The Heart Surgery Forum #2011-1127
15 (2), 2012 [Epub April 2012
doi: 10.1532/HSF98.20111127

Online address: http://cardenjennings.metapress.com

Clinical and Pathologic Comparison of Simple Left-to-Right Shunt Congenital Heart Disease and Transposition of the Great Arteries with Ventricular Septal Defect

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ABSTRACT

Background: This study aimed to compare clinical and pathologic data for selected patients with congenital heart disease (CHD) and severe pulmonary hypertension (PH) treated with a diagnostic-treatment-and-repair strategy and to compare results for patients with pulmonary vascular disease (PVD) with simple left-to-right shunt CHD with patients with transposition of the great arteries (TGA) and ventricular septal defect (VSD).

Methods: Group I comprised 38 patients with simple left-to-right shunt CHD and severe PH; group II included 11 older patients with TGA with VSD and severe PH; and group III comprised 6 autopsy cases of individuals with a normal circulation. The nature of the pulmonary arteries was determined by the Heath-Edwards classification system. All specimens were quantitatively analyzed.

Results: Group I showed 31 patients with a change to grade I, 3 patients were grade II, 3 patients were grade III, and only 1 patient was grade IV. Group II showed 7 patients with a change to grade I, 2 patients were grade II, 1 patient was grade III, and only 1 patient was grade IV. The media wall thickness percentage (%MT), the media wall area percentage (%MS), and arteriole density were significantly higher in groups I and II than in group III. %MS was significantly higher in group II than in group I; no significant differences in %MT and arteriole density could be found between groups I and II.

Conclusions: The PVD in these selected patients with CHD and severe PH who were cared for with a diagnostic-treatment-and-repair strategy is generally reversible, and the changes in PVD in the patients with TGA and VSD were similar to those in the patients with simple left-to-right shunt CHD.

INTRODUCTION

Whether congenital heart disease (CHD) with near-systemic pulmonary arterial pressures is operable remains controversial. Recently, advanced therapies for pulmonary hypertension (PH), including the availability of oral endothelin antagonists (e.g., bosentan and sitaxsentan) and the application of sildenafil (a type 5 phosphodiesterase inhibitor), have become available and have been effective in reducing pulmonary vascular resistance and symptoms in patients with near-systemic pulmonary arterial pressures and previously thought to have irreversible pulmonary vascular disease (PVD) [Dimopoulos 2008; Liu 2010a; Huang 2011]. CHD with near-systemic pulmonary arterial pressures has been successfully corrected at our institution, and early and middle-term results have been obtained [Yamaki 1981; Allcock 2003; Liu 2010b]. Whether the PVD in this subset of patients is reversible remains unknown. We hypothesized that the PVD in these selected patients is still reversible and that the changes in PVD for patients with transposition of the great arteries (TGA) and ventricular septal defect (VSD) are similar to those for patients with simple left-to-right-shunt CHD. Yamaki and Wagenvoort directly compared the histologic characteristics of lung tissue obtained at autopsy from VSD patients with TGA patients and found that the media of muscular pulmonary arteries is significantly thicker in VSD than in TGA [Klepetko 2004]. The present study aimed to compare clinical and pathology features for selected patients with CHD and severe PH by use of a diagnostic-treatment-and-repair strategy and to compare PVD in patients with simple left-to-right-shunt CHD with patients with TGA with VSD. Patients with severe PH received PH treatment to see whether they responded adequately to diagnostic treatment to determine whether they could undergo a repair operation.

Received August 28, 2011; accepted October 26, 2011.

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MATERIALS AND METHODS

Study Participants

Severe PH was defined as a mean pulmonary pressure >50 mm Hg or a systolic pulmonary/systemic pressure ratio >0.8, as derived from cardiac catheterization data of the patients while under general anesthesia. The patients included in this study all had severe PH associated with CHD. From January 1996 to October 2008, 49 patients who were selected for a diagnostic-treatment-and-repair strategy, underwent a complete repair, and had a lung biopsy sample taken during their cardiac operation were included in the study. Ventricular and atrial septal

defects and any patent ductus arteriosus were closed completely, and there were no fenestrations. Group I comprised 38 patients with a simple left-to-right shunt CHD and severe PH. Group II consisted of 11 older patients (>6 months) with PH, of whom 8 had TGA with VSD and 3 had Taussig-Bing hearts. For comparative analysis, we also studied 6 autopsy cases of individuals with an apparently normal cardiovascular system and pulmonary circulation (group III, control group). Patients with trisomy 21 were excluded from this study. The Medical Ethics Committee of Fuwai Cardiovascular Disease Hospital approved the study protocol and waived the need for patient consent for publishing follow-up data about these patients.

Diagnostic Treatment

All patients who underwent complete repair were selected after diagnostic treatment. Thirty-eight patients with simple left-to-right shunt CHD (group I) received conventional PH treatment (digoxin, hydrochlorothiazide, captopril, and prostaglandin E_1), 11 patients with TGA with VSD or with Taussig-Bing hearts (group II) received advanced PH treatment (nitric oxide, sildenafil). Conventional PH treatment lasted 16 to 150 days (mean ± SD, 43.3 ± 25.7 days) for patients with simple left-to-right shunt CHD; prostaglandin E_1 was used in 6 patients. Advanced PH treatment lasted 5 to 21 days (mean, 13.4 ± 5.3 days) and was used in cases of complex CHD. Patients with simple left-to-right shunt CHD with a transcutaneous oxygen saturation increased to 93% were deemed to have responded adequately to diagnostic treatment and to be eligible to undergo operation. Eleven patients who had complex CHD and received diagnostic treatment and who had a transcutaneous oxygen saturation increase of at least 5% (mean, 11.1% ± 6.2%) were deemed as having responded adequately and underwent complete repair. Table 1 summarizes the patient profiles.

Lung Biopsy

The specimens were obtained from the right middle lobe via open lung biopsy in patient groups I and II during cardiac operation and at autopsy in the group with an apparently normal cardiovascular system and pulmonary circulation (group III, control group). Lung tissue was formalin-fixed and paraffin-embedded. Serial sections 5 μm thick were stained with hematoxylin/eosin and with modified orcein for elastic fibers to allow identification of morphologic structures. In each case, the nature of the pulmonary arterial vessel was determined by using the histologic grading system proposed by Heath and Edwards. Specimens were examined with the aid of a microscopy/computer imaging analytical system (Leica Qwin image-processing and analysis application; Leica Microsystems, Beijing, China). We analyzed all specimens quantitatively and calculated values for the following pulmonary arteriole parameters: media wall area percentage (%MS), media wall thickness percentage (%MT), and arteriole density (number of arterioles per square centimeter [APSC]). %MT, %MS, and APSC were defined according to the following formulas:

$$\%MT = \frac{\text{Diameter of Outer Elastic Lamina} - \text{Diameter of Inner Elastic Lamina}}{\text{Diameter of Outer Elastic Lamina}} 100\%;$$

$$\%MS = \frac{\text{Area of Outer Elastic Lamina} - \text{Area of Inner Elastic Lamina}}{\text{Area of Outer Elastic Lamina}} 100\%;$$

$$APSC = \frac{\text{Number of Muscular Pulmonary Arterioles of the Slice}}{\text{Area of the Slice}} 100.$$

Lung biopsy results were not used to guide the decision for operation; all patients deemed to have achieved an

Table 1. Comparison of the Patient Profiles*

	Group I (n = 38)	Group II (n = 11)	Group III (n = 6)	*P*, Group I versus Group II
Sex, n				
Male	21 (55.3%)	7 (63.6%)	4 (66.7%)	.621
Female	17 (44.7%)	4 (36.4%)	2 (33.3%)	.621
Age at biopsy/autopsy, mo	37.4 23.1	33.4 26.9	15.6 16.8	.497
Body weight, kg	12.0 4.0	12.7 4.0	11.8 6.6	.539
Pre-mPAP, mm Hg	70.5 11.9	65.5 9.9		.215
Post-mPAP, mm Hg	30.7 10.9	31.1 11.8		.915
Q_P/Q_S	1.85 1.70	5.52 4.46		.000
Pre-PVR, dyn·s·cm^{-5}	1640.8 712.2	797.9 794.1		.002
Pre-SpO_2, %	90.8 5.1	76.1 6.5		.000
Drug-SpO_2, %	98.3 2.5	86.6 3.9		.000

*Data are presented as the mean SD where indicated. Pre-mPAP indicates preoperative mean pulmonary artery pressure; Post-mPAP, postoperative mean pulmonary artery pressure; Q_P/Q_S, ratio of pulmonary to systemic circulation; Pre-PVR, preoperative pulmonary vascular resistance; Pre-SpO_2, pretreatment transcutaneous oxygen saturation; Drug-SpO_2, transcutaneous oxygen saturation after diagnostic-treatment.

adequate response to diagnostic treatment underwent complete repair. Postoperative pulmonary artery pressure measurements were taken in the operating room at the end of the operation. Cardiac catheterization was carried out while the patient was under general anesthesia. Pulmonary artery pressure and pulmonary vascular resistance were measured preoperatively by the conventional cardiac catheterization protocol and the Fick method. In this study, early mortality was defined as death before hospital discharge or within 30 days of the operation.

Follow-up

All survivors discharged from the hospital were followed up until the end date of the study (November 2009). All survivors underwent chest radiography, electrocardiography, and echocardiography evaluations. The patients were followed up in our outpatient clinic once every 3 months. At the last follow-up, patients were contacted by telephone or interviewed directly in our outpatient clinic. The cardiothoracic ratio, the diameter of the aorta, the diameter of the main pulmonary artery, and the left ventricular end-diastolic anteroposterior diameter of all survivors at 6 to 12 months after the operation were compared with paired preoperative values to evaluate the changes that had occurred in the heart and the great arteries. The cardiothoracic ratio was measured via chest radiography, and aorta, main pulmonary artery, and left ventricular end-diastolic anteroposterior diameters were measured with echocardiography. Patients with persistent PH after discharge were administered oral sildenafil or bosentan for months or even years, and PH was estimated with echocardiography at follow-up.

Data Analysis

All data analysis was performed with SPSS software (version 13.0; SPSS, Chicago, IL, USA). Preoperative and postoperative data for continuous variables were evaluated statistically with paired Student *t* tests. Selected intraoperative and postoperative variables were evaluated with the χ^2 test, the Wilcoxon rank sum test, or the Kruskal-Wallis test, as appropriate. *P* values <.05 were considered statistically significant.

RESULTS

Clinical Results

There were no operative deaths. The pulmonary artery pressure in group 1 regressed significantly from a mean of 70.5 ± 11.9 mm Hg preoperatively to 30.7 ± 10.9 mm Hg postoperatively (*P* = .000); the pulmonary artery pressure in group II also regressed significantly, from a mean of 65.5 ± 9.9 mm Hg preoperatively to 31.1 ± 11.8 mm Hg postoperatively (*P* = .000). All patients recovered well and were discharged. The mean follow-up duration was 117.6 ± 56.6 months (range, 13-167 months). Forty-eight (98%) of 49 patients were in New York Heart Association (NYHA) class I. One patient with residual PH was in NYHA class II and was administered oral sildenafil. The cardiothoracic ratio and the diameter of the pulmonary artery decreased significantly for survivors (*P* = .000), with regression of PH occurring 6 to 12 months after the operation. The neoaorta grew postoperatively (*P* = .000). There were no late deaths or reoperations. No residual VSD or valvular insufficiency occurred, and all patients were in sinus rhythm.

Comparison of PVD

Of the 38 patients in group I with simple left-to-right shunt CHD and severe PH, 31 patients showed a change to grade I, 3 patients were grade II, 3 patients were grade III, and only 1 patient (with a plexiform lesion) was grade IV. Of the 11 patients in group II with ventriculoarterial discordance and severe PH, 7 showed a change to grade I, 2 were grade II, 1 was grade III, and only 1 patient, with a plexiform lesion, was grade IV (Table 2). The majority of the selected patients treated with the diagnostic-treatment-and-repair strategy had reversible and less advanced PVD. %MT, %MS, and APSC in patients with associated PH (groups I and II) were significantly higher than in the control group (group III). %MS was significantly higher in group II than in group I; however, we found no significant differences in %MT and APSC between patients with simple left-to-right shunt CHD (group I) and patients with TGA/VSD or Taussig-Bing hearts (group II) (Table 2).

Table 2. Analysis of Pulmonary Vascular Disease*

				P, Group Comparison		
	Group I (n = 38)	Group II (n = 11)	Group III (n = 6)	I versus II	II versus III	I versus III
%MS, %	52.8 ± 3.4	62.1 ± 11.4	27.0 ± 5.7	.000	.000	.000
%MT, %	37.4 ± 4.5	40.6 ± 5.0	16.7 ± 3.2	.053	.000	.000
APSC	129.7 ± 41.9	114.1 ± 36.5	43.5 ± 20.8	.269	.000	.001
PVD Grade						
I	31 (81.6%)	7 (63.6%)				
II	3 (7.9%)	2 (18.2%)				
III	3 (7.9%)	1 (9.1%)				
IV	1 (2.6%)	1 (9.1%)				

*%MS indicates percent media wall area; %MT, percent media wall thickness; APSC, number of arterioles per square centimeter; PVD, pulmonary vascular disease.

Table 3. Reversal of Pulmonary Vascular Disease in 2 Patients with Plexiform Lesions*

Patient No.	Diagnosis	Time	Age, y	NYHA Class	SPO_2, %	mPAP, mm Hg	Ao, mm	PA, mm
1	TGA/VSD	At operation	6	III	65	62	23	25
		Postoperative 6 mo	6.5	I	100	36	18	21
2	VSD	At operation	7	II	70	65	20	23
		Postoperative 8 mo	7.6	I	100	30	20	21

*NYHA indicates New York Heart Association; SPO_2; mPAP, mean pulmonary artery pressure; Ao, aorta diameter; PA, pulmonary artery diameter; TGA, transposition of the great arteries; VSD, ventricular septal defect.

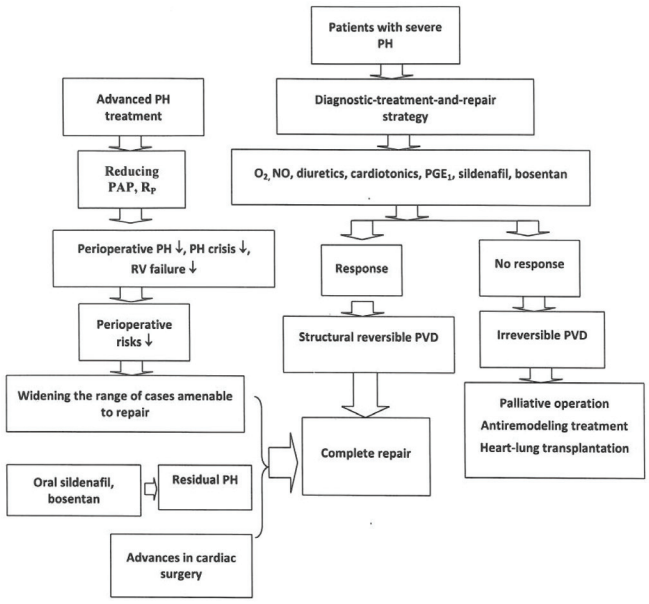
Follow-up data showed reversal of PVD in the 2 patients with plexiform lesions. Both are in NYHA class I. In these 2 patients, the mean pulmonary artery pressure decreased, the diameter of the pulmonary artery decreased, and transcutaneous oxygen saturation became normal (Table 3).

DISCUSSION

The surgical correctability of CHD with severe PH is well known to be highly dependent on the status of the pulmonary vasculature. Patients with VSD who are older than 2 years and patients with complete TGA associated with VSD or double outlet of the right ventricle who are older than 6 months can develop irreversible PVD. Older patients with near-systemic pulmonary arterial pressures and previously thought to have irreversible PVD have been considered ineligible for operation. These older patients are perceived to have irreversible obstructive PVD that puts them at a high perioperative risk, to have a low likelihood of benefiting from the procedure, and to be at high risk of right ventricular failure postoperatively. Right-to-left shunting in patients with PH in fact acts as a safety valve and forms the basis for performing atrial septostomy in patients with PH [Epting 2002; Micheletti 2006; Kurzyna 2007]. If the PVD is irreversible, repair of any intracardiac communication will worsen the prognosis of the patient. Therefore, appropriate assessment of PH is vital to the indication for repair. It remains unclear which patients with severe PH will tolerate surgery, have favorable outcomes, and have a regression of their PH; however, reports of studies of the surgical outcomes for the "inoperable" are few [Anderson 1967; Edgar 1974; Wagenvoort 1974, 1984]. We adopted a diagnostic-treatment-and-repair strategy to select the appropriate patients who might benefit from a complete repair. Patients with less advanced PVD and patients who demonstrate a significant response to such therapy are likely to be considered. These older patients with severe PH were treated diagnostically for approximately 1 or 2 months with oral cardiotonics and diuretics, and, if necessary, with inhaled oxygen, 10 to 20 ppm nitric oxide, and sildenafil or bosentan. Patients whose conditions improved were indicated for complete repair, whereas patients who did not improve were contraindicated for complete repair (Figure). We found that the majority of older patients, who were previously thought to have irreversible PVD, are still eligible for operation. Pulmonary artery pressure and pulmonary vascular resistance for these patients generally regressed postoperatively.

Clinical Comparison of Selected Simple Left-to-Right Shunt CHD Patients with Patients with TGA and VSD

The physiological factors believed to stimulate development of PVD in patients with dextro-TGA and patients with Taussig-Bing anomaly include an increased pulmonary blood flow, transmission of increased pressure to the pulmonary circulation, pulmonary venous hypertension, and systemic arterial hypoxemia [Nakajima 1996]. Calculating pulmonary vascular resistance with the Fick method in patients with dextro-TGA and in patients with Taussig-Bing anomaly is inaccurate. First, the pulmonary arterial oxygen saturation difference is usually narrow; hence, even minor errors in estimating oxygen saturation lead to major errors in estimating the pulmonary blood flow. Second, given that most of the bronchial collateral flow enters the peripheral pulmonary artery distal to the sampling site, the contribution of the bronchial flow to oxygen saturation is not taken into consideration when the pulmonary blood flow is calculated. The calculated pulmonary vascular resistance is minimal or underestimated because



Diagnostic-treatment-and-repair strategy. PH indicates pulmonary hypertension; PAP, pulmonary artery pressure; R_P, pulmonary resistance; NO, nitric oxide; PGE_1, prostaglandin E_1, RV, right ventricle; PVD, pulmonary vascular disease.

Table 4. Clinical Comparison of Selected Patients with Simple Left-to-Right Shunt Congenital Heart Disease (CHD) with Patients with Transposition of the Great Arteries (TGA) and Ventricular Septal Defect (VSD)*

	Simple CHD	TGA/VSD
Physiological factors	Pulmonary blood flow, transmission of increased pressure to the pulmonary circulation, pulmonary venous hypertension	Pulmonary blood flow, transmission of increased pressure to the pulmonary circulation, pulmonary venous hypertension, systemic arterial hypoxemia
Irreversible time	>2 y, acyanotic	>6 mo, cyanotic
Oxygen saturation in PA	Low	High
Q_P/Q_S	Low	High
PVR	High	Low
PVR calculated by Fick method	Accurate	Inaccurate
Degeneration of LV	No	Maybe
Eisenmenger syndrome	Cyanotic	More severely cyanotic
Natural history	4 or 5 decades	32% survive 1 y
Mode of death	Complications of Eisenmenger syndrome	Heart failure
Urgency for operation	Not so urgent	More urgent

*PA indicates pulmonary artery; Q_P/Q_S, ratio of pulmonary to systemic circulation; PVR, pulmonary vascular resistance; LV, left ventricle.

the measured value for the difference in arteriovenous oxygen saturation is inaccurately low and the calculated pulmonary blood flow is greater than the actual flow [Nakajima 1996; Allcock 2003]. The pulmonary vascular resistance calculated for the patients in our study was generally low, maybe because of errors in calculation. It is well known that survival prospects are poor for patients with TGA without treatment. In patients with TGA and VSD, the rate of early survival is 91% at 1 month, 43% at 5 months, and 32% at 1 year [Liebman 1969]. The mean survival time for patients who undergo an arterial switch operation and for patients with TGA/VSD and an increased pulmonary blood flow and pulmonary vascular resistance were 96.9 ± 1.8 months and 11.1 ± 2.4 months, respectively. Kaplan-Meier curves and log-rank test results (^{2} = 159.2; P < .000) showed that the survival rate of patients who underwent an arterial switch operation was much higher than that of patients who did not undergo this surgery. Repair of TGA and VSD in patients with severe PH is more imperative than repair in patients with a VSD or an atrial septal defect and severe PH [Liu 2010b] (Table 4). We assume that medial hypertrophy is suppressed in patients with TGA because of sustained vasodilation caused by the high oxygen saturation of pulmonary arterial blood. Pulmonary vascular resistance is lower in patients with TGA than in patients with VSD because of the vasodilation caused by the high oxygen saturation of pulmonary arterial blood in TGA cases [Liebman 1969].

Reversal of PH Associated with Plexiform Lesions

The plexiform lesion is generally considered a sign that a severe degree of PH has been present and that the PH is usually irreversible. The explanation for the dramatic regression of preoperative severe PH in the 2 patients despite a plexogenic pulmonary vascular pathology may be that the plexiform lesions were not representative of the entire pulmonary vasculature [Wagenvoort 1974, 1984]. Alternative explanations may involve the plexiform lesion. Mooi et al hypothesized that plexiform lesions, which are generally scarce, may have been overestimated in terms of their hemodynamic importance [Humbert 2004]. The potential of the pulmonary capillary bed to develop may also contribute to regression of pulmonary artery pressure. Our understanding of the pulmonary circulation and the mechanisms of PH remains incomplete [Mooi 2006]. As actual structurally irreversible PH is considered, antiremodeling treatment has recently become a potential therapeutic option to reverse pulmonary vascular remodeling and severe PH. The focus of PH treatment is turning toward strategies for inhibiting vascular proliferation and promoting vascular apoptosis to reverse pulmonary vascular remodeling [Huang 2010].

CONCLUSIONS

The PVD in these selected patients with CHD and severe PH treated with a diagnostic-treatment-and-repair strategy is generally reversible, and the changes observed in PVD in patients with TGA with VSD are similar to those in patients with simple left-to-right shunt CHD. The long-term benefits of complete repair for these selected patients with CHD and severe PH need to be demonstrated with a larger number of patients and a longer follow-up.

ACKNOWLEDGMENTS

This study was supported by the Ruikang Hospital Natural Science Foundation (grant no. RKZ201001).

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