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Case Report

Management of Functional Pulmonary Atresia with Isoproterenol in a Neonate with Ebstein's Anomaly

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Suzuki, H., Nakasato, M., Sato, S., Komatsu, H. and Hayasaka, K. *Management of Functional Pulmonary Atresia with Isoproterenol in a Neonate with Ebstein's Anomaly.* Tohoku J. Exp. Med., 1997, **181** (4), 459-465 —— Ebstein's anomaly is a rare congenital cardiac anomaly showing significant clinical manifestations with a high mortality rate in the neonatal period. The prognosis of the patient is essentially determined by the severity in morphological changes, however, high pulmonary vascular resistance in the neonatal period may aggravate tricuspid regurgitation and lead to functional pulmonary atresia. We describe a critically ill neonate with morphologically mild Ebstein's anomaly who was successfully managed with intensive care including isoproterenol administration for functional pulmonary atresia. Isoproterenol is a potent pulmonary vasodilator with inotropic and chronotropic effects, and seemed to decrease the pulmonary vascular resistance allowing increased antegrade blood flow to the pulmonary artery and improved cardiac output. If tachycardia is not present, isoproterenol administration is recommended in critically ill neonates with anatomically mild Ebstein's anomaly and no associated cardiac defects. —— isoproterenol; functional pulmonary atresia; Ebstein's anomaly; management

Ebstein's anomaly is a rare congenital cardiac anomaly characterized by downward displacement and dysplasia of the tricuspid valve (Anderson et al. 1979). Patients with Ebstein's anomaly present significant clinical manifestations with a high mortality rate in the neonatal period. The prognosis of the patient is essentially determined by the severity of morphological changes, however, high pulmonary vascular resistance in the neonatal period may aggravate tricuspid regurgitation and lead to functional pulmonary atresia (Boucek et al. 1976; Roberson and Silverman 1989; Celermajer et al. 1992; Nakazawa 1995). We report a critically ill neonate with Ebstein's anomaly who was successfully managed by intensive treatment including isoproterenol administration for func-

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tional pulmonary atresia.

Case Report

A 4,808 g female infant was born to a 34-year-old woman at 39 weeks of gestation by cesarean section because of latent fetal distress. Apgar score at 1 min was 10. Her mother was diagnosed as diabetes mellitus by glucose loading test after delivery. At 4 days of age, cyanosis was noted, and the infant was transferred to our hospital on day 6 under continuous infusion of lipo-prostaglandin E_1 (PGE_1) (5 ng/kg/min) for suspected ductus-dependent cyanotic congenital heart disease. Physical examination showed a moderately cyanotic infant with tachypnea and chest retraction. The heart rate was 130 beats/min and the systolic blood pressure was 94 mmHg. Moist rales were heard over both lungs and a grade 3/6 systolic murmur was at the left lower sternal border. The liver was 4 cm palpable below the right costal margin. Chest radiogram (Fig. 1) showed massive cardiomegaly with a cardiothoracic ratio of 0.78. There were diffuse pulmonary infiltrates and atelectasis of the left lower lobe. Electrocardiogram showed right atrial enlargement. Two-dimensional echocardiogram revealed mild downward displacement of the septal and posterior leaflets of the tricuspid valve, thick and redundant septal and anterosuperior leaflets of the tricuspid valve and mild enlargement of the right atrium (Fig. 2a). The size of the pulmonary artery was normal, but the right ventricular outflow tract was dilated. The pulmonary valve was weakly mobile (Fig. 2b). A secundum atrial septal defect with right-to-left shunting was noted. Pulsed-Doppler examination with the sample volume situated proximal to the pulmonary valve demonstrated retrograde flow from the pulmonary artery to the right ventricle and trivial anterograde flow to the pulmonary artery. Color-Doppler echocardiogram

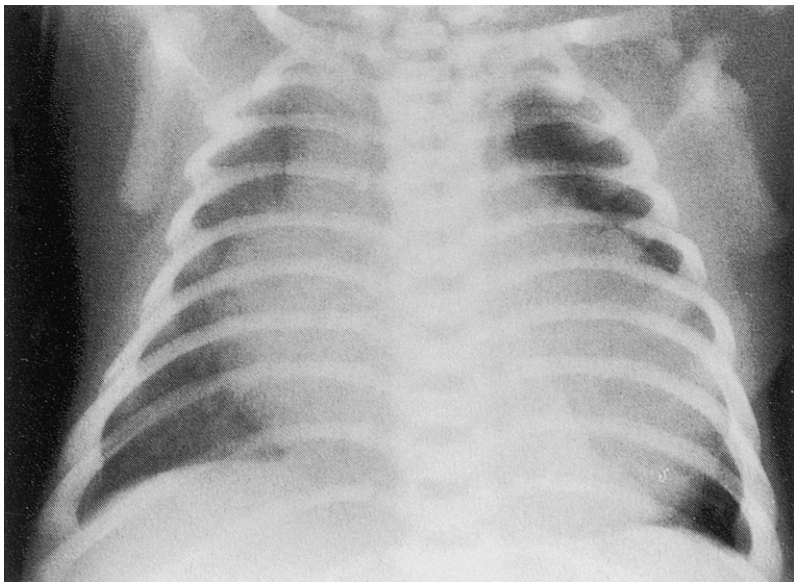

Fig. 1. Chest radiogram at presentation.

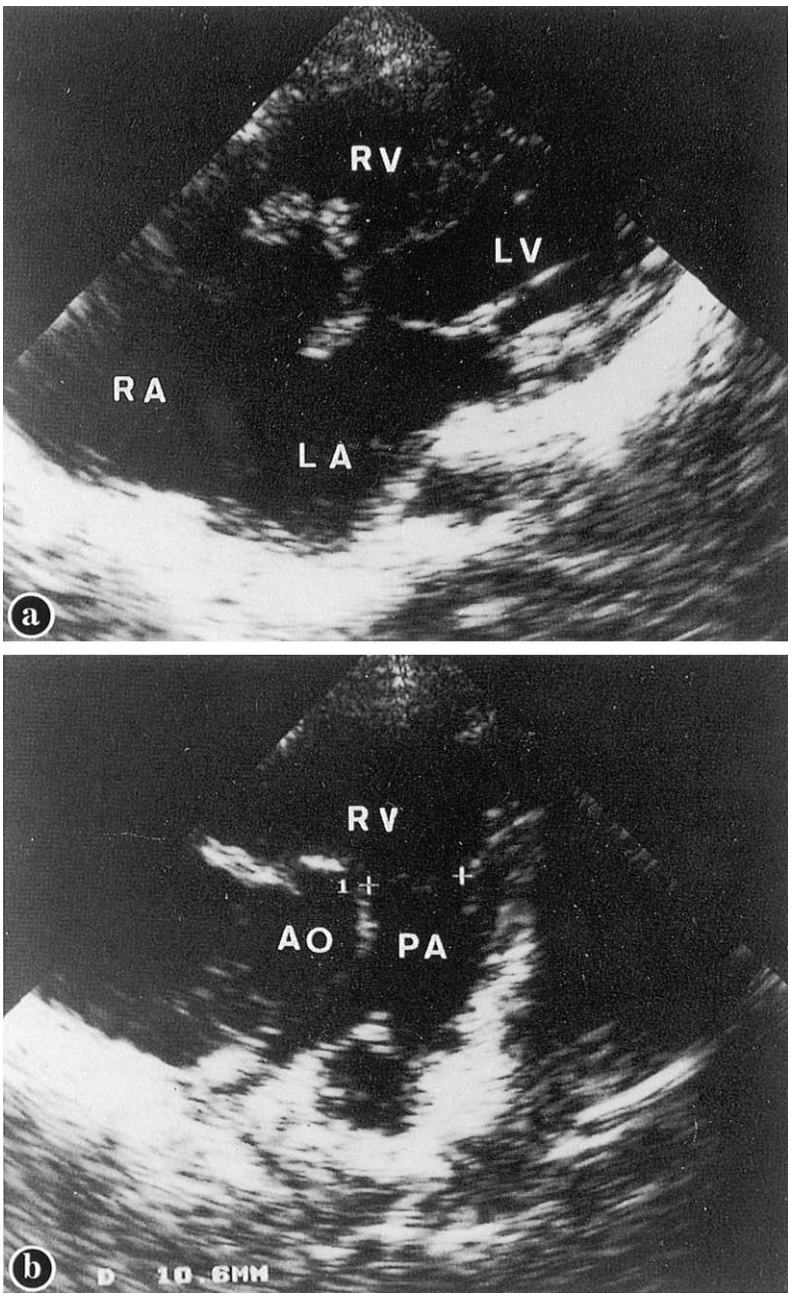

Fig. 2. (a): Two-dimensional echocardiogram, parasternal four-chamber view. Mild downward displacement of the septal leaflet of the tricuspid valve along with thick and redundant septal and anterosuperior leaflets of the valve.
(b): parasternal short-axis view. The size of the pulmonary artery was normal, but the right ventricular outflow tract was dilated. The pulmonary valve was weakly mobile.
AO, aorta; PA, pulmonary artery; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

showed severe tricuspid regurgitation with a peak velocity of 4.2 m/sec. The ductus arteriosus was widely patent with left-to-right shunting. The left ventricle was hypertrophied with the interventricular septal thickness and left ventricular posterior wall thickness, 5 mm and 4 mm, respectively. The left ventricular end-diastolic dimension was 24 mm and fractional shortening 0.41.

The laboratory findings were as follows: white blood cell count 14,400/μl; hematocrit 56.0%; blood glucose 94 mg/100 ml; serum calcium 4.2 mg/100 ml; serum sodium 129 mEq/liter; serum potassium 6.1 mEq/liter; serum chloride 89 mEq/liter; C-reactive protein 2.6 mg/100 ml. Blood gas analysis showed a respiratory acidosis, pH of 7.27, pCO_2 of 61 mmHg and base deficit of 0.2 mEq/liter. Arterial oxygen saturation by pulse oximetry was 87%. Frequent apneic spells with bradycardia led to immediate endotracheal intubation. The patient required ventilator settings of 22/4 cmH_2O at 40 breaths/min with 60% oxygen. Diazepam was used for sedation and therapy with antibiotics and calcium gluconate was begun. Over the following day, cyanosis did not improve and metabolic acidosis (pH 7.32, base deficit 8.8 mEq/liter) developed despite hyperventilation therapy with pCO_2 of 31 mmHg. Pulsed-Doppler echocardiogram demonstrated forward flow with a maximal velocity of 0.5 m/sec at the right ventricular outflow tract. Lipo-PGE_1 was discontinued and continuous intravenous infusion of isoproterenol (0.025 μg. kg^{-1}. min^{-1}) was begun for pulmonary vasodilation, which resulted in an improvement of arterial oxygen saturation to 92% and an increase of anterograde flow velocity in the right ventricular outflow tract to 0.9 m/sec on Doppler ultrasound. The heart rate increased to 180 beats/min. On day 8 the patient showed narrow QRS tachycardia of 250 beats/min, which responded to intravenous bolus of adenosine triphosphate, and therapy with digoxin was started. Color-Doppler echocardiogram showed gradual improvement of tricuspid regurgitation. On day 9, after withdrawal of isoproterenol, arterial oxygen saturation fell to 86% and Doppler interrogation just proximal to the pulmonary valve revealed a reduction in peak velocity to 0.4 m/sec. Isoproterenol was administered again and oxygenation improved rapidly. On day 13, isoproterenol was successfully discontinued. The serum calcium concentration was normalized with oral supplement of calcium lactate by 16 days

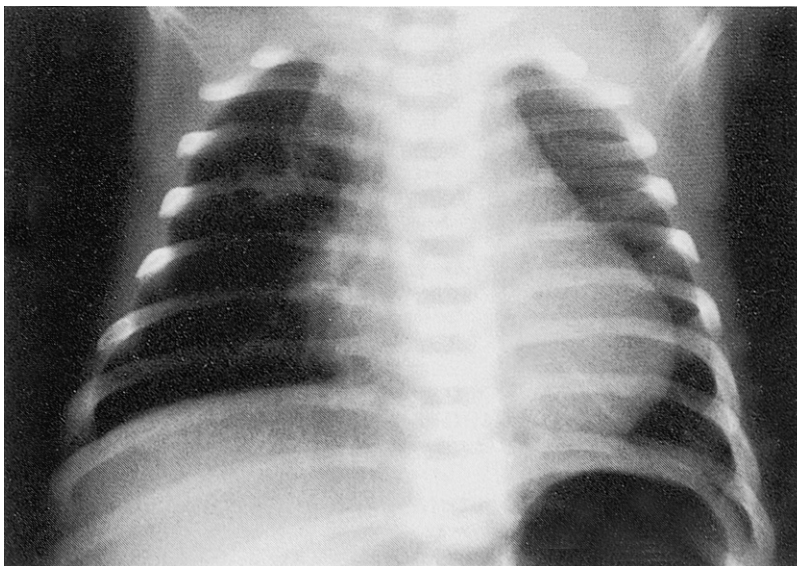

Fig. 3. Chest radiogram at 32 days of age.

of age. On day 19, chest radiogram showed improvement of pulmonary infiltrates and atelectasis of the left lower lobe. Color-Doppler echocardiogram showed no left-to-right shunting via the ductus arteriosus and mild tricuspid regurgitation with a maximal velocity of 2.3 m/sec on day 20. The patient was weaned from the ventilator by day 22. On day 32, chest radiogram showed a reduction in the size of the heart with a cardiothoracic ratio of 0.55 (Fig. 3). The infant discharged at 46 days of age with no signs of congestive heart failure.

At 1 year of age, the patient had no cyanosis, nor did signs of congestive heart failure. Echocardiogram showed moderate tricuspid regurgitation and trivial left-to-right shunting through the ductus arteriosus.

Discussion

Clinical manifestations of Ebstein's anomaly essentially depend on the degree of tricuspid valve deformity and the presence of associated cardiac defects (Roberson and Silverman 1989; Celermajer et al. 1992). Infants with Ebstein's anomaly presenting in the neonatal period, who often have either severe deformity of the tricuspid valve, associated cardiac anomalies, or both, do not respond to medical management and require surgical management (Roberson and Silverman 1989; Celermajer et al. 1992). Generally, the outcome is poor (Roberson and Silverman 1989; Celermajer et al. 1992). However, even patients with mild Ebstein's anomaly and no associated defects have congestive heart failure or cyanosis during this period and frequently improve spontaneously or by supportive management accompanied by a decrease in pulmonary vascular resistance (Roberson and Silverman 1989; Celermajer et al. 1992). Tricuspid regurgitation may be accentuated by high postnatal pulmonary vascular resistance and may impede antegrade blood flow to the pulmonary artery, resulting in functional pulmonary atresia with congestive heart failure (Giuliani et al. 1979; Silberbach et al. 1987; Roberson and Silverman 1989). Cyanosis may result from right-to-left shunting via a patent foramen ovale (Giuliani et al. 1979; Roberson and Silverman 1989).

During the neonatal period, the pulmonary vessels are very reactive and hypoxia and/or acidemia produce marked pulmonary vasoconstriction and result in an increase in pulmonary vascular resistance (Rudolph 1980). In neonates with functional pulmonary atresia, administration of PGE_1 and catecholamines, hyperventilation therapy and oxygen therapy have been employed to maintain pulmonary blood flow and cardiac output (Silberbach et al. 1987; Roberson and Silverman 1989; Yasui et al. 1989; Starnes et al. 1991; Tanaka et al. 1994; Toyohara et al. 1994). Extracorporeal membrane oxygenation may be useful in severely ill patients (Marsh and Shelton 1993).

Pharmacologic therapy should be directed to improving cardiac output and reducing pulmonary vascular resistance in neonates with functional pulmonary atresia. Catecholamines such as dopamine have been used for inotropic support (Roberson and Silverman 1989; Yasui et al. 1989; Tanaka et al. 1994). However,

dopamine and dobutamine have potentially adverse effects on pulmonary vascular resistance (Mentzer et al. 1976; Marter 1993). In contrast, isoproterenol is an inotropic and chronotropic agent with a potent vasodilative action on pulmonary arterioles (Mentzer et al. 1976; Zaritsky and Chernow 1984) and is recommended for neonates with functional pulmonary atresia. Because of its adverse effects including tachycardia and tachyarrhythmias, isoproterenol should not be administered to patients with tachycardia (Zaritsky and Chernow 1984; Marter 1993). To our knowledge, there has been only one neonate with Ebstein's anomaly who responded to isoproterenol administration (Yasui et al. 1989). Vasodilators including tolazoline, phenoxybenzamine or nitroprusside have been used in neonates with functional pulmonary atresia (Adams et al. 1978; Toyohara et al. 1994), however, they do not act specifically on pulmonary arterioles (Artman and Graham 1987) and were effective in few patients (Adams et al. 1978). PGE_1 has been used to maintain pulmonary blood flow by preventing closure of the ductus arteriosus and dilating the pulmonary arterioles (Silberbach et al. 1987; Roberson and Silverman 1989; Yasui et al. 1989; Starnes et al. 1991; Tanaka et al. 1994; Toyohara et al. 1994). Although PGE_1 has been administered to patients with Ebstein's anomaly, it sometimes causes a deterioration of clinical conditions (Toyohara et al. 1994). Increased pulmonary blood flow and transmission of systemic pressure to the pulmonary artery through the ductus arteriosus may impede the decrease in pulmonary vascular resistance and disturb anterograde blood flow from the right ventricle (Silberbach et al. 1987; Nakazawa 1995). Recently, inhaled nitric oxide, a potent selective pulmonary vasodilator, has been used in neonates with pulmonary hypertension (Wessel and Adatia 1995). It seems to be an ideal agent in neonates with functional pulmonary atresia.

As shown in this report, our patient clearly responded to isoproterenol administration. It is probable that isoproterenol decreased the pulmonary vascular resistance allowing increased forward right ventricular output and cardiac output due to the inotropic effect, leading to the improvement of functional pulmonary atresia. This case was also complicated by pneumonia, hypocalcemia and hypertrophic cardiomyopathy, probably associated with maternal diabetes. We could not deny the possibility that those factors may have attributed to pulmonary vasoconstriction and myocardial dysfunction. Isoproterenol administration should be further evaluated in critically ill patients with anatomically mild Ebstein's anomaly and no associated cardiac defects when there is no tachycardia.

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