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# Effects of High-Dose Mucosolvin on Lung Functions in Infant Patients with Cardiopulmonary Bypass

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## ABSTRACT

**Background:** Cardiopulmonary bypass may cause serious impairment of lung function. It has been reported that administration of mucosolvin can prevent acute respiratory insufficiency through the improvement of pulmonary surfactant.

**Objectives:** This study aimed to explore the effects of high-dose mucosolvin on infant lungs following cardiopulmonary bypass.

**Methods:** One hundred infants were randomly divided into 2 groups. In Group 1, patients did not receive any respiratory drug perioperatively and underwent conventional mechanical ventilation postoperatively. In Group 2, patients were administered mucosolvin (15 mg/kg per day) perioperatively, and doxofylline (15 mg/kg per day) and ipratropium bromide solution (200 μg) were administrated postoperatively. Mechanical ventilation parameters, pulmonary surfactant-related protein (SP-B), and cytokines were evaluated after induction of anesthesia and 30 minutes, 24 hours, and 48 hours after CPB.

**Results:** At the end of CPB, all PaO2/FiO2 values in Group 2 were higher than those in Group 1. Postoperative SP-B levels in Group 1 decreased significantly compared to the baseline value ($P < .05$). There was no significant difference in hospitalization time between both groups, but both mechanical ventilation time and intensive care unit time of infants in Group 2 were significantly shorter than those in group 1 ($P < .05$).

**Conclusions:** These findings indicate that high-dose mucosolvin has certain protective effects on respiratory functions in infants undergoing heart operations with CPB and that it that has no adverse effects.

## INTRODUCTION

The cardiopulmonary bypass (CPB) procedure is a prerequisite for the treatment of congenital heart disease; however, many factors, including mechanical factors, pulmonary ischemic reperfusion injury, and systemic inflammatory response syndrome (SIRS), can cause changes in respiratory function after CPB that may even induce acute lung injury (ALI). This is more serious for infants who undergo cardiac surgery, and infant mortality related to ALI can reach between 15% and 50% [Haslam 1997; Yamaki 1997; Milot 2001].

It has been reported that administration of mucosolvin between 27 to 34 completed weeks of pregnancy can prevent neonatal acute respiratory distress syndrome (ARDS) [Loaog-Fernandez 2000]. Patients suffering from ARDS are deficient in pulmonary surfactant (PS). After CPB, infants are prone to suffer from respiratory insufficiency and ALI. It remains unclear whether the PS in the infants is lost or deficient. The aim of this study was to test whether mucosolvin can reduce the loss of PS postoperatively and protect pulmonary function.

## MATERIALS AND METHODS

One hundred infants who underwent cardiac surgery between March 2009 and June 2010 were studied. The inclusion criteria for this study were as follows: infants aged less than 1 year who were definitely diagnosed with simple congenital heart disease that involved a left-to-right shunt. The procedure was explained to the guardians of the infants, who signed an informed consent form prior to the surgery. This study was approved by the Xijing Hospital Ethics Committee (NO. 20090210037).

The exclusion criteria were as follows: 1) the coexistence of complications, including pneumonia, heart failure, and systemic disease, among others; 2) a definite history of drug allergy; 3) failure to meet the inclusion criteria after enrollment; 4) serious adverse reactions to Mucosolvin; and 5) inability to continue receiving clinical observation.

Infants that met the inclusion criteria were divided into 2 groups in a randomized and double-blinded manner. Group 1, the control group, had 50 patients with a mean age of 5.23 ± 0.33 months and an average body weight of 5.38 ± 0.62 kg (Table 1); no other respiratory drug was administered to any of the patients in the control group during the perioperative CPB period, and a conventional respirator was used for respiratory assistance after CPB. The parameters for respirator assistance were set as follows: tidal volume, 10-15 mL/kg;

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Table 1. General Patient Demographics*

| | Age, mo | Body Weight, kg | Diseases |
|---|---|---|---|
| Control group (n = 50) | 5.23 ± 0.33 | 5.38 ± 0.62 | VSD50+ASD(18)+PDA(12)+PH(33) |
| Experimental group (n = 50) | 5.51 ± 0.43 | 5.26 ± 0.22 | VSD50+ASD(16)+PDA(10)+PH(36) |

*There was no significant difference in preoperative general information between groups. VSD indicates ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; PH, pulmonary hypertension.

frequency, 20-28 times/min; and positive end-expiratory pressure (PEEP), 3-5 mm Hg. If necessary, a respiratory bag was used for pulmonary inflation and sputum aspiration. Group 2, the experimental group, comprised 50 patients with a mean age of 5.51 ± 0.43 months and an average body weight of 5.26 ± 0.22 kg. Mucosolvin (15 mg/kg per day) was administered orally to these patients preoperatively; the same dosage of mucosolvin (15 mg/kg per day) was given by continuous pumping with a micro-pump intraoperatively and 5 days postoperatively. They received doxofylline (15 mg/kg per day) by intravenous injection and 200 μg ipratropium bromide solution by airway inhalation (4 times per day for 5 days) postoperatively. Each patient underwent surgery with the same set of surgeons, anesthetists, perfusionists, monitoring physicians, and nurses during the trial.

The tested parameters were as follows: 1) respiratory mechanics parameters, including pulmonary static compliance (Cstat), platform pressure (Pplat), and airway resistance (R); 2) SP-B; 3) cytokines, including tumor necrosis factor (TNF)-α) and interleukin-1 (IL-1); and 4) liver and renal function parameters, including glutamic-oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), bilirubin (BIL), creatinine clearance (Cr), and blood urea nitrogen (BUN). The time points for testing these parameters were as follows: 1) baseline values after the induction of anesthesia; 2) 30 minutes after CPB; 3) 24 hours after CPB; 4) 48 hours after CPB; and 5) repeat liver and renal function tests just before discharge. Furthermore, differences in mechanical ventilation times, the duration of time in intensive care unit (ICU), and the duration of hospitalization (in days) between both groups were also compared.

### *Respiratory Mechanics Measurement*

Mechanical ventilation was provided by Type-840 respirators, and the respirator parameters were as follows: tidal volume ($V_T$), 8-15 (mL/kg); inspiratory flow ($V_I$) waveform, square wave; inspiratory/expiratory rate, 1:1.5. Infants in the experimental group were given morphine (0.1 mg/kg) and midazolam (0.1 mg/kg) for sedation and vecuronium bromide (0.1 mg/kg) for muscular relaxation; after stable ventilation was achieved for 10 minutes and the inspiration control key was pressed for more than 1 second, the built-in system for testing respiratory mechanics parameters in the respirator started to measure respiratory mechanics parameters and to test and record hemodynamics parameters.

### *Determination of SP-B, TNF-α, and IL-1*

Arterial blood specimens were drawn from infants in accordance with the required volume intraoperatively and at 6:00 a.m. on the day after CPB under fasting conditions. Samples were immediately centrifuged, and the obtained supernatant was stored in a refrigerator at –20°C. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum SP-B, TNF-α (Yuanye Bio-Technology Limited, Shanghai, China), and IL-1 (Cell Sciences, Canton, MA, USA).

### *Statistical Analysis*

Numeric variables are expressed as mean ± standard deviation (M ± SD), and statistical analysis was performed with SPSS 14.0 for Windows (SPSS, Chicago, IL, USA). Probability values less than 0.05 were considered statistically significant.

## RESULTS

There were no differences in the preoperative demographic data, CPB time, or aorta occlusion time between infants in both groups (Tables 1 and 2, respectively). However, there were changes in the respiratory mechanics parameters of infants in both groups immediately after the completion of CPB; those in the control group changed more significantly (Table 3).

There was mainly a significant decrease of $C_{stat}$ at 1 hour and 24 hours after CPB in comparison to the baseline values ($P < .05$). In the test group, $C_{stat}$ at 1 hour after CPB was significantly lower than its baseline value ($P < .05$). $P_{Plat}$ at 1 hour after CPB and R values at 1 hour and 24 hours after CPB in the control group; additionally, R value at 24 hours after CPB in the test group were significantly higher than the respective baseline values ($P < .05$). $C_{stat}$ at 1 hour after CPB in the test group was significantly higher than that in the control group ($P < .05$), and R values at 1 hour and 24 hours after CPB in

Table 2. Immediate Postoperative Results in Both Groups*

| | CPB Time | Aorta Clamping Time | Mechanical Ventilation Time | ICU Time | Hospitalization Time |
|---|---|---|---|---|---|
| Control group (n = 50) | 63.09 ± 5.69 | 33.31 ± 5.79 | 19.28 ± 4.69 | 3.46 ± 0.48 | 19.58 ± 2.85 |
| Experimental group (n = 50) | 62.08 ± 2.02 | 32.05 ± 6.39 | 17.58† ± 6.88 | 3.02 ± 0.63† | 17.86 ± 1.59 |

*Cardiopulmonary bypass (CPB) time and occlusion time in both groups had no significant difference. ICU indicates intensive care unit.

†Mechanical ventilation and ICU time in the test group were significantly shorter than those in the control group ($P < .05$).

Table 3. Changes in Respiratory Mechanics at Different Time Points in Both Groups*

| | Control Group (n = 50) | | | Experimental Group (n = 50) | | |
|---|---|---|---|---|---|---|
| | Cstat | Plat | R | Cstat | Plat | R |
| Baseline value | 5.46 ± 2.98 | 16.00 ± 4.78 | 53.87 ± 6.81 | 5.48 ± 3.18 | 15.64 ± 3.96 | 51.96 ± 5.77 |
| CPB end | 4.84 ± 1.61 | 16.18 ± 3.82 | 63.79 ± 4.26 | 5.25 ± 1.69 | 16.01 ± 2.99 | 52.90 ± 6.51† |
| One hour after CPB | 4.30 ± 1.56‡ | 21.83 ± 3.33‡ | 68.73 ± 8.89‡ | 5.18 ± 1.62† | 18.08 ± 3.74 | 58.00 ± 9.83† |
| 24 hours after CPB | 4.47 ± 1.25‡ | 18.61 ± 3.98 | 57.25 ± 23.55‡ | 5.36 ± 1.86 | 16.64 ± 4.44 | 54.46 ± 11.15‡ |

*Compared with the baseline values, $C_{stat}$ after cardiopulmonary bypass (CPB) in both groups decreased with different degrees; 1-hour and 24-hour postoperative $C_{stat}$ values in the control group had significant differences in comparison to baseline values ($P < .05$). The postoperative $C_{stat}$ value at 1 hour in the test group was significantly lower than the baseline value; the 1-hour and 24-hour postoperative R values in the control group, as well as the 24-hour postoperative R value in the test group were significantly higher than the baseline values; the 1-hour postoperative $C_{stat}$ value in the test group was significantly higher than in the control group ($P < .05$); and the 1-hour and 24-hour postoperative R values in the test group were significantly lower than those in the control group ($P < .05$).

†In comparison to the control group ($P < .05$).

‡In comparison to the baseline value ($P < .05$).

the test group were significantly lower than those at the corresponding time points in the control group ($P < .05$).

After CPB, oxygenation parameters in both groups were significantly reduced, and the $PaO_2$ and $PaO_2/FiO_2$ values at the end of CPB were reduced significantly in both groups ($P < .01$; Figure 1). In the control group, $PaO_2/FiO_2$ values at all time points were significantly lower than their baseline values ($P < .05$ to $P < .01$). In the test group, $PaO_2/FiO_2$ values at 1 hour and 24 hours after CPB were significantly lower than the baseline values ($P < .05$) but higher than values at corresponding time points in the control group ($P < .05$). In the test group, $PaO_2/FiO_2$ values at 48 hours after CPB were not significantly different from the preoperative values ($P > .05$); due to different oxygen inhalation concentrations ($FiO_2$), postoperative $PaO_2$ changes were not of statistical significance (Figure 1). There were no differences in hospitalization time between both groups, but mechanical ventilation time and ICU time in infants in the test group were significantly shorter than those in the control group ($P < .05$; Table 2).

After the CPB procedure was completed, BIL, Cr, and BUN values in both groups had no significant changes in comparison to baseline values; however, GOT and GPT values at 24 hours and 48 hours after CPB were significantly higher than the baseline values ($P < .01$); before discharge, GOT and GPT values in both groups returned to normal levels. Compared with the control group, liver and kidney function parameters in the test group had no significant

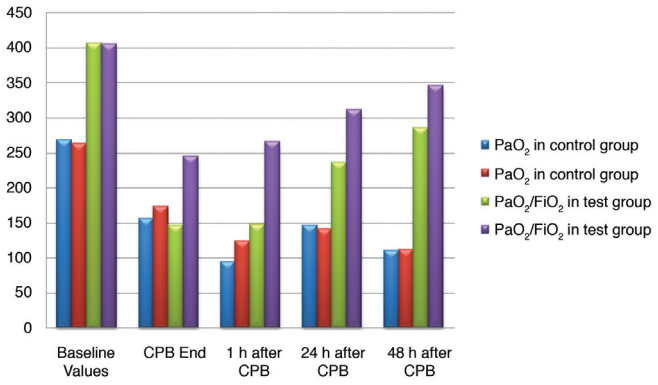


Figure 1. Oxygenation changes at different time points in both groups. Compared with baseline values, both $PaO_2$ and $PaO_2/FiO_2$ values at the end of cardiopulmonary bypass (CPB) were reduced significantly ($P < .01$). In the control group, $PaO_2/FiO_2$ values at all time points were significantly lower than baseline values ($P < .05$ ~ $P < .01$); 1-hour and 24-hour postoperative $PaO_2/FiO_2$ values were significantly lower than baseline values ($P < .05$); 48-hour postoperative $PaO_2/FiO_2$ levels were not significantly different from preoperative values ($P > .05$). In the test group, 1-hour and 24-hour postoperative $PaO_2/FiO_2$ values were significantly higher than those at corresponding time points in the control group ($P < .05$). Due to different oxygen inhalation concentrations ($FiO_2$), postoperative $PaO_2$ changes were not of statistical significance.

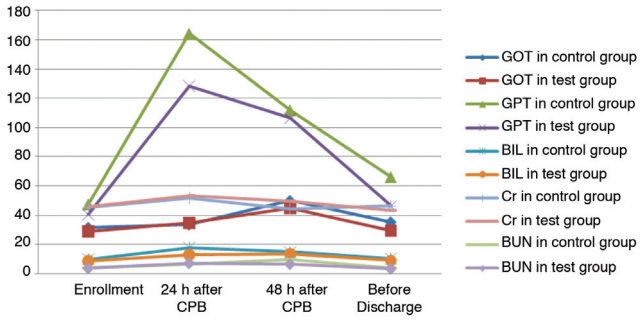


Figure 2. Liver and renal function changes for infants during the perioperative period. Compared with baseline values, 24-hour and 48-hour postoperative glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transanimase (GPT) values in both groups were significantly increased ($P < .01$); at discharge, GOT and GPT values in both groups decreased significantly, and there were no significant differences in comparison to preoperative values ($P > .05$); for other parameters, there were no significant differences in comparison to baseline values or between the 2 groups. GOT and GPT are measured in IU/L; bilirubin (BIL) and blood urea nitrogen (BUN) are measured in mmol/L; creatinine clearance (Cr) is measured in μmol/L.

differences (Figure 2). For infants in both groups, TNF-α and IL-1 during the perioperative period showed no significant changes, but postoperative SP-B in the control group decreased significantly in comparison to its baseline value ($P < .05$; Table 4).

## DISCUSSION

It is currently thought that changes of respiratory function in infants after CPB procedures are mainly caused by the increase in the permeability of pulmonary vessels, in addition to a decrease of PS. Pulmonary ischemic reperfusion injury during CPB may induce injury to pulmonary vessels, and permeability may increase as a consequence in lung capillaries. The generation of oxygen free radicals during CPB can further worsen damage to the pulmonary vessels. Meanwhile, CPB can inhibit PS synthesis and reduce its activity, thereby accelerating oxidative stress and worsening pulmonary insufficiency. Electron microscopy has proven that CPB can damage type II alveolar epithelial cells, decrease PS, and reduce its activity. Many factors cause an increase of alveolar tension and decrease of compliance, which easily induce atelectasis; thus, shear forces between the normal and alveoli affected with atelectasis increase, thereby causing ALI or ARDS in the more severe cases [Laoag-Fernandez 2000; Samir 2002; Gastiasoro-Cuesta 2006; Cui 2009; Fujii 2010].

Mucosolvin contains active agents that dissolve mucus and resist oxidation and inflammation. Furthermore, they promote surfactant generation and alleviate oxidative stress [Farkhutdinov 2010; Wiktorska 2010], which directly affects extracellular free radicals and decreases cytokine and leukotriene levels, prevents the degranulation of monocytes, mast cells, basophils, and other granulocytes, and promotes the generation of PS by type II alveolar epithelial cells.

Previous results have shown that after oral administration of 100-200 mg/kg mucosolvin for 3 or 6 days, type-II alveolar epithelial cells in mice enlarged and lamellated bodies in alveolar tissues increased significantly [Fu 2004]. Oral administration of 200 mg/kg mucosolvin was found to make tritium-labeled palmic acid enter into murine alveoli, and PS synthesis increased at the same time. Histological results demonstrated that after receiving 50 mg/kg mucosolvin by intraperitoneal injection twice a day for 3.5 days continuously, the phosphatide content in the pulmonary tissues of mice was higher than those in the control group.

There are only a few studies on the use of mucosolvin for the prevention of lung injuries in infants after CPB; however, numerous data have showed that mucosolvin can be used to prevent neonatal ARDS if given during the later stages of pregnancy and in premature neonates [Schmalisch 1999; Sweet 1999; Laoag-Fernandez 2000; Fan 2008].

In this study, we found that the PS-related protein SP-B decreased in both groups after CPB and that it decreased more significantly in the control group. Although SP-B in the test group was reduced, there were no statistically significant differences; this may be related to the administration of high-dose mucosolvin during perioperative period. After CPB, the changes in respiratory mechanics in the test group were smaller than those in the control group; this may be related to smaller changes in SP-B levels in the test group. We also found that at the end of CPB and in the early stage after CPB, oxygenation parameters in both groups were significantly lower than preoperative baseline values, which may be related to the decrease of SP-B. All postoperative $PaO_2/FiO_2$ values in the test group were significantly higher than those at the corresponding time points in the control group, which may be related to a smaller degree of variation in SP-B in the test group.

CPB has specific effects on the liver and renal function of infants, with greatly increased values of GOT, GPT, and BIL. In general, however, these changes can spontaneously resolve within a few days of CPB. Our study results also showed that GOT and GPT increased significantly after CPB; however, when compared with the control group, there were no notable changes in the liver and kidney function parameters of infants in the test group. The postoperative range of increase was smaller than that in the control group; this suggests that high-dose mucosolvin has no significant adverse effects on infants after cardiac surgery.

It has been reported that certain cytokines, including TNF-α and IL-1, in the serum of patients with ARDS were overly expressed, and mucosolvin can reduce serum levels of these factors [Su 2004; Li 2010]. However, this study did not replicate these findings. This may be because changes in respiratory function in infants after CPB are mainly related to the decrease in PS, and the correlation between these changes and systemic inflammatory response syndrome after CPB is low.

Our study results showed that mucosolvin has protective effects in the lungs of infants during the CPB perioperative period, and that it has no adverse systemic effects. However, these findings require further validation with a large-cohort trial.

Table 4. Changes in TNF-a, IL-1, and SP-B at Different Time Points in Infants of Both Groups*

| | Control Group (n = 50) | | | Experimental Group (n = 50) | | |
|---|---|---|---|---|---|---|
| | TNF-a | IL-1 | SP-B | TNF-a | IL-1 | SP-B |
| Preoperative | 0.16 ± 0.05 | 25.35 ± 9.38 | 0.15 ± 0.05 | 0.13 ± 0.03 | 24.46 ± 6.24 | 0.14 ± 0.03 |
| 24 hours after CPB | 0.16 ± 0.06 | 27.42 ± 6.13 | 0.12 ± 0.04† | 0.15 ± 0.04 | 25.19 ± 5.38 | 0.13 ± 0.05 |
| 48 hours after CPB | 0.14 ± 0.06 | 29.20 ± 8.46 | 0.13 ± 0.03 | 0.14 ± 0.05 | 27.28 ± 4.17 | 0.14 ± 0.04 |

*For infants in both groups, tumor necrosis factor (TNF)-a and interleukin-1 (IL-1) values during the perioperative period had no significant changes. SP-B indicates pulmonary surfactant-related protein; CPB, cardiopulmonary bypass.

†Compared with baseline value, postoperative SP-B value in the control group were significantly reduced ($P < .05$).

## REFERENCES

Cui Q, Zhou H, Zhao R, et al. 2009. The effects of open lung ventilation on respiratory mechanics and haemodynamics in atelectatic infants after cardiopulmonary bypass. J Int Med Res 37:113-20.

Fan YZ, Wen ZL. 2009. Efficacy of different dosages of ambroxol hydrochloride in the prevention of neonatal respiratory distress syndrome [in Chinese]. Zhongguo Dang Dai Er Ke Za Zhi 11:771-2.

Farkhutdinov UR, Farkhutdinov RR, Petriakov VV, Farkhutdinov ShU, Mirkhaidarov AM. 2010. Effect of mucolytic therapy on the production of reactive oxygen species in the blood of patients with an exacerbation of chronic obstructive pulmonary disease [in Russian]. Ter Arkh 82:29-32.

Fu XM, Yu JL, Liu GX, Deng B. 2004. Comparison of the effect of ambroxol and dexamethasone on the expression of pulmonary surfactant proteins in the fetal rat lungs [in Chinese]. Zhonghua Er Ke Za Zhi 42:450-3.

Fujii M, Miyagi Y, Bessho R, Nitta T, Ochi M, Shimizu K. 2010. Effect of a neutrophil elastase inhibitor on acute lung injury after cardiopulmonary bypass. Interact Cardiovasc Thorac Surg 10:859-62.

Gastiasoro-Cuesta E, Alvarez-Diaz FJ, Rey-Santano C, Arnaiz-Renedo A, Loureiro-Gonzalez B, Valls-i-Soler A. 2006. Acute and sustained effects of lucinactant versus poractant-alpha on pulmonary gas exchange and mechanics in premature lambs with respiratory distress syndrome. Pediatrics 117:295-303.

Haslam PL, Baker CS, Hughes DA, et al. 1997. Pulmonary surfactant composition early in development of acute lung injury after cardiopulmonary bypass: prophylactic use of surfactant therapy. Int J Exp Pathol 78:277-89.

Li L, Wang LX, Dong YQ. 2010. Effects of tetramethylpyrazine on fractalkine and tumor necrosis factor-alpha expression in patients with chronic pulmonary heart disease [in Chinese]. Zhongguo Zhong Xi Yi Jie He Za Zhi 30:373-5.

Laoag-Fernandez JB, Fernandez AM, Maruo T. 2000. Antenatal use of ambroxol for the prevention of infant respiratory distress syndrome. J Obstet Gynaecol Res 26:307-12.

Milot J, Perron J, Lacasse Y, Létourneau L, Cartier PC, Maltais F. 2001. Incidence and predictors of ARDS after cardiac surgery. Chest 119:884-8.

Samir K, Riberi A, Ghez O, Ali M, Metras D, Kreitmann B. 2002. Delayed sternal closure: a life-saving measure in neonatal open heart surgery; could it be predictable? Eur J Cardiothorac Surg 21:787-93.

Schmalisch G, Wauer RR, Böhme B. 1999. Changes in pulmonary function in preterm infants recovering from RDS following early treatment with ambroxol: results of a randomized trial. Pediatr Pulmonol 27:104-12.

Su X, Wang L, Song Y, Bai C. 2004. Inhibition of inflammatory responses by ambroxol, a mucolytic agent, in a murine model of acute lung injury induced by lipopolysaccharide. Intensive Care Med 30:133-40.

Sweet DG, Halliday HL. 1999. Current perspectives on the drug treatment of neonatal respiratory distress syndrome. Paediatr Drugs 1:19-30.

Wiktorska JA, Lewinski A, Stuss M, Nowak D, Pietras T, Sewerynek E. 2010. Effects of certain antioxidants on lipid peroxidation process in lung homogenates of L thyroxine-receiving rats. Neuro Endocrinol Lett 31:137-46.

Yamaki S, Abe A, Sato K, Takahashi T. 1997. Microatelectasis in patients with secundum atrial septal defect and its relation to pulmonary hypertension. Jpn Circ J 61:384-9.