

Late Onset Postcapillary Pulmonary Hypertension in Patients With Transposition of the Great Arteries and Mustard or Senning Baffles

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Background—There is a paucity of data regarding late-onset pulmonary hypertension (PH) in patients with transposition of the great arteries and atrial switch surgery.

Methods and Results—A retrospective cohort study was conducted on 140 adults with transposition of the great arteries and atrial switch surgery, age 37.3 ± 7.8 , 37.1% female, in order to assess the prevalence and characteristics of late-onset PH and explore associated factors. Patients were followed for a median of 32.3 years after atrial switch surgery and 10.0 years after their first referral visit. PH was detected in 18 of 33 (54.5%) patients who had invasive hemodynamic studies. Average age at diagnosis of PH was 33.9 ± 8.1 years. PH was postcapillary in all, with a mean pulmonary artery pressure of 36 ± 12 mm Hg and mean pulmonary capillary wedge pressure of 28 ± 8 mm Hg. PH was diagnosed in 13 of 17 (76.5%) patients who had cardiac catheterization for heart failure or decreased exercise tolerance. In multivariable analyses, systemic hypertension (odds ratio 9.4, 95% confidence interval 2.2–39.4, $P=0.002$) and heart failure or New York Heart Association class III or IV symptoms (odds ratio 49.8, 95% confidence interval 8.6–289.0, $P<0.001$) were independently associated with PH. Patients with PH were more likely to develop cardiovascular comorbidities including atrial ($P=0.001$) and ventricular ($P=0.008$) arrhythmias, require hospitalizations for heart failure ($P<0.001$), and undergo tricuspid valve surgery ($P<0.001$). Mortality was significantly higher in patients with PH (hazard ratio 9.4, 95% confidence interval 2.1–43.0], $P<0.001$).

Conclusions—Late-onset postcapillary PH is highly prevalent in adults with transposition of the great arteries and atrial switch surgery and is associated with an adverse prognosis. (*J Am Heart Assoc.* 2017;6:e006481. DOI: 10.1161/JAHA.117.006481.)

Key Words: atrial switch surgery • Mustard baffle • pulmonary hypertension • Senning baffle • transposition of great vessels

Complete transposition of the great arteries (D-TGA), whether isolated (simple) or associated with other congenital lesions (complex), is among the most common forms of cyanotic heart disease.¹ Untreated, it is associated with >90% mortality during the first year of life.² This dismal prognosis was dramatically altered by introduction of the atrial switch procedure by Åke Senning in 1959³ and William

Mustard in 1964.⁴ Atrial switch surgery became the procedure of choice for D-TGA until the 1980s, when it was progressively replaced by the arterial switch operation. Over 60% of patients with D-TGA and Senning or Mustard baffles remain alive after 30 years of follow-up,⁵ with most now in their third to fifth decades of life. Complications encountered in adult life are well characterized and include sinus node dysfunction, atrial arrhythmias, sudden death, systemic right ventricular dysfunction, tricuspid regurgitation, subvalvular pulmonary stenosis, and baffle obstructions and leaks.^{5–8}

Pulmonary hypertension (PH) has been described in patients with D-TGA and atrial switch surgery and has been associated with impaired functional capacity and quality of life.⁹ Precapillary PH was first observed early after atrial switch surgery, with more recent reports describing late-onset PH.^{9–11} The prevalence of late-onset PH is poorly defined, with studies suggesting rates between 2% and 7%, an age at diagnosis ranging between 14 and 34 years, and a predominance of precapillary PH with high pulmonary vascular resistance (PVR). Because of the high incidence of late

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Clinical Perspective

What Is New?

- Following an atrial switch procedure for D-transposition of the great arteries, late-onset pulmonary hypertension, particularly postcapillary pulmonary hypertension, is more common than previously thought and is associated with increased morbidity and mortality.
- Echocardiography is an insensitive screening tool to detect pulmonary hypertension in the context of D-transposition of the great arteries and Mustard or Senning surgery, given the low prevalence of detectable valve regurgitation associated with a subpulmonary morphologic left ventricle.

What Are the Clinical Implications?

- Systolic and diastolic dysfunction of the systemic right ventricle and noncompliance of rigid intra-atrial baffles appear to be important determinants of postcapillary pulmonary hypertension in patients with D-transposition of the great arteries and atrial switch surgery.

systemic ventricular failure in these patients, we hypothesized that late-onset PH, particularly postcapillary PH, is underrecognized. We therefore conducted a retrospective cohort study on adults with D-TGA and atrial switch surgery followed at the Montreal Heart Institute Adult Congenital Centre in order to assess the prevalence and characteristics of late-onset PH, and explore associated factors.

Methods

Study Population

The study population consisted of all patients ≥ 18 years of age with simple or complex D-TGA having undergone a Mustard or Senning baffle followed at the Montreal Heart Institute Adult Congenital Centre. Eligible patients were identified through the institutional tailored clinical and research informatics system for congenital heart disease, CONGENERATE, which contains comprehensive diagnostic and procedural codes for all patients followed at the Montreal Heart Institute Adult Congenital Centre since 1989. Patients with a double-outlet right ventricle, Rastelli procedure, or arterial switch operation were excluded. The study was approved by our local institutional review board with waiver of informed consent.

Pulmonary Hypertension

PH was defined as a mean pulmonary arterial pressure (PAP) ≥ 25 mm Hg at rest, as measured by cardiac catheterization.

PH was classified as precapillary if the pulmonary capillary wedge pressure (PCWP) was ≤ 15 mm Hg at rest or as postcapillary if the PCWP was > 15 mm Hg. Postcapillary PH was considered isolated if the diastolic pressure gradient (ie, diastolic PAP minus mean PCWP) was < 7 mm Hg in combination with PVR ≤ 3 Wood units. Patients with a PCWP > 15 mm Hg and a diastolic pressure gradient ≥ 7 mm Hg, PVR > 3 Wood units, or a transpulmonary gradient (ie, mean PAP minus mean PCWP) > 15 mm Hg were considered to have combined post- and precapillary PH.^{12,13}

Data Collection

Electronic and paper medical records were reviewed for all potentially eligible patients, including pertinent surgical, echocardiographic, and hemodynamic charts and databases, supplemented by secondary source material from referring hospitals. Variables of interest included standard demographic parameters (eg, age, sex, body mass index), associated congenital heart lesions (eg, pulmonary stenosis, ventricular septal defect), pharmacological therapies (eg, loop diuretics, β -blockers, angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blockers), electrocardiographic characteristics (eg, underlying rhythm, QRS duration), surgical details (eg, age at surgery, Mustard versus Senning baffle, surgery for associated defects, cardiac transplantation), residual hemodynamic lesions (eg, baffle leak or stenosis, tricuspid regurgitation, ventricular dysfunction), interventional procedures (eg, for baffle leak or stenosis, pacemaker, implantable cardioverter-defibrillator), New York Heart Association (NYHA) functional class, comorbidities (eg, current and past tobacco use, diabetes mellitus, systemic hypertension, dyslipidemia, noncardiac disease), brady- and tachyarrhythmias, heart failure-related hospitalizations, and all deaths. Data were extracted at the time of referral to the Montreal Heart Institute, at last follow-up, and at the time of cardiac catheterization, when relevant.

Echocardiograms (at first referral, last follow-up, and at the time of cardiac catheterization if performed) were reviewed for systemic right ventricular dimensions, right ventricular systolic function, and degree of tricuspid regurgitation. Right ventricular dimensions were qualitatively categorized as normal or mildly, moderately, or severely dilated. Right ventricular systolic dysfunction was characterized as absent, mild, moderate, or severe using visual assessment in combination with recommended indices of right ventricular function, namely, tricuspid annular plane systolic excursion, right ventricular myocardial performance index, right ventricular fractional area change, and right ventricular free-wall and septal systolic strain.¹⁴ The degree of tricuspid regurgitation was qualitatively assessed as absent, mild, moderate, or severe by color Doppler imaging in accordance with published guidelines.¹⁵

Data collected on hemodynamic studies performed during adulthood included indication for cardiac catheterization, age at time of study, and hemodynamic parameters: invasive systolic and diastolic arterial pressure; systolic, diastolic, and mean PAP; PCWP; PVR; and systemic and subpulmonary ventricular end-diastolic pressures.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation or median and interquartile range (25th, 75th percentile), depending on normality of distribution. Discrete variables are expressed as frequencies and percentages. Comparisons between continuous variables were performed using Mann-Whitney U tests. Discrete variables were compared using Fisher exact tests. Baseline characteristics listed in Table 1 were assessed for their association with PH in univariable and multivariable logistic regression models, from which odds ratios and associated 95% confidence intervals were derived. Highly correlated variables (correlation coefficients ≥0.6) were merged together for consideration in the multivariable model. More specifically, the correlation coefficient for “history of heart failure” and “NYHA functional class III or IV symptoms” was 0.71 such that a new dichotomous variable was created to code for patients with either 1 or the other (ie, “history of heart failure or NYHA functional class III or IV symptoms”). Variables associated with *P*<0.1 in univariable analyses were considered in the final automated stepwise multivariable regression model. Event-free survival was plotted using the Kaplan-Meier product-limit method, with censoring at the time of last follow-up or cardiac transplantation. Survival rates were compared by the log-rank test. The association between PH and mortality was assessed in univariable Cox regression analysis. Two-tailed *P*<0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY).

Results

Patient Population

From a total of 144 adults with D-TGA and Mustard or Senning baffles identified, 2 patients were excluded because of conversion to arterial switch surgery in childhood (ie, prior to referral to our center) and 2 due to double-outlet right ventricles. The study population is comprised of the remaining 140 patients, mean age 37.6±7.8 years, 37.1% female subjects. Baseline characteristics at the first referral visit to the Montreal Heart Institute Adult Congenital Centre are summarized in Table 1. Overall, 90 (64.3%) had simple D-TGA, and 50 (35.7%) had 1 or more associated lesions. A Mustard operation was performed in 118 (84.3%) patients, and a

Table 1. Baseline Characteristics

	N=140
Age at first referral, y	25.1±6.7
Sex (female), N (%)	52 (37.1)
Mustard baffle, N (%)	118 (84.3)
Age at atrial switch surgery,* months	20.9 (11.1, 32.3)
Diabetes mellitus, N (%)	2 (1.4)
Dyslipidemia, N (%)	1 (0.7)
Hypertension, N (%)	12 (8.6)
Obesity, N (%)	5 (3.6)
Active or past tobacco use, N (%)	26 (18.6)
New York Heart Association class III or IV symptoms, N (%)	6 (4.3)
Diagnosis of heart failure, N (%)	8 (5.7)
Sustained atrial arrhythmia, N (%)	37 (26.4)
Nonsustained or sustained ventricular tachycardia, N (%)	7 (5.0)
Permanent pacemaker, N (%)	43 (30.7)
Stenosis or thrombosis of the systemic baffle, N (%)	26 (18.6)
Associated lesions at birth, N (%)	
One or more associated lesions	50 (35.7)
Patent ductus arteriosus	21 (15.0)
Pulmonary or subpulmonary stenosis	16 (11.4)
Atrial septal defect	6 (4.3)
Ventricular septal defect	17 (12.1)
Residual lesions after surgery, N (%)	
One or more residual lesions	16 (11.4)
Atrial septal defect	6 (4.3)
Subpulmonary stenosis	6 (4.3)
Ventricular septal defect	5 (3.6)
Pulmonary artery stenosis	1 (0.7)
Electrocardiographic parameters	
Sinus rhythm, N (%)	82 (58.6)
QRS duration, ms	107.3±25.1
Ventricular pacing, N (%)	10 (7.1)
QRS duration excluding ventricular pacing, ms	104.1±18.5
Echocardiographic parameters, N (%)	
Moderate or severe right ventricular dilatation	80 (57.1)
Moderate or severe right ventricular systolic dysfunction	38 (27.1)
Moderate or severe tricuspid regurgitation	41 (29.3)
Pharmacologic therapy, N (%)	
Loop diuretic	7 (5.0)
β-Blocker	27 (19.3)
ACE inhibitor or angiotensin receptor blocker	63 (45.0)

ACE indicates angiotensin-converting enzyme.

*Nonnormally distributed continuous variables are presented as median (interquartile range).

Table 2. Characteristics at the Time of Cardiac Catheterization According to Whether or Not Patients Had PH

	PH (N=18)	No PH (N=15)	P Value
Age at catheterization, y	33.9±8.1	32.2±9.9	0.656
Female sex, N (%)	5 (27.8)	6 (40.0)	0.458
Associated congenital heart lesions, N (%)	7 (38.9)	6 (40.0)	0.948
Mustard surgery, N (%)	16 (88.9)	12 (80.0)	0.639
Age at atrial switch surgery,* months	26.0 (15.3, 43.2)	17.9 (5.3, 19.2)	0.211
Time from surgery to catheterization,* y	29.7 (26.0, 38.7)	29.2 (22.6, 35.3)	0.656
Residual lesion after atrial switch surgery, N (%)	4 (22.2)	2 (13.3)	0.665
Stenosis or thrombosis of systemic baffle, N (%)	4 (22.2)	5 (33.3)	0.697
Echocardiogram at time of catheterization			
Moderate or severe right ventricular dilatation, N (%)	8 (44.4)	7 (46.7)	0.898
Moderate or severe right ventricular dysfunction, N (%)	14 (77.8)	10 (66.7)	0.697
Moderate or severe tricuspid regurgitation, N (%)	12 (66.7)	7 (46.7)	0.247
At least mild mitral regurgitation, N (%)	4 (22.2)	5 (33.3)	0.697
At least mild pulmonary regurgitation, N (%)	8 (50.0)	4 (36.4)	0.696
Severe subpulmonary ventricular dysfunction, N (%)	4 (22.2)	0 (0.0)	0.108
Catheterization data			
Systolic arterial pressure, mm Hg	124±17	109±21	0.036
Diastolic arterial pressure, mm Hg	75±9	64±13	0.007
Systolic PAP, mm Hg	55±20	26±8	<0.001
Diastolic PAP, mm Hg	23±9	8±4	<0.001
Mean PAP, mm Hg	36±12	16±4	<0.001
PCWP, mm Hg	28±8	15±6	<0.001
PVR, Wood units	2.5±2.5	0.7±0.6	<0.001
Cardiac index, L/min per m ²	2.4±0.7	2.5±0.6	0.714
Systemic ventricular end-diastolic pressure, mm Hg	18±7	14±5	0.077
Subpulmonary ventricular end-diastolic pressure, mm Hg	13±6	8±5	0.077

PAP indicates pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

*Nonnormally distributed continuous variables are presented as median (interquartile range).

Senning operation in 22 (15.7%). Sixteen (11.4%) patients had 1 or more residual lesions after surgery.

Pulmonary Hypertension

Cardiac catheterization was performed in 33 (23.6%) patients for the following primary indications: heart failure or decreased exercise tolerance (N=17; 51.5%), superior systemic baffle stenosis (N=6; 18.2%), baffle leak (N=5; 15.2%), severe tricuspid regurgitation (N=3; 9.1%), pulmonary venous baffle stenosis (N=1; 3.0%), and pulmonary valve regurgitation after pacemaker extraction (N=1; 3.0%). As shown in Table 2, demographic and echocardiographic characteristics of patients with and without PH were similar. On the whole, PH was detected in 18 (54.5%) catheterized patients. The prevalence of PH was 76.5% in patients for whom cardiac

catheterization was indicated for heart failure or decreased exercise tolerance compared with 31.2% in patients with other reasons for cardiac catheterization ($P=0.014$).

PH was diagnosed at an average age of 33.9±8.1 years, a median of 32.2 (interquartile range 28.3, 40.6) years after atrial switch surgery. The mean PAP was 36.1±12.0 mm Hg, PCWP 27.6±7.8 mm Hg, and PVR 2.5±2.5 Woods units. PH was postcapillary in all cases, albeit combined in 2 patients. In 1 additional patient, PVR was not obtainable, thereby precluding classification as isolated postcapillary or combined PH. Of note, PAP could be estimated by pulsed Doppler echocardiography in only 1 patient. Subpulmonary systolic pressure was estimated at 49 mm Hg by echocardiography, in comparison to 55/34 (mean 43) mm Hg by catheterization. Pulmonary artery diastolic velocity could not be accurately measured in 8 of 18 (44.4%) patients with mild PH.

Table 3. Characteristics and Clinical Status of Individuals With PH

Indication for Catheterization	Pt #	Age at Surgery, Months	Type of Postcapillary PH	PAP S/D (Mean), mm Hg	PCWP, mm Hg	PVR, Wood Units	TPG, mm Hg	DPG, mm Hg	Specific Management	Clinical Status at Last Follow-Up
Heart failure or decreased exercise tolerance	1	49	Isolated	62/29 (40)	30	1.7	10	-1	Referral for cardiac transplantation	Improvement; removal from transplant list
	2	58	Isolated	55/34 (43)	29	2.1	14	5		No follow-up available
	3	5	Isolated	58/20 (30)	17	2.5	13	3		Heart transplant
	4	32	Isolated	47/17 (31)	23	1.9	8	-6		Listed for transplant; recurrent hospitalizations for heart failure
	5	43	Isolated	50/21 (33)	26	1.8	7	-5		Death
Severe tricuspid regurgitation	6	25	Combined	86/40 (60)	39	4.0	21	1	Pulmonary arterial hypertension therapy	Recurrent hospitalizations for heart failure
	7	21	Isolated	56/19 (36)	29	1.7	7	-10		Improvement
	8	43	Not determined	45/18 (32)	18	...	14	0		Death
	9	44	Isolated	34/16 (26)	22	0.8	4	-6		Improvement
	10	28	Isolated	50/20 (30)	25	0.8	5	-5		Death
	11	31	Isolated	45/21 (31)	24	1.3	7	-3		Improvement
	12	15	Isolated	45/20 (29)	20	2.1	9	0		Improvement
	13	9	Combined	117/45 (73)	32	10.2	41	13		Improvement
	14	17	Isolated	40/20 (28)	23	1.26	5	-3		No change
	15	152	Isolated	40/12 (30)	22	1.7	8	-10		Death
	16	18	Isolated	38/23 (31)	20	2.9	11	3		Improvement
Suspicion of superior systemic baffle stenosis	17	41	Isolated	48/26 (32)	25	1.5	7	1	TVR	No change
	18	4	Isolated	64/15 (35)	28	1.5	7	-13		No change

DPG indicates diastolic pressure gradient; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; S/D, systolic/diastolic; TPG, transpulmonary gradient; TVR, tricuspid valve replacement.

Table 3 provides a more detailed description of characteristics and clinical outcomes of the 18 patients with PH. During follow-up, 4 (22.2%) had tricuspid valve replacement, and 8 (44.4%) had moderate or severe tricuspid regurgitation treated medically. One patient received a heart transplant, and 3 died, 2 from sudden cardiac death and the third from sepsis with biventricular dysfunction. Among the 13 patients with cardiac catheterization for heart failure or decreased exercise tolerance, 9 received medical management for heart failure, of whom 4 responded favorably.

Factors Associated With PH

Baseline characteristics associated with PH in univariable and multivariable logistic regression analyses are summarized in Table 4. In multivariable analyses, systemic hypertension (odds ratio 9.4, 95% confidence interval 2.2-39.4, $P=0.002$) and history of heart failure or NYHA functional class III or IV symptoms (odds ratio 49.8, 95% confidence interval 8.6-289.0, $P<0.001$) were independently associated with PH. History of heart failure and NYHA class III or IV symptoms were highly correlated (ie, correlation coefficient 0.71, $P<0.001$) and, therefore, merged into a single variable.

Clinical Course During Follow-Up

Patients were followed for a median of 32.3 (interquartile range 27.0, 38.8) years after atrial switch surgery and 9.9 (interquartile range 5.8, 13.0) years following their baseline visit. As shown in Table 5, during the course of follow-up, patients with PH were more likely to develop comorbidities including diabetes mellitus, dyslipidemia, hypertension, and obesity. Patients with PH were more likely to have NYHA functional class III or IV symptoms, to be hospitalized for heart failure, to have moderate or severe right ventricular systolic dysfunction, and to receive loop diuretics, β -blockers, and ACE inhibitors or angiotensin receptor blockers. The need for tricuspid valve surgery and the prevalence of atrial and ventricular arrhythmias were higher in patients with PH. The

mortality rate, plotted in Figure, was significantly greater in patients with PH (hazard ratio 9.4, 95% confidence interval 2.1-43.0, $P<0.001$).

Discussion

The main findings of this cohort study of 140 patients with D-TGA and Mustard or Senning baffles are that late-onset PH is more common than previously suspected, it is predominantly postcapillary, and it is associated with increased morbidity and mortality. PH was detected in 54.5% of patients referred for cardiac catheterization. It was present in over three-quarters of those with cardiac catheterization for heart failure or worsening functional capacity and in nearly one-third of patients with hemodynamic studies for other indications. Although PH was postcapillary in all patients, a precapillary component (PVR >3 Wood units) was identified in 2 subjects. Earlier studies with shorter follow-up periods reported a prevalence of PH ranging from 2.6% to 7%.⁹⁻¹¹ Ebenroth et al described 4 (7%) patients with idiopathic PH, and although PCWP values were not available, indexed PVRs were high.⁹ Yehra et al detected PH in 6 of 103 (5.6%) patients, mean age 29 years, by echocardiographic screening.¹⁰ Three had postcapillary PH.

Pathophysiology of Postcapillary PH

The pathophysiology of postcapillary PH in TGA with atrial switch surgery remains to be elucidated. In contrast to prior reports,¹⁶⁻¹⁸ PH in our adult population was not associated with coexisting congenital heart defects, older age at surgery, residual hemodynamic lesions, or obstructed systemic atrial baffles. It may be hypothesized that the observed postcapillary PH is secondary to atrial and/or ventricular disease associated with the reconstructed atrial anatomy and systemic right ventricle. Some degree of right ventricular systolic dysfunction is the norm rather than the exception in adults with D-TGA and Mustard or Senning baffles, although PH was not associated with moderate or severe right ventricle dysfunction.

Table 4. Baseline Characteristics Associated With PH in Univariable and Multivariable Logistic Regression Analyses

N=140	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Systemic hypertension	6.3 (1.8, 22.8)	0.005	9.4 (2.2, 39.4)	0.002
Ventricular arrhythmias	5.9 (1.2, 28.9)	0.029		
History of heart failure or NYHA class III or IV	38.2 (7.1, 206.6)	<0.001	49.8 (8.6, 289.0)	<0.001
QRS duration, per ms	1.024 (1.006, 1.041)	0.008		
Moderate to severe tricuspid regurgitation	2.8 (1.0, 7.7)	0.044		

CI indicates confidence interval; NYHA, New York Heart Association.

Table 5. Characteristics at Last Follow-Up

	PH (N=18)	No Known PH (N=122)	P Value
Diabetes mellitus, N (%)	3 (16.7)	2 (1.6)	0.015
Dyslipidemia, N (%)	2 (11.1)	1 (0.8)	0.044
Hypertension, N (%)	6 (33.3)	16 (13.1)	0.039
Obesity, N (%)	4 (22.2)	5 (4.1)	0.016
Active or past tobacco use, N (%)	4 (22.2)	28 (23.0)	1.000
New York Heart Association class III or IV symptoms, N (%)	5 (27.8)	5 (4.1)	0.003
Hospitalization for heart failure, N (%)	9 (50.0)	2 (1.6)	<0.001
Sustained atrial arrhythmia, N (%)	16 (88.9)	58 (47.5)	0.001
Nonsustained or sustained ventricular tachycardia, N (%)	8 (44.4)	19 (15.6)	0.008
Permanent pacemaker, N (%)	11 (61.1)	49 (40.2)	0.094
Implantable cardioverter-defibrillator, N (%)	5 (27.8)	4 (3.3)	0.002
Tricuspid valve surgery (replacement or annuloplasty), N (%)	5 (27.8)	2 (1.6)	<0.001
Stenosis or thrombosis of the systemic baffle, N (%)	7 (38.9)	36 (29.5)	0.421
Echocardiographic parameters, N (%)			
Moderate or severe right ventricular dilatation	12 (70.6)	89 (73.6)	0.776
Moderate or severe right ventricular systolic dysfunction	11 (61.1)	41 (33.6)	0.024
Moderate or severe tricuspid regurgitation*	6 (33.3)	39 (32.0)	0.908
Pharmacologic therapy, N (%)			
Loop diuretic	9 (50.0)	6 (4.9)	<0.001
β-Blocker	15 (83.3)	44 (36.1)	<0.001
ACE inhibitor or angiotensin receptor blocker	11 (61.1)	41 (33.6)	0.024
Mortality			
Death of any cause, N (%)	3 (16.7)	4 (3.3)	0.045
Cardiovascular death, N (%)	3 (16.7)	3 (2.5)	0.028
Age at death, y	33.0±7.2	30.7±6.6	1.000

ACE indicates angiotensin-converting enzyme; PH, pulmonary hypertension.
 *Includes patients with moderate or severe tricuspid regurgitation following tricuspid valve surgery.

The geometric structure and myocardial fiber orientation of the morphologic right ventricle predisposes to an excessive hypertrophic response to systemic pressures, which can result in diastolic dysfunction.¹⁹ However, notwithstanding limitations associated with estimating systemic right ventricular end-diastolic pressures in the presence of tricuspid regurgitation, nonsignificantly higher values were observed in patients with PH. This argues against diastolic dysfunction as a primary driver of postcapillary PH. We cannot rule out the influence of valve disease on development of PH considering the numerically higher prevalence of moderate to severe tricuspid regurgitation in patients with compared with those without PH (ie, 67% versus 47%), despite the lack of statistical significance ($P=0.247$). At the atrial level, poor compliance of the baffle may lead to PH with no increase in systemic right ventricular end-diastolic pressure, as noted in our study. Poor atrial transport has been well characterized in this patient population.²⁰ Further studies

are required to clarify pathophysiology and explore potential modulating effects of acquired comorbidities and genetic factors that may influence the systemic right ventricle and tricuspid valve’s response to pressure and volume overload.

Echocardiographic Data in Patients With Postcapillary PH

Importantly, the echocardiographic data collected in our study suggest that it is an insensitive screening test for PH in this patient population irrespective of the quality of the acoustic images encountered. Noninvasive measure of PH by continuous Doppler flow imaging across the pulmonary valve is seldom possible due to the absence of regurgitation. Moreover, in contrast to the standard tricuspid valve in a subpulmonary right ventricle, the mitral valve in a subpulmonary left ventricle is far less likely to have detectible

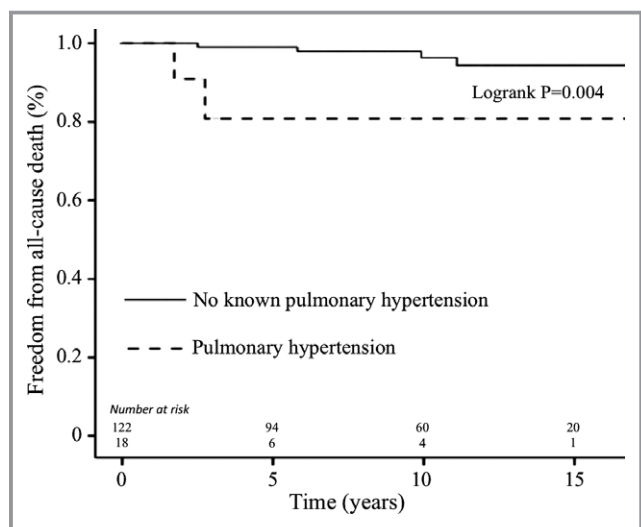


Figure. Kaplan-Meier curves depicting all-cause mortality according to the presence or absence of pulmonary hypertension.

regurgitation (ie, 22% of our study population). This likely reflects greater resilience of a mitral valve, which is normally subjected to systemic pressures, to leak when exposed to an increase in afterload. Although it could be argued that indirect echocardiographic signs may be useful metrics in assessing PH,^{9-11,21} we found no differences in ventricular chamber dimensions or function in patients with and without PH. Thus, echocardiographic signs seem to appear later in the evolution of PH in patients with D-TGA and Mustard or Senning baffles because of the resiliency of the subpulmonary morphologic left ventricle and its mitral valve. Consequently, cardiac catheterization may be required to diagnose PH in this patient population.

Comorbidities and Associated Factors in Patients With Postcapillary PH

In our analyses, heart failure metrics (ie, history of heart failure or NYHA class III or IV symptoms) and systemic hypertension were independently associated with PH. These findings should raise awareness about the association between heart failure and PH and provide a rationale for early detection. Although the association between systemic hypertension and PH has been described in patients with structurally normal hearts,²² it may be speculated that the impact of systemic hypertension on PH is more pronounced in the setting of a morphologic right ventricle given its reduced capacity to adapt to increased afterload. As a result, systemic hypertension should generally be managed aggressively in patients with D-TGA and Mustard or Senning baffles. Although our study was not designed to assess causal associations, the mortality rate was higher in patients with PH. It is possible that PH is simply a marker of poor prognosis. However, it may

well be implicated in a complex causal web with bidirectional interactions. For example, PH is associated with impaired functional capacity, which may predispose to the development of acquired comorbidities such as obesity and diabetes mellitus. Moreover, associations between PH and heart failure, atrial arrhythmias, ventricular arrhythmias, sudden death, and thromboembolic complications have been well documented in other populations.²³

Management of Patients With Postcapillary PH

Management of PH in patients with D-TGA and Mustard or Senning baffles remains unstudied. In our experience 50% of patients received loop diuretics, 61% ACE inhibitors or angiotensin receptor blockers, and 83% β -blockers. In addition, 28% had tricuspid valve surgery. Although some patients improved with standard heart failure medications, it is worth emphasizing that efficacy of these drugs has not been demonstrated in patients with systemic right ventricles.^{24,25} Safety and efficacy of endothelin receptor antagonists and other advanced PH-targeted therapies remain unclear in patients with D-TGA and Mustard or Senning baffles,^{10,11} particularly in the context of postcapillary PH with systemic right ventricular systolic and/or diastolic dysfunction.^{10,11} Finally, cardiac transplantation was performed in 1 patient in our series and remains an option in suitable candidates with end-stage heart failure, on condition that that PVR remains acceptable. Advanced PH may contraindicate single-organ heart transplantation, providing an additional rationale for early detection. Mechanical circulatory support may be considered in selected patients with systemic right ventricular dysfunction and PH as destination therapy or as a bridge to heart transplantation.²⁶

Limitations

The study is retrospective in nature and, hence, subject to associated limitations that arise from nonstandardized indications for cardiac catheterization, diagnostic assessments, detection of outcomes, and therapeutic decisions. Guidelines for the assessment of right ventricular dilatation, ventricular function, and severity of valvular regurgitation evolved during the 35-year observation period. Hemodynamic values were reported by different physicians over the span of the study. Diastolic pressure gradients near 0 are particularly sensitive to errors with fluid-filled catheter measurements. V waves from tricuspid regurgitation might have been variably integrated into mean PCWP measurements, contributing to negative diastolic pressure gradient values and larger differences between mean PCWP and systemic right ventricular end-diastolic pressures.²⁷ Although attempts were made to control for potential confounders in assessing the relationship

between clinical factors and PH, regression analyses cannot account for unknown or unmeasured variables. Finally, although restricting the study to a single center with a core group of adult congenital specialists may lessen the impact of variations in practice patterns, it also limits generalizability of the findings.

Conclusion

In this cohort of 140 adults with D-TGA and Mustard or Senning baffles, we observed a high prevalence of late-onset PH. These findings suggest that the phenomenon of post-capillary PH has been underappreciated in this patient population. This likely reflects the fact that echocardiography is an insensitive screening tool to detect PH in the context of a subpulmonary left ventricle that is resilient to high pulmonary artery pressures and associated with a low prevalence of mitral regurgitation. The pathophysiology of postcapillary PH remains to be elucidated, but it is speculated that impaired diastology resulting from a rigid atrial baffle plays a role. It appears important to identify PH considering its association with increased morbidity and decreased survival.

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Disclosures

None.

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