may influence the results. Further well-designed randomized control trials are required to analyze the therapeutic impact of early use of ARB.

Reintervention for PVS following TAPVC surgery, including reoperations and angioplasty/stenting, has been gradually regarded as a fundamental tool in a multimodal treatment strategy.[2,8,27] Our results confirm this belief as more than one-half of the patients (57%) in the valsartan group who concurrently received reoperations experienced disease attenuation. Nonetheless, reoperations alone cannot translate into an equivalent benefit in alleviating PVS progression, as evidenced by the poorer outcomes in the control group. This supports the notion that anatomical recanalization may be helpful in temporarily relieving pulmonary venous congestion but not affecting the primary pathophysiology of PVS wherein specific receptors and pathways play a key role in disease progression.[8,24,27] On the other hand, a number of patients with PPVS in both groups did not undergo reoperations and showed improved status over time. We cannot rule out the possibility that there may be patients with milder disease severity or misclassification of PPVS, which confounds our results.

Currently, valsartan has gained regulatory approval for pediatric use and is principally used in children with hypertension wherein its safety profile has been well described.[14,15] This study has some potential implications for extending its off-label use in treating pediatric PVS. In particular, it can be inferred from our results that younger infants with obstructed extracardiac TAPVC appeared to be more responsive patients. The dosage (1 mg/kg per day) in this series falls within the recommended range (0.1–4.6 mg/kg per day) derived from several landmark studies of valsartan in pediatric populations.[15,41] One important caveat is that the patients treated with valsartan in prior studies are older

compared with our population, in whom valsartan was initiated during infancy. Nevertheless, under the close surveillance by our TAPVC team, no significant adverse event or intolerance was observed during the treatment phase.

Limitations

First, although the design of study, which compared outcomes to a contemporary control group of patients treated with the same management algorithm (except the use of valsartan), was helpful to reduce bias, there were still some uncontrolled factors that may affect the results. For example, as the drug initiation was subject to parental consent, it is possible that patients with more severe disease were included in the control group. Additionally, patients in the valsartan group had a higher rate of CTA completion compared with the control group (88% versus 81%), although it was not statistically significant, which can also be a confounding factor because previous literatures[18,42] have shown that CTA-based surgical strategy contributes to procedural perfection and is associated with optimal locoregional hemodynamics. Second, although the dosage of valsartan in this study appeared to have therapeutic benefits in alleviating disease progression, serial drug concentrations after administration were not measured, which precluded a rigorous identification of the optimal plasma concentration range. Third, considering that the study participants were distinct with respect to cause of PVS (acquired PVS following TAPVC surgery), our findings may not generalize to patients with primary PVS wherein there may be a complex interplay between the inherent risk factors (eg, genetic variation, prematurity-associated conditions) and hemodynamic contribution.[27] Fourth, although there was no patient with trisomy-21 syndrome, other genetic syndromes cannot be identified. In addition, all patients were full-term newborns. Hence, generalization of our findings to these specific subpopulations requires further investigation. Fifth, whether valsartan therapy has a role in preventing in-stent PVS remains unknown because there may be different underlying mechanisms from the native vessel disease (eg, peristent vascular injury, thrombus, or hematoma formation after stent implantation). Sixth, we cannot rule out the possibility that technique variation among different surgeons might confound our results. Finally, the small sample size limited a sufficient power to precisely estimate the association between valsartan therapy and freedom from PPVS progression.

CONCLUSIONS

Our findings have shown that early administration of valsartan after TAPVC surgery is efficacious in alleviating progression of recurrent PVS and can be well tolerated in pediatric patients, suggesting the implication for its clinical utility in those at risk of developing acquired form of PVS. Specifically, ARB therapy serving as an adjunct to reoperation may play an important role in multimodal treatment for PVS.

ARTICLE INFORMATION

Received October 6, 2024; accepted December 17, 2024.

Affiliations

Department of Cardio-thoracic Surgery, Congenital Heart Center, Shanghai Children's Medical Center, School of Medicine (J.S., M.Z., Z.X., C.W., H.Z., Z.Z., H.C., G.S.), and Clinical Research Center, Shanghai Children's Medical Center, School of Medicine (H.C.), Shanghai Jiao Tong University, Shanghai, China; and Guizhou Branch of Shanghai Children's Medical Center Shanghai Jiaotong University School of Medicine, Shanghai, China (H.C.).

Acknowledgments

The authors sincerely thank Li Xie and Tienan Feng from Clinical Research Center, Shanghai Jiao Tong University School of Medicine, for their great assistance in statistical analyses.

Sources of Funding

This study is supported by the Chinese National Natural Science Foundation of China (grant nos. 81970267, 82170307), Science and Technology Commission of Shanghai Municipality (grant no. 22QA1405800, 23Y11902700), Interdisciplinary Program of Shanghai Jiao Tong University (grant nos. YG2022QN094), Program of Shanghai Shen-kang Hospital Development Centre (grant no. SHDC2022CRD014), Science and Technology Project of Guizhou Province (KXJZ[2024]035).

Disclosures

None.

Supplemental Material

Tables S1–S4
Figures S1–S5

REFERENCES

1. Prieto LR. In search of the holy grail for pediatric pulmonary vein stenosis. *J Am Coll Cardiol*. 2021;77:2819–2821. doi: 10.1016/j.jacc.2021.04.029
2. Patel JD, Mandhani M, Gray R, Pettus J, McCracken CE, Thomas A, Bauser-Heaton H, Kim DW, Petit CJ. Transcatheter recanalization of atretic pulmonary veins in infants and children. *Circ Cardiovasc Interv*. 2022;15:e011351. doi: 10.1161/CIRCINTERVENTIONS.121.011351
3. Simard T, Sarma D, Miranda WR, Jain CC, Anderson JH, Collins JD, el Sabbagh A, Jhand A, Peikert T, Reeder GS, et al. Pathogenesis, evaluation, and management of pulmonary vein stenosis: JACC review topic of the week. *J Am Coll Cardiol*. 2023;81:2361–2373. doi: 10.1016/j.jacc.2023.04.016
4. Latson LA, Prieto LR. Congenital and acquired pulmonary vein stenosis. *Circulation*. 2007;115:103–108. doi: 10.1161/CIRCULATIONAHA.106.646166
5. White BR, Ho DY, Faerber JA, Katcoff H, Glatz AC, Mascio CE, Stephens P Jr, Cohen MS. Repair of total anomalous pulmonary venous connection: risk factors for postoperative obstruction. *Ann Thorac Surg*. 2019;108:122–129. doi: 10.1016/j.athoracsur.2019.02.017
6. Shi G, Zhu F, Wen C, Yan Y, Zhang H, Zhu Z, Chen H. Cardiac-type total anomalous pulmonary venous return is not benign. *J Thorac Cardiovasc Surg*. 2023;165:449–459.e4. doi: 10.1016/j.jtcvs.2022.03.036
7. Shi G, Zhu F, Wen C, Qiu L, Zhang H, Zhu Z, Chen H. Single-institution outcomes of surgical repair of infracardiac total anomalous pulmonary venous connection. *J Thorac Cardiovasc Surg*. 2021;161:1408–1417.e2. doi: 10.1016/j.jtcvs.2020.06.023
8. Vanderlaan RD, Rome J, Hirsch R, Ivy D, Caldarone CA. Pulmonary vein stenosis: treatment and challenges. *J Thorac Cardiovasc Surg*. 2021;161:2169–2176. doi: 10.1016/j.jtcvs.2020.05.117

9. Vanderlaan RD. Commentary: targeting neointimal lesions in pulmonary vein stenosis: fact or fiction? *J Thorac Cardiovasc Surg*. 2020;160:794–795. doi: 10.1016/j.jtcvs.2020.02.021
10. Kato H, Fu YY, Zhu J, Wang L, Aafaqi S, Rahkonen O, Slorach C, Traister A, Leung CH, Chiasson D, et al. Pulmonary vein stenosis and the pathophysiology of "upstream" pulmonary veins. *J Thorac Cardiovasc Surg*. 2014;148:245–253. doi: 10.1016/j.jtcvs.2013.08.046
11. Zhu J, Ide H, Fu YY, Teichert AM, Kato H, Weisel RD, Maynes JT, Coles JG, Caldarone CA. Losartan ameliorates "upstream" pulmonary vein vasculopathy in a piglet model of pulmonary vein stenosis. *J Thorac Cardiovasc Surg*. 2014;148:2550–2557. doi: 10.1016/j.jtcvs.2014.07.050
12. Dimas VV. Pulmonary vein atresia: is there hope for a good outcome? *Circ Cardiovasc Interv*. 2022;15:e012172. doi: 10.1161/CIRCINTERVENTIONS.122.012172
13. Christopher C. *Pilot Trial: The Safety and Feasibility of Losartan for Pulmonary Vein Stenosis*. ClinicalTrial.gov. 2019 Accessed March 20, 2024. https://clinicaltrials.gov/study/NCT02769130.
14. Fogari R, Zoppi A. A drug safety evaluation of valsartan. *Expert Opin Drug Saf*. 2011;10:295–303. doi: 10.1517/14740338.2011.543416
15. Schaefer F, Coppo R, Bagga A, Senguttuvan P, Schlosshauer R, Zhang Y, Kadwa M. Efficacy and safety of valsartan in hypertensive children 6 months to 5 years of age. *J Hypertens*. 2013;31:993–1000. doi: 10.1097/HJH.0b013e32835f5721
16. Greenberg JH, Zappitelli M, Devarajan P, Thiessen-Philbrook HR, Krawczeski C, Li S, Garg AX, Coca S, Parikh CR; for the TRIBE-AKI Consortium. Kidney outcomes 5 years after pediatric cardiac surgery: the TRIBE-AKI study. *JAMA Pediatr*. 2016;170:1071–1078. doi: 10.1001/jamapediatrics.2016.1532
17. Bussler S, Vogel M, Pietzner D, Harms K, Buzek T, Penke M, Händel N, Körner A, Baumann U, Kiess W, et al. New pediatric percentiles of liver enzyme serum levels (alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase): effects of age, sex, body mass index, and pubertal stage. *Hepatology*. 2018;68:1319–1330. doi: 10.1002/hep.29542
18. Shi G, Zhu Z, Chen J, Ou Y, Hong H, Nie Z, Zhang H, Liu X, Zheng J, Sun Q, et al. Total anomalous pulmonary venous connection: the current management strategies in a pediatric cohort of 768 patients. *Circulation*. 2017;135:48–58. doi: 10.1161/CIRCULATIONAHA.116.023889
19. Lee EY, Jenkins KJ, Muneeb M, Marshall AC, Tracy DA, Zurakowski D, Boiselle PM. Proximal pulmonary vein stenosis detection in pediatric patients: value of multiplanar and 3-D VR imaging evaluation. *Pediatr Radiol*. 2013;43:929–936. doi: 10.1007/s00247-013-2647-8
20. Abeysekera WWM, Sooriyarachchi MR. Use of Schoenfeld's global test to test the proportional hazards assumption in the cox proportional hazards model: an application to a clinical study. *J Natl Sci Found Sri Lanka*. 2009;37:41–51.
21. Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. *Bone Marrow Transplant*. 2020;55:675–680. doi: 10.1038/s41409-019-0679-x
22. Hair JF, Hult GTM, Ringle CM, Sarstedt M, Danks NP, Ray S. An introduction to structural equation modeling. *Partial Least Squares Structural Equation Modeling (PLS-SEM) Using R*. Cham: Springer; 2022:1–29. doi: 10.1007/978-3-030-80519-7_1
23. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
24. Kuo JA, Petit CJ. Pulmonary vein stenosis in children: a programmatic approach employing primary and anatomic therapy. *Children (Basel)*. 2021;8:663.
25. Patel JD, Briones M, Mandhani M, Jones S, Suthar D, Gray R, Pettus J, McCracken C, Thomas A, Petit CJ. Systemic sirolimus therapy for infants and children with pulmonary vein stenosis. *J Am Coll Cardiol*. 2021;77:2807–2818. doi: 10.1016/j.jacc.2021.04.013
26. Jadcherla AV, Backes CH, Cua CL, Smith CV, Levy PT, Ball MK. Primary pulmonary vein stenosis: a new look at a rare but challenging disease *NeoReviews*. 2021;22:e296–e308. doi: 10.1542/neo.22-5-e296
27. Vanderlaan RD, Caldarone CA. Pulmonary vein stenosis: incremental knowledge gains to improve outcomes. *Children (Basel)*. 2021;8:481.
28. Rehman M, Jenkins KJ, Juraszek AL, Connor JA, Gauvreau K, Muneeb M, Sena LM, Colan SD, Saia T, Kieran MW. A prospective phase II trial of vinblastine and methotrexate in multivessel intraluminal pulmonary vein stenosis in infants and children. *Congenit Heart Dis*. 2011;6:608–623. doi: 10.1111/j.1747-0803.2011.00574.x
29. Callahan R, Kieran MW, Baird CW, Colan SD, Gauvreau K, Ireland CM, Marshall AC, Sena LM, Vargas SO, Jenkins KJ. Adjunct targeted biologic inhibition agents to treat aggressive multivessel intraluminal pediatric pulmonary vein stenosis. *J Pediatr*. 2018;198:29–35.e5. doi: 10.1016/j.jpeds.2018.01.029
30. Davies PF. Flow-mediated endothelial mechanotransduction. *Physiol Rev*. 1995;75:519–560. doi: 10.1152/physrev.1995.75.3.519
31. Tamargo IA, Baek KI, Kim Y, Park C, Jo H. Flow-induced reprogramming of endothelial cells in atherosclerosis. *Nat Rev Cardiol*. 2023;20:738–753. doi: 10.1038/s41569-023-00883-1
32. Hammer PE, McEnaney K, Callahan R, Baird CW, Hoganson DM, Jenkins KJ. The role of elevated wall shear stress in progression of pulmonary vein stenosis: evidence from two case studies. *Children (Basel)*. 2021;8:729. doi: 10.3390/children8090729
33. Cooley BC, Nevado J, Mellad J, Yang D, St. Hilaire C, Negro A, Fang F, Chen G, San H, Walts AD, et al. TGF-β signaling mediates endothelial-to-mesenchymal transition (EndMT) during vein graft remodeling. *Sci Transl Med*. 2014;6:227ra34. doi: 10.1126/scitranslmed.3006927
34. Souilhol C, Serbanovic-Canic J, Fragiadaki M, Chico TJ, Ridger V, Roddie H, Evans PC. Endothelial responses to shear stress in atherosclerosis: a novel role for developmental genes. *Nat Rev Cardiol*. 2020;17:52–63. doi: 10.1038/s41569-019-0239-5
35. Numata R, Takigiku K, Obinata H, Akazawa Y, Takei K. Assessment of left atrial deformation in patients with total anomalous pulmonary venous connection by two-dimensional speckle-tracking echocardiography. *Heart Vessel*. 2023;38:825–838. doi: 10.1007/s00380-023-02232-1
36. Fujimoto Y, Urashima T, Kawachi F, Akaike T, Kusakari Y, Ida H, Minamisawa S. Pulmonary hypertension due to left heart disease causes intrapulmonary venous arterialization in rats. *J Thorac Cardiovasc Surg*. 2017;154:1742–1753.e8. doi: 10.1016/j.jtcvs.2017.06.053
37. Ricci M, Elliott M, Cohen GA, Catalan G, Stark J, de Leval MR, Tsang VT. Management of pulmonary venous obstruction after correction of TAPVC: risk factors for adverse outcome. *Eur J Cardiothorac Surg*. 2003;24:28–36. doi: 10.1016/S1010-7940(03)00180-5
38. Lacour-Gayet F, Zoghbi J, Serraf AE, Belli E, Piot D, Rey C, Marçon F, Bruniaux J, Planché C. Surgical management of progressive pulmonary venous obstruction after repair of total anomalous pulmonary venous connection. *J Thorac Cardiovasc Surg*. 1999;117:679–687. doi: 10.1016/S0022-5223(99)70287-4
39. Karamlou T, Gurofsky R, Al Sukhni E, Coles JG, Williams WG, Caldarone CA, van Arsdell GS, McCrindle BW. Factors associated with mortality and reoperation in 377 children with total anomalous pulmonary venous connection. *Circulation*. 2007;115:1591–1598. doi: 10.1161/CIRCULATIONAHA.106.635441
40. Yamaki S, Tsunemoto M, Shimada M, Ishizawa R, Endo M, Nakayama S, Hata M, Mohri H. Quantitative analysis of pulmonary vascular disease in total anomalous pulmonary venous connection in sixty infants. *J Thorac Cardiovasc Surg*. 1992;104:728–735. doi: 10.1016/S0022-5223(19)34743-9
41. Flynn JT, Meyers KE, Neto JP, de Paula Meneses R, Zurowska A, Bagga A, Mattheyse L, Shi V, Gupte J, Solar-Yohay S, et al. Efficacy and safety of the angiotensin receptor blocker valsartan in children with hypertension aged 1 to 5 years. *Hypertension*. 2008;52:222–228. doi: 10.1161/HYPERTENSIONAHA.108.111054
42. Matsuhisa H, Oshima Y, Higuma T, Matsushima S, Hasegawa S, Wada Y, Matsuoka M, Tanaka T. Computed tomography-based surgical strategy for total anomalous pulmonary venous connection. *Eur J Cardiothorac Surg*. 2020;58:237–245. doi: 10.1093/ejcts/ezaa028