

Early Transient Neonatal Cyanosis Related to Interatrial Right-to-Left Shunting at an Altitude of 1890 Meters: A Report of Five Cases

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Abstract

Background: We report five term neonates born at an altitude of 1890 meters with transient early neonatal cyanosis due to right-to-left shunting at atrial level through patent foramen ovale.

Case Presentation: The five neonates with no clinical sign or symptom other than marked cyanosis were examined in two neonatal units of Erzurum city. Hematologic and radiologic examinations were normal. Partial oxygen pressure (PO₂) in the arterial blood samples was lower than 45 mmHg in all of the patients, and did not increase more than 15 mmHg in any of the patients after inhalation of 100% oxygen. Echocardiography revealed normal intracardiac structure. The right-to-left interatrial shunt at diastole was detected through a patent foramen ovale in all of these infants. By only observation with no treatment, diastolic right-to-left shunt disappeared in 40.15±9.52 hours. Oxygen saturation was increased from 69.80±9.55 percent to 90.40±8.80 percent. The patients were discharged from the hospital at 5.6±0.4 days of life. Follow up for 6 months revealed no clinical problem in any of the cases.

Conclusion: Transient cyanosis can be seen in the very early neonatal period because of interatrial right-to-left shunting in some healthy term neonates born at an altitude of 1890 meters. Decreased right atrial compliance due to relative hypoxia at that altitude can be speculated to be the causative mechanism.

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Introduction

Cyanosis is one of the most important aspects of neonatal practice. Various disorders can cause

cyanosis in the neonatal period. In neonates, especially in preterm babies, respiratory distress of any origin can cause cyanosis that is highly responsive to oxygen^[1]. Cyanosis of the central

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type with no response to oxygen can manifest in congenital cardiac anomalies or persistent fetal circulation^[2,3].

There occurs an obligatory right to left shunt through patent foramen ovale in fetal life because of the nature of fetal circulation^[4]. After birth, with the first breath, the pulmonary arterial pressure drops and the atrial level shunt reverses until spontaneous closure of oval foramen occurs^[5]. If a right-to-left shunt is detected in a neonate, there is probably some resistance to flow through right cardiac chambers into the pulmonary arterial system^[6].

Important respiratory and cardiovascular changes have been demonstrated in healthy children native to high altitude^[7,8]. At high altitude, oxygen uptake in the lungs is enhanced by increases in ventilation, lung compliance, and pulmonary diffusion. With respect to decreased arterial oxygen tension at high altitude, this seems a useful adaptation^[8]. On the other hand, infants native to high altitude may have persistent right ventricular predominance, right ventricular hypertrophy and dysfunction, and mild pulmonary hypertension associated with increased pulmonary vascular resistance^[8,9]. All of these altitude-related changes may contribute to a decrease in right atrial compliance and may cause diastolic right-to-left shunt at the atrial level.

Herein we report five term neonates born at an altitude of 1890 meters with transient early neonatal cyanosis and diastolic right-to-left shunting at atrial level.

Cases Presentation

Between May 2008 and December 2009, cyanosis of the central type non-responsive to 100% oxygen was detected in a total of 45 term neonates in two different neonatal units in Erzurum, which is the perinatal center of eastern Anatolia. It is a big city of roughly half of a million people living at an altitude of 1890 meters.

Of these 45 patients, 13 were diagnosed with persistent pulmonary hypertension of neonate. Twenty-six neonates were diagnosed with cyanotic congenital cardiac disease. Pulmonary arterio-venous fistula was diagnosed by contrast echocardiography in another patient. The remaining five patients were otherwise healthy neonates with no clinical sign or symptom other than marked cyanosis. They were all born at full term from spontaneous vaginal delivery with full antenatal care and no perinatal problem. Apgar scores were normal at one and five minutes in all patients. All of them were 21 to 36 hours of age at the time of first evaluation. The characteristics of individual cases are given in Table 1.

The mean rate of transcutaneous oxygen saturation was 69.80 ± 9.55 percent. Partial oxygen pressure (PO_2) in the arterial blood samples was lower than 45 mmHg and methemoglobin levels were below 2% in all of the patients. PO_2 did not increase more than 15 mmHg in any of the patients after inhalation of 100% oxygen. The mean partial pressure of carbon dioxide (PCO_2) was 45.40 ± 7.55 mmHg, and none of the patients

Table 1: The characteristics of individual cases

Patients	1	2	3	4	5	Mean
Weight , kg	3.05	3.75	3.48	3.27	3.66	3.44±0.68
Age at first exam, hours	29	21	36	27	30	28.6±5.21
Sat O ₂ at first exam, percent	70	67	73	71	68	69.80±9.55
PO ₂ initially, mmHg	41	36	42	34	44	39.4±6.6
PCO ₂ , mmHg	48	48	41	44	46	45.40 ± 7.55
Hgb, gr	18.2	17.6	18.9	16.9	18.4	18.0 ± 4.4
Hct, percent	54.8	54.1	56.8	52.1	55.6	54.6 ± 5.0
PO ₂ after 100% oxygen, mmHg	48	47	47	40	51	46.6±8.2
Disappearance of R-L shunt, days	3	4	3	3	3	3.2±0.4
Sat O ₂ before discharge, percent	88	91	90	94	89	90.40±8.80
Age at discharge, days	5	7	5	5	6	5.6±0.4

Sat O₂: oxygen saturation, PAP: Pulmonary arterial pressure, PO₂: Partial oxygen pressure, PCO₂: Partial carbon-dioxide pressure, Hgb: Hemoglobin, Hct: Hematocrit.

had a PCO₂ value of greater than 50 mmHg. The mean hemoglobin level was 18.0±4.4 gr/dl, and the mean hematocrit level was 54.6±5.0 percent. Mean plasma glucose level was 66.77±9.04 mg/dl. None of the patients had anemia, polycythemia or hypoglycemia.

There was no clinical or culture support for sepsis. Cranial ultrasound examination yielded normal results. Chest x-rays revealed normal sized and shaped heart shadow with clear lung fields. Echocardiography confirmed normal cardiac anatomies except diastolic right-to-left shunt through a patent foramen ovale in all patients. Pulmonary artery systolic pressure estimated by tricuspid regurgitation jet was 41 mmHg in one of the patients while simultaneous systemic blood pressure was 72 mmHg.

Pulmonary artery systolic pressure was lower than 26 mmHg in the remaining four patients. As the right-to-left intracardiac shunt due to suprasystemic pulmonary artery pressure is the rule in persistent pulmonary hypertension in neonates, the low pulmonary artery pressures in our patients easily excluded the diagnosis of persistent pulmonary hypertension.

Tissue Doppler examination of the lateral tricuspid annulus was performed for the assessment of RV systolic and diastolic function. Early diastolic annular velocity (e') and ratio of early to late diastolic annular velocities (e'/a') were found to be lower than normal values for newborns^[10], while systolic annular velocity (s') and late diastolic annular velocity (a') were within normal limits (Table 2).

We observed those cyanotic neonates in the neonatal intensive care unit with continuous monitoring of vital signs and daily echocardiographic examination. No treatment was begun for any patient. The diastolic right-to-left shunt disappeared in 3.2±0.4 days. The mean oxygen saturation increased to 90.40±8.80 percent. The

patients were discharged from hospital at 5.6±0.4 days of life. At discharge from hospital the mean hemoglobin and hematocrit levels decreased to 16.6±3.9 gr/dl and 49.8±4.6 percent, respectively. Tissue Doppler examination at discharge demonstrated normal values of lateral tricuspid annular parameters. Follow up for 6 months revealed no clinical problem in any of the cases.

Discussion

Fetuses respond to long-term, high-altitude hypoxia with down-regulation of NO synthesis in fetal pulmonary vessels in utero^[11]. In addition, fetal cardiac output is decreased secondary to a decrease in myocardial cell contractile function in response to high altitude long-term hypoxemia^[12]. At high levels of altitude, a baby may be born with a persistence of high pulmonary vascular resistance and right ventricular hypertrophy and dysfunction. The degree of ventricular hypertrophy depends on the vasoconstrictor pulmonary response, the intensity of vascular resistance and the level of altitude, and therefore on the degree of hypoxemia^[13]. Both of these changes may contribute to the decrease in right atrial compliance in the early neonatal period and may cause right-to-left shunting at the atrial level.

Huicho et al recently showed that the molecular signatures of children of chronic mountain sickness (CMS) patients show impaired adaptation to hypoxia^[14]. Based on these findings, the authors suggested that childhood gene expression may predict subsequent CMS. Preliminary data from the highlands also suggest that perinatal exposure to chronic hypoxia increases susceptibility to the later development of maladaptation to life in chronic hypoxia^[15]. Fortunately, most of the

Table 2: Tricuspid lateral annular parameters of patients at initial examination and before discharge

Parameters	Initial examination	Before discharge	P Value*
s', cm/s	6.8 (1.3)	6.9 (1.1)	NS
e', cm/s	6.6 (1.2)	7.5 (1.4)	0.01
a', cm/s	9.0 (1.3)	9.1 (1.3)	NS
e'/a', cm/s	0.73 (0.19)	0.82 (0.20)	0.02

*paired t test was used for comparison of the results

newborns adapt quickly to these environmental conditions and no clinically apparent cyanosis develops. Tibetans, for example, with a longer history of high altitude residence, seem well adapted. They show lower frequency of intrauterine growth retardation, better neonatal oxygenation, lower pulmonary artery pressure and resistance, and lower frequency of CMS.

The cause of right-to-left atrial shunting despite normal intracardiac pressures and normal or near-normal pulmonary function through a patent foramen ovale (PFO) still has not been completely clarified^[16]. The anatomic-embryological features of the right atrium and compliances of the right heart chambers are proposed as causative mechanisms. The right ventricular diastolic dysfunction is thought to be responsible for right-to-left shunting through PFO by some authors^[17]. Early neonatal right ventricular diastolic dysfunction in the absence of pulmonary arterial hypertension is the possible cause of the decrease in right atrial compliance in our cases. Tissue Doppler imaging is demonstrated to be valuable in the assessment of RV functions in infancy^[18]. We assessed the RV diastolic function of our cases by tissue Doppler imaging and found some minor alterations which were normalized before discharge.

Although the altitude of Erzurum city is not sufficiently high to be classified as 'high altitude', relative hypoxia at that altitude might have caused these cardiac changes and finally resulted in marked cyanosis.

The right-to-left shunt at atrial level may be obligatory, like that seen in fetal circulation^[4] or tricuspid atresia, or may be bidirectional. The shunt was bidirectional in all of our cases; the direction is left-to-right at the ventricular systole and right-to-left at the ventricular diastole. It is this mixing that saves the life of many newborns with transposition of the great arteries until palliation or surgery. Actually there occurs some right-to-left shunt through all PFOs, but this shunt is too small to be detected by echo or to cause any desaturation^[19]. It is important for an examiner not to overlook the right-to-left shunt occurring only at diastole. At subcostal coronal view, atrial septum and oval foramen must be assessed carefully frame-by-frame to avoid any diagnostic error.

Conclusion

This report of five cases suggests that in a newborn native to high altitude with cyanosis of the central type, with no response to oxygen, no cardiac structural anomaly including ductus arteriosus or persistent fetal circulation, a clinician should ask for a diastolic right-to-left shunt through a patent foramen ovale. Decrease in right atrial compliance caused by transient right ventricular diastolic dysfunction seems to be responsible for transient cyanosis.

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