

Effect of a Low-Carbohydrate Diet on Respiratory Quotient of Infants with Chronic Lung Disease

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Objective: To compare the respiratory quotient in infants with chronic lung disease before and after receiving a modular diet with slightly lower carbohydrate content.

Material and Method: Infants with chronic lung disease from the King Chulalongkorn Memorial Hospital were enrolled and assessed for nutritional status, severity of chronic lung disease and dietary intake. Indirect calorimetry was performed using a custom-made airtight canopy with O₂ and CO₂ sensors. Respiratory quotient (RQ) was calculated from VCO₂/VO₂ during the period they were fed low carbohydrates (37% of total calories) for at least 24 hours vs. a standard diet (47% carbohydrate). These two formulas were similar in terms of caloric density and protein content. Each patient received at least 100-150 kcal/kg/day during the study period. Respiratory quotients of the same patient receiving the two diets were compared by using Wilcoxon signed-rank test.

Results: A total of 14 patients (median age 7 months, range 1-26 months) were recruited. Twelve children had weight for age Z-score below -2SD. Their median weight for age Z-score, length for age Z-score and weight for length Z-score were -2.89, -3.08 and -1.24, respectively. The median RQ measured during the low carbohydrate diet was 0.96 (interquartile range 0.95-0.97), significantly lower than the median RQ during the standard diet, which was 1.04 (0.97-1.10). However, the respiratory rate revealed no significant difference. Two participants with underlying gastroesophageal reflux disease showed higher RQ after low carbohydrate formula feeding, which might be a result of hypersecretion due to its high fat content.

Conclusion: Diet with slightly lower carbohydrate content can reduce the RQ in infants with chronic lung disease compared to the standard enteral formula. A 10-percent reduction of carbohydrate content may provide a sizeable effect in this group of patients. Nevertheless, the clinical significance of this finding requires further investigation.

Keywords: Respiratory quotient, Chronic lung disease, Low carbohydrate formula

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Chronic lung disease, despite having no conclusive definition, usually refers to a group of pulmonary diseases that chronically damage the peripheral airways or lung parenchyma. The etiology of chronic lung disease in children includes bronchopulmonary dysplasia, asthma, chronic interstitial lung disease, pulmonary fibrosis and bronchiectasis⁽¹⁾.

Infants with chronic lung disease are at risk of malnutrition and failure to thrive due to decreased appetite, impaired intestinal absorption, increased energy expenditure and restricted fluid intake⁽²⁻⁴⁾. Several studies have found that infants with chronic

lung disease may have increased energy expenditure by 15-25%; moreover, those with recurrent illness may require up to 140-150 kcal/kg/day^(5,6). To meet the high-energy requirement despite some degree of fluid restriction is a major challenge for this group of patients. Increasing the caloric density of the enteral formula by increasing either carbohydrate or fat content presents some drawbacks since inadequate ventilation and gastroesophageal reflux are common in this age group. Respiratory quotient (RQ) is the ratio of carbon dioxide production (VCO₂) and oxygen consumption (VO₂) and can be measured by indirect calorimetry (IC). Previous studies have shown that the RQ of glucose is approximately 1.0 and the RQ of fat is approximately 0.7, while the RQ from the process of lipogenesis may be as high as 8.0^(7,8). High RQ could potentially increase the work of breathing, which may lead to respiratory failure, especially in patients with underlying pulmonary

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disease^(7,9). Since fat oxidation results in the lowest production of carbon dioxide, a modular formula for chronic lung disease has been developed by reducing the proportion of carbohydrate and increasing the fat. However, the number of studies of diet modification in pediatric patients with chronic lung disease is limited. Most studies have been on adults with chronic obstructive pulmonary diseases, which are characterized by different pathology and patient progression⁽¹⁰⁻¹²⁾. In addition, the proportion of carbohydrate used in the previous studies of chronic lung disease was often lower than the standard formula by 15-30%⁽¹³⁻¹⁵⁾ and thus the fat component was higher by the same proportion. Increasing the fat content of the diet to around 15-30% of total calories is difficult in infants with chronic lung disease because they usually have gastroesophageal reflux disease and delayed gastric emptying time⁽¹⁶⁾. Therefore, the aim of this study is to investigate whether the modular diet, which has a slightly lower carbohydrate than standard infant formula by only 10%, can reduce CO₂ production and RQ in infants with chronic lung disease. This slight reduction in carbohydrate content may lessen the possible complications such as gastroesophageal reflux disease, fat malabsorption and poor growth^(17,18).

Material and Method

Study design

The present study was a cross-sectional, open-label, interventional trial comparing RQ between low and standard carbohydrate formulas in the same subjects with chronic lung disease. The present study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand. The researchers described the present study

to the parents before obtaining signed informed consent.

Subjects

Infants diagnosed with chronic lung disease who were below two years of age and weighed less than 12 kilograms were recruited from the Nutrition and Pulmonology Clinic at the King Chulalongkorn Memorial Hospital between 1 March 2013 and 31 March 2014. Criteria for diagnosing chronic lung disease were the presence of the underlying conditions related to chronic lung disease (e.g. chronic aspiration, bronchopulmonary dysplasia, chronic respiratory infection) and at least one of the following: chronic respiratory symptoms and signs such as cough, dyspnea, tachypnea, adventitious lung sounds or abnormal chest x-ray compatible with the chronic lung disease⁽¹⁾.

Infants who had unstable clinical symptoms such as current respiratory infection, chronic diseases that may affect the VCO₂ and VO₂ measurement as well as those with history of cow milk protein allergy or intolerance were excluded from the present study.

Study protocol

The low carbohydrate formula used in this study was developed by the Nutrition Division, Department of Pediatrics, King Chulalongkorn Memorial Hospital⁽¹⁹⁾. Composition of the two formulas is shown in Table 1. The proportion of carbohydrate in the low carbohydrate formula was reduced to 37% of total energy while the regular infant formula provided carbohydrate approximately 43-47% of total energy. This modular formula was composed of a lactose-free formula blended together with vegetable oil. It was

Table 1. Composition of standard and low carbohydrate formulas

Composition per 100 mL	Standard formula ¹	Low carbohydrate formula ²
Energy (kcal)	100	100
Carbohydrate (g)	11.6 sucrose 47%, corn syrup 53% ³	9.3 dextrin 100%
Protein (g)	2	1.9
Fat (g)	4.9	6.1
CHO: protein: fat ⁴	47: 8: 45	37: 8: 55
Osmolality (mOsm/kgH ₂ O)	322	266

¹ Standard formula was prepared by using 19.5 grams of similac lactose free formulaTM and then adding water up to 100 mL.

² Low carbohydrate formula was prepared by using 17.3 grams of Nan AL110 plus 1.5 mL of rice bran oil and then adding water up to 100 mL.

³ Percentage by weight.

⁴ Caloric distribution.

easy to prepare and could be used in an ambulatory setting.

After informed consent, all patients underwent anthropometric and dietary assessments. Complementary food was recorded separately from the formula in terms of energy, carbohydrate, protein and fat content. The total energy intake from formula and complementary food was prescribed at between 100-150 kcal/kg/day, either in the form of low carbohydrate or standard formula, depending on the patients' current feeding regimen. Indirect calorimetry was performed after they received the study formula as main source of diet for at least 24 hours. After the VCO_2 and VO_2 were measured, the feeding regimen was switched to the other formula (with equivalent total energy intake) for at least 24 hours before the second calorimetry was carried out.

Respiratory quotient

RQ is the ratio of CO_2 production and O_2 consumption⁽²⁰⁻²²⁾ calculated as follows:

$$RQ = VCO_2 (\text{ml/kg/min}) / VO_2 (\text{ml/kg/min})$$

In order to measure VCO_2 and VO_2 by indirect calorimetry, the infants were placed in a custom-made airtight canopy for a period of 15-30 minutes, two hours after their last meal. This indirect calorimetry model was developed by the Physiology Department, Faculty of Medicine, Chulalongkorn University. The machine consisted of three major parts:

1) Airtight canopy for patients to stay in. This is a transparent box, size 100x50x50 cm, placed on a flat surface. The O_2 and CO_2 sensors, connected to the gas analyzer, were attached to the canopy. This canopy was tested for air leakage by pushing air pressure above 300 mmHg before use.

2) Gas analyzer (model ML 866, serial 430-0394) was developed by ADInstrument® (Colorado, USA). We tested the accuracy by known standard gases (25% O_2 , 5% CO_2). The accuracy of oxygen and carbon dioxide was $\pm 0.1\%$ and $\pm 0.3\%$, respectively.

3) Computer, programmed with Chart™ Pro® version 5 (ADInstrument, Colorado, USA), was attached to the gas analyzer to analyze the percentage of carbon dioxide emitted and the percentage of oxygen available to the patient. The reading of VCO_2 and VO_2 was performed while the patient was quiet and the values remained stable.

Statistical analysis

The sample size was calculated according to findings from previous studies of the effect of low

carbohydrate diet on RQ. The difference in mean RQ of 0.064 that would represent the minimal clinically significant difference was used⁽¹³⁾. To provide 90% power and significance of 0.05, a minimum of eight participants was needed.

SPSS version 20 was used for statistical analysis and significance was defined as $p < 0.05$. Wilcoxon signed-rank test was used to evaluate differences in the respiratory quotient between low carbohydrate and standard formula within the same patient. Median and interquartile range were used to describe the data.

Results

Demographic data

Fourteen participants were enrolled. The median age of participants was seven months (range 1-26 months) and there were nine boys and five girls. Nine out of 14 patients (64%) were diagnosed with bronchopulmonary dysplasia, two patients (14%) had diaphragmatic hernia, one had pulmonary sling with tracheal stenosis, one had infantile spasm, and the other had laryngomalacia. Five out of 14 subjects (36%) still required long-term oxygen therapy. Eight patients (57%) were treated with either inhaled bronchodilator or inhaled corticosteroids and three patients (21%) were treated with diuretics. Six participants (43%) were fed by a nasogastric or nasojejunal tube.

Nutritional status and dietary assessment

Twelve out of 14 participants (86%) suffered from undernutrition; stunting was more prevalent than wasting (Table 2). The median weight for age Z-score, length for age Z-score and weight for length Z-score were -2.89, -3.08 and -1.24, respectively. In general, these 12 patients with preexisting undernutrition had improved nutritional status as shown by the mean weight for length and a BMI Z-score that was higher than length for age Z-score. More than half of the patients had no acute malnutrition as demonstrated by normal weight for length and BMI Z-score.

The mean total energy intake was 126 ± 14.39 kcal/kg/day, mainly derived from formula. Only two subjects received complementary food but the amount and energy distribution was similar during the two-day period of low and standard carbohydrate formula.

Respiratory quotient

The measurements from indirect calorimetry are shown in Table 3. Although there was no significant difference between VO_2 of these infants during the

Table 2. Anthropometric data

Z-score ¹	Weight for age	Length for age	Weight for length ²	BMI
Normal	14.28% (2) ³	28.57% (4)	61.53% (8)	50% (7)
<-2SD	42.86% (6)	21.43% (3)	7.70% (1)	7.14% (1)
<-3SD	42.86% (6)	50% (7)	30.77% (4)	42.86% (6)
Median	-2.89	-3.08	-1.24	-1.69
Interquartile range	-4.40 - (-2.26)	-5.03 - (-0.41)	-3.46 - (-0.59)	-3.33 - (-1.03)

¹Z-score was calculated using WHO Anthro Plus® (version 3.2.2, January 2011, available from www.who.int/childgrowth/software)

²n was 13 due to no reference data for one premature infant (subject No. 9)

³Data were presented as % (n)

period of low carbohydrate and standard diet, VCO₂ and RQ were reduced significantly after the low carbohydrate formula. Nonetheless, the RQ of the two participants who had severe gastroesophageal reflux disease was higher than that of the standard.

It is noted that there was no significant difference in the respiratory rate between these subjects during the period they received either the standard or low carbohydrate formula (36.00 vs. 35.50 times/min, $p = 0.59$). However, other clinical outcomes, such as pulmonary function test and arterial blood gases, were not collected in the present study.

Discussion

The present study aimed to compare the respiratory quotient in infants with chronic lung disease after they were fed with low vs. normal carbohydrate formulas. The authors found that although the difference in the proportion of carbohydrate was only 10%, the RQ was altered significantly. In spite of this, the respiratory rate was not changed along with the varying levels of the RQ.

Custom-made indirect calorimetry equipment with an airtight canopy was invented for this study because the conventional device was made for adults or infants who were supported by a mechanical ventilator; thus, the equipment could be connected directly to a mechanical ventilator circuit. In the present study, participants were infants who were not supported by a mechanical ventilator. They neither had an endotracheal tube nor were able to breathe into a mouthpiece. The researchers needed to create a closed-space for measuring the gas exchange in order to calculate VO₂ and VCO₂. Therefore, only subjects who weighed less than 12 kilograms or age below two years were recruited due to the limitation of the airtight canopy's size. Furthermore, their main dietary intake

was milk, for which it was easy to manipulate the total energy and carbohydrate content.

Few previous studies have compared the RQ in patients with chronic lung disease. Van den Berg B et al⁽¹¹⁾ administered low-carbohydrate feeding (28% carbohydrate) to 32 ventilator-dependent adults and standard isocaloric feeding (53% carbohydrate) to 15 patients. Low carbohydrate feeding was associated with significantly lower RQ compared with the standard regimen; the mean RQ was 0.91±0.01 and 1.00±0.02, respectively. However, no significant difference was found in the PaCO₂ between the two feeding groups. Efthimiou et al⁽¹²⁾ conducted a study in 10 elderly men with severe chronic obstructive lung disease (average age of 69.2 years) comparing diet with carbohydrate proportion of 53% and 27% of total energy. They reported the significantly higher VCO₂ and RQ in the standard carbohydrate group, which correlated with a decrease in the mean six-minute walking distance. Kashyap et al⁽¹³⁾ conducted a study in 62 low-birth weight infants receiving enteral nutrition. The patients received similar energy intake but different proportion of carbohydrate at 35%, 50% and 65% of total energy intake. The RQ was significantly different between the three groups (0.87±0.04, 0.93±0.06, and 0.98±0.07, respectively), the highest in the group receiving 65% carbohydrate. Chessex et al⁽¹⁴⁾ conducted a study in 10 chronic lung disease infants, who were supported by a mechanical ventilator and received parenteral nutrition. The RQ was higher in the group on a carbohydrate-rich parenteral nutrition regimen (70% of total energy) than those on the standard carbohydrate (50%) regimen (1.05±0.02 vs. 0.96±0.01; $p < 0.02$). Pereira et al⁽¹⁵⁾ studied 10 premature infants with bronchopulmonary dysplasia, comparing the enteral formulas with 22% and 52% carbohydrate. They showed that the low carbohydrate group had lower VCO₂ (6.6±0.3 vs. 7.4±0.4 mL/kg/min;

Table 3. Demographic data and data from indirect calorimetry

Subject No.	Gender ¹	Age (months)	Severity	Feeding methods ²	Standard formula		Low carbohydrate formula				
					VCO ₂ ³	VO ₂ ⁴	RQ	VCO ₂	VO ₂	RQ	
1	M	18	Oxygen dependent	1 LPM	NG	7.07	6.51	1.09	6.65	6.93	0.95
2	M	7	Oxygen dependent	2 LPM	NG	7.11	6.29	1.13	5.83	6.83	0.83
3	M	1	Room air		NG	11.55	10.59	1.09	11.5	13.05	0.88
4	M	6	Oxygen dependent	0.5 LPM	NG	7.1	7.29	0.97	6.36	6.54	0.97
5	M	14	Room air		Oral	5.59	5.79	0.97	4.23	4.43	0.96
6	M	13	Room air		Oral	4.02	3.87	1.04	3.23	3.42	0.96
7	M	9	Room air		Oral	4.95	4.37	1.13	4.95	5.15	0.96
8	F	7	Oxygen dependent	1 LPM	NJ	10.81	10.08	1.07	11.69	10.35	1.13
9	F	26	Oxygen dependent	1 LPM	NJ	7.74	8.12	0.95	5.96	6.19	0.96
10	F	12	Room air		Oral	6.78	6.57	1.03	6.66	6.86	0.97
11	F	5	Room air		Oral	8.23	8.51	0.97	7.81	8.24	0.95
12	M	2	Room air		Oral	9.89	8.47	1.17	8.87	8.19	1.08
13	F	4	Room air		Oral	7.85	7.7	1.02	7.4	7.8	0.95
14	M	5	Room air		Oral	5.47	5.37	1.02	5.42	5.82	0.93
Median (interquartile range)		7 (4.75-13.25)				7.11 (5.56-8.65)	6.93 (5.69-8.48)	1.04 ⁵ (0.97-1.10)	6.90 ⁵ (5.30-8.08)	7.13 (5.65-8.20)	0.96 ⁵ (0.95-0.97)

¹ M = male, F = female

² NG = nasogastric tube, NJ = nasojejunostomy tube

³ VCO₂ was carbon dioxide production (mL/kg/min)

⁴ VO₂ was oxygen consumption (mL/kg/min)

⁵ Wilcoxon signed-rank test, significantly different between standard formula and low carbohydrate formula ($p = 0.01$)

$p < 0.05$) and consequently lower RQ (0.8 ± 0.02 vs. 0.94 ± 0.01 ; $p < 0.05$). Nevertheless, there was no change in pulmonary function tests, namely minute ventilation, dynamic compliance, total lung resistance and work of breathing. From these studies, it seems that lowering the proportion of carbohydrate by around 15-30% could lower the RQ in patients with chronic lung disease. In the present study, only a 10% reduction of carbohydrate could reveal differences in the respiratory quotient. However, the authors cannot demonstrate the clinical significance of this change in RQ because neither detailed pulmonary function testing nor functional exercise capacity could be easily performed in this population.

The present study decided on 37% carbohydrate for the low carbohydrate formula due to the following reasons: 1) an extremely low carbohydrate proportion might adversely affect the growth rate of infants^(17,23-26) and 2) a very high fat content might delay gastric emptying time and worsen pre-existing gastroesophageal reflux disease⁽¹⁸⁾. Similac LFTM was chosen as a representative of standard formula due to the highest carbohydrate content (47%) and thus made up the 10 percent difference in carbohydrate distribution from the low carbohydrate formula.

Patients with chronic lung disease are at risk for CO₂ retention that affects the work of breathing and subsequent growth⁽²⁻⁴⁾. One factor affecting hypercapnia is the diet. Some nutrients may lead to increased CO₂ production in the body and subsequently to respiratory failure. It might be explained as follows: 1) within the same amount of energy, glucose oxidation gives more CO₂ than fat by 22%, and 2) excessive energy from glucose will be used for lipogenesis and thus the RQ increases⁽⁷⁾.

Therefore, a modular formula developed for chronic lung disease patients would lower the proportion of carbohydrate and increase the proportion of fat to reduce hypercapnia. At present, such formula has been developed for adults with chronic lung disease by drastically reducing the proportion of carbohydrate. This makes it difficult to use in pediatric patients. The low carbohydrate formula used in the present study was modified from a lactose-free infant formula by increasing the proportion of energy from fat with vegetable oil. It is a simple way to make appropriate food for young patients and is easy to prepare at home. However, the high proportion of fat in the formula could be a problem for patients with some co-morbidity, such as severe gastroesophageal reflux disease, which might worsen due to delayed gastric

emptying time. In the present study, two participants with underlying gastroesophageal reflux disease showed higher VCO₂ after being fed with the low carbohydrate formula. This observation could be a result of their worsening gastroesophageal reflux disease, which causes hypersecretion followed by CO₂ retention. However, previous studies⁽¹³⁻¹⁵⁾ did not mention this type of co-morbidity or the side-effects of a low carbohydrate and high fat formula. One experiment was carried out using low carbohydrate, high fat parenteral nutrition that did not result in a hypersecretion problem⁽¹⁴⁾. In clinical practice, a low carbohydrate formula might be useful in infants with chronic lung disease who have CO₂ retention; however, it should be avoided in those who have uncontrolled severe gastroesophageal reflux disease or evidence of fat malabsorption.

Conclusion

Diet with a lightly lower carbohydrate content can reduce the respiratory quotient in infants with chronic lung disease more than the standard enteral formula. A 10-percent reduction of energy from carbohydrate content may provide a sizeable effect in this group of patients but the clinical significance is yet to be studied. However, long-term use of this low carbohydrate and high fat formula in chronic lung disease of infancy still requires long-term follow-up on nutritional status and growth as well as the side effects, such as delayed gastric emptying time, gastroesophageal reflux and fat malabsorption.

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Potential conflicts of interest

None.

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ผลของอาหารคาร์โบไฮเดรตต่ำต่อค่า respiratory quotient ในผู้ป่วยเด็กโรคปอดเรื้อรัง (effect of a low-carbohydrate diet on respiratory quotient of infants with chronic lung disease)

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วัตถุประสงค์: เพื่อเปรียบเทียบค่า Respiratory quotient (RQ) ของอาหารที่มีปริมาณคาร์โบไฮเดรตต่ำกับอาหารที่มีปริมาณคาร์โบไฮเดรตปกติ ในผู้ป่วยเด็กโรคปอดเรื้อรัง

วัสดุและวิธีการ: ผู้มีพันธบัตรตรวจประเมินภาวะทางโภชนาการและความรุนแรงของโรคปอดเรื้อรังในผู้ป่วยอายุน้อยกว่า 2 ปีที่เป็นโรคปอดเรื้อรังก่อนให้โภชนาบำบัดด้วยนมชนิดคาร์โบไฮเดรตต่ำ (คาร์โบไฮเดรต 37% ของพลังงานทั้งหมด) โดยกำหนดพลังงานที่ได้รับอยู่ระหว่าง 100-150 กิโลแคลอรีต่อกิโลกรัมต่อวันต่อเนื่องเป็นระยะเวลาอย่างน้อย 24 ชั่วโมง และได้รับการวัดค่า RQ (VCO_2/VO_2) ด้วยเครื่อง indirect calorimetry หลังจากนั้นผู้ป่วยคนเดียวกันได้รับนมชนิดคาร์โบไฮเดรตปกติ (คาร์โบไฮเดรต 47% ของพลังงานทั้งหมด) ต่อเนื่องอีกอย่างน้อย 24 ชั่วโมง ในปริมาณพลังงานเท่ากัน และได้รับการวัดด้วยวิธีเดียวกันเพื่อเปรียบเทียบความแตกต่างของ RQ ในระหว่างได้รับนมแต่ละสูตรโดย Wilcoxon sign rank test

ผลการศึกษา: ผู้ป่วยเข้าร่วมวิจัยทั้งหมด 14 ราย (อายุเฉลี่ย 7 เดือน) มีผู้เข้าร่วมวิจัย 12 รายที่มีน้ำหนักน้อยกว่า -2SD โดยค่าเฉลี่ยของ weight for age Z-score, height for age Z-score และ weight for height Z-score มีค่าเท่ากับ -2.89, -3.08 และ -1.24 ตามลำดับ RQ ระหว่างที่ผู้ป่วยได้รับนมที่มีสัดส่วนคาร์โบไฮเดรตต่ำมีค่าต่ำกว่า RQ ระหว่างได้รับนมที่มีสัดส่วนคาร์โบไฮเดรตปกติอย่างมีนัยสำคัญทางสถิติ (RQ 0.96 (IQR 0.95-0.97) และ 1.04 (IQR 0.97-1.10) ตามลำดับ โดยที่อัตราการหายใจไม่แตกต่างกันแต่มีผู้เข้าร่วมวิจัยจำนวน 2 รายที่มี RQ สูงขึ้นแม้ได้รับนมที่มีสัดส่วนคาร์โบไฮเดรตต่ำ โดยผู้เข้าร่วมวิจัยทั้งสองมีโรคกรดไหลย้อนร่วมด้วย ทั้งนี้อาจเป็นไปได้ว่าการได้รับนมที่มีสัดส่วนคาร์โบไฮเดรตต่ำแต่สัดส่วนไขมันสูงกว่าปกติอาจทำให้เกิดภาวะเสมหะคั่งมากขึ้น

สรุป: อาหารที่มีสัดส่วนคาร์โบไฮเดรตที่ลดลงจากปกติเพียง 10% สามารถลด RQ ได้อย่างมีนัยสำคัญในผู้ป่วยเด็กที่เป็นโรคปอดเรื้อรัง อย่างไรก็ตามควรมีการศึกษาเพิ่มเติมต่อในอนาคตว่า RQ ที่ลดลงมีผลต่อการเปลี่ยนแปลงผลลัพธ์ทางคลินิกหรือไม่
