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Original Article

COPD Patients with Acute Exacerbation Who Developed Refeeding Syndrome during Hospitalization Had Poor Outcome: A Retrospective Cohort Study

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SUMMARY

Background: The study retrospectively investigated risk factors for refeeding syndrome in COPD patients with acute exacerbation and its impact on clinical outcomes.

Methods: We retrospectively reviewed discharge notes of patients with primary diagnosis of COPD with acute exacerbation from August 2014 to December 2015. Demographic data, BMI, the last post-bronchodilator FEV_1, case-mixed index (CMI), APACHE-II score, average daily total energy intake (TEI) and adjusted by current BW to obtain average daily total energy intake index (TEII) of the first four hospitalization days, the initial ABG with calculated P_aO_2/F_iO_2 were collected. Laboratory RFS was arbitrarily defined as either serum P or Mg declined 15% or more after feeding in comparison with the pre-feeding one and fell below the lower limit of normal ranges.

Results: 61 patients were eligible for analysis and 38% had RFS. Univariate analyses showed that advanced age, low BMI, high TEII, low post-bronchodilator FEV_1, high APACHE-II score, low P_aO_2/F_iO_2, high P_aCO_2, low pH, and leukocytosis at admission were risk factors for RFS. However, multiple logistic regression revealed that only BMI, TEII and the last post-bronchodilator FEV_1 were the risk predictors for RFS. Those who developed RFS had high risk to suffer from delirium, be intubated and receive invasive mechanical ventilation with difficult weaning from the ventilator, and have longer LOS. No in-hospital mortality was found.

Conclusion: RFS should not be overlooked in COPD patients with acute exacerbation. Awareness of this feeding-related complication is mandatory for early diagnosis and appropriate management to prevent morbidity and mortality.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a range of pathologic changes contributing to a highly variable clinical manifestations and extensive heterogeneity. The consequences of COPD experienced by patients include exercise intolerance, acute exacerbations, weight loss, impaired health status, and finally death. The complexity of the disease is often underestimated by traditional approach that focuses only on the presence of chronic airflow limitation and medications to relive airflow obstruction. Global Initiative for Chronic Obstructive Lung Disease (GOLD) was established in 1998 and its first clinical guideline[1] was released in 2001 with goals to increase awareness and improve the prevention and management of COPD. Since 2003, the GOLD guideline has been updated almost annually, however, the GOLD guideline mentioned little about the COPD-related malnutrition.[2]

Refeeding syndrome (RFS) is described as a series of biochemical and metabolic derangements that occur as a consequence of refeeding after a period of starvation or fasting.[3] It is a commonly overlooked life-threatening condition affecting patients with malnutrition or negative energy balance for more than 10 days on starting nutritional support.[4] COPD patients with acute exacerbation are at high risk for malnutrition due to increased energy consumption and decreased food intake. Dyspnea-related difficult

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swallowing, pathophysiology-related (hypoxemia, hypercapnia, acidosis) and medication-related (theophylline, etc) anorexia/nausea can impede energy intake. RFS might develop when they are orally supplemented, fed enterally or parenterally during hospitalization.

There is no data concerning the RFS in patients with COPD who are admitted due to acute exacerbation. The purpose of the study was to retrospectively investigate the incidence of RFS in COPD patients with acute exacerbation, its risk factors and impact on clinical outcomes.

This study protocol had been reviewed by the hospital ethic committee and was approved based on no violation of medical ethic code.

2. Materials and methods

We retrospectively reviewed discharge notes of patients with primary diagnosis of COPD with acute exacerbation from August 2014 to December 2015. Demographic data including sex, age, body mass index (BMI), the last post-bronchodilator FEV_1, case-mixed index (CMI), APACHE-II (Acute Physiology and Chronic Health Evaluation-II) score, the initial arterial blood gas with calculated P_aO_2/F_iO_2 were collected. Phosphate (P), magnesium (Mg), potassium (K), and random blood sugar were checked at the emergence service or the first day of hospitalization, and the second or the nadir ones were determined within the 4th day of hospitalization. Daily average total energy intake (TEI) was calculated from intravenous fluid and/or glucose solution, polymeric diets and oral nutritional supplementations, and adjusted by current body weight (BW) to get daily average total energy intake index (TEII) of the first four hospitalization days.

The reason why the energy intake was summed, averaged and adjusted by current body weight for the first four days after admission was based on the prospective cohort study by Marik et al, which showed hypophosphatemia developed soon after refeeding was started at 1.9 ± 1.1 days (mean + SD).[5] The maximal time point deduced from 1.9 ± 1.1 days was around 4 days (mean + 2 SD = 1.9 + 2 × 1.1 = 4.1). The 2nd blood sample drawn for electrolyte and glucose measurements was set no longer 4 days after admission based on the same reason.

Hypophosphatemia after feeding was universally considered as a hallmark of RFS, but hypomagnesemia and hypokalemia were always accompanied it.[4] Severe hypophosphatemia was mentioned, but the issue on "how was severe" was not clearly defined, and inter-laboratory and/or intra-laboratory variations were not considered. Currently there was no international consensus on clinical and laboratory definitions of RFS,[3] in this study we arbitrarily defined the laboratory RFS as either serum P (normal range: 2.80–4.70 mg/dL) or Mg (normal range: 1.90–2.50 mg/dL) declined 15% or more after feeding in comparison with the pre-feeding one and fell below the lower limit of normal ranges. The reason why we arbitrarily set a cut-point of 15% or more reduction in serum concentration of intracellular ions after diet intake was to avoid random bias and intra-laboratory variations.

Beta-adrenergic agonists can induce hypokalemia,[6] but it is an important pharmacologic modality to treat obstructive airway diseases with critical illness. Even though all patients received inhaled unit-dose Combivent® aerosol which contains short-acting beta-agonist Salbutamol and short-acting muscarinic antagonist Ipratropium, we could not definitely evaluate the extent of their hypokalemic effect, but the incidence of hypokalemia (normal K range: 3.5–4.5 mEq/L) was also assessed using the same criteria.

We also tried to elucidate the association of RFS with leukocytosis at admission, tracheal intubation, delirium during hospitalization, ventilator dependence, hospitalization length of stay (LOS) and in-hospital mortality.

The following patients were excluded for analysis: (1) Those who had impaired renal function with an estimated glomerular filtrate rate (eGFR) < 30 mL/h (2) Patients who had long-term used or during admission had to used medications which will affect the intestinal absorption or the renal loss of electrolytes (proton pump inhibitors,[7] diuretics, etc) or transcellular shift from the serum to the intracellular compartment, and (3) Those who had clinically evident gastrointestinal loss of electrolyte (such as diarrhea, vomiting, nasogastric drainage of gastric or gastroduodenal fluids) were also excluded.

Statistical analyses were conducted using the SPSS software (IBM SPSS Statistics for Windows, version 19.0: IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD and categorical variables as frequency. Independent student T test and X^2 test were used to test the null hypothesis of no difference between groups of continuous and categorical variables respectively. A two-sided value of $P < 0.05$ was considered statistically significant. In case of univariate analyses of RFS risk factors showing a $P < 0.05$, multiple logistic regression analysis with backward stepwise elimination was performed. Relative risk (RR) and odd ratio (OR) with 95% confidence intervals (95% CI) were calculated for some items.

3. Results

There were 65 patients admitted due to COPD with acute exacerbation, who showed no symptomatic relief after unit-dose Combivent® aerosol inhalation and intravenous steroid at the emergency service. After admission, all patients received intravenous fluid and electrolytes. Dieticians were consulted, tube-fed calorie and/or oral supplementation was prescribed.

After hospitalization they all were on mask non-invasive ventilation with BiPAP mode and systemic steroid was continued until the cardiopulmonary status improved and the patient felt well-being. If the condition deteriorated with conscious disturbance or severe respiratory acidosis with pH < 7.00, tracheal intubation with mechanical ventilation was performed.

No patients received total parenteral nutrition (TPN) during hospitalization, only intravenous saline and/or glucose water was administered to facilitate medications. Patients in severe respiratory distress received nasogastric feeding of polymeric diets, and those in rather respiratory stability might take oral nutritional supplementations.

Sixty one cases were eligible for analysis (Fig. 1). Among them, 23 patients developed laboratory RFS after admission, and the other 38 patients were used as control group. 38% of COPD patients with acute exacerbation experienced laboratory RFS. The incidences of hypophosphatemia, hypomagnesemia and hypokalemia were 38%, 30% and 34% respectively. Sex had no statistic difference ($P = 0.7153$) between groups, but age ($P = 0.0262$) seemed to be a risk factor for RFS. The baseline P, Mg, and blood sugar had no statistic difference between groups, but the RFS (+) group had statistically low data of the 2nd or nadir P and Mg in comparison with the RFS (−) group. Blood sugar at the 2nd or nadir electrolyte measurement also showed no statistic difference between groups. (Table 1).

In addition to age, BMI, the last post-bronchodilator FEV_1, APACHE-II score, P_aO_2/F_iO_2, P_aCO_2, pH and presence of leukocytosis at admission were all statistically different between groups ($P < 0.05$) with univariate analysis, and CMI did not seem to be a risk factor. Although the average total energy intake (TEI) of the first four hospitalization days showed no statistical significance ($P = 0.2143$) between two groups, but the RFS (+) received more TEII than RFS (−) ($P < 0.0001$) (Table 2). However, multiple logistic

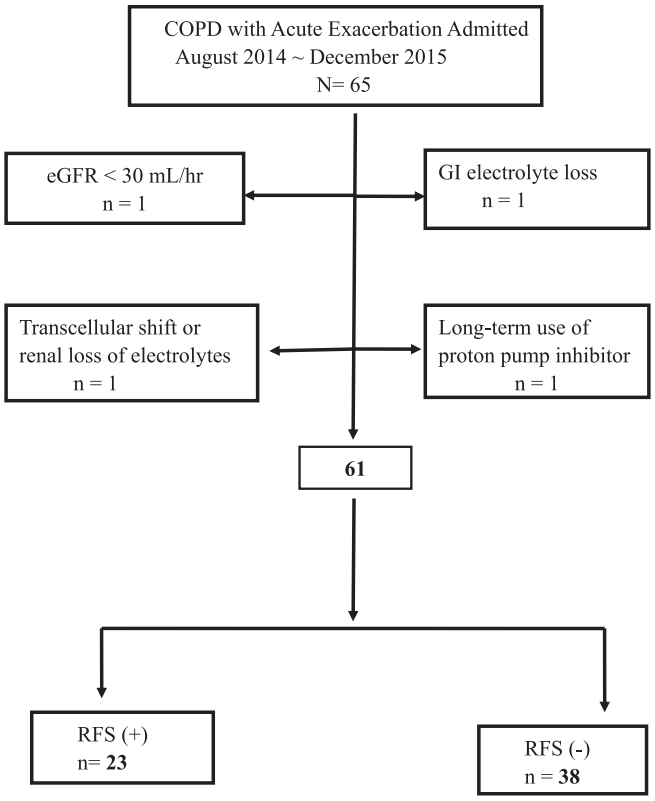

Fig. 1. The study flow chart.

Table 1
The initial and the 2nd or nadir electrolyte and blood sugar profiles.

	RFS (+)	RFS (−)	P
Baseline P (mg/dL)	3.51 ± 0.48	3.61 ± 0.39	0.3776
Baseline Mg (mg/dL)	2.14 ± 0.35	2.23 ± 0.41	0.3844
Baseline K (mEq/L)	4.14 ± 0.35	4.21 ± 0.32	0.4273
Baseline blood sugar (mg/dL)	84.3 + 10.7	86.7 ± 11.2	0.4129
The 2nd or nadir P (mg/dL)	2.41 ± 0.49	2.88 ± 0.21	<0.0001
The 2nd or nadir Mg (mg/dL)	1.75 ± 0.37	2.13 ± 0.39	0.0004
The 2nd or nadir K (mg/dL)	3.16 ± 0.39	3.88 ± 0.36	<0.0001
The 2nd blood sugar (mg/dL)	138.9 ± 12.5	133.4 ± 13.4	0.1166

RFS (+): Presence of RFS; RFS (−): Absence of RFS.

regression revealed that only BMI (95% CI = 0.56–0.89), TEII (95% CI = 1.05–1.41) and the last post-bronchodilator FEV_1 (95% CI = 0.65–0.94) were risk predictors for RFS (Table 3).

The impact of developing RFS during hospitalization was investigated (Table 4). Those patients who had RFS had high risk of developing delirium (RR = 8.26, 95% CI = 1.03–66.37), being intubated and receiving invasive mechanical ventilation (RR = 8.26, 95% CI = 1.03–66.37), and longer hospitalization LOS (P < 0.0001). The contribution of RFS (+) to ventilator dependence was also significant (RR = 8.26, 95% CI = 1.03–66.37). There was no mortality case in both groups.

Table 2
Binary analysis of risk factors for RFS.

	RFS (+)	RFS (−)	P
Gender (male/female)	22/1	37/1	0.7153
Age (years)	75.3 ± 10.8	67.2 ± 14.8	0.0262
BMI (kg/m^2)	20.7 ± 2.2	24.3 ± 2.3	<0.0001
TEI (kcal/day)	1090 ± 175	1030 ± 186	0.2143
TEII (Kcal /kg/day)	20.4 ± 2.2	16.2 ± 2.1	<0.0001
Post-bronchodilator FEV_1 (L)	1.56 ± 0.23	1.96 ± 0.31	<0.0001
APACHE-II score	14.8 ± 3.1	12.9 ± 3.2	0.0266
CMI	4.09 ± 1.28	3.77 ± 1.34	0.3618
P_aO_2/F_iO_2 (mmHg)	187.6 ± 34.5	207.9 ± 32.9	0.0254
P_aCO_2 (mmHg)	61.4 ± 4.3	58.7 ± 4.9	0.0332
pH	7.24 ± 0.13	7.32 ± 0.14	0.0302
Leukocytosis (Yes/No)	10/13	6/32	0.0172

Table 3
Multiple logistic regression analysis with backward stepwise elimination to assess the associated risk factors for RFS.

	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
Age (years)	1.02 (0.92–1.24)	0.167		
BMI (kg/m^2)	0.76(0.63–0.84)	<0.001	0.73(0.56–0.89)	0.017
TEII (Kcal /kg/day)	1.13(1.09–1.34)	<0.001	1.18(1.05–1.41)	0.012
Post-bronchodilator FEV_1	0.91(0.79–0.94)	<0.001	0.89(0.65–0.94)	0.032
APACHE-II score	1.26(0.76–1.62)	0.072		
P_aO_2/F_iO_2	0.86(0.74–1.35)	0.083		
P_aCO_2	1.34(0.72–1.86)	0.094		
pH	0.65(0.53–1.12)	0.079		
Leukocytosis (Yes/No)	1.18 (0.88–1.45)	0.134		

Table 4
The impact of RFS on outcome profiles.

	RFS (+)	RFS (−)	P	RR (95% CI)
Delirium (Yes/No)	5/18	1/37	0.0152	8.26(1.03–66.37)
Intubation (Yes/No)	5/18	1/37	0.0152	8.26(1.03–66.37)
VD (Yes/No)	5/18	1/37	0.0152	8.26(1.03–66.37)
Hospital LOS (days)	24.3 ± 7.6	14.9 ± 6.2	<0.0001	
In-hospital survival	23/23	38/38	Not assessed	

VD: Ventilator dependence.

4. Discussion

Clinical presentations compatible with RFS was first reported in medical literature in Far East military prisoners after the 2nd world war,[8] which showed that malnourished military prisoners starting to eat again after prolonged starvation seemed soon to precipitate cardiac failure and neurological crisis. The reported incidence of RFS of hospitalized patients was variable depending on the inconsistent laboratory and clinical definition of RFS, the nutritional status of specific patient groups and clinicians' awareness of it. Mild symptoms of RFS remain frequently unrecognized and low serum electrolytes are often assumed to be associated with other disorders. According to a study of 10,197 hospitalized patients,[9] the incidence of severe hypophosphatemia was 0.43%. In the other study, 100% of patients who received TPN without phosphate supplementation developed hypophosphatemia, and 38% TPN patients had hypophosphatemia even though TPN solution was supplemented with phosphate preparation.[10] Classically, patients at risk of RFS[11] were those with kwashiorkor or marasmus, anorexia nervosa, chronic systemic inflammatory disorders, chronic alcoholism, and prolonged fasting. The easy availability of parenteral and enteral nutrition in current clinical practice and lack of awareness of RFS had made the situation worse.[12–14]

We found in this study that those COPD patients with acute exacerbation who had advanced age, low BMI, high TEII, low post-bronchodilator FEV_1, high disease severity (APACHE-II score), more severely impaired gas exchange with acidosis, and leukocytosis at admission had higher risk to develop RFS. However, multiple logistic regression revealed that only BMI, TEII and the last post-bronchodilator FEV_1 were the best risk predictors for RFS. Patients with low BMI (20.7 ± 2.2 vs 24.3 ± 2.3), high TEII (20.4 ± 2.2 vs 16.2 ± 2.1) and severely impaired pulmonary function

represented by the last post-bronchodilator FEV_1 (1.56 ± 0.23 vs 1.96 ± 0.31) were prone to developing RFS. It could be interpreted as that RFS resulted from the interaction of severity of malnutrition, aggressiveness of caloric intake in the acute phase of critical illness, and severity of underlying disease process.

Those who developed RFS had high risk for suffering from delirium, being intubated and receiving invasive mechanical ventilation, difficulty with weaning from mechanical ventilation (duration > 21 days), and longer hospital LOS. It seemed in this study that malnourished COPD patients with acute exacerbation receiving hypocaloric nutrition had low risk for RFS and carried better outcomes, which was consistent with a research by Krishnan JA et al.[15] They conducted a prospective cohort study to investigate the effect of caloric intake in the early phase of acute illness on clinical outcomes in two teaching hospitals. Patients in medical ICUs with LOS > 4 days were enrolled and total 187 patients were eligible for analysis. The caloric intake was compared to ACCP (American college of Chest Physicians) guideline recommendations of 30 kcal/kg/day and divided by tertiles. The results showed that: (1) Caloric intake was in proportional to numbers of gastric residual volume < 100 mL, but not to disease severity, nutritional status, or routes of feeding (enteral or parenteral). (2) Moderate caloric intake (9–18 kcal/kg/day) was associated with better outcomes based on discharge survival rate and ICU ventilator weaning rate, but the incidence of sepsis during ICU stay was similar among three groups. Overfeeding in the acute phase of critical illness had proved to be associated with poor outcomes,[16,17] and now we should also pay more attention to the disadvantage of eucaloric feeding in the acute phase of critical illness.

RFS was associated with neuropsychiatric disorders, such as delirium[18,19] and central pontine myelinolysis.[20–22] When patients presented clinically with shortness of breath and mental confusion, clinical deterioration was always impressed and they were prone to being intubated for airway protection and mechanical ventilation. In this study, patients who developed RFS had a RR of 8.26 to be intubated in comparison with those who did not. Six patients, including 5 in RFS (+) group and 1 in RFS (−) group, went through the process of being intubated and difficult weaning from ventilator. Those 6 patients requiring endotracheal intubation had abnormal gas exchanges and developed delirium in advance, in this situation and before intubation it was difficult to measure Pimax (maximal peak inspiratory pressure) representative of diaphragmatic contraction strength due to its need of patient's cooperation in non-intubated status. Persistent abnormal gas exchanges, refractory respiratory distress, and mental confusion or delirium are major risk factors for tracheal intubation in the acute phase of COPD with acute exacerbation, but ventilator-induced diaphragmatic dysfunction and ICU-acquired weakness play important roles in weaning difficulty.

Cardiovascular complications were also reported in patients with RFS,[23,24] but in this study we did not found events of hypomagnesemia-related tachyarrhythmias. Respiratory muscle strength and endurance can be impaired with electrolyte abnormalities, and there were several reports of acute respiratory failure caused by RFS in patients without lung pathology.[25–30] In patients with lung pathology such as COPD, the development of RFS might aggravate the respiratory dysfunction and result in poor prognosis.

This study had some limitation. First, this was a retrospective analysis with some important relevant data missing, such as body weight change. Increased body weight due to fluid retention was common during RFS[31] and could be used as a clinical marker of RFS. Every patients had body weight checked at admission in our hospital, but not every day. Second, the sample size was small, statistic inference might be misleading.

In summary, nutrition is good for the malnourished patients,[32–36] but it might turn bad if some precautions are not taken in advance during nutritional implementation. RFS is diet-induced and presents itself with a wide spectrum of clinical manifestations, from rather no or nonspecific symptoms to potentially life-threatening complications[37] in patients who are malnourished from whatever cause, but it is preventable. The first step in the prevention of RFS is clinical awareness of it. In the acute phase (the first 3–4 days) of critical illness, Stanga et al suggested caloric intake should be initiated from 10 kcal/kg/day and progress slowly,[4] plasma intracellular ions (P, Mg, and K) should be monitored closely and supplemented if indicated. Routine thiamin supplementation is mandatory to prevent Wernicke's encephalopathy and Korsakoff syndrome.[38] Only when the catabolic phase and systemic inflammatory response syndrome of critical illness are over, nutritional support to pursue recommended goal of energy intake and positive nitrogen balance could be feasible and beneficial to the patients, and do no harm.

Conflict of interest

The authors have no conflict of interest to declare.

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