# Late clinical manifestations of mitral valve disease and severe pulmonary hypertension in a patient diagnosed with premature closure of foramen ovale during fetal life

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Case report

***Background:*** **The patency of foramen ovale (FO) in fetal circulation is very important, and premature closure of FO could be associated with several pathological conditions.**

***Methods:*** **We report a patient in whom premature closure of FO in fetal life was associated with late clinical onset of mitral valve stenosis and subsequent development of irreversible pulmonary hypertension (PH).**

***Results:*** **The patient showed persistent PH after birth, which completely regressed at the age of 8 months. However, the patient developed heart failure due to mitral valve lesions (hammock valve) at the age of 11 months and underwent artificial valve replacement. The patient subsequently developed severe PH, which was refractory to anti-PH therapy with sildenafil and bosentan in addition to home oxygen.**

***Conclusions:*** **This case illustrates that mitral stenosis can be overlooked during early neonatal life, and thus emphasizes the need for close follow-up for potential existence of mitral stenosis and later clinical manifestation in patients with premature FO closure even when initial careful examination of the mitral valves does not indicate any abnormalities. In addition, premature closure of FO could cause pulmonary vascular disease, which may lead to later development of irreversible PH.**

***World J Pediatr 2011;7(2):182-184***

***Key words:*** **foramen ovale;**
**mitral valve;**
**premature closure;**
**pulmonary hypertension**

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doi: 10.1007/s12519-011-0276-6


## Introduction

Premature closure of foramen ovale (FO) could result in several pathological conditions associated with right heart volume overload or left heart volume underload, including right ventricular (RV) failure, fetal hydrops, supraventricular tachycardia, and left heart obstructive defects.[1] Closure of FO can also result from increased left atrial (LA) pressure due to cardiac disease with left ventricular (LV) inflow obstruction, such as aortic stenosis, mitral stenosis, or ventricular diastolic dysfunction.[1,2] We report a case in which premature FO closure was associated with late clinical onset of mitral valve stenosis and a later development of irreversible pulmonary hypertension. This case raises several important issues, and could help improve the management of children with premature closure of FO.

## Case report

The patient was transferred to our hospital at the gestational age of 37 weeks with suspected congenital cardiac anomaly. The fetal echocardiogram revealed a small LV cavity with a smaller mitral valve annulus (5.6 mm) compared to that of the tricuspid valve (10 mm)

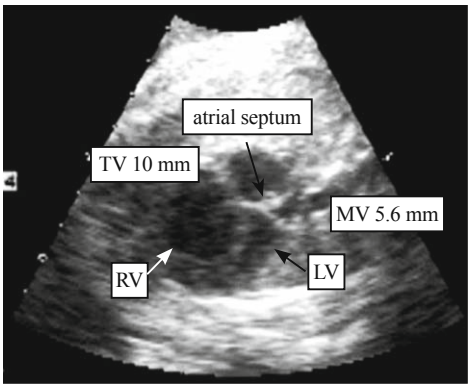


**Fig. 1.** Fetal echocardiogram taken one day before delivery indicated diminished cavity volume of the left ventricle with a small mitral valve annulus. The atrial septum looked thick and closed. TV: tricuspid valve; RV: right ventricle; MV: mitral valve; LV: left ventricle.

(Fig. 1). The diameter of the ascending aorta was also smaller (4.6 mm) than that of the pulmonary artery (10 mm). We made a tentative diagnosis of hypoplastic left heart syndrome (HLHS) with aortic and mitral stenoses complicated with closed (or restrictive) FO (Fig. 1). However, the patient (boy) was born without any symptoms of cardiac or respiratory distress. Although the atrial septum was thick and completely closed, there was a reasonable left heart size: the diameters of the ascending aorta, mitral valve annulus, and LV end-diastolic cavity were 8 mm, 9 mm, and 20 mm, respectively (Fig. 2A). There were no apparent structural abnormalities in the mitral valves or papillary muscles (Fig. 2B), and LV inflow by color/pulse Doppler echocardiography showed no acceleration (Figs. 2C and 2D). Consistent with these echocardiographic findings, the patient showed stable circulatory condition except for the balanced pulmonary hypertension (PH) evidenced by increased flow velocity of tricuspid regurgitation (TR), which persisted for a week after birth even on oxygen therapy. PH of the patient gradually decreased to the levels of 40-50 mmHg (60%-70% of systemic blood pressure) thereafter, and the patient was discharged from the hospital 23 days after birth, and treated with oral administration of a vasodilator (beraprost) and home oxygen therapy.

During the follow-up at the outpatient clinic, PH gradually regressed, and finally normalized at the age of 8 months. Chest X-ray also showed normal cardiac size (Fig. 3A). However, the patient developed heart failure due to mitral valve stenosis (Fig. 4A; peak LV inflow velocity of 2.1 m/s and mean velocity of 1.2 m/s) and regurgitation of grade III (Fig. 4B) at the age of 11 months (Chest X-ray also showed cardiomegaly; Fig. 3B). There was no evidence of PH (no TR and round-shape interventricular septum). At the age of 14 months, the patient underwent mitral valve replacement by a 19 mm artificial valve. There was still no TR at surgery, but mildly elevated pulmonary artery pressure was suspected from the emerging pulmonary regurgitation (PR) and its pressure gradient of 25 mmHg. Operative finding indicated hammock valve with all chordae fused together. Postoperative course was uneventful, but mild degree of PH was suspected on echocardiography (Fig. 4C); the inter-ventricular septum was not completely round during systole in short axis view (there was no TR or PR). The patient subsequently developed severe PH three months after surgery, characterized by increased TR flow velocity (4 m/s) and dilated right ventricular cavity. Cardiac catheterization confirmed PH, which was not responsive to inhalation of 100% oxygen (Table), suggesting the possibility of irreversible histopathological changes in the pulmonary arterial bed. The patient did not have any systemic disease possibly causing PH. Although we

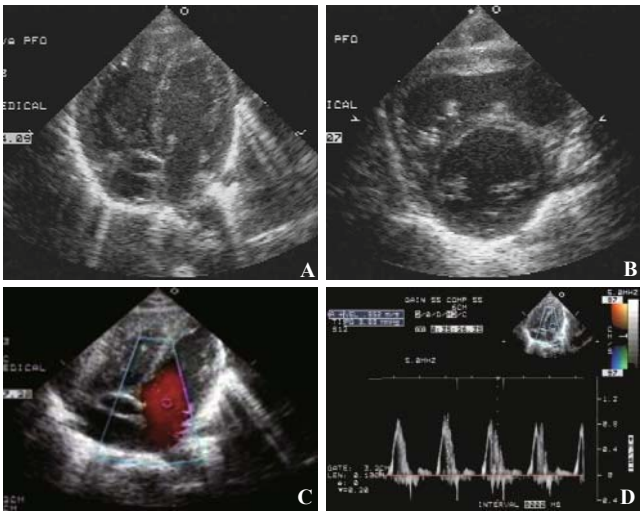


**Fig. 2.** Echocardiogram taken at day one after birth. Four-chamber view indicated reasonable size of left heart (**A**). Mitral valve opening and structure were considered normal (**B**). There was no acceleration in left ventricular inflow by color Doppler (**C**) or pulsed Doppler (**D**).

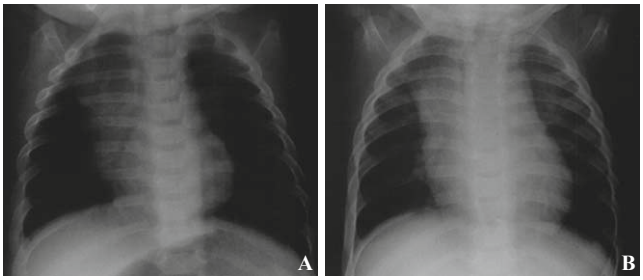


**Fig. 3.** Chest X-ray taken before (**A**) and after (**B**) development of mitral valve stenosis/regurgitation.

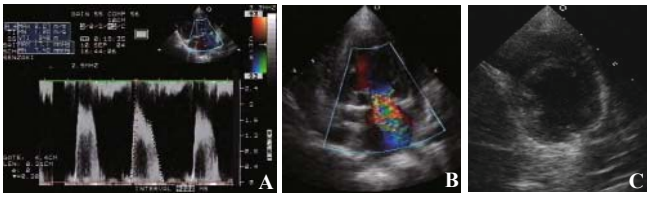


**Fig. 4. A:** pulse Doppler finding indicating mitral stenosis; **B:** color Doppler finding indicating mitral regurgitation; **C:** Short axis view demonstrating only slightly compressed inter-ventricular septum (arrows).

**Table.** Cardiac catheterization findings during room air breathing and inhalation of 100% oxygen

| Variables | Room air breathing | Inhalation of 100% oxygen |
|---|---|---|
| Pulmonary artery pressure (mmHg) | 61/35 (44) | 77/41 (56) |
| Descending aorta pressure (mmHg) | 72/48 (56) | 86/69 (70) |
| Cardiac output (mL/min/m$^2$) | 2.69 | 3.37 |
| Pulmonary artery resistance (units×m$^2$) | 13.75 | 13.92 |
| Pulmonary arterial wedge pressure (mmHg) | 7 | 9 |
| Left ventricle end-diastolic pressure (mmHg) | 8 | No data |

Numbers in parentheses are mean values. Left and right pulmonary arterial wedge pressures were identical.

could not completely rule out the possibility of multiple small pulmonary thrombi as a cause of PH, the patient had no evidence of thrombus formation or coagulation abnormalities. The PH exists to date (4 years of age) despite anti-PH therapy with sildenafil and bosentan in addition to home oxygen.

## Discussion

The present case highlights two important issues. First, mitral valve disease may underlie premature closure of FO, even if the echocardiography indicates no mitral valve lesion during the neonatal period. Second, premature FO closure may cause pulmonary vascular disease that could lead to irreversible PH possibly due to increased fetal pulmonary blood flow.[3]

Because the left heart size normalized after birth, FO closure in our patient was suspected as a secondary event subsequent to increased LA pressure caused by mitral stenosis. It was very difficult to obtain convincing findings of abnormal mitral valve even by a retrospective review of echocardiographic recordings. The present report highlights the importance of meticulous examination of the mitral valve, and close follow-up even if the initial appearance looks normal whenever premature FO closure is evidenced during fetal life.

Another issue that deserves discussion is the association between premature closure of FO and the development of pulmonary vascular obstructive disease. The catheterization data and clinical course (refractoriness to anti-hypertensive therapy) of our patient strongly suggest that established pulmonary vascular obstructive disease underlies PH. Although there is no clear evidence that premature closure of FO is a cause for the development of pulmonary vascular obstructive disease, several lines of evidence suggest this possibility. FO closure inevitably causes increase in pulmonary blood flow due to additional blood flow from the placenta that should enter the LV through FO if FO is patent. Increased oxygen content in the pulmonary artery due to a more oxygenated blood from the placenta may synergistically contribute to an increase in pulmonary flow by lowering pulmonary arterial resistance. In this regard, a 13% increase in oxygen saturation resulted in a 3-fold increase in pulmonary blood flow in fetal lamb.[3] Increased pulmonary flow in the fetus by ductus restriction produces anatomic changes in small pulmonary arteries,[4,5] similar to neonates with idiopathic persistent PH.[6] In addition, more oxygenated blood in the pulmonary artery as a result of FO closure could accelerate the development of pulmonary vascular disease. Furthermore, it is well known that FO closure in fetus with HLHS, a more severe form of LV inflow obstruction than mitral stenosis of the present patient, is associated with PH with histopathological changes in the pulmonary vascular bed including pulmonary veins.[7] The present case may represent a continuum in the degree of pulmonary vascular disease and clinical manifestation of PH due to FO closure in LV inflow obstructive disease.

In summary, it should be kept in mind that mitral stenosis can be overlooked during early infancy. Thus, a close follow-up for potential existence of mitral stenosis and later clinical manifestation is recommended in patients with premature closure of FO even when the initial extensive examination of the mitral valves is normal. In addition, premature closure of FO could cause pulmonary vascular disease, which may subsequently lead to development of irreversible PH.

**Funding:** This study was supported by grants from the Japan Society for the Promotion of Science and Medical Research (no. 8025127), Nipro Corporation, Kawano Memorial Foundation, and Tenshindo Medical Institution.
**Ethical approval:** This study was approved by Saitama Medical University Ethical Committee.
**Competing interest:** None.
**Contributors:** Iwamoto Y wrote the main body of the article under the supervision of Senzaki H. Tamai A, Kawasaki H, and Taketazu M provided advice on medical aspects. Senzaki H is the guarantor.

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*Received September 29, 2009*
*Accepted after revision May 4, 2010*