

## Clinical Anesthesia File

# Acute respiratory alkalosis associated with low minute ventilation in a patient with severe hypothyroidism

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**Purpose:** Patients with severe hypothyroidism present unique challenges to anesthesiologists and demonstrate much increased perioperative risks. Overall, they display increased sensitivity to anesthetics, higher incidence of perioperative cardiovascular morbidity, increased risks for postoperative ventilatory failure and other physiological derangements. The previously described physiological basis for the increased incidence of postoperative ventilatory failure in hypothyroid patients includes decreased central and peripheral ventilatory responses to hypercarbia and hypoxia, muscle weakness, depressed central respiratory drive, and resultant alveolar hypoventilation. These ventilatory failures are associated most frequently with severe hypoxia and carbon dioxide (CO<sub>2</sub>) retention. The purpose of this clinical report is to discuss an interesting and unique anesthetic presentation of a patient with severe hypothyroidism.

**Clinical features:** We describe an unique presentation of ventilatory failure in a 58 yr old man with severe hypothyroidism. He had exceedingly low perioperative respiratory rate (3-4 bpm) and minute ventilation volume, and at the same time developed primary acute respiratory alkalosis and associated hypocarbia (P<sub>ET</sub>CO<sub>2</sub> ≈ 320-22 mmHg).

**Conclusion:** Our patient's ventilatory failure was based on unacceptably low minute ventilation and respiratory rate that was unable to sustain adequate oxygenation. His profoundly lowered basal metabolic rate and decreased CO<sub>2</sub> production, resulting probably from severe hypothyroidism, may have resulted in development of acute respiratory alkalosis in spite of concurrently diminished minute ventilation.

**Objectif :** Les patients atteints d'hypothyroïdie sévère représentent tout un défi pour les anesthésiologistes étant donné les risques périopératoires très élevés. Dans l'ensemble, ils affichent une grande sensibilité aux anesthésiques, une forte incidence de morbidité cardiovasculaire périopératoire, des risques importants d'insuffisance ventilatoire postopératoire et d'autres désordres physiologiques. Les bases physiologiques, précédemment décrites, de l'incidence accrue d'insuffisance ventilatoire postopératoire chez ces patients comprennent des réponses ventilatoires centrales et périphériques diminuées à l'hypercapnie et à l'hypoxie, la faiblesse musculaire, la baisse de stimulation respiratoire centrale et l'hypoventilation alvéolaire qui en résulte. Ces défaillances ventilatoires sont le plus souvent associées à une hypoxie sévère et à une rétention de gaz carbonique (CO<sub>2</sub>). L'objectif du présent article est de commenter la présentation anesthésique unique et intéressante d'un patient atteint d'hypothyroïdie sévère.

**Éléments cliniques :** Il s'agit d'un homme de 58 ans atteint d'hypothyroïdie sévère. Il présentait une fréquence respiratoire (3-4 bpm) et une ventilation-minute périopératoires extrêmement basses et il a, au même moment, développé une alcalose respiratoire primaire aiguë et une hypocarbie associée (P<sub>ET</sub>CO<sub>2</sub> ≈ 320-22 mmHg).

**Conclusion :** La défaillance ventilatoire était basée sur d'inacceptables basses fréquence respiratoire et ventilation-minute qui ne permettaient pas d'entretenir une oxygénation suffisante. La vitesse extrêmement faible du métabolisme basal et la production réduite de CO<sub>2</sub>, résultant probablement de l'hypothyroïdie sévère, ont pu conduire au développement d'une alcalose respiratoire aiguë malgré la diminution simultanée de la ventilation-minute.

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**W**E were asked by the surgical staff to evaluate a 58 yr old male patient weighing 80 kg for emergency sigmoid colectomy. He presented to the hospital emergency room with a hematocrit of 21%. Work-up by the medical service eventually revealed actively bleeding and obstructing sigmoid colon cancer. In addition to anemia, the patient was found to have severe hypothyroidism [free T4 < 1 µg·dl<sup>-1</sup> (normal = 4.5-12), TSH = 51 µIU·ml<sup>-1</sup> (normal = 0.38-4.7)]. Unfortunately, thyroid hormone supplementation was not started preoperatively. Preoperative anesthetic assessment was not possible until 30 min before operation and preoperative arterial blood gas analysis was not performed. The patient was actively bleeding and had already received six units of packed red blood cells over 24 hr to maintain hematocrit > 25%. Due to the emergent nature, it was decided to proceed with the operation.

Our patient's additional medical problems included chronic depression and poorly controlled hypertension. Moreover, he was a heavy smoker and had, in the past, abused intravenous drugs and alcohol. The patient's preoperative medications included metoprolol, ranitidine, lorazepam and thiamin.

In the holding area, the patient appeared to be extremely lethargic, inattentive to the surroundings, and had poor responses to questions and verbal commands. His blood pressure (BP) and heart rate (HR) were 150/80 mmHg and 60 bpm, respectively. Moreover, his respiratory rate at this point was noted to be 3-4 bpm. His preoperative physical examination was remarkable for obtunded mental status, sluggish deep tendon reflexes and scaly dry skin. Routine preoperative laboratory values were normal except for the hematocrit of 28%. It was unclear at this time whether the patient's depressed mental status was due to his hypothyroidism or to his anemia. The patient did not receive lorazepam for 24 hr preoperatively.

Hypothyroidism is a common disease, afflicting about 0.5-1.8% of the adult population.<sup>1</sup> Based on laboratory tests and clinical manifestations, hypothyroidism can be graded into three categories;<sup>1</sup> subclinical, mild, and severe (or overt). In addition, based on serum TSH levels, hypothyroidism can be divided into primary (intrinsic thyroid pathology and higher than normal TSH) or secondary (hypothalamic or pituitary pathology and lower than normal TSH). In primary hypothyroidism, more severely hypothyroid patients tend to have higher serum TSH levels. In addition, patients with severe hypothyroidism tend to have markedly depressed T4 serum levels and display clinical symptoms of hypothyroidism. These clinical symptoms would include lethargy, depression, dry skin,

cold intolerance, fatigue, sluggish tendon reflexes, skin edema, slow mentation and memory impairment, and constipation.

Previous clinical reports have demonstrated that patients with severe hypothyroidism display considerably increased risks when they undergo general anesthesia. They can have severe cardiovascular decompensation on induction, intraoperative hemodynamic instability, electrolyte abnormalities, adrenocortical insufficiency, increased sensitivity to anesthetics, and profound hypothermia.<sup>1-6</sup>

Our patient's preoperative lethargy and low respiratory rate need discussion. Medication induced respiratory depression can be ruled out. Retrospectively, the most likely explanation for his respiratory depression would be his severely hypothyroid state. The initial concern was the development of severe respiratory acidosis secondary to respiratory depression. In fact, the previously described physiological basis for the increased incidence of postoperative ventilatory failure in hypothyroid patients includes decreased respiratory responses to hypercarbia and hypoxia, muscle weakness, depressed central respiratory drive, and resultant alveolar hypoventilation.<sup>7-10</sup> These ventilatory failures are associated most frequently with severe hypoxia and carbon dioxide (CO<sub>2</sub>) retention.

Our patient presented with severe gastrointestinal bleeding associated with his colon cancer. Gastrointestinal bleeding occurs with increased incidence in severely hypothyroid patients.<sup>5</sup> The pathophysiological mechanism includes increase capillary fragility, impaired tissue healing and reduction in coagulation factors VIII and XI.<sup>1,5</sup> The patient also displayed severe gastrointestinal obstruction. Adynamic ileus is a recognized complication of severe hypothyroidism.<sup>1</sup>

### Actual Course

In the operating room (OR), standard monitors were applied. The SpO<sub>2</sub> breathing room air was 95%. A 20 G left radial arterial line was inserted and arterial blood gas was obtained during induction. The patient's spontaneous respiratory rate at this point was noted to be 3-4 bpm with shallow tidal volume. His ventilatory mechanics did not appear to improve with verbal commands and, therefore, spontaneous denitrogenation/preoxygenation was limited. Before the result of the first blood gas was available, rapid sequence general anesthesia was induced with 14 mg etomidate *iv* followed by 120 mg succinylcholine *iv*. A cuffed 8 mm- internal diameter endotracheal tube was placed via direct laryngoscopy. Based on his low respiratory rate and tidal volumes, we expected a return of high P<sub>ET</sub>CO<sub>2</sub>. To our surprise, the capnometer tracing ranged between 18-20 mmHg

TABLE Arterial blood gas results

Time	Event	pH	PaCO <sub>2</sub>	PaO <sub>2</sub>	BE	BICARB	FIO <sub>2</sub>	MODE	RATE
	Preop.	—	—	—	—	24	—	—	3-4
1400	Induction	7.51	28	156	+1	23	100%	FM	3-4
1500	Intraop.	7.49	28	102	-1	22	50%	SIMV	6
1700	Recovery	7.5	29	161	0	25	70%	SIMV	6
1830	Recovery*	7.44	35	91	+1	24	40%	CPAP	8-10
2030	Recovery*	7.44	35	96	+1	24	60%	FM	8-12

Results of arterial blood gas analysis obtained in the OR (first two gases, 1400 indicates time of induction) and in the recovery room (last 3 gases). PaO<sub>2</sub> and PaCO<sub>2</sub> are measured in mmHg, and bicarbonate (BICARB) is measured in mEq/L. Mode indicates method of ventilation.

\* indicate gases obtained after levothyroxine therapy.

### Other abbreviations:

BE = base excess

FIO<sub>2</sub> = fractional inspired O<sub>2</sub> concentration in percent

MODE = mode of ventilation

FM = face mask

SIMV = synchronized intermittent mechanical ventilation

CPAP = continuous positive airway pressure

RATE = respiratory rate per minute

immediately after tracheal intubation. We initially suspected that endo-esophageal intubation had occurred. However, correct placement of the endotracheal tube was verified via palpation of the cuff in the trachea, bilaterally equal breath sounds, persistent O<sub>2</sub> saturation > 98%, and maintained, although low, CO<sub>2</sub> capnogram tracing.

Anesthesia was maintained with isoflurane (expired %~0.9-1.1), O<sub>2</sub> (FIO<sub>2</sub>~50%) and air. The fresh-gas flow into the breathing circuit was maintained at ~ 1-1.5 L·min<sup>-1</sup>. The SpO<sub>2</sub> ranged from 95-98% and esophageal temperature was maintained between 35.5-36.5°C. Intermittent boluses of fentanyl were given to a total of 400µg over four hours of surgery. Systolic BP and HR remained between 110-190 mmHg and 50-70 bpm, respectively.

Blood gas analysis obtained during induction of anesthesia revealed acute respiratory alkalosis (Table). Moreover, P<sub>ET</sub>CO<sub>2</sub> remained between 20-21 mmHg throughout the case even with reduced tidal volume of ~300 ml and SIMV of 5-6 bpm (minute ventilation ~1500-1800 ml). A second arterial blood gas obtained one hour later demonstrate persistent acute respiratory alkalosis as we continued to maintain low minute ventilation volume (Table).

After completion of sigmoid resection, muscle relaxation was reversed with 3.5 mg neostigmine and 0.6 mg glycopyrrolate. The patient immediately

assumed spontaneous ventilation, and was alert and responsive to verbal commands. However, his P<sub>ET</sub>CO<sub>2</sub> remained low (20-25 mmHg) and he was breathing only at spontaneous respiratory rates of ~4-6 bpm with tidal volumes of ~100-150 ml (minute ventilation volume~400-900 ml). However, when instructed, he was able to generate tidal volume of > 750 ml. His SpO<sub>2</sub> remained > 98% during this period. The trachea remained intubated and he was transferred to the recovery room.

In the recovery room, the patient was immediately started on levothyroxine *iv*. He was initially ventilated on SIMV and was gradually weaned to CPAP. The first blood gas obtained in the recovery room showed persistent respiratory alkalosis (Table). However, the tidal volume and respiratory rate increased over the evening with simultaneous and paradoxical normalization of pH and PaCO<sub>2</sub>. The trachea was extubated uneventfully in the recovery room. The spontaneous tidal volume and respiratory rate were ~ 200-300 ml and 8-12 bpm at this time, respectively. On postoperative day #2, the patient was breathing at a respiratory rate of 10-14 bpm with satisfactory tidal volumes. Plasma bicarbonate concentration, which was normal preoperatively, decreased to 21 mEq·L<sup>-1</sup> (normal=24-28) on postoperative day #1, demonstrating compensatory metabolic acidosis. On postoperative day #2, the serum bicarbonate level returned to normal.

Management of anesthesia for severely hypothyroid patients is demanding.<sup>1-6</sup> Severely hypothyroid patients have profoundly increased morbidity during anesthesia and surgery secondary to highly disturbed physiological and metabolic processes.<sup>1-3</sup> The choice of induction agent is important for hypothyroid patients as they tend to have decreased circulating blood volume.<sup>1,5</sup> Cardiac arrest has been reported on induction with 200 mg thiopental.<sup>5,6</sup> Etomidate was chosen as an induction agent for rapid sequence intu-

bation because of its relative hemodynamic stability. Ketamine was considered but was not used because of the concern for postoperative agitation and hallucinations. One should keep in mind, however, the potential for adrenal gland suppression with etomidate especially in a severely hypothyroid patient who may have pituitary abnormality.<sup>1</sup> Controlled mechanical ventilation should be titrated down to maintain  $P_{ET}CO_2$  as normal as possible, but at the same time maintaining adequate oxygenation. Severe hypocapnia and resultant decrease in cerebral blood flow could be dangerous since cerebral  $O_2$  consumption, per se, is not reduced in hypothyroidism.<sup>1</sup> Other detrimental effects of severe respiratory alkalosis include reduced cardiac output and coronary blood flow, diminished lung compliance, left-ward shift in  $O_2$ -hemoglobin dissociation curve (decreased  $O_2$  availability), lowered plasma potassium and calcium.<sup>7</sup>

Patients with severe hypothyroidism are known to exhibit abnormalities in ventilatory function including increased fatigue and dyspnea on exertion, impaired ventilatory drive to hypoxia and hypercapnia, and decreased respiratory muscle force.<sup>8-10</sup> These manifestations are responsible for occasional life-threatening postoperative ventilatory failure, desaturation, hypoventilation, profound  $CO_2$  retention and, sometimes,  $CO_2$  narcosis. Hypothyroid patients with  $CO_2$  retention have been most frequently described to present with hypoventilation.<sup>1</sup> Therefore, our patient's clinical presentation was unique in that profoundly reduced perioperative respiratory rate and minute ventilation were associated with a pure and acute respiratory alkalosis (hyperventilation).

Intraoperatively, we maintained a tidal volume of ~300 ml ( $3.75 \text{ ml}\cdot\text{kg}^{-1}$ ) and minute ventilation volume of  $1500\text{--}1800 \text{ ml}\cdot\text{min}^{-1}$  ( $18.75\text{--}22.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) to maintain  $P_{ET}CO_2 > 20 \text{ mmHg}$ . Upon termination of sigmoid resection, the patient's spontaneous tidal volume and minute ventilation decreased to  $\sim 100\text{--}150 \text{ ml}$  ( $\sim 1.25\text{--}1.86 \text{ ml}\cdot\text{kg}^{-1}$ ) and  $\sim 400\text{--}900 \text{ ml}\cdot\text{min}^{-1}$  ( $5\text{--}11.25 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), respectively. These tidal volumes and minute ventilation volumes are considerably less than the average values reported for an 80 kg man.<sup>11</sup>

Although our patient was fully alert and responsive to commands at the termination of the sigmoid resection, it was decided not to extubate his trachea due to his low respiratory rate and minute ventilation. Initially, we anticipated a need for postoperative mechanical ventilation because of our concern for potential respiratory muscle weakness, increased sensitivity to anesthetics and narcotics, possible intractable hypothermia, prolonged recovery from the inhalation-

al agent, and reduced ventilatory effort in response to hypoxia and hypercarbia in this severely hypothyroid patient. Our patient did not meet any of these criteria but did develop severe respiratory alkalosis associated with very low respiratory rate and minute ventilation.

Before tracheal intubation, we expected a primary respiratory acidosis based on the low minute ventilation and respiratory rate. Alveolar hypoventilation and impaired ventilatory drive to hypercarbia are known to occur in patients with severe hypothyroidism.<sup>1-3,8-9,12</sup> However, hypoventilation, by definition, should result in respiratory acidosis with retention of plasma  $CO_2$ . In fact, previous clinical reports describe ventilatory failure in hypothyroid patients that was associated with impaired ventilatory drive to hypercarbia and worsening hypercarbia.<sup>8-12</sup> However, our patient developed acute respiratory alkalosis and, at the same time, displayed a clinical picture inconsistent with respiratory alkalosis and alveolar hyperventilation. The arterial pH of 7.51 with plasma  $PCO_2$  of 28 mmHg during induction of general anesthesia represents an appropriate and acute shift in pH (for every 10 mmHg decrease in plasma  $PCO_2$ , pH should increase by approximately by 0.1 unit<sup>13</sup>).

The reason for our patient's respiratory alkalosis associated with a low respiratory rate is not clear but can be speculated upon. The low respiratory rate did not stem from increased sensitivity to anesthetics and narcotics, as he underwent rapid sequence intubation and was not premedicated before induction. Inadequate muscle relaxant reversal was ruled out in the OR. Preoxygenation before intubation in the OR appeared very limited but may, in fact, have increased his minute ventilation and caused respiratory alkalosis. However, this does not explain persistent intraoperative respiratory alkalosis even with unusually low mechanical minute ventilation. Perhaps, his central respiratory drive had been adjusted as a consequence of his chronic hypothyroidism.<sup>9,10</sup> Our patient appears to have a severely reduced demand for ventilation. In patients who are severely hypothyroid there are a diminished basal metabolic rate and a lowered  $CO_2$  production.<sup>1,2,4</sup> Although we did not measure the metabolic rate for our patient, his threshold for developing respiratory alkalosis may have been reduced as his baseline metabolic rate may have been diminished. This reduction in metabolic rate may have reflected on his low  $P_{ET}CO_2$ . In addition, general anesthesia can further depress metabolic rate and could have further contributed to respiratory alkalosis.<sup>1-3</sup> Even at very low minute ventilation, our patient was hyperventilated with regard to his metabolic demands for  $CO_2$  elimination. It is interesting that our patient was able

to generate adequate tidal volumes when instructed to do so. However, these tidal volumes were not steadily maintained on his own.

We also examined the relationship between  $\text{PaCO}_2$  tension and respiratory rate for our patient (Table). Under normal physiological condition,  $\text{PaCO}_2$  and respiratory rate have an inverse relationship, that is, increasing respiratory rate would reduce  $\text{PaCO}_2$ . However, in our patient, increased respiratory rate initiated with thyroid hormone replacement therapy paradoxically increased his  $\text{PaCO}_2$  (Table). Increased metabolic initiated with thyroid hormone therapy could have increased plasma  $\text{CO}_2$ .

Thyroid hormone replacement therapy is most often achieved with synthetic triiodothyronine (T3) or levothyroxine (T4). The use of levothyroxine is more wide spread as it has a longer half-life (7-8 days) and a more gradual and steady onset of action (onset to start on average of 6-12 hr and peak metabolic effect occurring within 10-12 dy) than triiodothyronine.<sup>1</sup> It is known that the T3 form of thyroid hormone (triiodothyronine) has quicker effect in restoring euthyroid state than has the T4 form (levothyroxine). However, rapid correction of hypothyroidism may precipitate myocardial ischemia and adrenal insufficiency. Because of these concerns, we utilized levothyroxine to treat our patient's hypothyroidism. Thyroxine supplementation rapidly increased his minute ventilation and, at the same time, resulted in correction of his respiratory alkalosis.

In summary, we describe a unique and counterintuitive clinical presentation of perioperative ventilatory failure in a severely hypothyroid patient. Our patient appeared to have diminished  $\text{CO}_2$  production and displayed very low respiratory rate that are associated with acute respiratory alkalosis. Decreased metabolic rate may have resulted in a profoundly lowered threshold in creating acute respiratory alkalosis upon undergoing controlled mechanical ventilation. Surgical emergencies may not be avoidable in all cases, however, surgery should be delayed until treatment with thyroid hormone replacement has been instituted in severely hypothyroid patients.

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