International Journal of Cardiology 386 (2023) 160–166

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Late left ventricular myocardial remodeling after pulmonary artery banding for end-stage dilated cardiomyopathy in infants: an imaging study

Matteo Ponzoni [a,1], Luca Zanella [a,1], Elena Reffo [b,1], Annachiara Cavaliere [c,1], Alice Pozza [b,1], Biagio Castaldi [b,1], Giovanni Di Salvo [b,1], Vladimiro L. Vida [a,1], Massimo A. Padalino [a,1,*]

[a] Pediatric and Congenital Cardiac Surgery Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy
[b] Pediatric Cardiology Unit, Department of Woman and Child Heath, University of Padova, Padova, Italy
[c] Pediatric Radiology, UOC Neuroradiology, Department of Integrated Diagnostic, Universty of Padova, Italy

ARTICLE INFO

Keywords:
Pulmonary artery banding
Dilated cardiomyopathy
Magnetic resonance imaging
Myocardial remodeling

ABSTRACT

Background: Understanding the macroscopic biventricular changes induced by pulmonary artery banding (PAB) in children with dilated cardiomyopathy (DCM) represents the first step to unraveling the regenerative potential of the myocardium. We herein investigated the phases of left ventricular (LV) rehabilitation in PAB responders, using a systematic echocardiographic and cardiac magnetic imaging (CMRI) surveillance protocol.
Methods: We prospectively enrolled all patients with DCM treated with PAB from September-2015 at our institution. Among 9 patients, 7 positively responded to PAB and were selected. Transthoracic 2D echocardiography was performed before PAB; and 30, 60, 90, and 120 days after PAB; and at the last available follow-up. CMRI was performed before PAB (whenever possible) and one year after PAB.
Results: In PAB responders, LV ejection fraction showed a modest 10% increase 30–60 days after PAB, followed by its almost complete normalization after 120 days (median of 20[10–26]% vs 56[44.5–63.5]%, at baseline and 120 days after PAB, respectively). Parallelly, the LV end-diastolic volume decreased from a median of 146 (87–204)ml/m2 to 48(40–50)ml/m2. At the last available follow-up (median of 1.5 years from PAB), both echocardiography and CMRI showed a sustained positive LV response, although myocardial fibrosis was detected in all patients.
Conclusions: Echocardiography and CMRI show that PAB can promote a LV remodeling process, which starts slowly and can culminate in the normalization of LV contractility and dimensions 4 months later. These results are maintained up to 1.5 years. However, CMRI showed residual fibrosis as evidence of a past inflammatory injury whose prognostic significance is still uncertain.

1. Introduction

Relying on ventricular-ventricular positive interactions [1–4] and the hypothesized reactivation of the reparative potential of the myocardium [5], surgically performed pulmonary artery banding (PAB) has been proposed as a bridge to transplant or recovery strategy in infants with dilative cardiomyopathy (DCM) with preserved right ventricular (RV) function [2,6].

By generating an acute leftward shift of the interventricular septum, which determines a reshaping of the dilated left ventricle (LV) in the context of DCM, together with amelioration of LV preload and its intrinsic contractility [1,5,7,8], PAB may be a promising alternative to conventional organ replacement-based options for pediatric heart failure. Recent multicenter studies documented LV functional recovery after PAB in 29% to 56% of treated patients [2,7], suggesting a causative role of PAB in positively modifying the natural clinical history of DCM.

Abbreviations: CMRI, cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricle; MCS, mechanical circulatory support; MV, mitral valve; PAB, pulmonary artery banding; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.

* Corresponding author at: Pediatric and Congenital Cardiac Surgery Unit, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy.
E-mail address: massimo.padalino@unipd.it (M.A. Padalino).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2023.05.040
Received 30 March 2023; Received in revised form 19 May 2023; Accepted 21 May 2023
Available online 23 May 2023

However, the global experience with this technique still suffers from limited numbers of treated patients and relatively short follow-up times [2]. Moreover, surgical indications and patient selection criteria have been derived from clinical experience rather than evidence-based knowledge of the mechanisms of action of PAB in DCM [3,5].

Understanding the early and late ventricular remodeling process in PAB responders may contribute to eligibility criteria refinement and help identify those patients who could benefit the most from this strategy as bridge to recovery. Moreover, documenting the macroscopic correlates of the hypothesized underlying molecular pathways promoted by PAB might provide novel insights into the regenerative/reparative potential of the human heart [9,10]. We herein systematically assessed the acute and chronic changes in biventricular function and anatomic structure in PAB responders, by seriate 2D echocardiography and cardiac magnetic resonance imaging (CMRI).

2. Methods

2.1. Study design and population

We prospectively enrolled all consecutive pediatric patients affected by end-stage DCM and treated with PAB from September 2015 at our institution. Indication to PAB was determined via multidisciplinary evaluation according to our institutional protocol for pediatric end-stage heart failure [6]. Eligibility and exclusion criteria for PAB have been published previously [4,6]. Parental consent to the procedure and the study was obtained in all cases. The study was approved by our institutional Ethics Committee (protocol #5372/AO/22) and it conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

All patients who positively responded to PAB (defined by symptoms and clinical status improvement, amelioration of LV function at echocardiography, and avoidance of durable mechanical circulatory support [MCS] or heart transplantation) were selected for the present study. Demographic and clinical characteristics, in-hospital events, laboratory data, echocardiographic and CMRI measures, and follow-up status were collected prospectively via electronic medical records. The follow-up was concluded on December 2022 (100% completeness).

2.2. Echocardiographic and CMRI parameters

Transthoracic 2D echocardiography was performed before PAB; and 30, 60, 90, and 120 days after PAB; and then at the last available follow-up (according to the clinical status of the patient). Biventricular function and dimensions, atrioventricular valves competence, and gradients across PAB were monitored in all patients by the same operators (BC, GDS).

Cardiac magnetic resonance imaging was performed before PAB (whenever possible) and approximately one year after PAB. Each CMRI examination was carried out by one cardiologist and one radiologist (ER, AC) with the same CMRI scanner (Achieva 1.5 Tesla, Philips Healthcare; Best, the Netherlands). For every patient, LV and RV function and volumes were registered, as well as evidence of myocardial fibrosis (late gadolinium enhancement [LGE] positivity) by PSIR sequences and myocardial edema by T2w TSE sequences with fat saturation [11,12].

2.3. Pulmonary artery banding procedure

Preoperative medical management was initiated at the time of admission based on the protocol by Scharnz et al. [3]. Complete anti-congestive medical therapy, including a beta-blocker (bisoprolol or metoprolol, with target heart rate < 120 bpm), lisinopril (0.1–0.2 mg/kg/die), and spironolactone (1 mg/kg/die), was administered to all patients. Diuretics (furosemide) were used if marked pulmonary congestion and/or fluid overload were present. In case of hemodynamic instability catecholamines (epinephrine and/or milrinone) were administered. If tolerated, a dose of levosimendan was provided. The surgical PAB was performed as described elsewhere [4,6]. In particular, after median sternotomy, invasive measurement of pre-PAB pulmonary arterial pressure and systemic pressure was placed. Then, the main pulmonary artery was gently encircled with a PTFE band whose length was initially tailored according to Trusler's rule [13]. Under continuous transesophageal echocardiography monitoring, the band was tightened to obtain a leftward shift of the interventricular septum, with a RV invasive pressure of approximately 60% of the systemic one. Finally, the length of the banding stripe was fixed with 6–0 polypropylene suture, obtaining a balloon-dilatable band. The chest (and the pericardium) was routinely left open, to allow further PAB tightening in the first post-operative h, if necessary. To reduce the risk of acute RV decompensation, we avoided aggressive PAB tightening intraoperatively and we closely monitored the patient's early response to PAB. If the patient was hemodynamically stable with the presence of good RV function, normal tricuspid annular plane systolic excursion (TAPSE), and not linear intraventricular septum, we performed an additional tightening of PAB. Subsequently, once hemodynamics were optimal, the pericardium and the sternum were definitively closed.

2.4. Statistical analysis

Continuous variables are summarized as median and interquartile range (IQR) and categorical variables are expressed as numbers and percentages. Given the relatively small number of patients, no statistical tests were run to compare echocardiographic and CMRI data variation during follow-up. Statistical analysis was performed using SPSS statistic software v.24 (IBM Corporation, Armonk, NY). The data that supports the findings of this study is available from the corresponding author upon reasonable request.

3. Results

3.1. Treated population

Since 2015, nine patients (M/F: 4/5) were admitted for end-stage heart failure due to DCM unresponsive to conventional medical treatment, and selected for PAB according to our protocol [6]. Median age and weight at PAB were 7.1 (IQR 4.0–8.8) months and 6.3 (IQR 5–7.7) kg, respectively. The etiology of heart failure (confirmed by histological examination of specimens collected during PAB) was chronic viral myocarditis in 3 (33%), idiopathic DCM in 3 (33%), acute lymphocytic myocarditis in 2 (22%), and LV non-compaction with a genetic diagnosis of heterozygous mutation of TPM1 gene (de novo) and of ABCC9 gene (parental) in 1 (11%). Five patients (56%) were in PEDIMACS class 3 and 4 (44%) in PEDIMACS class 1. Seven patients (78%) required pre-operative mechanical ventilation and 1 (11%) ECMO implantation due to incipient cardiogenic shock before PAB. In 7 (78%) cases, a preoperative dose of levosimendan was administered. The median time from hospital admission to PAB was 27 (9–33) days. Complete demographic and clinical characteristics are summarized in Table 1.

Seven patients (78%) responded positively to PAB and were selected for the present study (Supplemental Fig. 1). One PAB non-responder (3.5-year-old child) required intraoperative implantation of ECMO (associated with atrial septostomy), followed by Berlin Heart EXCOR implantation, and underwent a successful heart transplantation 13 months later. We hypothesized that a reduced regenerative potential due to older age may be the reason for PAB failure in this patient [5,9]. Subsequently, we modified our maximal age threshold for PAB to 1 year of age [6]. In the second case (with associated LV non-compaction), the PAB strategy was initially successful, allowing discharge to home. However, 3 months after PAB, the patient developed acute pneumonia, which destabilized RV function, causing RV decompensation and cardiogenic shock. The patient was treated with Berlin Heart EXCOR implantation, followed by successful heart transplantation 3 days later [5,6]. All patients are alive at the last available follow-up (median of 3.4

Table 1
Demographic and clinical characteristics of patients at the time of PAB.

Patient	Age (months)	Weight (kg)	Gender	DCM etiology	Genetic syndrome	PEDIMACS class	Preoperative invasive ventilation	Preoperative MCS	Admission to PAB time (days)	BNP at admission (ng/l)	Heart rate at admission (bpm)	Heart rate prior to PAB (bpm)	Associated procedures during PAB	ICU stay (days)	Total hospital stay (days)	PAB responder
#1	8.8	8	Male	LV non-compaction	*TPM1* and *ABCC9* (heteroz. mutation)	1	Yes	No	16	10,226	150	105	None	20	70	No
#2	42.9	12	Male	Chronic viral myocarditis	None	1	Yes	No	6	3565	135	112	Atrial septostomy + ECMO	60	14 months*	No
#3	4	5.9	Male	Acute lymphocytic myocarditis	None	3	Yes	No	36	3664	177	120	None	33	54	Yes
#4	12.7	7.7	Female	Chronic viral myocarditis	None	3	Yes	No	27	18,421	152	95	None	10	36	Yes
#5	5.8	4.8	Male	Acute lymphocytic myocarditis	None	3	No	No	43	4833	140	120	None	15	92	Yes
#6	8.3	7	Female	Chronic viral myocarditis	None	3	No	No	29	17,614	178	115	None	8	21	Yes
#7	1.9	3.7	Female	Idiopathic DCM	None	3	Yes	No	9	8691	140	135	None	42	73	Yes
#8	7.1	6.3	Female	Idiopathic DCM	None	1	Yes	No	6	210	135	110	8 mm atrial flow regulator insertion + ECMO (weaned off after 2 days)	34	99	Yes
#9	3.8	5	Female	Idiopathic DCM	None	1	Yes	ECMO	33	70,020	180	120	None	23	42	Yes

* The patient underwent Berlin Heart implantation and heart transplant during the same hospital admission.

[0.6–4.9] years from PAB).

3.2. Clinical course of PAB responders

Among the 7 PAB responders, tightening of PAB in the first days after the operation was necessary in 4 cases (57%) due to reduction of intracavitary RV pressure to <60% of systemic pressure, in the presence of preserved RV function. One patient experienced postoperative low-cardiac output syndrome, requiring venous-arterial ECMO implantation. Subsequently, the child developed left ventricular thrombosis, which was treated by apical thrombus removal and placement of apical vent via left mini-thoracotomy. After 2 days of support, the patient was successfully weaned from ECMO without complications. The median heart rate decreased from 152 (140–178) at hospital admission to 120 (113−120) prior to PAB and 109 (88–110) at last available follow-up.

All patients were discharged home after a median of 54 (39–83) days of hospitalization, with improved clinical and echocardiographic status. Full anticongestive medical regimen was administered in all cases, including a beta-blocker, lisinopril, and spironolactone according to Schranz et al. [3]. Diuretics were administered immediately after PAB and suspended gradually before discharge. Erythropoietin 150 IU/kg was used after PAB for 4 to 12 weeks, together with vitamins and Co-enzyme Q10.

At a median follow-up of 1.5 (0.5–3.8) years, four patients underwent PAB dilatation due to increasing estimated RV intracavitary pressures. Currently, 6/7 patients are in Ross heart failure class I and 1/7 in class II; 6/7 patients have been delisted from heart transplantation.

3.3. Echocardiographic follow-up

The longitudinal echocardiographic evaluation of PAB responders revealed a progressive amelioration of LV ejection fraction, which increased from a baseline median value of 20% (10–26%) to 61% (37–65.5%) at the last available echocardiographic follow-up (median of 1.5 [0.3–4.2] years from PAB) (Fig. 1 and Table 2). Simultaneously, the indexed LV end-diastolic volume decreased from a median baseline value of 146 (87–204) ml/m2 to 53 (44–74) ml/m2 at the last follow-up. Supplemental Fig. 2 shows exemplificative echocardiographic and CMRI images of positive LV remodeling after PAB. Mitral valve (MV) regurgitation severity (scored qualitatively as 0: absent; 1: trivial; 2: mild; 3: moderate; 4: severe) reduced from a median baseline value of 3 (2–4) to 1 (0.8–2.3). Similarly, MV inflow Doppler E/A ratio decreased from 1.7 (1.6–3.6) before PAB to 1.2 (1.1–1.5) at last follow-up (Supplemental Fig. 3). Left ventricular global longitudinal strain ameliorated from a median value of −6% (−8.1 to −3.5%) before PAB to −15% (−12.1 to −17.5%) at last follow-up (Supplemental Table 1).

Right ventricular function, expressed as TAPSE, showed an early deflection after PAB, with subsequent return to baseline values at the last follow-up (Supplemental Fig. 3). Tricuspid valve (TV) regurgitation (scored qualitatively as 0: absent; 1: trivial; 2: mild; 3: moderate; 4: severe) remained stable during follow-up (Table 2 and Supplemental Fig. 3).

3.4. CMRI assessment

Among the 7 PAB responders, in 2 cases it was not possible to perform CMRI before PAB, while the last 2 treated patients are still awaiting to perform the 1-year follow-up CMRI. Table 3 summarizes CMRI findings at baseline and at a median follow-up of 1.5 (1.1–3.3) years after PAB.

Preoperative CMRI showed large LV volumes and severely reduced LV function, which improved in all cases at follow-up. In 4/5 patients LV contractility and dimensions almost returned to the normal ranges, while in patient #7 we noticed a mild LV remodeling and improvement in systolic function. Right ventricular function and dimensions were preserved, both at baseline and, more importantly, at follow-up. Most of the patients presented with areas of LV fibrosis (at LGE study) preoperatively, while all patients displayed LV myocardial fibrosis at the 1-year follow-up study. Conversely the RV was spared from myocardial fibrosis at baseline, while 4/5 patients developed areas of RV fibrosis at last follow-up (Supplemental Fig. 4).

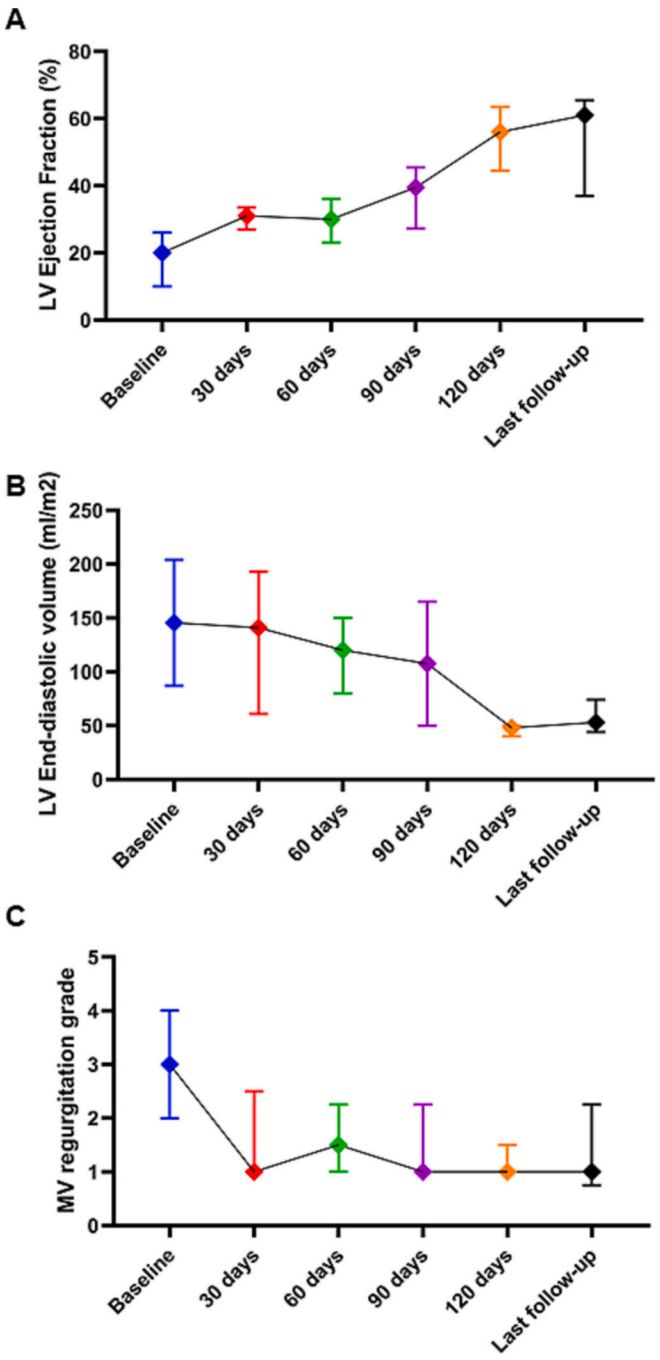

Fig. 1. Longitudinal changes of LV ejection fraction (panel A), indexed LV end-diastolic volume (panel B), and MV regurgitation severity (panel C) in PAB responders ($n = 7$), measured using echocardiography. Represented values are median (central dot) and IQR. LV: left ventricle; MV: mitral valve.

4. Discussion

The use of PAB as a treatment strategy for end-stage pediatric DCM is a particularly attractive option in smaller infants, in whom MCS and heart transplantation still do not provide optimal outcomes [14–19]. In

Table 2
Echocardiographic changes of biventricular function in PAB responders (n = 7) during follow-up. Last available echocardiographic follow-up is at a median of 1.5 (0.3–4.2) years from PAB.

	Baseline	30 days	60 days	90 days	120 days	Last follow-up
Variable	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
LV ejection fraction (%)	20 (10–26)	31 (27–33.5)	30 (23–36)	39.5 (27.3–45.5)	56 (44.5–63.5)	61 (37–65.5)
Indexed LV end-diastolic volume (ml/m2)	146 (87–204)	141 (61–193)	120 (80–150)	108 (50–165)	48 (40–50)	53 (44–74)
MV regurgitation grade*	3 (2–4)	1 (1–2.5)	1.5 (1–2.3)	1 (1–2.3)	1 (1–1.5)	1 (0.8–2.3)
MV inflow Doppler E wave (m/s)	0.8 (0.6–1.3)	0.7 (0.6–0.8)	0.9 (0.6–1.0)	0.9 (0.8–0.9)	0.9 (0.8–1.0)	1.0 (0.8–1.1)
MV inflow Doppler A wave (m/s)	0.4 (0.4–0.5)	0.5 (0.4–0.6)	0.7 (0.6–0.9)	0.7 (0.6–0.8)	0.7 (0.5–0.7)	0.7 (0.6–0.8)
E/A ratio	1.7 (1.6–3.6)	1.2 (1.1–1.3)	1.1 (1.0–1.2)	1.2 (1.2–1.4)	1.3 (1.2–1.5)	1.2 (1.1–1.5)
TAPSE (mm)	15 (10.3–22.8)	9 (7.5–11)	8.7 (7.1–14.5)	16 (11–16)	14.5 (12–15)	14.5 (12.9–15.6)
TV regurgitation grade*	2 (1–2)	2 (1–2)	2 (1–2.3)	1.5 (1–2.5)	2 (1–2)	1.5 (1–2)
PAB gradient (mmHg)	–	35 (25–55)	–	50 (40–50)	67.5 (55–80)	42.5 (20.8–61.3)

* Scored qualitatively as 0: absent; 1: trivial; 2: mild; 3: moderate; 4: severe.

Table 3
CMRI findings in PAB responders (n = 7) at baseline and at a median follow-up of 1.5 (1.1–3.3) years from PAB.

Variable	Baseline					Follow-up				
	Case #4	*Case #6*	*Case #7*	*Case #8*	*Case #9*	*Case #3*	*Case #4*	*Case #5*	*Case #6*	*Case #7*
Indexed LV end-diastolic volume (ml/m2)	143	263	170	250	165	50	75	92	98	134
Indexed LV end-systolic volume (ml/m2)	118	220	150	218	148	17	30	40	58	103
LV ejection fraction (%)	17	16	10	12.5	10	66.4	60	56	41	24
LV stroke volume (ml/m2)	25	43	20	–	–	33	45	52	40	31
LV cardiac output (l/min)	1.3	2	0.5	–	–	2	2.5	2.2	2	1.4
LV cardiac index (l/min/m2)	3.42	5.1	2.5	–	–	3.47	3.78	4	4.8	3.7
LV mass (g/m2)	56	–	77	–	76	–	–	65	–	71
LV global longitudinal strain (%)	–	–	−9.2	−10	−0.4	−21.4	–	–	–	−15.4
LV global circumferential strain (%)	–	–	−4.5	−5.7	−6.1	−10.7	–	–	–	−11.0
Indexed RV end-diastolic volume (ml/m2)	38	60	10	109	65	68	66	71	72	76
Indexed RV end-systolic volume (ml/m2)	16	13	37	82	23	34	20	25	30	29
RV ejection fraction (%)	59	45	76	24	64	51	70	65	58	62
RV stroke volume (ml/m2)	22	47	27	–	–	34	46	46	42	47
RV cardiac output (l/min)	1.2	2	–	–	–	2	2.5	1.9	2	1.9
RV cardiac index (l/min/m2)	3.15	5.1	–	–	–	3.47	3.78	1	4.8	5
LV myocardial edema	No	No	No	No	No	No	No	No	No	No
LV myocardial fibrosis										
Subendocardial	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes
Intramyocardial	Yes	No	Yes	No	No	No	Yes	Yes	No	Yes
RV myocardial edema	No	No	No	No	No	No	No	No	No	No
RV myocardial fibrosis										
Subendocardial	No	No	No	No	No	No	No	Yes	Yes	Yes
Intramyocardial	No	No	No	No	No	Yes	No	Yes	Yes	Yes

this population, PAB has its greatest potential in positively remodeling the LV [20] and possibly (re)activating the regenerative properties of human cardiomyocytes [5,9,10]. However, suffering from a worldwide limited number of treated patients [2,7] and the shortage of specific animal models [21], the underlying tissue-based and molecular mechanisms sustained by PAB are still unknown. With the present study, we aimed to define systematically the macroscopic changes that occur in the LV and RV after PAB, using a strict echocardiographic follow-up protocol, implemented with CMRI. We found that, in PAB responders, as soon as 30 days after PAB, the LV can enter a positive remodeling process that culminates in a normalization of size and function at about 4 months after PAB (Fig. 1). These findings remained durable and were confirmed 1.5 years after PAB, both by echocardiography and CMRI, suggesting that, when successful, PAB can produce a sustained positive response, that allowed most patients to be delisted from heart transplantation waiting list.

As documented in the US and World Network Report multicenter studies [2,7], a modest amelioration of LV ejection fraction is noticed in PAB responders at discharge echocardiography, in addition to LV reshaping and reduction of LV dilatation. In particular, LV ejection fraction increased from baseline values of 20–21% to 26–27% early after PAB both in the US and German cohorts [7,22], followed by its normalization (50–60%) at longer follow-times [2,7]. However, a structured evaluation of biventricular response to PAB in DCM is still lacking and the diversity of adopted follow-up times and protocols does not allow for precisely tracking the evolution of LV and RV performance after PAB.

In the present study, we collected major echocardiographic and CMRI values of interest in PAB responders, using a standardized protocol. We better delineated how the LV undergoes a slow remodeling phase early (30–60 days) after PAB when a 10% increase of LV ejection fraction (starting from extremely depressed baseline values) and a small reduction of indexed end-diastolic volume are noticed. However, at a medium-term follow-up (90–120 days after PAB) this process becomes more prominent, with complete normalization of LV contractility and dimensions 4 months after PAB (LV ejection fraction of 56 [44.5–63.5] % and LV indexed end-diastolic volume of 48 [40–50] ml/m2, Fig. 1). On the other hand, the improvement of MV regurgitation grade (despite the limits of a qualitative assessment) and LV diastolic function (assessed by MV inflow Doppler E/A) was considerable even at the 30-day echocardiographic follow-up. We hypothesize that PAB can positively act in pediatric DCM in a dual manner [5]. The immediate effect of PAB is the increase in RV pressure, which causes a leftward shift of the interventricular septum, reducing LV and MV annular dilatation [20]. Moreover, LV preload is ameliorated, reducing left atrial volume overload which can further increase MV regurgitation in a vicious cycle [4]. These hemodynamic changes can account for the early modest improvements in LV function and dimensions and the concomitant transitory impairment

of RV contractility (shown by a 5–6 mm reduction in TAPSE 30 to 60 days after PAB, Supplemental Fig. 3). After this initial insult, the RV is known to activate several mechanisms of adaptation which lead to a compensated RV response to increased afterload. In response to pressure overload, a metabolic change from beta-oxidation to glycolysis occurs, as well as a rise of antioxidant defenses (heat-shock protein production) [23,24], and an increase of protein expression levels for myocardial structural components [25]. Interestingly, proteomics analysis of PAB animal models revealed that this molecular adaptive response involves both the RV and LV [24,26,27], suggesting the presence of molecular crosstalk between the two ventricles which the failing LV can benefit from. We speculate that these mechanisms could represent the molecular bases of the substantial and progressive amelioration of LV performance we measured at the medium-term follow-up, which cannot be simply explained by the initial changes in biventricular hemodynamics, as well as the return of TAPSE to baseline values 90 days after PAB (Supplemental Fig. 3). Experimental efforts should be directed to address the molecular bases of LV rehabilitation induced by PAB in DCM, which, to date, still need for evidence-based validation [5].

At a longer follow-up (median of 1.5 years from PAB), LV recovery was maintained in all responders, without any evidence (clinical or by imaging) of relapse of heart failure. Both echocardiographic and CMRI data support favorable LV reshaping and almost normalization of LV contractility parameters (see Table 2 and Table 3). Similarly, RV function was preserved, as well as RV dimensions, thanks to careful echocardiographic monitoring and prompt balloon dilatation of PAB to maintain RV intracavitary pressures of 50–60% of systemic values [3]. However, 4/5 patients developed de-novo RV myocardial fibrosis at follow-up (Supplemental Fig. 4); the long-term impact of this on RV performance remains unknown. A lower initial PAB target gradient (or abstaining from early PAB tightening during open-chest approach) and an inferior threshold for catheter-based de-banding might help avoid the long-term fibrotic sequelae of RV pressure overload while achieving sufficient LV remodeling.

In our cohort, 5/9 treated patients (4/7 PAB responders) displayed a myocarditis-related etiology of DCM, which has been addressed as one potential confounding factor of the efficacy of PAB in DCM [3,5]. In fact, a possible concern may be the possibility of having selected a subgroup of patients with higher chances of spontaneous recovery from DCM. However, recovery rates usually range between 10 and 20% of patients with DCM [28,29]. Moreover, the healing process requires years, with a cumulative recovery rate as low as 1.2% in the first year after DCM diagnosis, which increases only to 12.1% after 5 years [29]. This drastically contrasts with our findings, where 7/9 (78%) of patients positively responded to PAB and, when successful, PAB promoted (or accelerated) an almost complete LV recovery as soon as 1.5 years after PAB. On the other hand, the presence of persisting myocardial fibrosis at CMRI assessment late after PAB even in PAB responders may represent a scar of the past inflammatory injury. In Giessen's experience, LGE positivity was rarely seen in pediatric DCM patients [30] and this differs from our findings (7/7 patients with LV fibrosis at 1-year follow-up CMRI). However, when present, LGE positivity was mainly observed in patients with chronic myocarditis [30], suggesting a causative role of the inflammatory process. In this view, given the considerable prevalence of a myocarditis-based etiology of DCM in our treated cohort, the high rate of LGE positivity at follow-up seems to support this hypothesis and it might insinuate an underlying inflammatory etiology even in idiopathic forms of DCM. This must dictate an active surveillance protocol, since the long-term efficacy of this technique is still to be determined and a very late relapse of DCM cannot be completely excluded.

5. Limitations

The worldwide evidence of PAB-sustained LV remodeling/regeneration in pediatric patients with DCM still suffers from the small size of treated cohorts [5]. Similarly, the major limitation of our series is the number of enrolled patients. This has not enabled comparative statistical analyses and limits the generalization of our findings. Moreover, due to preoperative hemodynamic instability in 2 cases and a < 1-year follow-up in 2, only 3 patients so far possess both a preoperative and a long-term CMRI study. On the other hand, having a standardized surgical, echocardiographic, and monitoring protocol has enabled us to systematically assess the longitudinal modifications of biventricular function after PAB in our cohort, which aligns with previously published data. Left ventricular strain analysis was not part of our routine echocardiographic protocol, thus it was not available at each time point. We hope that our work will stimulate the prospective and multi-center enrolment of a larger number of patients, using a rationale and standardized surveillance protocol, to be considered for this treatment.

6. Conclusions

A systematic echocardiographic and CMRI monitoring protocol allowed us to delineate the different phases of LV rehabilitation promoted by PAB in infants with DCM. Following an initial phase of modest improvement in LV function and geometry and a concomitant transitory impairment of RV contractility, which can be derived from the optimization of biventricular hemodynamics, a more prominent LV remodeling occurs. This process culminates in almost complete normalization of LV contractility and dimensions at about 4 months after PAB, which is maintained up to a median follow-up of 1.5 years. The underlying tissue-based and molecular mechanisms supporting this late regeneration of biventricular performance should be the target of future investigations of PAB in DCM.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.05.040.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the University of Padua (protocol #5372/AO/22).

CRediT authorship contribution statement

Matteo Ponzoni: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Luca Zanella:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Elena Reffo:** Methodology. **Annachiara Cavaliere:** Methodology. **Alice Pozza:** Methodology. **Biagio Castaldi:** Methodology. **Giovanni Di Salvo:** Supervision. **Vladimiro L. Vida:** Supervision. **Massimo A. Padalino:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

We thank Hannah N. Kozlowski, PhD for the English review of this paper.

References

[1] H. Latus, P. Hachmann, K. Gummel, S. Recla, I. Voges, M. Mueller, J. Bauer, C. Yerebakan, H. Akintuerk, C. Apitz, D. Schranz, Biventricular response to pulmonary artery banding in children with dilated cardiomyopathy, J. Hear. Lung Transplant. Off. Publ. Int. Soc. Hear. Transplant. 35 (2016) 934–938, https://doi.org/10.1016/j.healun.2016.04.012.

[2] D. Schranz, H. Akintuerk, L. Bailey, Pulmonary artery banding for functional regeneration of end-stage dilated cardiomyopathy in young children: world network report, Circulation. 137 (2018) 1410–1412, https://doi.org/10.1161/CIRCULATIONAHA.117.029360.

[3] D. Schranz, S. Recla, I. Malcic, G. Kerst, N. Mini, H. Akintuerk, Pulmonary artery banding in dilative cardiomyopathy of young children: review and protocol based on the current knowledge, Transl. Pediatr. 8 (2019) 151–160, https://doi.org/10.21037/tp.2019.04.09.

[4] A. Di Candia, B. Castaldi, G. Bordin, A. Cerutti, E. Reffo, R. Biffanti, G. Di Salvo, V. L. Vida, M.A. Padalino, Pulmonary artery banding for ventricular rehabilitation in infants with dilated cardiomyopathy: early results in a single-center experience, Front. Pediatr. 8 (2020) 347, https://doi.org/10.3389/fped.2020.00347.

[5] M. Ponzoni, B. Castaldi, M.A. Padalino, Pulmonary artery banding for dilated cardiomyopathy in children: returning to the bench from bedside, Children. 9 (2022) 1392, https://doi.org/10.3390/children9091392.

[6] M. Ponzoni, A.C. Frigo, B. Castaldi, A. Cerutti, G. Di Salvo, V.L. Vida, M. A. Padalino, 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 45 (2021) 1543–1553, https://doi.org/10.1111/aor.14057.

[7] Z.A. Spigel, A. Razzouk, J.J. Nigro, T.B. Karamlou, M.N. Kavarana, M.E. Roeser, I. Adachi, Pulmonary artery banding for children with dilated cardiomyopathy: US experience., Semin. Thorac. Cardiovasc. Surg. Pediatr. Card, Surg. Annu. 23 (2020) 69–76, https://doi.org/10.1053/j.pcsu.2020.03.002.

[8] D. Schranz, U. Krause, G. Kerst, A. Esmaeili, T. Paul, Functional regeneration of dilated cardiomyopathy by transcatheter bilateral pulmonary artery banding: first-in-human case series, Eur. Hear. J. - Case Reports. 7 (2023), https://doi.org/10.1093/ehjcr/ytad052.

[9] A. Traister, R. Patel, A. Huang, S. Patel, J. Plakhotnik, J.E. Lee, M.G. Medina, C. Welsh, P. Ruparel, L. Zhang, M. Friedberg, J. Maynes, J. Coles, Cardiac regenerative capacity is age- and disease-dependent in childhood heart disease, PLoS One 13 (2018), e0200342, https://doi.org/10.1371/journal.pone.0200342.

[10] L. Zhang, A. Yeganeh, M. Bartkevics, A. Perri, C. Brown, J. Coles, J.T. Maynes, Mesenchymal stromal cells isolated from patients with congenital heart disease reveal an age-dependent proinflammatory phenotype, JACC Adv. 1 (2022), 100050, https://doi.org/10.1016/j.jacadv.2022.100050.

[11] A.R. Patel, C.M. Kramer, Role of cardiac magnetic resonance in the diagnosis and prognosis of nonischemic cardiomyopathy, JACC Cardiovasc. Imaging 10 (2017) 1180–1193, https://doi.org/10.1016/j.jcmg.2017.08.005.

[12] D.R. Messroghli, J.C. Moon, V.M. Ferreira, L. Grosse-Wortmann, T. He, P. Kellman, J. Mascherbauer, R. Nezafat, M. Salerno, E.B. Schelbert, A.J. Taylor, R. Thompson, M. Ugander, R.B. van Heeswijk, M.G. Friedrich, Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imagi, J. Cardiovasc. Magn. Reson. 19 (2017) 75, https://doi.org/10.1186/s12968-017-0389-8.

[13] G.A. Trusler, W.T. Mustard, A method of banding the pulmonary artery for large isolated ventricular septal defect with and without transposition of the great arteries, Ann. Thorac. Surg. 13 (1972) 351–355, https://doi.org/10.1016/S0003-4975(10)64866-7.

[14] D.L.S. Morales, I. Adachi, D.M. Peng, P. Sinha, A. Lorts, K. Fields, J. Conway, J. D. St Louis, R. Cantor, D. Koehl, J.P. Jacobs, J.K. Kirklin, E.D. Blume, J.W. Rossano, Fourth annual pediatric interagency registry for mechanical circulatory support (Pedimacs) report, Ann. Thorac. Surg. 110 (2020) 1819–1831, https://doi.org/10.1016/j.athoracsur.2020.09.003.

[15] J.W. Rossano, T.P. Singh, W.S. Cherikh, D.C. Chambers, M.O. Harhay, D.J. Hayes, E. Hsich, K.K. Khush, B. Meiser, L. Potena, A.E. Toll, A. Sadavarte, A. Zuckermann, J. Stehlik, The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: twenty-second pediatric heart transplantation report - 2019; focus theme: Donor and recipient size match, J. Hear. Lung Transplant. Off. Publ. Int. Soc. Hear. Transplant. 38 (2019) 1028–1041, https://doi.org/10.1016/j.healun.2019.08.002.

[16] R. Kirk, A.I. Dipchand, R.R. Davies, O. Miera, G. Chapman, J. Conway, S. Denfield, J.G. Gossett, J. Johnson, M. McCulloch, M. Schweiger, D. Zimpfer, L. Ablonczy, I. Adachi, D. Albert, P. Alexander, S. Amdani, A. Amodeo, E. Azeka, J. Ballweg, G. Beasley, J. Böhmer, A. Butler, M. Camino, J. Castro, S. Chen, M. Chrisant, U. Christen, L. Danziger-Isakov, B. Das, M. Everitt, B. Feingold, M. Fenton, L. Garcia-Guereta, J. Godown, D. Gupta, C. Irving, A. Joong, M. Kemna, S. K. Khulbey, S. Kindel, K. Knecht, A.K. Lal, K. Lin, K. Lord, T. Möller, D. Nandi, O. Niesse, D.M. Peng, A. Pérez-Blanco, A. Punnoose, Z. Reinhardt, D. Rosenthal, A. Scales, J. Scheel, R. Shih, J. Smith, J. Smits, J. Thul, R. Weintraub, S. Zangwill, W.A. Zuckerman, ISHLT consensus statement on donor organ acceptability and management in pediatric heart transplantation, J. Hear. Lung Transplant. Off. Publ. Int. Soc. Hear. Transplant. 39 (2020) 331–341, https://doi.org/10.1016/j.healun.2020.01.1345.

[17] T.M.M.H. de By, C.F.J. Antonides, M. Schweiger, J. Sliwka, B. Davies, F. Berger, M. Hübler, M. Özbaran, B. Maruszewski, C. Pace Napoleone, D. Zimpfer, E. Sandica, H. Antretter, B. Meyns, O. Miera, The European registry for patients with mechanical circulatory support (EUROMACS): second EUROMACS Paediatric (Paedi-EUROMACS) report, Eur. J. Cardio-Thoracic Surg. Off. J. Eur. Assoc. Cardio-Thoracic Surg. 57 (2020) 1038–1050, https://doi.org/10.1093/ejcts/ezaa132.

[18] F. Zafar, J. Conway, M.S. Bleiweis, M. Al-Aklabi, R. Ameduri, A. Barnes, D. W. Bearl, H. Buchholz, S. Church, N.L. Do, V. Duffy, J.C. Dykes, P. Eghtesady, L. Fisher, J. Friedland-Little, S. Fuller, F. Fynn-Thompson, K. George, J.G. Gossett, E.R. Griffiths, M. Griselli, B. Hawkins, O. Honjo, A. Jeewa, A. Joong, S. Kindel, P. Kouretas, A. Lorts, D. Machado, K. Maeda, A. Maurich, L.J. May, P. McConnell, M. Mehegan, M. Mongé, D.L.S. Morales, J. Murray, R.A. Niebler, M. O'Connor, D. M. Peng, C. Phelps, J. Philip, M. Ploutz, M. Profsky, A. Reichhold, D.N. Rosenthal, A.S. Said, K.R. Schumacher, M.-S. Si, K.E. Simpson, J. Sparks, J.S. Louis, M. E. Steiner, C. VanderPluym, C. Villa, Berlin heart EXCOR and ACTION post-approval surveillance study report, J. Hear. Lung Transplant. Off. Publ. Int. Soc. Hear. Transplant. 40 (2021) 251–259, https://doi.org/10.1016/j.healun.2021.01.010.

[19] K. Thangappan, F. Zafar, A. Lorts, I. Adachi, D. Rosenthal, J. Rossano, K. Maeda, D. L.S. Morales, MILESTONE: more than 1,200 children bridged to heart transplantation with mechanical circulatory support, ASAIO J. 68 (2022) 577–583, https://doi.org/10.1097/MAT.0000000000001635.

[20] H. Latus, K. Gummel, S. Rupp, M. Mueller, C. Jux, G. Kerst, H. Akintuerk, J. Bauer, D. Schranz, C. Apitz, Cardiovascular magnetic resonance assessment of ventricular function and myocardial scarring before and early after repair of anomalous left coronary artery from the pulmonary artery, J. Cardiovasc. Magn. Reson. Off. J. Soc. Cardiovasc. Magn. Reson. 16 (2014) 3, https://doi.org/10.1186/1532-429X-16-3.

[21] C. Yerebakan, J. Boltze, H. Elmontaser, U. Yoruker, H. Latus, M. Khalil, S. Ostermayer, B. Steinbrenner, C. Apitz, M. Schneider, M. Suchowski, R. Ruetten, K. Mueller, G. Kerst, D. Schranz, H. Akintuerk, Effects of pulmonary artery banding in doxorubicin-induced left ventricular cardiomyopathy, J. Thorac. Cardiovasc. Surg. 157 (2019) 2416–2428.e4, https://doi.org/10.1016/j.jtcvs.2019.01.138.

[22] D. Schranz, S. Rupp, M. Müller, D. Schmidt, A. Bauer, K. Valeske, I. Michel-Behnke, C. Jux, C. Apitz, J. Thul, D. Hsu, H. Akintürk, Pulmonary artery banding in infants and young children with left ventricular dilated cardiomyopathy: a novel therapeutic strategy before heart transplantation, J. Hear. Lung Transplant. Off. Publ. Int. Soc. Hear. Transplant. 32 (2013) 475–481, https://doi.org/10.1016/j.healun.2013.01.988.

[23] M.J. Faber, M. Dalinghaus, I.M. Lankhuizen, K. Bezstarosti, D.H.W. Dekkers, D. J. Duncker, W.A. Helbing, J.M.J. Lamers, Proteomic changes in the pressure overloaded right ventricle after 6 weeks in young rats: correlations with the degree of hypertrophy, Proteomics. 5 (2005) 2519–2530, https://doi.org/10.1002/pmic.200401313.

[24] M.J. Faber, M. Dalinghaus, I.M. Lankhuizen, K. Bezstarosti, A.J.M. Verhoeven, D. J. Duncker, W.A. Helbing, J.M.J. Lamers, Time dependent changes in cytoplasmic proteins of the right ventricle during prolonged pressure overload, J. Mol. Cell. Cardiol. 43 (2007) 197–209, https://doi.org/10.1016/j.yjmcc.2007.05.002.

[25] I. Friehs, D.B. Cowan, Y.-H. Choi, K.M. Black, R. Barnett, M.K. Bhasin, C. Daly, S. J. Dillon, T.A. Libermann, F.X. McGowan, P.J. del Nido, S. Levitsky, J.D. McCully, Pressure-overload hypertrophy of the developing heart reveals activation of divergent gene and protein pathways in the left and right ventricular myocardium, Am. J. Physiol. Heart Circ. Physiol. 304 (2013) H697–H708, https://doi.org/10.1152/ajpheart.00802.2012.

[26] Y. Cao, Y. Li, M. Wu, J. Song, M. Zhang, Y. Duan, K. Jiang, X. Zhou, Y. Zhang, RNA-sequencing analysis of gene expression in a rat model of acute right heart failure, Pulm. Circ. 10 (2020), https://doi.org/10.1177/2045894019879396, 2045894019879396.

[27] M. Ponzoni, J.G. Coles, J.T. Maynes, Rodent models of dilated cardiomyopathy and heart failure for translational investigations and therapeutic discovery, Int. J. Mol. Sci. 24 (2023) 3162, https://doi.org/10.3390/ijms24043162.

[28] D.-H. Kim, E.S. Choi, B.S. Kwon, C.S. Park, S.G. Cha, J.S. Baek, J.J. Yu, Y.-H. Kim, T.-J. Yun, Development of cardiac events and functional recovery prediction models for pediatric dilated cardiomyopathy, Front. Pediatr. 9 (2021), 736872, https://doi.org/10.3389/fped.2021.736872.

[29] P.-Y. Wang, W.-C. Tseng, C.-M. Fu, M.-H. Wu, J.-K. Wang, Y.-S. Chen, N.-K. Chou, S.-S. Wang, S.-N. Chiu, M.-T. Lin, C.-W. Lu, C.-A. Chen, Long-term outcomes and prognosticators of pediatric primary dilated cardiomyopathy in an Asian cohort, Front. Pediatr. 9 (2021), 771283, https://doi.org/10.3389/fped.2021.771283.

[30] H. Latus, K. Gummel, K. Klingel, A. Moysich, M. Khalil, N. Mazhari, J. Bauer, R. Kandolf, D. Schranz, C. Apitz, Focal myocardial fibrosis assessed by late gadolinium enhancement cardiovascular magnetic resonance in children and adolescents with dilated cardiomyopathy, J. Cardiovasc. Magn. Reson. 17 (2015) 34, https://doi.org/10.1186/s12968-015-0142-0.