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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Age is not a good predictor of irreversibility of pulmonary hypertension in congenital cardiac malformations with left-to-right shunt

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Abstract

Objective: Congenital cardiac malformations with high pulmonary blood flow and pressure due to left-to-right shunts are usually repaired in early infancy for both the benefits of early relief of heart failure and the fear that the concomitant pulmonary hypertension may become irreversible unless these defects are corrected at an early age. Age, however, has been a poor predictor of irreversibility of pulmonary hypertension in our experience, which is presented here.

Design: A retrospective observational study. We defined "late" as age ≥2 years. We examined clinical, echocardiographic, and hemodynamic data from all patients aged ≥2 years with such malformations referred to us from 2004 untill 2015.

Setting: Department of Pediatric Cardiology and Cardiac Surgery, University Hospital of Vaud, Lausanne, Switzerland.

Patients: There were 39 patients, aged 2–35 years (median: 5 years), without chromosomal abnormalities. All had malformations amenable to biventricular repair, and all had high systolic right ventricular pressures by echocardiography prior to referral.

Interventions: All patients underwent catheterization for assessment of pulmonary hypertension. If this was reversible, surgical correction was offered.

Outcome measures: (1) Operability based on reversibility of pulmonary hypertension. (2) When surgery was offered, mortality and evidence of persisting postoperative pulmonary hypertension were examined.

Results: Eighteen patients had no pulmonary hypertension, 5 of variable ages were inoperable due to irreversible pulmonary hypertension, and 16 had reversible pulmonary hypertension. Therefore, 34 patients underwent corrective surgery, with no immediate or late mortality. Pulmonary arterial and right ventricular pressures decreased noticeably in all operated patients. This is sustained to date; they are all asymptomatic with no echocardiographic evidence of pulmonary hypertension at a median follow-up of 7 years (range 2–13 years).

Conclusions: Pulmonary hypertension may still be reversible in many surprisingly old patients with left-to-right shunt lesions, who may therefore still be operable.

KEYWORDS

congenital heart disease, Eisenmenger syndrome, left-to-right shunt, pulmonary hypertension, pulmonary vascular disease

1 | INTRODUCTION

Congenital cardiac malformations with high pulmonary blood flow and pressure due to left-to-right shunts are usually repaired in early infancy for both the benefits of early relief of heart failure and the fear that the concomitant pulmonary hypertension may become irreversible (patients become inoperable) unless these defects are corrected early.[1–4] Indeed, it is generally thought that if such defects are not corrected by the age of one or two years, it may be already too late.[5–8] However, age has been a poor predictor of irreversibility of pulmonary hypertension in our experience, which includes a number of delayed repairs due to late presentation and referral. That experience is presented here to illustrate this point.

2 | MATERIALS AND METHODS

This study was approved by our institutional review board (Ethics' committee of the University Hospital of Vaud, Lausanne, Switzerland). The board agreed that no consent was required from patients or their families given that this study is retrospective, no experiments were carried out, and patients' identities are not revealed. All authors had full access to all data included in this study, and take responsibility for its integrity.

2.1 | Patients

Patients with high pulmonary blood flow and pressure due to left-to-right shunts are frequently treated in our unit. Many of them are referred from abroad; these are patients with limited economic means referred to us from countries with limited services for congenital heart disease. They are diagnosed by their local cardiologists and referred to us for treatment. Despite the limitations in services in those countries, the majority of their patients are detected and referred early such that treatment is offered in a timely fashion. However, some are detected late with echocardiographic features suggestive of pulmonary hypertension, and no information available on how their disease had evolved previously (whether or not, to what degree, and for how long they had been in heart failure). These patients are also referred to us for assessment and surgical correction if considered operable. Assessment of operability is made by us at our unit; such assessment may not be done locally due to lack of facilities. These patients that are presented late form the subject of this study.

We defined late presentation, or late referral, as age of at least 2 years, as this is the upper age limit suggested in the literature for safe surgical correction of malformations with high pulmonary blood flow and pressure due to of left-to-right shunts, as mentioned above. There were 39 such patients (28 male, 11 female) with a median age of 5 years (range: 2–35 years) referred to us from 2004 to 2015. Three were from Kosovo and 36 from West Africa. None had trisomy 21 or any dysmorphic feature suggestive of other chromosomal abnormalities. All had cardiac defects that were amenable to biventricular repair. They all had high estimated systolic right ventricular pressures (RVP) by echocardiography prior to referral. The commonest malformation was ventricular septal defect (VSD); this was the case in 27 patients. The other malformations were complete atrioventricular septal defect (5 cases), double outlet right ventricle with subaortic VSD (3 cases), common arterial trunk (2 cases), one case of interruption of the aortic arch with open arterial duct, and one patient with persistent arterial duct and subaortic stenosis. Symptoms ranged from mild heart failure to failure to thrive. They all underwent cardiac catheterization for more detailed assessment of pulmonary hypertension and operability by Acute Vasoreactivity Testing (AVT), which consists in measuring pulmonary vascular resistance index (PVRI) and its response to pulmonary vasodilators (oxygen ± nitric oxide).

2.2 | Assessment of pulmonary hypertension and operability

Pulmonary hypertension was diagnosed, and operability assessed, based on internationally accepted criteria that are published in the joint guidelines of the American Heart Association and the American Thoracic Society (AHA/ATS).[1] In the context of congenital heart disease with left-to-right shunts, these criteria are the following:

1. Echocardiography is considered a reasonable way of assessing pulmonary hypertension, but only as a screening method, not as firm proof of diagnosis or reversibility of this. Diagnosis may only be established by catheterization, which should be carried out in the presence of clinical and echocardiographic features of pulmonary hypertension.
2. At catheterization, the diagnosis of pulmonary hypertension requires a mean pulmonary arterial pressure (mPAP) $\geq$ 25 mm Hg and a PVRI $\geq$ 3 indexed Wood Units (WU $\times$ m^2)
3. Patients with PVRI up to 6 WU $\times$ m^2, or with a ratio of pulmonary to systemic vascular resistances (PVR/SVR) up to 0.3, would benefit from surgical correction and should be considered operable.
4. Patients with PVRI greater than 6 WU $\times$ m^2 or with PVR/SVR $>$ 0.3 would be operable if both these parameters drop to below these levels in response to pulmonary vasodilators without any reduction in cardiac output.

Although the AHA/ATS guidelines do consider echocardiography an acceptable screening method for pulmonary hypertension, they do not outline specific echocardiographic diagnostic features other than a high RVP, which, they state, should be expressed as a ratio of the systemic systolic pressure (SSP). However, no specific figure is provided as to what is meant by a high RVP. Such a figure was arbitrarily chosen in our unit to assess surgical results. Surgical results are considered good in our unit if systolic RVP is no more than 50% of SSP (RVP/SSP $\leq$ 0.50).

2.3 | Data collection

The following data were recorded for each patient preoperatively:

- Age, sex, and diagnosis
- RVP/SSP ratio measured at catheterization

- mPAP, PVRI, PVR/SVR ratio, Qp/Qs and their response to pulmonary vasodilators, thus assessing operability

In all patients that underwent surgery, systolic RVP was measured intraoperatively after termination of cardiopulmonary bypass. Those with postbypass systolic RVPs higher than one-third SSP (RVP/SSP $\geq$ 0.33), were arbitrarily considered at higher risk of postoperative pulmonary hypertensive crises, and were fitted with a pulmonary arterial catheter for more accurate postoperative monitoring of pulmonary arterial pressures.

The following data were collected postoperatively:

- Mortality
- In patients that had been equipped with a pulmonary arterial catheter, three measurements were recorded: (i) mPAP on arrival on the ICU, (ii) the peak level of mPAP reached while the catheter was in place, and (iii) the last mPAP reading just prior to removal of this catheter (on postoperative day 3 or 4).
- Episodes of postoperative pulmonary hypertensive crises
- Postoperative RVP/SSP ratio (while in hospital) by echocardiography
- RVP/SSP ratio (also by echocardiography) at 6 weeks after hospital discharge
- Treatment with oral pulmonary vasodilators at discharge (phenoxybenzamine or sildenafil)

After the 6-week follow-up assessment, if there are no concerns, patients return to their countries of origin where they are followed-up by their local cardiologists. The local cardiologists keep us informed with respect to the progress of these patients and whether or not we need to make arrangements to see them again. They also communicate their echocardiographic findings, but do not carry out any catheterization.

3 | RESULTS

All 39 patients are presented individually in Table 1 in age sequence (youngest first), together with their preoperative catheterization data. The three patients from Kosovo are number 23, 30, and 35; the other patients are from West Africa.

At catheterization, systolic RVP was measured first. This was at, or nearly at systemic level (RVP/SSP ratios of 0.9 to 1.1) in 22 (56%) patients. In the remaining 17 (44%) patients, RVP/SSP ratios varied from 0.55 to 0.85. Therefore, RVP/SSP ratios were high in all patients (median ratio of 0.90, range: 0.55 to 1.1). In addition, all patients had mPAPs greater than 25 mm Hg (range: 30–72 mm Hg). They all underwent AVT to assess operability.

With AVT, 16 (41%) patients had basal PVRI $<$ 3 WU $\times$ m^2 and PVR/SVR $<$ 0.30. Clearly, these 16 patients did not have pulmonary hypertension and were operable.

There were 18 patients with either PVRI or PVR/SVR or both greater than 3 WU $\times$ m^2 and 0.30, respectively, in whom these parameters responded to AVT. These patients were also considered operable.

Five (13%) patients were considered inoperable—patients number 18, 22, 29, 33, and 39 in Table 1. These were at least 5 year old, four of whom had more complex malformations. In these 5 patients, both PVRI and PVR/SVR were high without responding to pulmonary vasodilators. All 5 were amongst the 22 cases that had preoperative RVPs at systemic level. These 5 patients were returned to their respective countries and have not been followed by us.

All 34 (87%) operable patients underwent surgical correction of their malformation via median sternotomy using cardiopulmonary bypass and cold blood cardioplegia. Systolic RVPs measured intraoperatively after termination of cardiopulmonary bypass had diminished noticeably in all cases—in 20 of them to one-third SSP or less.

There was no immediate or late mortality. Their postoperative data are presented in Table 2 in exactly the same sequence as in Table 1 (youngest first), such that the same patient number in both tables represents each patient.

Postoperative pulmonary hypertensive crises occurred in 10 (26%) patients. In 7 of these 10 cases, preoperative PVRIs were amongst the highest in our series (4.54-9.35 WU $\times$ m^2) while in the other 3 patients these were quite low (1.22-2.58 WU $\times$ m^2). All 10 patients had quite high preoperative RVPs—at systemic level in 7 cases, and between 70% and 85% of systemic pressures in 3 cases. In addition, they were all amongst the 19 patients whose RVP/SSP ratio after termination of cardiopulmonary bypass was higher than 0.33 and who were fitted with a pulmonary arterial catheter for postoperative monitoring of pulmonary arterial pressures. All episodes of crisis were managed successfully with the usual and recognized measures—adequate sedation and analgesia, ventilation modes that optimize functional residual capacity without excessively increasing airway pressure, avoidance of acidosis and hypoxia, and using nitric oxide.[1,9]

In the 19 patients that had a pulmonary arterial catheter, mPAP measurements showed that these diminished postoperatively. Preoperative mPAP measurements in these patients had revealed an average of 48 mm Hg (range 30–71 mm Hg). Their mPAPs on arrival on the ICU were lower, with an average of 24 mm Hg (range: 12–48 mm Hg). These increased temporarily 6–12 hour later, with an average of 46 mm Hg (range: 27–78 mm Hg). Measurements just prior to removal of these catheters (3 or 4 days later) revealed an average of 28 mm Hg (range: 19–49 mm Hg).

Postoperative echocardiographic RVP/SSP ratio was used as a measure of physiologic outcome in all cases. These were compared to preoperative values (preoperative median of 0.90, range 0.55-1.1). Postoperative RVP/SSP ratios were measured between the first and the third postoperative days. These revealed a median of 0.35 (range: 0.20-0.55). At follow-up, 6 weeks after hospital discharge, there was a median of 0.30 (range: 0.20–0.45).

Eleven of the 34 operated patients were treated with oral pulmonary vasodilators for 6 months following surgery. This precaution was taken in patients that either had suffered from episodes of pulmonary hypertensive crises in the postoperative period, or whose preoperative RVP was very high, or both.

Based on information provided by the local cardiologists of these operated patients, they all remain alive and asymptomatic, without any

TABLE 1 Preoperative data of all patients, arranged in order of age (youngest first)

Pt. No.	Age (years)	Sex	Dx	Preop RVP/SSP	Basal mPAP (mm Hg)	Basal Qp/Qs	Basal PVRI (WU × m^2)	Basal PVR/SVR	AVT mPAP (mm Hg)	AVT Qp/Qs	AVT PVRI (WU × m^2)	AVT PVR/SVR	Comment
1	2	F	VSD	0.70	37	3.10	1.86	0.12	33	4.62	0.70	0.06	
2	2.5	M	DORV	1	53	0.58	9.35	1.89	27	2.54	1.23	0.18	
3	2.5	M	VSD	0.95	36	2.12	2.08	0.39	27	3.22	1.50	0.20	
4	2.5	M	VSD	0.85	32	2.17	2.24	0.28	25	2.72	1.05	0.13	
5	2.5	M	VSD	1	38	3.33	1.89	0.16	42	5.48	1.33	0.10	
6	2.5	M	VSD	0.70	33	1.88	1.36	0.15	31	2.19	1.32	0.21	
7	2.5	F	VSD	0.75	40	1.47	5.76	0.48	30	5.44	0.55	0.09	
8	3	M	VSD	0.90	39	1.54	2.47	0.33	33	2.89	1.00	0.20	
9	3	M	CAT	1	51	2.63	2.58	0.27	51	5.25	2.18	0.14	
10	3.5	M	VSD	0.90	33	3.80	1.22	0.15	35	5.90	0.49	0.06	
11	3.5	F	VSD	0.90	62	1.31	6.24	0.67	57	2.44	2.57	0.33	
12	4	F	VSD	0.55	29	1.58	1.79	0.14	26	2.18	1.61	0.14	
13	4	F	VSD	1	59	1.92	5.89	0.41	48	2.64	2.83	0.21	
14	4	M	VSD	0.80	48	3.80	1.93	0.12	45	5.30	2.13	0.14	
15	4	M	VSD	0.75	71	2.70	1.80	0.19	37	5.70	0.35	0.03	
16	4	M	VSD	0.95	49	3.44	2.48	0.20	41	5.01	1.00	0.10	
17	4	M	VSD	1.1	64	2.50	6.93	0.29	62	3.28	2.67	0.24	
18	5	F	VSD	0.95	61	1.56	5.40	0.59	63	1.62	4.83	0.60	Inoperable
19	5	M	DORV	0.85	46	1.57	4.54	0.46	44	3.40	2.48	0.18	
20	5	M	VSD	0.55	32	1.90	2.05	0.18	31	2.56	1.45	0.18	
21	5.5	M	VSD	0.70	54	3.11	4.27	0.21	37	2.57	1.41	0.17	
22	6	M	IAA/Duct	1	68	0.77	13.60	0.95	72	0.57	4.16	0.79	Inoperable
23	6	F	AVSD	1	39	1.92	5.14	0.27	40	2.44	3.84	0.22	
24	7	F	VSD	0.90	41	3.00	2.78	0.19	41	3.54	2.03	0.14	
25	7.5	M	VSD	0.80	54	2.01	2.77	0.28	44	2.96	0.77	0.12	
26	8	M	DORV	0.75	39	1.75	2.36	0.32	34	4.62	0.83	0.13	
27	8	M	VSD	1	53	2.75	3.22	0.23	50	3.90	2.62	0.16	
28	8.5	M	VSD	0.60	44	2.01	4.64	0.26	39	2.91	1.58	0.16	
29	9.5	M	AVSD	1	72	0.54	12.26	2.29	70	0.99	10.67	1.15	Inoperable
30	10	M	VSD	1	62	1.46	6.52	0.58	59	2.49	4.38	0.25	
31	10	F	VSD	0.90	45	4.75	3.59	0.19	44	6.50	1.37	0.11	
32	11	M	VSD	0.75	48	2.67	3.91	0.23	45	3.37	2.44	0.18	
33	12	M	CAT	1	62	0.93	11.41	0.96	62	0.79	6.84	1.61	Inoperable
34	12	M	AVSD	0.60	39	1.63	3.55	0.58	39	1.70	2.89	0.30	
35	13	M	AVSD	0.55	30	2.69	2.23	0.08	28	2.51	1.23	0.05	
36	13	M	PDA/SAS	0.65	50	2.17	2.47	0.37	48	3.64	1.28	0.20	
37	14	F	VSD	0.95	58	4.40	2.14	0.12	49	5.11	1.24	0.09	
38	16	M	VSD	1	36	5.80	1.63	0.07	32	4.49	1.45	0.05	
39	35	F	AVSD	1	66	3.25	9.18	0.23	57	3.93	7.47	0.17	Inoperable

Abbreviations: Pt. No., patient number; Dx, diagnosis; RVP/SSP, ratio of systolic right ventricular pressure to the systemic systolic pressure; Basal, study done while ventilating with air; AVT, Acute Vasoreactive Testing (ie, study done while ventilating with 100% oxygen or with nitric oxide); Qp/Qs, ratio of pulmonary to systemic blood flow; PVRI, pulmonary vascular resistance index expressed in Wood units × m^2; mPAP, mean pulmonary arterial pressure; PVR/SVR, ratio of pulmonary to systemic vascular resistances; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; CAT, common arterial trunk; PDA/SAS, persistent ductus arteriosus and subaortic stenosis; IAA/Duct, interrupted aortic arch and persistent arterial duct; DORV, double outlet right ventricle with subaortic VSD; Com., comment.

TABLE 2 Postoperative data of all patients, arranged in order of age (youngest first)

Pt. No.	Vent	PHC	ICU	Hosp	Arrival mPAP (mm Hg)	Peak mPAP (mm Hg)	Last mPAP (mm Hg)	Preop RVP/SSP	Postop RVP/SSP	6 weeks RVP/SSP	Treatment on discharge
1	1d	–	3	11	14	33	19	0.70	0.35	0.20	–
2	3d	+	8	11	19	51	20	1	0.35	0.35	PBZ
3	2d	–	4	8				0.95	0.25	0.25	–
4	3d	–	3	7				0.85	0.20	0.25	–
5	2d	–	4	10	24	29	26	1	0.40	0.25	PBZ
6	4d	+	10	13	33	38	26	0.70	0.35	0.35	–
7	3d	+	9	14	14	29	27	0.75	0.35	0.30	–
8	3hr	–	2	7				0.90	0.35	0.35	–
9	6d	+	7	13	17	56	29	1	0.30	0.30	PBZ
10	6d	+	9	15	12	50	24	0.90	0.30	0.35	PBZ
11	2d	–	11	15				0.90	0.40	0.25	–
12	1d	–	4	8				0.40	0.30	0.25	–
13	2d	+	6	9	35	78	27	1	0.50	0.40	PBZ
14	3	–	6	12	17	31	28	0.80	0.40	0.35	PBZ
15	1d	–	4	17	16	36	22	0.75	0.35	0.30	–
16	1d	–	7	16				0.95	0.25	0.30	–
17	2	+	7	18	44	65	35	1.1	0.45	0.30	PBZ
18	Inoperable							0.95			
19	5d	+	6	14	13	53	25	0.85	0.30	0.25	PBZ
20	2hr	–	3	7				0.55	0.25	0.25	–
21	1d	–	4	6				0.70	0.30	0.20	–
22	Inoperable							1			
23	23d	+	45	54	34	75	35	1	0.55	0.25	–
24	3hr	–	2	10				0.90	0.30	0.30	–
25	1d	–	4	6				0.80	0.30	0.30	–
26	3hr	–	4	8				0.75	0.35	0.35	–
27	1d	–	3	7	23	34	37	1	0.50	0.25	–
28	1d	–	4	7				0.60	0.25	0.35	–
29	Inoperable							1			
30	9d	+	20	31	48	72	49	1	0.55	0.45	PBZ + Sil
31	1d	–	2	9	15	27	23	0.90	0.40	0.45	–
32	1d	–	5	7				0.75	0.40	0.35	–
33	Inoperable							1			
34	2d	–	3	9	29	43	37	0.60	0.40	0.45	PBZ
35	1d	–	6	14	25	40	36	0.50	0.40	0.35	–
36	1d	–	3	8	25	37	24	0.65	0.35	0.30	–
37	1d	–	6	16				0.95	0.50	0.35	Sil
38	1d	–	4	8				1	0.35	0.30	–
39	Inoperable							1			

Pt. No., patient number; Vent, duration of postoperative ventilation in days (d) or hours (h); PHC, whether or not there were episodes of pulmonary hypertensive crises postoperatively; ICU, ICU stay in days; Hosp, hospital stay in days; mPAP, mean pulmonary arterial pressure, on arrival on ICU, Peak mPAP, the maximum mPAP reached while the catheter was in place, Last mPAP, the last mPAP reading prior to removal of the catheter; Postop RVP/SSP, ratio of systolic right ventricular pressure to the systemic systolic pressure in the postoperative period (between the first and the third postoperative days); 6 weeks RVP/SSP, ratio of systolic right ventricular pressure to the systemic systolic pressure 6 weeks after hospital discharge; Rx, treatment with pulmonary vasodilators for 6 months after surgery, PBZ, phenoxybenzamine, Sil, sildenafil.

echocardiographic evidence of pulmonary hypertension, at a median of 7 years' follow-up (range 2–13 years).

4 | DISCUSSION

Age is not a consistent and reliable predictor of irreversibility of pulmonary hypertension in congenital heart disease with left-to-right shunts. This may not surprise clinicians working in parts of the world where late referrals may be common, or those involved in humanitarian work similar to ours who may likewise come across such patients repeatedly. However, to our knowledge, this has not been clearly highlighted in the literature. Even when this issue was noticed by other investigators, it was not emphasized in their publications, as this was not the main focus of their work.[10–12] The main and only focus of this work, conversely, is precisely to point this issue out, illustrating it with our series of 39 patients.

All patients in this series were at least 2 year old, most of them much older. Therefore, they were all old enough to be at high risk of having irreversible pulmonary hypertension according to the current literature.[5–8] However, this was found in only 5 (13%) patients. One of these 5 inoperable patients was 35 years old—the oldest patient in our series. The other 4, however, were of various ages and were not the oldest ones in our series. The other 34 patients underwent surgical correction with no early or late mortality and marked reduction in mPAP and/or RVP in every case after repair.

Although mPAP and/or RVP dropped significantly in all patients after repair, mPAP did increase temporarily 6–12 hours after surgery in the 19 patients where this was measured. This may be explained by the fact that surgical correction requires cardiopulmonary bypass, which is well known to cause a systemic inflammatory reaction. This reaches its peak several hours after the operation and damages the pulmonary endothelium. Such damage is thought to lead to a reduction in nitric oxide and increase in endothelin-1 release, thus temporarily causing pulmonary hypertension.[13,14]

Pulmonary hypertension is defined as mPAP > 25 mm Hg, generally without taking any other criteria (PVRI, PVR/SVR, or RVP) into account, as stated in the AHA/ATS guidelines.[1] This also applies to children older than three months if born at term; three months being long enough for pulmonary arterial pressures to fall to normal adult levels. However, this diagnostic simplicity is problematic in the context of congenital heart disease such that additional criteria may be required. This is because the use of mPAP as the sole diagnostic marker is sound only if pulmonary blood flow is normal (ie, equal to the total systemic flow). But this is often not the case in congenital heart disease where pulmonary blood flow may vary from less than half to several times the total systemic flow. A high pulmonary blood flow would result in a high mPAP by physical necessity, even if PVRI is low, and vice versa. This is seen in this study—all patients had a preoperative mPAP > 25 mm Hg without much response to AVT, even when PVRI and PVR/SVR diminished significantly in response to AVT (or were low to begin with).

These diagnostic pitfalls and ambiguities led the AHA/ATS to stipulate the use of PVRI and PVR/SVR in conjunction with mPAP as diagnostic criteria for pulmonary hypertension in congenital heart disease, as described above.[1] This adjustment compensates for the relative influences of high or low pulmonary blood flow on the diagnostic process. However, pulmonary blood flow becomes normal if and when the cardiac malformations are corrected, in which case the general and simpler definition of pulmonary hypertension (based solely on mPAP) may be applied. This is why we confidently report postoperative progress based only on pressures, while our preoperative assessments were much more based on PVRI and PVR/SVR.

This study has several important limitations that must be recognized. First and foremost, it has in-built potential for selection bias, as these patients are sent to us from other countries where we have no control over the patient selection process. It is easy to imagine that only the operable ones may be sent to us. We are told that this is not the case and that all detected patients are referred given that facilities for assessment of operability are not available locally. But we have no way of verifying this. In addition, despite all detected patients being referred to us, they may still be preselected by the virtue of the fact that they were able to survive long enough to be detected and referred; it is possible that some had died before they could be detected. Second, this study does not include any long-term follow-up by us, given that these patients live abroad. Follow-up is done by the local cardiologists, although they do provide us with clinical and echocardiographic data, which have been favorable in all operated patients so far. Third, follow-up was not really long-term (a median of 7 years); longer-term outcome remains unknown. Specifically, we do not know whether or not these patients are more likely to develop pulmonary hypertension later in life. Fourth, it is retrospective, thus limiting us significantly in what data we may gather. Fifth, only about one third of patients received a pulmonary arterial catheter at the time of surgery for postoperative mPAP monitoring. In addition, we do not know the ventilator settings when the measurements were recorded. This may affect pulmonary arterial pressures such that readings at different times may not be comparable. Had this study been prospective, all patients would have been fitted with such a catheter and measurements would have been made under standardized conditions. Sixth, again due to the retrospective nature of this study, we are unable to provide a precise algorithm that may have been used regarding the decision to initiate medical therapy (pulmonary vasodilators for 6 months following surgery) in some patients, beyond the explanation given already in the results section. Seventh, there is no control group for comparison, that is, a group of younger patients. We could not form such a group, as younger patients are rarely catheterized, and therefore lack data for comparison. Lastly, this study does not include any patient destined to univentricular palliation or any with trisomy 21 or other chromosomal abnormalities. Therefore, our findings may not be applicable to these groups.

Despite these limitations, this study shows that many surprisingly old patients with these cardiac malformations may still be operable. Conversely, although not included in this study, some patients much younger than two years are occasionally found to be inoperable, as is well known to most workers in the field of congenital heart disease. Clearly, age alone should not be viewed as a contraindication to

proceeding with surgical correction, although it remains a risk factor (5 of our 39 patients were inoperable). No patient should be denied surgical correction without formal assessment by catheterization.

This does not mean that all patients with such malformations should undergo catheterization to rule out irreversibility of pulmonary hypertension. In fact, catheterization is rarely used in this respect. Catheterization is indicated to confirm or refute this diagnosis only when other findings (both clinical and echocardiographic) raise this possibility. However, when clinical and echocardiographic findings indicate absence of pulmonary hypertension (ie, clinical evidence of heart failure, dilated left-sided cardiac chambers without rectification or leftward shift of the ventricular septum, left-to-right shunting throughout systole and high shunt velocity), no catheterization is required for confirmation.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTIONS

Concept/Design: Hosseinpour, Perez, Longchamp, Sekarski, Di Bernardo

Data collection: Hosseinpour, Perez, Longchamp, Hurni, Di Bernardo

Data analysis/interpretation: Hosseinpour, Perez, Longchamp, Di Bernardo

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