

# Successful Management of Pulmonary Arterial Hypertension by Monitoring N-Terminal Pro-B-Type Natriuretic Peptide Serum Levels in a Preterm Infant with Chronic Lung Disease: A Case Report

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## Abstract

We measured the serial changes in N-terminal probrain natriuretic peptide (NT-proBNP) levels in a 6-month-old male infant with chronic lung disease (CLD) complicated by pulmonary arterial hypertension (PAH). The patient was born at the 24th week of gestation weighing 695 g. At 1 month after birth, an echocardiogram confirmed the diagnosis of CLD with PAH. He was treated with inhaled nitric oxide (iNO) and oral sildenafil and discharged from the hospital. At 190 days of age, the patient was readmitted to our department because of a viral upper respiratory infection. At 195 days of age, his respiratory condition worsened with pulmonary edema and his NT-proBNP level was determined to be 10,117 pg/mL. The patient was immediately administered iNO, and his respiratory condition improved, and NT-proBNP levels decreased. However, he experienced repeated severe cyanosis attacks. Before the attacks, his NT-proBNP level was > 1,000 pg/mL. Therefore, we continuously administered iNO until his NT-proBNP level decreased to < 1,000 pg/mL. We safely discontinued iNO administration at 473 days of age. In conclusion, serial change in NT-proBNP is a surrogate marker with prognostic value in patients with PAH associated with CLD.

## Keywords

- ▶ NT-proBNP
- ▶ bronchopulmonary dysplasia
- ▶ chronic lung disease
- ▶ pulmonary arterial hypertension
- ▶ tracheobronchomalacia

Pulmonary arterial hypertension (PAH) complicates the course of chronic lung disease (CLD) in newborns and contributes to later morbidity and mortality during infancy, especially in the context of bronchopulmonary dysplasia (BPD). Earlier studies showed that patients with CLD and later-onset PAH represent a very high-risk population that exhibits increased morbidity and mortality.<sup>1</sup> Among infants with BPD, 20 to 40% develop PAH at some point during their initial hospital course, and PAH is an important risk factor for mortality in this population.<sup>2,3</sup> Echocardiography is often used both to screen for and monitor the progression of PAH in infants with BPD. However, it has been reported that echocardiographic screening at 28 days of life fails to identify many late-developing cases of PAH in

extremely low-birth-weight infants.<sup>4</sup> There are many causes for failed or late diagnosis of PAH in CLD, such as poor imaging due to over-inflation caused by CLD, the complexities of evaluating PAH by echocardiography, and dramatic changes in the hemodynamic status of PAH in CLD due to the patient's unstable respiratory condition. Recently, N-terminal probrain natriuretic peptide (NT-proBNP) levels and BNP levels have been useful in screening for PAH in preterm infants with CLD who are at risk for death.<sup>5,6</sup> However, few studies have elucidated the changes in NT-proBNP levels over time in CLD complicated by PAH. In this report, we determined the serial changes in NT-proBNP levels in a 6-month-old male infant with CLD complicated by PAH.

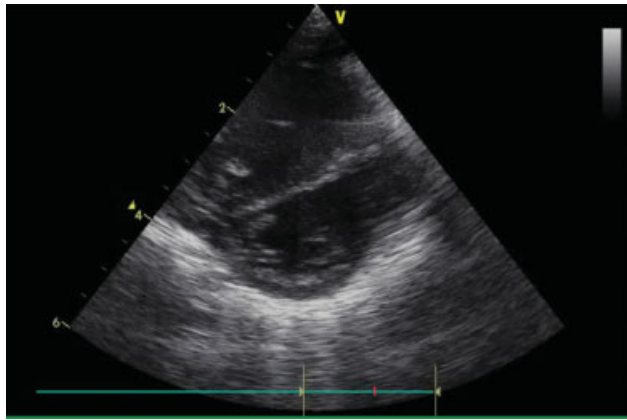
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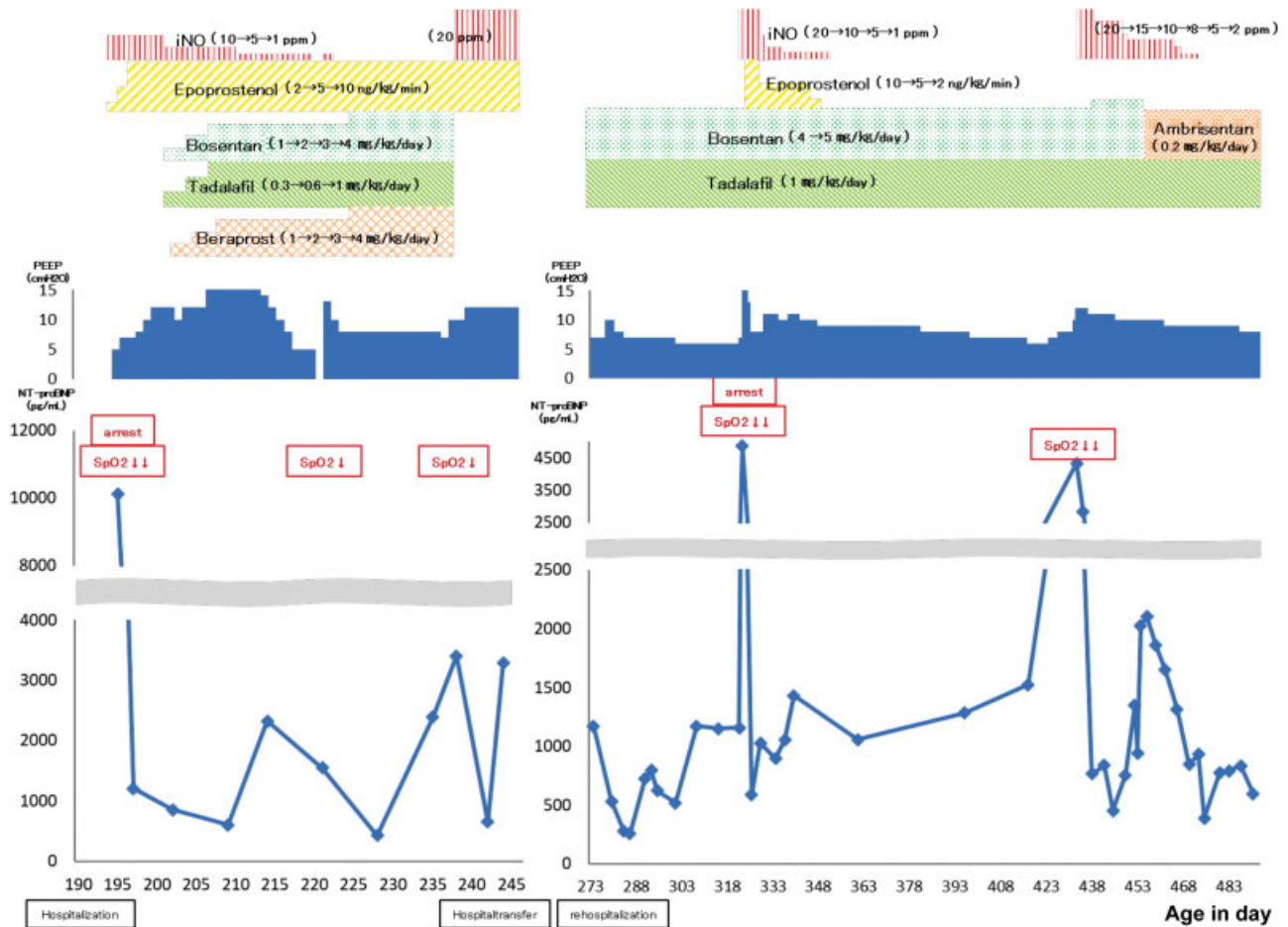


**Fig. 1** Echocardiography (aortic valve short axis image). Observation of flattening of the ventricular septum.

### Patient Report

The patient's mother was referred to our department for premature rupture of the membranes at the 24th week of gestation. An emergency cesarean section was required because of oligohydramnios and indications of fetal distress. The patient's birth weight was 695 g and his Apgar's scores

were 3 and 7 at 1 and 5 minutes, respectively. The patient was immediately intubated with surfactant and admitted to our newborn intensive care unit. His respiratory condition was poor and he could not be weaned from mechanical ventilator support. One month after birth, an X-ray examination was performed, and the patient was diagnosed with CLD. His oxygenation level was poor. An echocardiogram revealed no congenital heart disease, but PAH was observed with right atrial enlargement, right ventricular dilation, and septal flattening (–Fig. 1). He was treated with inhaled nitric oxide (iNO), oral sildenafil, diuretics, and intravenous and inhaled steroids. Progressive improvement in his respiratory condition led to subsequent extubation and, at 169 days of age, his weight had increased to 2,568 g. At this time, the patient was discharged and prescribed supplemental oxygen (1.0 L/min by nasal cannula). At 190 days of age, he was readmitted to our department due to a viral upper respiratory infection. At 195 days of age, his respiratory condition and oxygenation level worsened and he developed pulmonary edema. His peripheral capillary oxygen saturation (SpO<sub>2</sub>) was 67% and he developed cardiopulmonary arrest. We immediately performed successful cardiopulmonary resuscitation. His clinical course is shown in –Fig. 2. His laboratory findings were: white blood cells, 10,070/μL; C-reactive protein level, 0.03 mg/dL;



**Fig. 2** Serial change in NT-proBNP level and the patient's clinical course. Over the course of treatment, there were six instances during which the NT-proBNP levels increased, of which three instances were associated with severe cyanosis attacks. iNO, inhaled nitric oxide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SpO<sub>2</sub>, oxygen saturation of peripheral artery.

and NT-proBNP level, 10,117 pg/mL, as indicated by an Elecsys 2010 analyzer with a chemiluminescent immunoassay kit (Roche Diagnostics, Mannheim, Germany). The protocol for this assay has been previously described.<sup>7</sup> We could not determine the NT-proBNP levels during his stay in the neonatal intensive care unit because echocardiography performed after he was treated with iNO, oral sildenafil, and diuretics showed improvement of the characteristic PAH signs (right atrial enlargement, right ventricular dilation, and septal flattening). After his condition stabilized, we continued the administration of iNO, catecholamines, and epoprostenol and measured his NT-proBNP levels two to three times per week. His SpO<sub>2</sub> level increased and his respiratory condition improved after treatment, with the levels of NT-proBNP decreasing to 1,201 pg/mL at 197 days of age. However, echocardiography indicated that his PAH did not improve; therefore, we added oral bosentan and tadalafil to his treatment regimen and, at 201 days of age, we were able to discontinue the iNO. We were not able to wean the patient from mechanical ventilator support and we transported him to another institution to perform a tracheotomy while maintaining oral bosentan and tadalafil. During his stay at the other institution, there were no episodes of pulmonary hypertension. After the tracheotomy was performed, we performed a bronchoscopy and confirmed a diagnosis of tracheobronchomalacia. High positive-end expiratory pressure (PEEP) therapy was started for the tracheobronchomalacia and the patient's respiratory condition was improved. We then started to wean him from mechanical ventilator support. At the age of approximately 300 days, when the PEEP setting was decreased from 7 to 6 mm Hg, the patient's NT-proBNP level slightly increased to 1,171 pg/mL at 308 days of age.

However, at 323 days of age, he suddenly experienced a severe cyanosis attack (after crying), and the suspected cause was PAH or uncontrolled tracheobronchomalacia. Cardiopulmonary resuscitation was initiated and iNO, catecholamines, and epoprostenol were administered. High PEEP therapy was performed for tracheobronchomalacia which was difficult to control. Furthermore, the patient experienced repeated severe cyanosis attacks at 427 days of age after ending iNO therapy. His NT-proBNP levels were slightly increased and were always > 1,000 pg/mL when tracheobronchomalacia was hard to manage and he exhibited unstable respiratory conditions. We continued to administer iNO even when the NT-proBNP values were < 1,000 pg/mL. At 454 days of age, the patient's NT-proBNP value had slightly increased and we suspected the re-emergence of an unstable respiratory condition due to tracheobronchomalacia. After we maintained 10 mm Hg PEEP, his NT-proBNP level decreased. He was subsequently weaned from iNO therapy and his medication was changed from bosentan to ambrisentan. Subsequently, his NT-proBNP values decreased to < 1,000 pg/mL and iNO therapy was stopped at 473 days of age. His respiratory condition, which was caused by tracheobronchomalacia, gradually stabilized and high PEEP therapy was reduced. When the patient was 2 years and 2 months of age, we performed cardiac catheterization. His mean pulmonary arterial pressure was 24 mm Hg and, under treatment with tadalafil and ambrisentan, there was no evidence of PAH. Furthermore, at 2 years and 4 months

of age, his NT-proBNP value was 350 pg/mL. He was discharged with a home respiratory machine, supplemental oxygen, and ongoing treatment with tadalafil and ambrisentan. After discharge, these therapies will be carefully tapered since infants with CLD have increased risks of mortality due to respiratory failure, unremitting pulmonary hypertension with cor pulmonale, or acquired infection (pneumonia or sepsis).

## Discussion

We determined the serial changes in NT-proBNP levels in a 6-month-old male infant with CLD complicated by PAH retrospectively. Our patient experienced five cyanotic attacks, including two requiring CPA. Before his severe cyanotic attacks developed, the NT-proBNP levels were nearly always slightly increased to > 1,000 pg/mL. The elevated NT-proBNP was a cause of one CPA, while the others might have been due to the PAH. When we failed to wean him off the iNO therapy for PAH twice, his NT-proBNP levels were unstable and exceeded 1,000 pg/mL. Hence, we decided to maintain the iNO therapy until the NT-proBNP dropped to less than 1000 pg/mL after which the iNO was successfully stopped.

NT-proBNP is the precursor of brain natriuretic peptide. This peptide is released from the myocardial tissue of the right and left ventricles when stretched. NT-proBNP is helpful in diagnosing heart failure; however, it does not distinguish between left or right ventricular failure. In the present case, NT-proBNP levels increased with hemodynamic changes associated with PAH and respiratory instability. NT-proBNP and BNP are two different types of peptides but, as reported previously, there is a strong correlation between NT-proBNP and BNP levels during childhood.<sup>8</sup> It is also possible that the measurement results of these peptides reflect the time lag between the time of specimen collection and measurement. Since NT-proBNP has a longer half-life (70 minutes) than atrial NP (12 minutes) or BNP (15 minutes),<sup>9</sup> it is likely less influenced by stress on the heart just prior to blood collection. In adults, NT-proBNP correlates with right ventricle function in PAH and has been shown to be of prognostic value in PAH.<sup>10,11</sup> In the present case, the serial changes in NT-proBNP levels were observed to correlate with the patient's respiratory condition and the hemodynamic changes associated with PAH. While no optimal cut-off value of NT-proBNP, such as 1,000 pg/mL, has been determined, Cuna et al previously reported that a BNP value of > 220 pg/mL might serve as a prognostic marker of all-cause mortality in extremely low-birth-weight infants with BPD-associated PAH.<sup>12</sup> Sugimoto et al<sup>8</sup> reported a strong correlation between BNP and NT-proBNP levels, where  $NT\text{-}proBNP = 9.080 \times BNP^{0.923}$ . We speculated that at a threshold of approximately 2000 pg/mL, NT-proBNP might serve as a prognostic indicator, and that our patient's level (< 1000 pg/dL) might be a safe level at which to control the CLD complicated by PAH. We speculated that the serial changes in NT-proBNP levels observed in this case were associated with the patient's PAH with CLD. Furthermore, high levels of NT-proBNP might be useful in predicting the risk of severe cyanotic attacks.

Echocardiography is often used both to screen for and to monitor the progression of PAH in infants with CLD. Right ventricular structural or functional abnormalities, as determined by an echocardiogram, are used as indirect indicators of PAH, including septal flattening, right atrial enlargement, right ventricular hypertrophy, dilation, and decreased function. Certain quantitative echocardiographic parameters used to screen for PAH, such as tricuspid annular plane systolic excursion, tricuspid regurgitant jet velocity, and/or pulmonary systolic time intervals, are supported by the 2015 guidelines from the American Heart Association.<sup>13</sup> However, these parameters have not been validated in preterm infants. There are several causes for failed or late diagnosis of PH in CLD, such as poor electrocardiogram quality due to CLD-induced over-inflation, as in the present case. While an echocardiogram obtained upon admission revealed severe PAH, as indicated by right atrial enlargement, right ventricular dilation, and septal flattening, we were unable to confirm PAH using echocardiography due to the unstable respiratory conditions and high PEEP therapy. Recently, consensus recommendations for the care of children with bronchopulmonary dysplasia-PAH<sup>14</sup> were published. Serial NT-proBNP levels may be useful in monitoring disease progression/regression and response to therapy and in modulating decision making, but these biomarkers should be used in conjunction with echocardiography rather than in isolation. We suggest that NT-proBNP level may be a useful biochemical marker in predicting the presence of PAH in CLD infants.

Tracheobronchomalacia is an acquired complication of BPD and is more common in infants and children with classic BPD who are treated with prolonged positive pressure ventilation. Tracheobronchomalacia is characterized by abnormally compliant, collapsible central airways and may be associated with barotrauma, chronic or recurrent infection, chronic aspiration, and endotracheal intubation. Tracheobronchomalacia can improve with age, as the tracheal cartilage matures and becomes less compliant.<sup>15</sup> Our patient was diagnosed with tracheobronchomalacia after undergoing a tracheotomy. After this diagnosis, he experienced at least two severe cyanotic attacks induced by PAH. Interestingly, tracheobronchomalacia is easily inducible by PAH, which requires long-term control by a respiratory machine that in turn, sometimes induces unstable respiratory conditions, such as desaturation, hypercapnia, and apneic attack.

## Conclusion

In conclusion, serial changes in NT-proBNP levels can serve as a surrogate marker in place of an electrocardiogram. These changes have been shown to have good prognostic value in patients with PAH associated with CLD. Patients who exhibit higher and unstable levels of NT-proBNP might be developing a serious respiratory and hemodynamic condition. As a result, PAH with CLD should be evaluated carefully and the therapeutic strategy used should be mindful of potential complications, such as tracheobronchomalacia.

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## Conflicts of Interest

The authors of this manuscript do not have any potential, perceived, or real conflicts of interest, including any financial arrangement to disclose.

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