ELSEVIER

https://www.jhltopen.org/

Pulmonary artery banding to treat end-stage heart failure in infants and young children: A multicenter study

Massimo A. Padalino, MD, PhD,[a,b,*] Domenico Crea, MD,[a] Matteo Ponzoni, MD,[a] Luca Vedovelli, PhD,[a] Andrzey Kansy, MD,[c] Thierry Bove, MD,[d] Joseph Panzer, MD, PhD,[e] Marc Gewillig, MD,[f] Bjorn Cools, MD,[f] Thomas Salaets, MD,[f] Dexter Cheng, MD,[g] Andrea Francavilla, MD,[a] Alessia Cerutti, MD,[h] Vladimiro Vida, MD, PhD,[a] Giovanni Di Salvo, MD, PhD,[h] and Biagio Castaldi, MD[h]

[a]*Department of Cardiothoracic and Vascular Sciences and Public Health, University of Padova, Padova, Italy*
[b]*Department of Precision and Regenerative Medicine and Jonian Area, University of Bari, Bari, Italy*
[c]*Children's Memorial Health Institute Warsaw, Warsaw, Poland*
[d]*Kliniekhoofd Hartchirurgie, Department of Cardiac Surgery Universitair Ziekenhuis Gent, University Hospital of Ghent, Ghent,Belgium*
[e]*Kliniekhoofd Kindercardiologie, Department of Pediatrics Universitair Ziekenhuis Gent, University Hospital of Ghent, Ghent, Belgium*
[f]*Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium*
[g]*The Medical City Hospital, Manila, Philippines*
[h]*Department of Woman and Child's Health, University of Padova, Padova, Italy*

KEYWORDS:
multicenter study;
end-stage heart failure;
dilated cardiomyopathy;
pulmonary artery banding

BACKGROUND: Conventional treatment options for end-stage heart failure (ESHF) in children include heart transplantation (HT) and ventricular assist device (VAD), both with significant drawbacks in the pediatric population. Pulmonary artery banding (PAB) strategy embedded in a protective cardiovascular drug regime has been effectively used for functional cardiac regeneration and as a bridge to HT in pediatric ESHF. We herein describe the early and mid-term clinical outcomes from a multicenter international experience.

METHODS: This is a multicenter retrospective study including children admitted for ESHF caused by dilated cardiomyopathy of any etiology, who were treated with PAB. The primary outcome was the freedom from death/VAD/HT. Data are summarized as median (interquartile range) and count and percentages.

RESULTS: Thirty-one patients (median age 210 days [131-357]) with ESHF underwent PAB in 5 centers. Pediatric interagency registry for mechanically assisted circulatory support score was I to III in 90%; 15 patients were intubated preoperatively. Preoperative left ventricular (LV) ejection fraction was < 30% in 68%, with LV dilation in all cases. Postoperatively, median PAB gradient was 29 mm Hg (23-34), and complications occurred in 14 patients (45%), with 4 (13%) early deaths. Twenty-seven patients were successfully discharged home on cardiac protective medical therapy. At a median follow-up of 2.9 years, there were 1 late death and 3 HTs. Freedom from death/VAD/HT was 77.3% (95%

*Corresponding author: Massimo A. Padalino, MD, PhD, Pediatric and Congenital Cardiac Surgery, Department of Precision and Regenerative Medicine and Jonian Area, University of Bari "Aldo Moro," Piazza Giulio Cesare, 11, 70124 Bari, Italy.
E-mail address: massimo.padalino@uniba.it.

https://doi.org/10.1016/j.jhlto.2024.100143

confidence interval [CI] = 58%-88.4%), 77.3% (95%CI = 58%-88.4%), and 73.2% (95%CI = 53.2%-85.5%) at 6 months, 1 year, and 2 years of follow-up, respectively. All 23 survivors with a native heart had gradual normalization of LV function and dimensions.

CONCLUSIONS: PAB can be an effective procedure to treat ESHF in selected infants, as an innovative conservative strategy for bridging to transplant or recovery.

JHLT Open xxxx;xxx:xxx

Background

The ultimate therapy for end-stage heart failure (ESHF) is heart transplantation (HT), which, unfortunately, is not readily available in all infants and children.[1,2] Therefore, novel therapeutic strategies are needed. Durable ventricular assist devices (VAD) can be effective even in infants and children with ESHF,[3] even if clinical experience is still limited when compared to the adult setting. The extracorporeal Berlin Heart EXCOR and PediMag/CentriMag are currently the only available VADs for pediatric patients < 10 kg.[4] Nevertheless, despite ongoing enhancements, the occurrence of significant, life-threatening, or debilitating complications remains noteworthy,[5] with only a few cardiac centers accumulating sufficient expertise to ensure satisfactory results. Based on the experience with left ventricular (LV) retraining for congenitally corrected transposition of the great arteries, pulmonary artery banding (PAB) has been reinvented as a bridge-to-transplant or recovery strategy in infants with dilated cardiomyopathy (DCM) and preserved right ventricular (RV) function.[6] PAB is thought to harness the inherent regenerative capacity of the heart, particularly in infants and young children, who possess a more robust stem cell pool.[7] By creating controlled pressure overload, PAB may trigger signaling pathways that promote cardiomyocyte proliferation and tissue repair.

The global experience with PAB for DCM has been recently recapitulated by 2 multicenter studies, which reported satisfactory although diverse results in very heterogeneous cohorts of children.[8,9] Currently, there is no scientific consensus regarding indications or age cut-offs, and whether this procedure is effective for myocardial recovery,[10] or can be safely proposed as an alternative strategy to VAD for bridging patients to HT. Moreover, the tissue-level correlates of functional LV rehabilitation promoted by PAB (documented by imaging and hemodynamic studies[11-13]) are still unknown. We herein present the most recent multicenter experience with PAB for DCM in infants and children, to outline its best indications and the clinical and functional mid-term outcomes.

Methods

This is a multicenter retrospective clinical study, including infants and children with ESHF due to DCM of any etiology treated with PAB from January 2012 to December 2023 in 5 centers. Indication to PAB was determined via multidisciplinary evaluation across all centers. During the study period, with the increasing and varied experiences across centers, certain facilities integrated PAB into the standard care for ESHF in infants,[5] while others employed PAB as a form of rescue therapy. Inclusion criteria across all centers were all the same: age < 3.5 years; evidence of severe LV dysfunction (ejection fraction [EF] < 35%), with preserved RV function (fractional area change > 30%, tricuspid annular plane systolic excursion [TAPSE] > 8 mm); failure of weaning from inotropic therapy.[5,14] Excluded were patients with biventricular failure, severe tricuspid regurgitation (qualitative assessment), and idiopathic or reactive pulmonary hypertension (mean pulmonary artery pressure > 25 mm Hg).

Preoperative, intraoperative, postoperative, and follow-up data were collected and entered into a common REDCAP database. The local ethics committee from each center approved the review of medical records and data-sharing. The anonymized data collected in the common database with patient follow-up until December 2023 were compiled into a unique dataset and forwarded to the data-processing center at the University of Padua (after ethics approval for centralized data collection and analysis, protocol 5372/AO/22). A team of experienced ESHF clinicians abstracted and reviewed all data for completeness. Outlier data were checked and validated with their submitting center. This study is in compliance with the ISHLT Ethics statement.

The primary outcome was the freedom from death, VAD, and HT (composite end-point of PAB failure). Secondary outcomes were the incidence of early and late adverse events, as well as the modifications in biventricular function and structure as measured by echocardiography.

Before PAB, all patients were administered anticongestive and cardiac-protecting medical therapy (bisoprolol, lisinopril, and spironolactone), as recommended by Schranz et al.[13,14] Whenever clinical conditions were unstable, the patient was admitted to the pediatric intensive care unit (ICU), intubated and mechanically ventilated, and intravenous infusion of inotropes as milrinone and levosimendan were started, and catecholamines added if necessary. All patients underwent cardiac transplant work-up, but the inclusion in the active waiting list depended on center-specific protocols.

The primarily echocardiographic evaluation was focused on the 4ch-view with and without color-Doppler movies having a first, subjective impression of the preoperative and

postoperative ventriculo-ventricular interaction, (left) atrial congestion or even hypertension and existing of an atrial communication. Measured data were LV EF (Simpson's method), LV dimensions, and mitral and tricuspid valve regurgitation (according to ESC recommendations).[15] RV function was additionally assessed using TAPSE. Postoperative trans-PAB pressure gradient was assessed by continuous Doppler velocity gradient,[2] and related to the actual TAPSE measurements. When available, the echocardiographic assessment was reported before PAB, at discharge, and after 3, 6, and 12 months from surgery or at the last available follow-up. Patients were excluded from the imaging follow-up after undergoing VAD implantation or HT.

All patients underwent PAB through a midline sternotomy as previously described,[5,6] under continuous transesophageal echocardiography (TEE) monitoring. In particular, PAB was secured with sequential 6.0 and 7.0 polypropylene stitches to facilitate catheter-based debanding during follow-up, if needed. Pulmonary artery pressure and RV pressure were monitored continuously during the procedure by direct measurement. PAB was tightened to obtain an RV pressure equal to 50% to 70% of a still stable systemic arterial pressure, or until TEE was showing a leftward shift of the interventricular septum, or TAPSE reduction, or increasing tricuspid valve regurgitation.[5,6,13,14] Chest closure was delayed according to the surgeon's preference.

Statistical analysis

Data are expressed as counts and percentages and median and interquartile range (IQR), as appropriate. Comparisons between categorical variables were performed by Fisher's test, while for continuous variables the nonparametric Kruskal-Wallis test was used with pairwise comparison by Dunn's test and *p*-value adjusted by Holm's method. Freedom from death, VAD, and HT was estimated with the Kaplan–Meier method along with the 95% confidence interval (CI) at 6 months, 1 year, and 2 years of follow-up from PAB. Univariate logistic regression analysis was performed to identify preoperative variables associated with PAB failure (composite event: death/VAD/HT). The risk was quantified using odds ratio (OR) with 95% CI. Given the small sample size and the low number of events, multivariate analysis was not performed. The analyses were performed using R (R Core Team, 2022).

Results

Baseline characteristics

Thirty-one patients (male/female = 18/13) with a median age of 210 days (IQR: 131-357, range 45-1,288 days) and median weight of 6.4 kg (IQR: 5.2-8.15) underwent PAB for ESHF (Ross class III and IV in all) in 5 international centers (mean of 6.2 procedure/center, range 4-8).

On admission, all patients underwent two-dimensional echocardiographic evaluation (Table 1), while 12 had cardiac magnetic resonance imaging (CMRI) assessment (39%). At two-dimensional echocardiography, the median baseline LV EF was 25% (IQR: 16.8%-28.3%), and it was < 30% in 21 patients (68%); mitral valve regurgitation was > moderate in 54%; median TAPSE was 10.8 mm (IQR: 9-14.4). Tricuspid regurgitation was < moderate in all. All admission echocardiography data were collected before or shortly after the initial medical treatment. The most frequent etiology of ESHF was idiopathic DCM in 15 patients (48%, Table 1) and associated congenital heart diseases were present in 3 (anomalous left coronary artery from the pulmonary artery [ALCAPA] in 2 and patent ductus arteriosus in 1). Fifteen patients (48%) were mechanically ventilated before PAB, while 1 patient required extracorporeal membrane oxygenation (ECMO) support (Table 2). A preoperative endomyocardial biopsy was performed in 9 patients (29%). At admission, the pediatric interagency registry for mechanically assisted circulatory support (PEDIMACS) class was I to III in 28 patients (90%), and 22 patients (71%) underwent Levosimendan intravenous infusion before PAB. Most patients (74%) were listed for HT; this varied according to local center protocols rather than patients' conditions.

Surgical results

All patients undergoing PAB had a smooth intraoperative course, and cardiopulmonary bypass was electively used only in 3 patients requiring concomitant surgical repair of ALCAPA (2 cases), and creation of a restrictive ASD (1 patient). One patient had a patent ductus arteriosus closure (without cardiopulmonary bypass).

The band was tightened gently to obtain a leftward displacement of the interventricular septum (possible in 87% of patients), with a median PAB gradient at the end of the procedure of 29 mm Hg (IQR: 23-34). After PAB, TEE monitoring showed an acute decrease in mitral valve regurgitation severity in 13 (42%) cases. Seven patients (all in 1 center, as part of the institutional protocol) underwent a delayed sternal closure after a median time of 3 days (range 2-9 days).

The perioperative course was complicated in 14 patients (47%), with low cardiac output syndrome occurring in 5 patients (Table 2). Thirteen patients required an early reintervention: surgical PAB tightening in 6, and mechanical cardiac support in 4 patients (1 of whom required temporary ECMO support, while 3 underwent an LVAD-Berlin Heart EXCOR implantation) during the same hospitalization, because of inadequate myocardial recovery and inotropic support dependence. The remaining complications are listed in Table 2.

The median ICU stay was 13 days (IQR: 7-24). There were 4 early deaths (13%), following low cardiac output syndrome in 3 and sepsis in 1. Of note, 2 of these infants were not supported on ECMO because of specific center protocols, which exclude infants from ECMO support.

Table 1 Demographics of Patients Undergoing PAB for DCM

Variable	N	%
Age at PAB (days, median, IQR)	210 (131-357)	
Weight at PAB surgery (kg, median, IQR)	6.4 (5.20-8.15)	
Male	18	58
Associated congenital heart disease	3	10
– ALCAPA	2	
– Patent ductus arteriosus	1	
Etiology of ESHF		
Idiopathic DCM	15	48
Acute viral myocarditis	2	7
Chronic viral myocarditis	5	16
LV noncompaction	1	3
Genetic DCM	5	16
	1	7
– Heterozygotic carrier of new molecular variant in PRDM16 gene	1	3
– Heterozygotic carrier of new molecular variant in MYBPC3 gene	1	
– Heterozygotic carrier of 2 molecular variants in MYL2 gene	1	
– Heterozygotic carrier of new molecular variant in MYH7 gene	1	
– Mitochondrial disease	2	
Postischemia	1	
Other (not specified)		
Endomyocardial biopsy	9	29
Normal	1	
Inconclusive, but excluding viral myocarditis	1	
Inflammatory DCM with endocardial fibroelastosis	2	
Chronic active myocarditis	2	
	1	
– Parvovirus-B19-induced	1	
Active lymphocytic myocarditis	1	
Interstitial disease	1	
Mitochondrial cardiomyopathy		
Associated genetic syndrome	2	7
Pre-PAB NT-pro-BNP (pg/ml, median, IQR)	9,927 (3,346-14,991) ($n = 23$)	

Abbreviations: ALCAPA, anomalous left coronary artery from the pulmonary artery; BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; ESHF, end-stage heart failure; IQR, interquartile range; LV, left ventricle; PAB, pulmonary artery banding.

Except for those 2 on VAD support, all the remaining survivors (25/27, 81%) were discharged home in good clinical conditions (Ross class < III in 25/27 survivors), with cardiac protective medical therapy (Table 2).

Medium-term outcomes

At a median follow-up of 2.9 years (IQR: 1.2-4.85), there was 1 late death during VAD support, because of progressive multiorgan failure and a stroke. Eight patients (30%) experienced at least 1 adverse event: 3 patients underwent a successful HT (1 of whom was preceded by ECMO and VAD support), VAD implantation in 1, and other minor procedures in 3 (Tables 3 and 4).

Freedom from death/VAD/HT was 77.3% (95% CI = 58%-88.4%), 77.3% (95%CI = 58%-88.4%), and 73.2% (95%CI = 53.2%-85.5%) at 6 months, 1 year, and 2 years of follow-up, respectively (Figure 1). All survivors with their native hearts are alive and well (Ross class I in 79%), on sinus rhythm, and cardiac protective medical therapy, with progressive improvement of symptoms.

During follow-up, 5 patients (19%) required at least 1 cycle of Levosimendan infusion within 3 months from PAB, with good benefit (3 patients required 2 or more cycles). Elective percutaneous PAB balloon dilation was performed in 14 patients (61%) at variable timing (range 2-13 months). The indication for partial debanding was progressive RV hypertension and hypertrophy, with worsening tricuspid regurgitation. This procedure was well tolerated and effective in all patients, who had a substantial benefit from partial debanding.

Univariate logistic regression analysis revealed that female sex was a protective factor against PAB failure (OR: 0.09, 95%CI: 0.00-0.60, $p = 0.034$). Although not statistically significant, age > 1 year displayed a trend toward a higher risk of PAB failure (OR: 4.00, 95%CI: 0.73-23.4, $p = 0.11$). Having a viral myocarditis etiology did not represent a protective factor against PAB failure.

Table 2 Operative Data of Patients Undergoing PAB for DCM

Variable	N	%
Echocardiography assessment on admission	31	100
CMRI assessment on admission	12	39
PEDIMACS level		
Critical cardiogenic shock (I)	3	10
Progressive decline (II)	6	19
Stable but inotrope dependent (III)	19	61
Resting symptoms (IV)	1	3
Exertion intolerance (V)	1	3
Exertion limitation (VI)	1	3
Listed for HT	23	74
Preoperative intubation	15	48
Preoperative ECMO	1	3
Preoperative infusion of levosimendan	22	71
Procedure before PAB	6	19
– ALCAPA repair	2	
– Balloon atrial septostomy	*4*	
Cardiopulmonary bypass during cardiac surgery + cardioplegic arrest	1	3
Associated surgical procedure	3	10
– Restrictive atrial septostomy + ECMO	1	
– PDA transection	1	
– ALCAPA repair	1	
PAB peak-gradient at the end of procedure (mm Hg, median, IQR)	29 (23-34) ($n = 30$)	
Leftward interventricular septum displacement after PAB	27	87
Mitral regurgitation reduction after PAB	13	42
Delayed chest closure	7	23
– Within 48 hours	3	
– Within 72 hours	1	
– After 72 hours	3	
Length of ICU stay (days, median, IQR)	13 (7-24) ($n = 30$)	
Postoperative complications (n)	14 ($n = 30$)	47
Low cardiac output syndrome	*5*	
Bleeding requiring reoperation	1	
Acute kidney injury	2	
Chilotorax	1	
Pleural effusion requiring chest tubes > 3 days	1	
Infection requiring antibiotic therapy for > 7 days	4	
Bradyarrhythmias	1	
Tachyarrhythmias	1	
Other:	6	
– Subglottic stenosis (Cotton grade III)	1	
– Hypotension and LV thrombosis requiring vent placement	1	
– Pericardial effusion requiring surgical drainage	1	
– Peripheral vein thrombosis	1	
– Progressive LV failure requiring VAD implantation	1	
Intubation time after PAB		
Less than 24 hours	5	16
24-72 hours	11	36
More than 72 hours	15	48
Early death (n)	4	13
– Cardiac failure	*3*	
– Sepsis	*1*	
Early reintervention (n)	13	42
– Surgical PAB tightening	*6*	
– Delayed chest closure	7	
– ECMO	1	
– VAD	3	
– Tamponade	1	
Home therapy	25	81
ACE-inhibitors or ARB	24	77
Beta-blockers	24	77
Diuretics	24	77
Warfarin	1	3
Aspirin or antiaggregation therapy	10	32
Other:	7	23
– L-carnitine and Q coenzyme	1	
– Clonidine	1	
– Digoxin	2	
– Enoxaparin	2	
– Immunosuppression after HTX	1	
NYHA/Ross class at discharge (n)	27	
I	6	22
II	17	63
III	2	7
IV	2	7
Echocardiography at discharge	22	74

Abbreviations: ALCAPA, anomalous left coronary artery from pulmonary artery; ARB, angiotensin receptor blockers; CMRI, cardiac magnetic resonance imaging; ECMO, extracorporeal membrane oxygenation; HT, heart transplantation; ICU, intensive care unit; IQR, interquartile range; LV, left ventricle; PAB, pulmonary artery banding; PDA, patent ductus arteriosus; PEDIMACS, pediatric interagency registry for mechanically assisted circulatory support; VAD, ventricular assist device.

Echocardiographic and CMRI assessment

Echocardiographic monitoring during follow-up (Tables 5 and 6) demonstrated that the LV EF gradually increased, mostly after 3 months from PAB, from a median baseline value of 25% (IQR: 16.8%-28.3%) to 60% (IQR: 52.5%-65%) at the last follow-up (Figure S1). Similarly, the LV diameter Z-Score gradually decreased from a median value of 9.72 (IQR: 6.54-12.63) at baseline to 2.52 (IQR −0.05 to 3.27) at the last follow-up (Figure S2). At the last echocardiography, mitral regurgitation was absent or trivial in most patients, while tricuspid regurgitation was always less than moderate, with a median TAPSE of 16 mm (IQR: 15.3-16.8).

Six patients had CMRI at follow-up (Table S1), after a median time of 1.4 years (IQR: 1-4) from PAB, which showed improvement in the LV EF from a baseline value of 17% (12.5-20.5) to 56% (41-60) at follow-up. Similarly, we observed LV remodeling, with progressive reduction of LV EDV from 170 ml/m^2 (138-242.5) at baseline to 85.2 ml/m^2 (78.8-96.5) at follow-up. RV function was preserved. Of note, a significant quote of patients developed areas of late-gadolinium

Table 3 Follow-up Data of Patients Undergoing PAB for DCM

Variable	N	%
Follow-up (years, median, IQR)	2.9 (1.2-4.85)	
Total patients (*n*)	27	87
Late death (*n*)	1	4
Adverse event other than death during FU	8	30
Surgical adverse events	*7*	
– HT	*2*	
– ECMO + VAD + HT	1	
– VAD	1	
Nonsurgical adverse events	1	
– Progressive congestive heart failure	1	
Therapy at last FU	26	89
ACE-inhibitors or ARB	23	
Diuretics	14	
Beta-blockers	17	
Antiaggregation	*3*	
Other	*7*	
PAB dilation during follow-up	14 (*n* = 23)	61 71
Once	10	29
More than once	4	
Sinus rhythm at last follow-up	27	100
NYHA class in survivors (*n*)	27	
I	22	81
II	4	15
III	0	0
IV	1	4
Levosimendan infusion therapy after PAB	5	19
Number of cycles		
One cycle	2	40
Two cycles	1	20
More than 2	2	40
Timing		
Within 1 month from discharge	2	40
Within 3 months from discharge	3	60
CMRI at follow-up	6	22

Abbreviations: ARB, angiotensin receptor blockers; CMRI, cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; HT, heart transplant; IQR, interquartile range; PAB, pulmonary artery banding; VAD, ventricular assist device.

Table 4 Univariate Logistic Regression Analysis Between Preoperative Variables and PAB Failure (Composite Event: Death/VAD/HT)

Variable	N	OR	95% CI	*p*-value
Age at PAB	31			
< 12 months		-	-	
> 12 months		4.00	0.73-23.4	0.11
Gender	31			
Male		-	-	
Female		0.09	0.00-0.60	0.034
ESHF etiology	31			
Viral myocarditis (acute + chronic)		-	-	
All others		0.83	0.13-5.47	0.85
PEDIMACS class	31			
Class I+II		-	-	
Class III or more		0.21	0.04-1.06	0.063
Preoperative Levosimendan	31	4.00	0.58-80.9	0.20
Preoperative intubation	31	2.36	0.50-13.4	0.30
Delayed chest closure	31	0.69	0.09-3.81	0.70

Abbreviations: CI, confidence interval; ESHF, end-stage heart failure; HT, heart transplantation; OR, odds ratio; PAB, pulmonary artery banding; PEDIMACS, pediatric interagency registry for mechanically assisted circulatory support; VAD, ventricular assist device.

enhancement positivity in both ventricles at last evaluation, whose clinical significance is unknown.

Discussion

Based on the findings in this multicenter study, we show that in selected infants, a reversible PAB associated with aggressive use of pharmacotherapy represents a promising treatment for functional cardiac regeneration and an alternative strategy to LVAD for bridging pediatric patients to HT. The concept of ventricular remodeling is well-established and aligns with the modern understanding of congestive heart failure with reduced EF. It includes the potential for reverse remodeling of a failing left ventricle using VAD, as thoroughly reviewed by Braunwald.[16] Also, the use of VAD involves a "reverse remodeling" and probably a profound change in the structure and function of the myocardium, which occasionally leads to explantation of the device.[17] Despite current outcomes of HT and VAD have also improved in the pediatric population, the intrinsic limitations of these organ replacement-based strategies have directed recent research efforts toward novel regenerative-inspired approaches to pediatric ESHF.[7,10] Recruiting the healing ability of the native heart has the concrete potential to overcome not only the well-known shortage of heart donors in the youngest age classes,[1] but also the multiple side-effects of chronic immunosuppressive regimen,[18,19] and the hemorrhagic/thromboembolic concerns of VAD.[3,4,20]

A surgically performed reversible PAB is now entering the portfolio for the management of pediatric ESHF, as a promising alternative to preserve the native heart, especially when considering that VAD in pediatric patients is still utilized in few pediatric cardiac centers. However, from the first description by Schranz et al[21] to the more recent multicenter studies,[8,9] the number of children with ESHF treated with PAB is still limited, as well as data on their late response.[13] In the current work, we aimed at providing an up-to-date insight into the efficacy and safety of PAB as a regenerative strategy for pediatric ESHF, by collecting a multicenter cohort from 5 international hospitals. This project was proposed within different cardiac surgical societies, having as an example the previously published multicenter study by Schranz et al.[8] Despite intrinsic differences in patient management among participating centers, the adopted standard of practice (in terms of patient selection, inclusion criteria, and treatment) was the same in

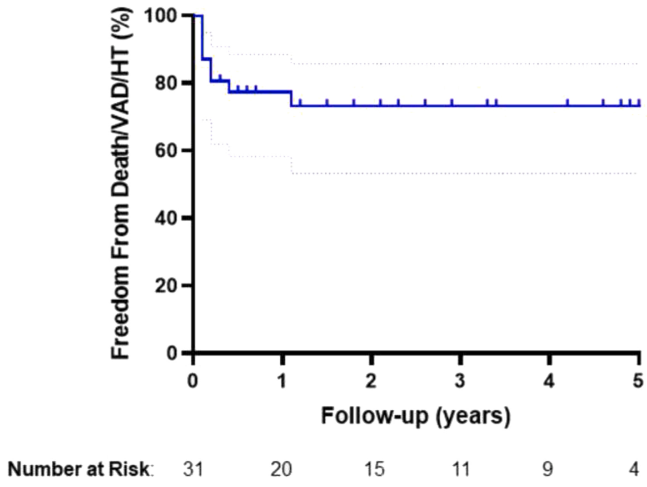

Figure 1 Kaplan–Meier plot of freedom from death/VAD/HT with 95% CI. CI, confidence interval; VAD, ventricular assist device.

all centers, following the Giessen protocol.[14] From the present work, PAB was a successful bridge to recovery in 23/31 patients, without precluding the HT pathway, resulting in a freedom from death/VAD/HT of 73.2% (95%CI = 53.2%-85.5%) at 2 years of follow-up (Figure 1). Clinical results of PAB for DCM have shown discrepancies among different groups. In the Giessen experience, PAB promoted myocardial recovery in 10/12 patients (83.3%), avoiding VAD and HT.[6] These promising results were subsequently confirmed by the first multicenter study, which highlighted a low medium-term mortality (8/61, 13.1%) and a high rate of LV function recovery (complete recovery: 34/61, 55.7%; partial recovery 8/61, 13.1%).[8] Conversely, in the subsequent US multicenter experience, LV functional recovery was achieved in only 4/14 cases (28.6%), while 2/14 (14.3%) died and 8/14 (57.1%) underwent HT.[9] Intercenter variations in selection criteria, age at PAB, etiology of ESHF, preoperative clinical status, and most importantly, a totally different and heterogeneous perioperative treatment concept should be considered and may explain this contrasting results.[22]

The cardiac repair potential is known to be age-dependent, with children < 1 year of age showing the most robust intrinsic stem cell capacity.[7] During embryonic and fetal development, cardiomyocytes possess replicative activity, which is subsequently lost after birth.[23] This negatively impacts the repair modality of the mammalian heart after injury: loss of myocardial tissue in the fetal or early neonatal mouse heart can be replaced with cardiomyocyte proliferation, while irreversible fibrosis and contractile tissue loss predominate later.[24] As shown in LV retraining in congenitally corrected transposition of the great arteries, the ventricular myocardium can benefit from controlled pressure overload mostly in younger age classes.[25,26] On the other hand, Rohde et al recently showed that, in the EUROMACS series of 303 children < 19 years who

Table 5 Echocardiographic Evaluation at Admission, Discharge and at 3-Month Follow-up

Variable	Admission		Discharge		3-month follow-up	
	N		N		N	
LV EF (%, median, IQR)	31	25 (16.8-28.3)	22	31 (25.5-34.8)	12	33.5 (29.3-41.8)
PAB peak-gradient (mm Hg, median, IQR)	6	0 (0-4.5)	20	33 (25-43)	7	50 (47.5-55)
Mitral valve regurgitation (*n*, %)	26		21		12	
None		3 (12)		1 (5)		0
Mild		3 (12)		6 (29)		5 (42)
Mild-moderate		3 (12)		5 (24)		3 (25)
Moderate		14 (54)		4 (19)		3 (25)
Severe		3 (12)		5 (24)		1 (8)
LV dilatation, qualitative (*n*, %)	21		19		7	
None		0		0		1 (14)
Mild		0		0		0
Mild-moderate		0		0		0
Moderate		2 (10)		5 (26)		3 (43)
Severe		19 (90)		14 (74)		3 (43)
LV end-diastolic diameter (mm, median, IQR)	25	43 (39.3-45.8)	18	40.5 (33.5-43.8)	6	31 (26.3-35.8)
LV end-diastolic diameter Z-score (median, IQR)	25	9.72 (6.54-12.63)	18	8 (11.66-5.32)	6	7.72 (12.06-3.1)
TAPSE (mm, median, IQR)	16	10.8 (9-14.4)	13	10 (9-12)	8	10 (9-13)
Tricuspid valve regurgitation (*n*, %)	25		22		13	
None		9 (36)		4 (18)		6 (46)
Mild		14 (56)		16 (73)		6 (46)
Mild-moderate		2 (8)		2 (9)		1 (8)
Moderate		0		0		0
Severe		0		0		0
RV pressure estimate if TR (mmHg, median, IQR)	9	32.5 (30-44.5)	12	40 (31-50)	2	52 mm Hg; 24 mm Hg

Abbreviations: EF, ejection fraction; IQR, interquartile range; LV, left ventricle; PAB, pulmonary artery banding; RV, right ventricle; TAPSE, tricuspid annular plane excursion; TR, tricuspid regurgitation.

Table 6 Echocardiographic Evaluation at 6-Month, 12-Month, and the Last Available Follow-up

Variable	6-month follow-up		12-month follow-up		Last follow-up	
	N		N		N	
LV EF (%, median, IQR)	9	46 (38-55)	10	60 (48-63.5)	20	60 (52.5-65)
PAB peak-gradient (mm Hg, median, IQR)	6	55 (38.8-70.5)	9	55 (39.5-79)	19	40 (27-50)
Mitral valve regurgitation (*n*, %)	9		7		20	
None		0		2 (29)		7 (35)
Mild		5 (56)		4 (57)		10 (50)
Mild-moderate		1 (11)		1 (14)		2 (10)
Moderate		2 (22)		1 (14)		1 (5)
Severe		1 (11)		1 (14)		0
LV dilatation, qualitative (*n*, %)	6		19		7	
None		2 (33)		0		1 (14)
Mild		0		0		0
Mild-moderate		0		0		0
Moderate		2 (33)		5 (26)		3 (43)
Severe		2 (33)		14 (74)		3 (43)
LV end-diastolic diameter (mm, median, IQR)	6	33 (25-40.5)	9	32 (31-33.5)	17	35.5 (32.8-38.3)
LV end-diastolic diameter Z-score (median, IQR)	6	6.92 (8.65-2.54)	9	1.96 (2.38-1.03)	17	2.52 (–0.05 to 3.27)
TAPSE (mm, median, IQR)	5	14 (10.5-16)	7	15 (12-15)	16	16 (15.3-16.8)
Tricuspid valve regurgitation (*n*, %)	9		9		20	
None		4 (44)		4 (44)		8 (40)
Mild		4 (44)		5 (56)		10 (50)
Mild-moderate		0		0		2 (10)
Moderate		1 (12)		0		0
Severe		0		0		0
RV pressure estimate if TR (mm Hg, median, IQR)	4	47 (39.8-53)	3	50 (39.5-67.5)	8	37.5 (21.8-58.5)

Abbreviations: EF, ejection fraction; IQR, interquartile range; LV, left ventricle; PAB, pulmonary artery banding; RV, right ventricle; TAPSE, tricuspid annular plane excursion; TR, tricuspid regurgitation.

underwent a successful Berlin heart EXCOR implantation,[27] the rates of myocardial recovery were remarkably high in children < 1.3 years and BSA < 0.53 m^2. These data may support using a PAB instead of a VAD in younger and smaller patients, who appear to have a higher recovery rate (approximately 70% in this series, compared to 21.8% in Rohde's experience).

In previous multicenter reports of PAB for DCM, age at surgery showed a significant variability (mean of 266 ± 310 days and median of 5 months (IQR 3.5-10), in the international and US studies, respectively[8,9]). In our cohort, the median age at PAB was lower (210 days, IQR 131-357), and only patients < 3.5 years were considered eligible for PAB (< 1 year in some institutions[5]). A greater myocardial repair potential could be hypothesized in our cohort, contributing to the high recovery rate after PAB. In addition, although it did not reach statistical significance, univariate logistic regression analysis revealed a trend toward a higher risk of PAB failure for patients > 1 year (OR: 4.00, 95%CI: 0.73-23.4, $p = 0.11$). Moreover, female sex was found to be a protective factor against PAB failure (OR: 0.09, 95%CI: 0.00-0.60, $p = 0.034$). These findings further support the utilization of PAB to treat ESHF in younger patients, where this strategy may display its greater benefit, and dictate particular clinical vigilance in male patients, who are expected to experience a higher rate of PAB failure.

A worse preoperative clinical status has been documented in the US cohort, in which PAB was adopted as a rescue strategy to avoid high-risk VAD implantation.[9] In our study, the vast majority of patients were in PEDIMACS class I to III, requiring invasive mechanical ventilation in almost 50% of cases, suggesting a very challenging clinical setting. The etiology of ESHF is intrinsically linked to the myocardial recovery rate.[5] In particular, an inflammatory myocarditis-like etiology of ESHF has been previously raised as a possible confounding factor of the efficacy of PAB in this population.[10] However, in the present study, we documented a particularly "unfavorable" distribution of ESHF etiologies, with a low prevalence of acute/chronic myocarditis (23%) and high rates of idiopathic DCM (48%) and genetic variants (16%, although genetic testing was not performed consistently across all centers). In this cohort, a very low spontaneous recovery rate can be anticipated,[28,29] supporting a causative role of PAB in promoting early and sustained LV recovery in 23/31 patients. Although the perioperative course was complicated in 47% of patients, early mortality was low (13%) and almost all survivors (25/27, 81%) were discharged home in good clinical conditions, with cardiac protective medical therapy. Due to careful echocardiographic monitoring and planned catheter-based partial debanding, we reported a very low rate of disease relapse at a median follow-up of 2.9 years (IQR: 1.2-4.85), with 23/31 patients who are alive and well with their native heart and without VAD. Based on these promising results, we are establishing a new treatment protocol for pediatric ESHF to be implemented across the centers involved in this

study. This protocol includes the use of PAB with aggressive cardiac protective medical therapy in selected cases as the new standard of care.

The functional biventricular response to PAB has been previously described by Latus et al, who retrospectively analyzed baseline and late CMRI of 15 children with DCM treated with PAB.[12] At 1-year follow-up, PAB promoted LV remodeling and improved LV contractility, diastolic function, and intra- and interventricular synchrony. Similarly, a rise in RV mass and strain, associated with a leftward shift of the interventricular septum, was documented.[12] More recently, Ponzoni et al confirmed these results, tracking the evolution of LV and RV performance after PAB with a seriate echocardiographic/CMRI monitoring protocol in PAB responders.[13]

In the present study, we documented on a larger sample that the LV undergoes an initially slow remodeling phase in the first 3 to 6 months after PAB when a reduction of LV pathological enlargement and a modest increase in LV global function are noticed (Figure S1 and S2). Subsequently, 6 to 12 months after PAB, almost complete normalization of LV contractility and dimensions is evident and maintained up to 2.9 years of follow-up. Although these data further contribute to the understanding of the macroscopic functional and morphological LV response to PAB, the need for adequate preclinical models[10,30] and the investigation of the cellular and molecular bases of LV rehabilitation[7,10] are now imperative. Moreover, the long-term consequences of LV and RV fibrosis (unmasked by CMRI) on the biventricular function of survivors are unknown. Further clinical and experimental studies are warranted to support the role of PAB as a valuable treatment option for pediatric ESHF.

Limitations

Significant limitations are the retrospective design of the study, the relatively small number of treated patients, and the short follow-up time, which prevents long-term cardiac function assessment. Moreover, since data were collected retrospectively from multiple centers, the timing of echocardiographic follow-up, scanning protocols, as well as the inclusion of CMRI, were not uniform, leading to missing functional data. The completeness of imaging data at the various time points was variable, thus caution should be used in longitudinally comparing the imaging data across the time points. Given the small sample size and the low incidence of adverse events, multivariate analysis was not performed. Some centers included in the present study have previously published their single-center[5] or shared experience,[8] leading to possible cohort overlap with already published patient data. However, we separately analyzed the cohort of unpublished patients and did not find any significant difference in the main outcomes. Additionally, we believe that including these patients is justified, as they have been evaluated over a longer follow-up period and contribute to validating the long-term effectiveness of this strategy.

Conclusions

In this multicenter study, PAB in conjunction with cardiac protective medical therapy and rigorous clinical monitoring emerges as a potentially effective strategy for treating ESHF in selected infants and children, with a freedom from death/VAD/HT of 73.2% (95%CI = 53.2%-85.5%) at 2 years of follow-up. Notably, female patients exhibited the most favorable response to PAB and there was a positive trend observed in patients under 12 months of age. At mid-term follow-up, individuals responding to PAB displayed a gradual clinical recovery, a marked improvement in LV function, and a reduction in LV dilatation and mitral regurgitation. We hypothesize that LV remodeling is a slow and gradual process triggered by the restoration of interventricular geometry induced by PAB, requiring 6 to 12 months to stabilize. Additional research is essential to elucidate the precise mechanisms governing ventricular remodeling and the action mechanisms of aggressive cardiac protective medical therapy. This will help to distinguish between "responders" and "nonresponders" to this strategy. Such insights could potentially enhance the survival rates of infants with ESHF and contribute to normalizing the long-term prognosis for these children. Importantly, this approach holds particular promise for implementation in low-income countries where mechanical assist devices may be unavailable.

We believe that the primary goal of pediatric health care today should be to focus on cardiac regeneration to spare children, especially infants, from HT. This approach should take precedence over addressing the well-known shortage of heart donors and the complications associated with HT immunosuppression and VAD.

CRediT authorship contribution statement

Massimo Padalino conceptualized and designed the study, design the data collection instruments, carried out complete analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. Domenico Crea and Matteo Ponzoni designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed and revised the manuscript. Luca Vedovelli and Andrea Francavilla designed the data collection instruments, carried out the statistical analyses, and critically reviewed and revised the manuscript. Andrzey Kansy, Thierry Bove, Joseph Panzer, Marc Gewilling, Bjorn Cools, Thomas Salaets, and Dexter Cheng collected data and coordinated and supervised data collection, and critically reviewed and revised the manuscript. Biagio Castaldi and Alessia Cerutti supervised data collection and critically reviewed and revised the manuscript for important intellectual content. Giovanni Di Salvo and Vladimiro L. Vida supervised data collection and critically reviewed and revised the manuscript for important intellectual content.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments and Funding: None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100143.

References

1. Zangwill S. Five decades of pediatric heart transplantation: challenges overcome, challenges remaining. Curr Opin Cardiol 2017;32:69-77.
2. de By TMMH, Schweiger M, Waheed H, et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first EUROMACS Paediatric (Paedi-EUROMACS) report. Eur J Cardiothorac Surg 2018;54:800-8.
3. Morales DLS, Adachi I, Peng DM, et al. Fourth Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Report. Ann Thorac Surg 2020;110:1819-31.
4. Zafar F, Conway J, Bleiweis MS, et al. Berlin Heart EXCOR and ACTION post-approval surveillance study report. J Heart Lung Transplant 2021;40:251-9.
5. Ponzoni M, Frigo AC, Castaldi B, et al. Surgical strategies for the management of end-stage heart failure in infants and children: a 15-year experience with a patient-tailored approach. Artif Organs 2021;45:1543-53.
6. Schranz D, Rupp S, Müller M, et al. Pulmonary artery banding in infants and young children with left ventricular dilated cardiomyopathy: a novel therapeutic strategy before heart transplantation. J Heart Lung Transplant 2013;32:475-81.
7. Traister A, Patel R, Huang A, et al. Cardiac regenerative capacity is age- and disease-dependent in childhood heart disease. PloS One 2018;13:e0200342. e0200342-e.
8. Schranz D, Akintuerk H, Bailey L. Pulmonary artery banding for functional regeneration of end-stage dilated cardiomyopathy in young children: World Network Report; 2018:1410-12.
9. Spigel ZA, Razzouk A, Nigro JJ, et al. Pulmonary artery banding for children with dilated cardiomyopathy: US experience. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2020;23:69-76.
10. Ponzoni M, Castaldi B, Padalino MA. Pulmonary artery banding for dilated cardiomyopathy in children: returning to the bench from bedside. Children 2022;9:1392.
11. Yerebakan C, Boltze J, Elmontaser H, et al. Effects of pulmonary artery banding in doxorubicin-induced left ventricular cardiomyopathy. J Thorac Cardiovasc Surg 2019;157:2416-28.
12. Latus H, Hachmann P, Gummel K, et al. Biventricular response to pulmonary artery banding in children with dilated cardiomyopathy; 2016:934-8.
13. Ponzoni M, Zanella L, Reffo E, et al. Late left ventricular myocardial remodeling after pulmonary artery banding for end-stage dilated cardiomyopathy in infants: an imaging study. Int J Cardiol 2023;386:160-6.
14. Schranz D, Recla S, Malcic I, Kerst G, Mini N, Akintuerk H. Pulmonary artery banding in dilative cardiomyopathy of young children: review and protocol based on the current knowledge. Transl Pediatr 2019;8:151-60.
15. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611-44.
16. Braunwald E. Heart failure. JACC Heart Fail 2013;1:1-20. https://doi.org/10.1016/j.jchf.2012.10.002.
17. Yacoub MH, Terracciano CM. Bridge to recovery and the search for decision nodes. Circ Heart Fail 2011;4:393-5. https://doi.org/10.1161/CIRCHEARTFAILURE.111.963058.
18. Kirk R, Dipchand AI, Davies RR, et al. ISHLT consensus statement on donor organ acceptability and management in pediatric heart transplantation; 2020:331-41.
19. Lipshultz SE, Law YM, Asante-Korang A, et al. Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association. Circulation 2019;140:e9-68.
20. Thangappan K, Zafar F, Lorts A, et al. MILESTONE: more than 1,200 children bridged to heart transplantation with mechanical circulatory support. ASAIO J 2022;68:577-83.
21. Schranz D, Veldman A, Bartram U, Michel-Behnke I, Bauer J, Akintürk H. Pulmonary artery banding for idiopathic dilative cardiomyopathy: a novel therapeutic strategy using an old surgical procedure. J Thorac Cardiovasc Surg 2007;134:796-7.
22. Schranz D. Treatment strategies for dilated cardiomyopathy in children: scientific statement from the American Heart Association-a real advance! But please more specific!. Pediatr Cardiol 2024;45:699-701. https://doi.org/10.1007/s00246-023-03314-7.
23. Sedmera D, Reckova M, DeAlmeida A, et al. Spatiotemporal pattern of commitment to slowed proliferation in the embryonic mouse heart indicates progressive differentiation of the cardiac conduction system. Anat Rec A Discov Mol Cell Evol Biol 2003;274:773-7.
24. Porrello ER, Mahmoud AI, Simpson E, et al. Transient regenerative potential of the neonatal mouse heart. Science (New York, NY) 2011;331:1078-80.
25. Myers PO, del Nido PJ, Geva T, et al. Impact of age and duration of banding on left ventricular preparation before anatomic repair for congenitally corrected transposition of the great arteries. Ann Thorac Surg 2013;96:603-10.
26. Ibrahimiye AN, Mainwaring RD, Patrick WL, Downey L, Yarlagadda V, Hanley FL. Left ventricular retraining and double switch in patients with congenitally corrected transposition of the great arteries. World J Pediatr Congenit Heart Surg 2017;8:203-9.
27. Rohde S, Sandica E, Veen K, et al. Outcomes in small children on Berlin Heart EXCOR support: age and body surface area as clinical predictive factors. Eur J Cardiothorac Surg 2022;63.
28. Kim D-H, Choi ES, Kwon BS, et al. Development of cardiac events and functional recovery prediction models for pediatric dilated cardiomyopathy. Front Pediatr 2021;9:736872.
29. Wang P-Y, Tseng W-C, Fu C-M, et al. Long-term outcomes and prognosticators of pediatric primary dilated cardiomyopathy in an Asian Cohort. Front Pediatr 2021;9:771283.
30. Ponzoni M, Coles JG, Maynes JT. Rodent models of dilated cardiomyopathy and heart failure for translational investigations and therapeutic discovery. Int J Mol Sci 2023;24:3162.