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# Lung biopsy findings in previously inoperable patients with severe pulmonary hypertension associated with congenital heart disease☆,☆☆

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ABSTRACT

*Background:* Congenital heart disease with near-systemic pulmonary arterial pressures, previously thought to have irreversible pulmonary vascular disease (PVD), has been successfully corrected at our institution recently. Whether the PVD is reversible remains unknown. This study aimed to examine the nature of the pulmonary arterial vessels in these selective patients.

*Methods:* All patients with congenital heart disease and severe pulmonary hypertension (PH) were selected using Diagnostic-treatment to undergo radical repair ($n=49$). Lung biopsy specimens were obtained during operation. The nature of PVD was determined by Heath–Edwards classification system. All specimens were quantitatively analyzed by calculating percentage media wall area, percentage media wall thickness and arteriole density.

*Results:* Transcutaneous oxygen saturation of all selected patients increased significantly after Diagnostic-treatment ($P<0.001$). There were no operative deaths. Mean pulmonary artery pressure and pulmonary vascular resistance regressed significantly postoperatively ($P<0.001$). The incidence of postoperative PH was 59.2% (29/49). Of 49 selected patients with severe PH, 38 (77.6%) showed grade I change, 5 (10.2%) showed grade II change, 4 (8.2%) showed grade III change and only 2 (4%) showed grade IV change with plexiform lesion. The percentage media wall area, percentage media wall thickness and arteriole density were significantly increased in patients associated with PH than in normal subjects ($P<0.001$). Follow-up data showed the reversal of PVD in these 2 patients with plexiform lesions.

*Conclusions:* The PVD in these selective patients with congenital heart disease and severe PH using a Diagnostic-treatment-and-Repair strategy is generally reversible and these patients are operable in current era.



☆ The authors claim that none of the material in the paper has been published or is under consideration for publication elsewhere, and there are no relationships with industry and financial associations that might pose a conflict of interest in connection with the submitted article. All authors have seen the manuscript and approved to submit to your journal.

☆☆ Congenital heart disease with near-systemic pulmonary arterial pressures, previously thought to have irreversible pulmonary vascular disease (PVD), has been successfully corrected at our institution recently. Whether the PVD is reversible remains unknown. This study aimed to examine the nature of the pulmonary arterial vessels in these selective patients. All patients with congenital heart disease and severe pulmonary hypertension (PH) were selected using Diagnostic-treatment to undergo radical repair ($n=49$). Lung biopsy specimens were obtained during operation. The nature of PVD was determined by Heath–Edwards classification system. All specimens were quantitatively analyzed by calculating percentage media wall area, percentage media wall thickness and arteriole density. Transcutaneous oxygen saturation of all selected patients increased significantly after Diagnostic-treatment ($P<0.001$). There were no operative deaths. Mean pulmonary artery pressure and pulmonary vascular resistance regressed significantly postoperatively ($P<0.001$). The incidence of postoperative PH was 59.2% (29/49). Of 49 selected patients with severe PH, 38 (77.6%) showed grade I change, 5 (10.2%) showed grade II change, 4 (8.2%) showed grade III change and only 2 (4%) showed grade IV change with plexiform lesion. The percentage media wall area, percentage media wall thickness and arteriole density were significantly increased in patients associated with PH than in normal subjects ($P<0.001$). Follow-up data showed the reversal of PVD in these 2 patients with plexiform lesions. The PVD in these selective patients with congenital heart disease and severe PH using a Diagnostic-treatment-and-Repair strategy is generally reversible and these patients are operable in current era.

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## 1. 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 applications 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, previously thought to have irreversible pulmonary vascular disease (PVD) [1–4]. CHD with near-systemic pulmonary arterial pressures has been successfully corrected at our institution and early and middle term results were obtained [5]. Whether the PVD in these subset patients is reversible remains unknown. Data of this subset patient are rare. We hypothesized that the PVD in this selective patients is still reversible. This study aimed to examine the nature of the pulmonary arterial vessels in these selective patients.

## 2. Materials and methods

### 2.1. Subjects

Severe PH was defined as mean pulmonary pressure >50 mm Hg from cardiac catheterization data of patients under general anesthesia. Preoperative cardiac catheterization data were available in all patients ($n=49$). Cardiac catheterization was taken under general anesthesia. Preoperative pulmonary artery pressure and pulmonary vascular resistance were measured by the conventional cardiac catheterization protocol and Fick method. The measurements of postoperative pulmonary artery pressure were taken in operation room at the end of the case. The patients included in this study all had severe PH associated with CHD, previously thought to have irreversible PVD. From January 1996 to October 2008, 49 patients were selected using a Diagnostic-treatment-and-Repair strategy to undergo radical repair ($n=49$, Group I) and from whom lung biopsy was obtained during cardiac operation. In Group I, mean operation age was 36.5±23.8 months (range, 8 to 96), mean operation body weight 12.2±4.0 kg (range, 6 to 20), 29 males and 20 females, 44 in WHO class II, 5 in WHO class III. The patient profile is given in Table 1. Patients with 21 trisomy were excluded from this study.

For comparative analysis, autopsy cases of apparently normal cardiovascular system and pulmonary circulation were studied in Group II ($n=6$, control Group). In Group II, mean age was 20.8±13.5 months (range, 9 to 48), mean body weight 11.2±3.8 kg (range, 8 to 16), 4 males and 2 females.

### 2.2. Diagnostic-treatment

Inhaled oxygen test was completed in 38 patients. Inhaled oxygen test was deemed as positive when mean pulmonary arterial pressure deceased 20% when 100% oxygen was inhaled for 20–30 min. Inhaled oxygen test was positive in 10 (10/38, 26.3%), negative in 28 (28/38, 73.7%). We did not use inhaled oxygen test to assess the reversibility of the PH. Otherwise, we adopted a Diagnostic-treatment to assess the reversibility of the PH. All patients who underwent radical repair ($n=49$) were selected using Diagnostic-treatment. 38 patients received conventional PH treatment (Digoxin, Hydrochlorothiazide, Captopril and Prostaglandin $E_1$ iv), 11 received advanced PH treatment (Nitrogen oxide, Sildenafil and Bosentan). Duration of conventional PH treatment lasted 16 to 150 days in simple CHD with left-to-right shunts, including the use of Prostaglandin $E_1$ in 6 patients. Advanced PH treatment lasted 5 to 21 days in complex CHD. Patients with simple CHD with left-to-right shunts whose transcutaneous oxygen saturation increased to 93% or more were deemed as adequate response to Diagnostic-treatment and operable. Complex CHD was more difficult to evaluate because of cyanosis. In our study, 11 patients with complex CHD received Diagnostic-treatment whose transcutaneous oxygen saturation increased at least 5% (11.1%±6.2%) were deemed as adequate response and underwent radical repair. The exact treatment patients received is presented in Table 1.

### 2.3. Lung biopsy

The specimens were obtained from the right middle lobe by open lung biopsy in Group I patients during cardiac operation and at autopsy in Group II (control Group) patients with apparently normal cardiovascular system and pulmonary circulation. Lung tissue was formalin-fixed and paraffin-embedded. Serial 5-μm-thick sections were stained with hematoxylin and eosin and modified orcein for elastic fibers to allow identification of morphologic structures. In each case, the nature of the pulmonary arterial vessel was determined using the histologic grading system proposed by Heath and Edwards. Specimens were examined under the microscope-computer image analytical system (Leica QWin image processing and analysis application). All specimens were quantitatively analyzed and the parameters of pulmonary arterioles, including percentage media wall area (%MS), percentage media wall thickness (%MT) and arteriole density (arterioles per square centimeter, APSC), were calculated. %MT, %MS, and APSC are defined as following formulas:

$$\%MT = [(\text{diameter of outer elastic lamina} - \text{diameter of inner elastic lamina}) / (\text{diameter of outer elastic lamina}] \times 100\%;$$

$$\%MS = [(\text{area of outer elastic lamina} - \text{area of inner elastic lamina}) / \text{area of outer elastic lamina}] \times 100\%;$$

$$APSC = (\text{number of muscular pulmonary arterioles of the slice} / \text{area of the slice}) \times 100.$$

Lung biopsy was not used to guide operability, all patients who were deemed as adequate response to Diagnostic-treatment underwent radical repair.

### 2.4. Follow up

All patients discharged from the hospital were followed up to the end date of the study (November, 2009). The patients were directly interviewed in our outpatient clinic. All patients were investigated with X-ray chest film, electrocardiogram and echocardiogram.

Informed consent was obtained for all procedures, usually from the parents, and all research protocols were approved by the Fuwai Hospital Ethics Committee.

### 2.5. Data analysis

Statistical analysis was performed with SPSS version 13.0 software (SPSS Inc, Chicago, Ill). Analysis of continuous variables was performed with the Student $t$ test. A value of $P<0.05$ was considered significant.

## 3. Results

PH treatment, operative, follow-up and pathological results of each patient are presented in Table 1.

### 3.1. Results of Diagnostic-treatment

Transcutaneous oxygen saturation of all patients underwent radical repair selected by Diagnostic-treatment-and-repair strategy increased significantly from pre-Diagnostic-treatment 87.5±8.2 to post-Diagnostic-treatment 95.8±5.6 ($P<0.001$) (Table 2).

### 3.2. Operative results

There were no operative deaths. Mean pulmonary artery pressure regressed significantly from preoperative 69.4±11.6 mm Hg to postoperative 30.8±11.0 mm Hg ($P<0.001$), and pulmonary vascular resistance also regressed significantly from preoperative 1640.8±712.2 dyn s cm$^{-5}$ to postoperative 736.1±290.4 dyn s cm$^{-5}$ ($P<0.001$) (Table 2). Of 49 patients, mean pulmonary artery pressure of 20 (20/49) regressed to normal postoperatively. The incidence of postoperative PH was 59.2% (29/49), mild PH (mPAP 25 to 30 mm Hg) 14.3% (7/49), moderate PH (mPAP 30 to 50 mm Hg) 36.7% (18/49), severe PH (mPAP >50 mm Hg) 8.2% (4/49). All the patients were administered with drugs for PH, 77.6% (38/49) with conventional PH therapy (Digoxin, Hydrochlorothiazide, Captopril and Prostaglandin $E_1$ iv), 22.4% (38/49) with conventional and advanced PH therapy (Nitrogen oxide, Sildenafil and Bosentan). All patients recovered well and were discharged (Table 1).

### 3.3. Follow-up results

Mean follow-up duration was 117.6±56.6 months (range, 13 to 167). 98% (48/49) were in WHO class I. 1 patient with residual PH was in WHO class II, who was administered with oral Sildenafil.

### 3.4. Lung biopsy findings

Of 49 selected patients with severe PH, 38 (77.6%) showed grade I change, 5 (10.2%) showed grade II change, 4 (8.2%) showed grade III