

# Neonatal Thyrotoxicosis and Persistent Pulmonary Hypertension Necessitating Extracorporeal Life Support

Jon Oden, MD\*; and Ira M. Cheifetz, MD, FCCM‡

**ABSTRACT.** We report a case of neonatal Graves' disease involving an infant with severe persistent pulmonary hypertension (PPHN) associated with neonatal thyrotoxicosis that necessitated extracorporeal membrane oxygenation. Hyperthyroidism, although uncommon in the newborn period, has been associated with pulmonary hypertension among adults. The exact mechanisms responsible for this effect on pulmonary vascular pressure are not well understood. Recent studies have provided evidence that thyrotoxicosis has direct and indirect effects on pulmonary vascular maturation, metabolism of endogenous pulmonary vasodilators, oxygen economy, vascular smooth muscle reactivity, and surfactant production, all of which may contribute to the pathophysiologic development of PPHN. Therefore, because PPHN is a significant clinical entity among term newborns and the symptoms of hyperthyroidism may be confused initially with those of other underlying disorders associated with PPHN (eg, sepsis), it would be prudent to perform screening for hyperthyroidism among affected newborns. *Pediatrics* 2005;115:e105–e108. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2004-0554](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-0554); *Graves' disease, persistent pulmonary hypertension of the newborn, extracorporeal life support, extracorporeal membrane oxygenation, shock, respiratory failure, neonate, hypoxia, hypotension, tachycardia, oxygen delivery, thyrotoxicosis, thyroid, hyperthyroidism.*

ABBREVIATIONS. PPHN, persistent pulmonary hypertension; PVR, pulmonary vascular resistance; ECMO, extracorporeal membrane oxygenation; NO, nitric oxide; NOS, nitric oxide synthase; TTF-1, thyroid transcription factor-1; ADMA, asymmetric N<sup>G</sup>,N<sup>G</sup>-dimethyl-L-arginine.

Hyperthyroidism, although uncommon in the newborn period, has been associated with pulmonary hypertension among adults.<sup>1,2</sup> The exact mechanisms responsible for this effect on pulmonary vascular pressure are not well understood. Persistent pulmonary hypertension (PPHN), a major cause of morbidity and death among term newborns,<sup>3</sup> is associated with perinatal asphyxia and perhaps chronic intrauterine hypoxia. Acute hypoxemia induces pulmonary vasoconstriction, whereas

prolonged hypoxia causes hypertrophy of the smooth muscle layer of the small pulmonary arterioles, resulting in persistently elevated pulmonary vascular tone.<sup>3</sup> In either situation, increased pulmonary vascular resistance (PVR) causes a subsequent increase in right ventricular pressure, a patent foramen ovale, and a patent ductus arteriosus in the postnatal period. The resultant, potentially severe, right-to-left shunting is the hallmark of PPHN. Infants with severe PPHN may require extracorporeal membrane oxygenation (ECMO) for adequate oxygen delivery until the elevated PVR resolves.

Although the pathophysiologic development of PPHN is multifactorial, certain conditions, such as congenital diaphragmatic hernia, cyanotic congenital heart disease, and sepsis, predispose infants to elevated PVR. These conditions are associated with hypoxia, acidosis, and elevated levels of proinflammatory cytokines. This environment promotes altered vasodilator synthesis and increased vasoconstriction through several poorly defined pathways. Interestingly, thyrotoxicosis is associated with similar clinical and biochemical findings.

The association between hyperthyroidism and pulmonary hypertension is unclear. Thyroid hormone has dramatic and contrasting effects on the cardiovascular system, inasmuch as hyperthyroidism produces a decrease in systemic vascular resistance but increases in cardiac output, heart rate, and intravascular volume.<sup>4</sup> However, the effects of elevated thyroid hormone concentrations on lung development and function are less well defined. Several studies reported the association between increased thyroid hormone concentrations and pulmonary hypertension.<sup>1,2,4</sup> Marvisi et al<sup>1</sup> demonstrated significantly increased pulmonary artery pressures among patients with untreated hyperthyroidism, compared with control patients. Those investigators postulated that explanations could include both direct and indirect adverse effects of thyroxine on pulmonary physiologic processes, including (1) alterations in the growth and development of pulmonary vascular cells, resulting in changes in vascular dynamics; (2) increased metabolism of endogenous pulmonary vasodilators such as nitric oxide (NO); and (3) decreased surfactant production and function.<sup>5</sup> Thyrotoxicosis also increases metabolic demand, elevates serum concentrations of proinflammatory cytokines, and promotes a state of hypoxia. Elevated thyroid hormone levels may, therefore, contribute to the development of PPHN.

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We report the first successful use of ECMO to support a newborn infant with PPHN associated with Graves' disease. We also present a review of several pertinent studies, to better define the role of thyroid hormone in pulmonary development and function and to characterize the significance of thyrotoxicosis as a potential cause of PPHN.

### CASE REPORT

The patient was a 36[2/7]-week infant, appropriate for gestational age, born to a 17-year-old mother (G<sub>1</sub>P<sub>0</sub>) with poor prenatal care, through normal spontaneous vaginal delivery. Spontaneous membrane rupture (clear amniotic fluid) occurred 4 hours before delivery. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively, and the infant was transferred to the newborn nursery.

At 12 hours of age, the infant developed progressive tachypnea. Chest radiographs revealed a right-sided pneumothorax, a chest tube was placed, and the patient was transferred to a local intensive care unit. The patient's clinical status deteriorated, necessitating intubation and conventional ventilation. Blood gas analysis revealed a continued decline in gas exchange, and high-frequency oscillating ventilation was initiated (fraction of inspired oxygen: 1.0; amplitude: 38; frequency: 8 Hz; mean arterial pressure: 17). Inhaled NO was instituted the next day, at 20 ppm. The infant was transferred to Duke University Medical Center on day of life 4, for additional treatment and evaluation for ECMO. The mother was then noted to have a history of Graves' disease treated with propylthiouracil. The admission physical examination for the newborn revealed a heart rate of 200 beats per minute, an enlarged thyroid gland, and exophthalmos, suggesting neonatal thyrotoxicosis. Thyroid function tests were ordered.

The infant's initial (day of life 1) thyroid function test results included a total thyroxine level of 14  $\mu\text{g/dL}$  and a thyroid-stimulating hormone concentration of 0.88 mIU/mL (normal for age). Maternal prenatal thyroid function and the fetal heart rate in utero are unknown. However, repeat thyroid function testing after admission to Duke University Medical Center showed a free thyroxine level of 6.68 ng/dL (markedly elevated) and a thyroid-stimulating hormone concentration of <0.05 mIU/mL (suppressed). Treatment with propylthiouracil (5 mg/kg per day, divided into doses administered every 8 hours), Lugol's solution, and hydrocortisone (35 mg/m<sup>2</sup> per day) was initiated.

Shortly after admission to Duke University Medical Center, an echocardiogram failed to show evidence of congenital heart disease but confirmed PPHN and demonstrated a severely dilated and hypertrophied right ventricle, with markedly diminished function. The right ventricular pressure was estimated to be suprasystemic. Inotropic management of the PPHN was difficult because of the extreme sinus tachycardia, which was presumably related to the hyperthyroidism. The infant's sinus tachycardia was unresponsive to fluid boluses or improvements in arterial oxygenation. The infant was treated with a dopamine infusion (7  $\mu\text{g/kg}$  per minute). Treatment with  $\beta$ -adrenergic receptor blockers was not initiated for the hyperthyroidism because of concerns regarding complete cardiovascular collapse related to the severe right ventricular dysfunction.

The patient's cardiorespiratory status continued to deteriorate. The sinus tachycardia increased to 235 beats per minute, with a systemic blood pressure of 58/30 mm Hg. Arterial blood gas analysis revealed the following: pH, 7.31; arterial carbon dioxide pressure, 53 mm Hg; arterial oxygen pressure, 50 mm Hg; oxygen saturation, 94%. Ventilator settings were as follows: fraction of inspired oxygen, 1.0; rate, 50 breaths per minute; peak inspiratory pressure, 21; positive end-expiratory pressure, 6. Inhaled NO remained at 20 ppm. Gas exchange could not be improved by altering the conventional ventilator parameters, manually ventilating, or changing to high-frequency oscillatory ventilation. Chest radiographs revealed clear lung fields with normal expansion.

The combination of continued decline in the infant's cardiorespiratory status and the extreme risks of either increasing inotropic support to treat the PPHN and right ventricular failure or adding a  $\beta$ -blocker to treat the hyperthyroidism prompted the decision to proceed with ECMO. Cannulation for venoarterial ECMO occurred without complication (8F arterial cannula and 12F venous cannula).

An esmolol infusion was initiated during the ECMO course

because of persistent tachycardia (185 beats per minute) and hypertension. The ECMO course was otherwise uneventful. Unfortunately, the details of pulmonary arterial pressures were not documented in the patient's records and thus cannot be included in our report. ECMO was continued for 113 hours, at which time the PPHN resolved and decannulation was performed. Concurrently, thyroid hormone levels normalized, and  $\beta$ -blocker therapy was gradually discontinued. The infant was extubated 2 days after decannulation and was weaned to room air the following day. Antithyroid medication, iodide, and hydrocortisone were adjusted to maintain a euthyroid state.

### DISCUSSION

#### Neonatal Thyrotoxicosis

Neonatal thyrotoxicosis is relatively uncommon. The prevalence of Graves' disease among pregnant women has been estimated to be 0.1 to 0.4%, and only 0.6 to 9.6% of infants born to these women develop hyperthyroidism.<sup>5</sup> One possible explanation involves variable maternal thyroid-stimulating immunoglobulin concentrations, which increase in the first trimester but decrease in the third trimester, secondary to the immune suppression encountered during late pregnancy.<sup>5,6</sup> This reduces the concentration of thyroid-stimulating immunoglobulin presented to the fetus and thus limits vertical transmission. After delivery, affected infants may be clinically hyperthyroid for 4 to 20 weeks.<sup>5</sup> Acute management includes antithyroid medications (the thionamides, ie, propylthiouracil and methimazole), glucocorticoids, saturated potassium iodine solutions, and  $\beta$ -blockers. Neonates generally present with symptoms consistent with hyperthyroidism and cardiovascular compromise but have been reported to experience pulmonary vascular and/or parenchymal disease.

#### Thyroid Hormone and Lung Development

Thyroid hormone action in cardiopulmonary development is not fully understood. Knowledge of the presence and activity of nuclear thyroid hormone receptors has proven useful. The concentrations of thyroid hormone receptors in fetal lung tissue have been shown to increase during gestation,<sup>7,8</sup> whereas the majority of thyroid hormone receptors are found within alveolar type II cells among adults.<sup>9,10</sup> The presence and relative concentrations of thyroid hormone receptors during fetal life suggest an important role for thyroid hormone in pulmonary differentiation and function. In fact, several groups have discovered that triiodothyronine stimulates epithelial differentiation and regulates lung structural maturity and alveolar septation.<sup>7</sup> Similarly, Morishige and Joun<sup>11</sup> showed, by inducing hypothyroidism in rat pups, that thyroid hormone was necessary during lung maturation, although only through optimization of glucocorticoid actions. Interestingly, serum thyroglobulin, levels of which are elevated in hyperthyroidism, inhibits the expression of thyroid transcription factor-1 (TTF-1), a necessary factor for normal lung epithelial differentiation and tissue organization.<sup>5,12</sup> Thyrotoxicosis could, secondarily, down-regulate TTF-1 and thus affect regulated pulmonary epithelial cell maturation and development. However, as Losada et al<sup>13</sup> reported, glucocorticoids

also induce TTF-1 expression and may overcome the inhibition produced by increased thyroglobulin levels. Therefore, the data suggesting that thyroid hormones play a primary role in lung development are incomplete.

A recent publication describing a child born with undetectable thyroid hormone concentrations and normal lung function calls into question the importance of thyroxine in pulmonary development.<sup>14</sup> Similarly, Biswas et al<sup>15</sup> demonstrated that triiodothyronine supplementation for premature infants failed to improve clinical outcomes. Some current data thus suggest that thyroid hormone plays an indirect role in lung maturation by augmenting the actions of glucocorticoids and plays only a minor role in directly stimulating epithelial differentiation, which may be overridden through redundant pathways in deficiency or excess states.

During the initial phase of fetal transition to extrauterine life, it is imperative that PVR decrease sharply, allowing adequate perfusion of the alveolar capillaries and subsequent gas exchange. NO, a well-known vasodilator, plays a crucial role in pulmonary vascular expansion during fetal transition.<sup>16</sup> Unlike adult vascular tissue, the pulmonary vasculature in newborn infants displays marked reactivity to variations in NO concentrations, especially in an hypoxic environment.<sup>16</sup> Direct effects of thyroid hormone on endogenous NO metabolism have been investigated. The production of NO is positively controlled through the enzyme NO synthase (NOS). This enzyme can be inhibited by endogenous L-guanine analogs such as asymmetric  $N^G,N^G$ -dimethyl-L-arginine (ADMA), *N*-monomethyl-L-arginine, and *N*-nitro-L-arginine methyl ester.<sup>16,17</sup> Conflicting data exist regarding the effects of NOS inhibitors on pulmonary vasoconstriction and subsequent increases in PVR among adults. Adult patients treated with NOS inhibitors failed to show significant increases in PVR. Similar results were found with isolated pulmonary arterial tissue.<sup>16</sup> However, among human subjects and in other species, there is a significant increase in hypoxic pulmonary vasoconstriction when a NOS inhibitor is introduced. In contrast to children and adults, neonates have proved to be quite dependent on NO to reduce PVR during and immediately after birth. Studies have indicated that basal NO production in fetal and newborn pulmonary circulation is relatively high.<sup>16</sup> A reduction in NO synthesis among newborns has been associated with significant increases in pulmonary vascular pressures, inasmuch as the administration of NOS inhibitors to newborn lambs resulted in increased pulmonary vasoconstriction.<sup>16</sup>

Interestingly, thyroxine up-regulates protein methylase I, the enzyme responsible for the production of the NO inhibitor ADMA.<sup>17</sup> Investigators revealed direct correlations between elevated thyroxine concentrations, elevated ADMA concentrations, and reduced systemic NO synthesis.<sup>17</sup> Unfortunately, that study did not measure pulmonary responses to the reduction in NO synthesis. As indicated by previous work, however, this reduction in NO expression may result in elevated PVR. Because

the production of NO is dependent on an adequate supply of oxygen,<sup>16</sup> the hypoxemia resulting from PPHN may augment NOS inhibitor activity and produce a more profound effect. Although the exact mechanism of PPHN has not yet been defined, a reduction in NO synthesis seems to be a common factor.

Smooth muscle is critical for maintaining vascular tone in certain segments of the pulmonary vascular tree, given the wide fluctuations in vascular and intraalveolar pressures.<sup>18</sup> The contraction of smooth muscle requires interactions between a myosin light chain kinase, calmodulin, and calcium. A detailed review of the interactions between smooth muscle cells and thyroid hormone is beyond the scope of this article. However, several groups have proposed that thyroid hormone reduces smooth muscle contractility by altering the interaction of myosin light chain kinase with calmodulin.<sup>19–21</sup> Unfortunately, the effects of thyrotoxicosis on this relationship remain uncertain, because the vasodilatory effect is obscured by an augmented vasoconstrictor response to norepinephrine in the hyperthyroid state.<sup>22</sup> More focused investigation is warranted.

In the adult lung, thyroid hormone receptors are found principally within type II alveolar cells, which are responsible primarily for surfactant production.<sup>10,23,24</sup> Triiodothyronine augments phosphatidylcholine and thus surfactant production by increasing choline phosphate cytidyltransferase activity.<sup>25</sup> Thyrotoxicosis, however, reduces critical surfactant protein production through 2 indirect mechanisms. First, the hyperthyroid state increases levels of proinflammatory cytokines.<sup>26–28</sup> Transforming growth factor- $\beta$  is associated with the inhibition of surfactant protein expression in human lung cell cultures.<sup>8</sup> Therefore, in the hyperthyroid state, the increase in transforming growth factor- $\beta$  levels causes a lack of adequate surfactant production and release. Similarly, high levels of thyroglobulin associated with increased thyroid hormone production inhibit the expression of TTF-1, which is also involved in the production and turnover of surfactant.<sup>29</sup> Inadequate surfactant production/action results in reduced pulmonary compliance and respiratory distress syndrome. These latter states reduce gas exchange and promote hypoxia, potentially contributing to the pathophysiologic development of PPHN.

#### PPHN and Graves' Disease

The association between PPHN and neonatal Graves' disease is unclear. Thyroid hormone has several important effects on pulmonary development, as indicated by the presence of thyroid hormone receptors on multiple fetal lung cell types. An association between thyrotoxicosis and the development of PPHN is supported by several lines of evidence. First, the increased metabolic demand of hyperthyroidism might result in chronic intrauterine and extrauterine hypoxia, which would predispose infants to PPHN. Second, hyperthyroidism induces a decrease in systemic vascular resistance. To compensate for the decrease in systemic vascular resistance,

thyroxine stimulates the production of NOS inhibitors responsible for reducing NO synthesis and increasing its catabolism. Reductions in NO synthesis may be augmented in the hypoxic environment associated with PPHN and hyperthyroidism. Finally, the negative effect of increased serum thyroglobulin concentrations on TTF-1, a potent activator of pulmonary epithelial differentiation and surfactant production,<sup>30</sup> potentially alters lung tissue organization, reduces gas exchange, and promotes hypoxia. Thyroid hormone affects pulmonary vascular contractility. However, the contrasting effects of thyroid hormone and catecholamines obscure the predominate outcome. Our patient presented not simply with PPHN but also with a pneumothorax, which could be explained on the basis of reduced surfactant production secondary to the effects of hyperthyroidism. The resolution of PPHN paralleled the improvement in thyroid hormone status. This case underscores the clinical importance of thyroid hormone effects on cardiopulmonary function during the perinatal period.

### CONCLUSIONS

Neonatal hyperthyroidism can be associated with significant cardiopulmonary morbidity. We report the first case of neonatal Graves' disease associated with PPHN necessitating extracorporeal life support. The data suggest that thyroid hormone plays both direct and indirect roles in the pathophysiologic development of PPHN. Therefore, it seems advisable to screen for hyperthyroidism among affected neonates, because concomitant illnesses (eg, sepsis) may obscure the initial clinical findings of neonatal thyrotoxicosis. Rapid detection and treatment of neonatal hyperthyroidism may limit the need for invasive procedures such as ECMO and may improve clinical outcomes.

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