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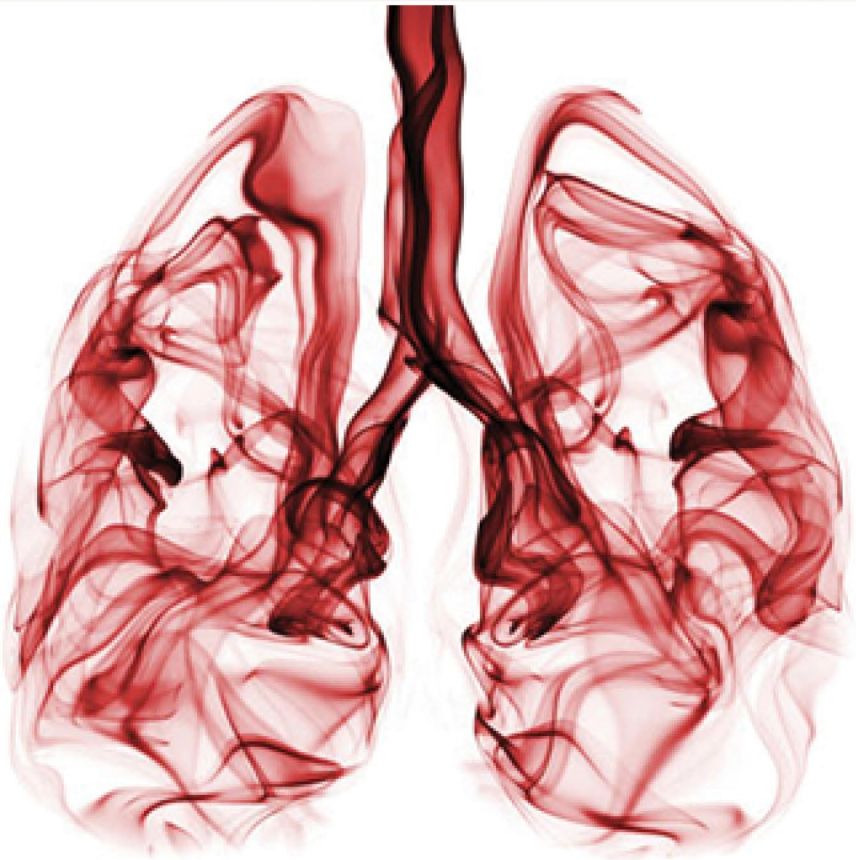
ISSN 2377-1658

PULMONARY RESEARCH AND RESPIRATORY MEDICINE

Open Journal



| December 2017 | Volume 4 | Issue 2 |

Openventio PUBLISHERS

PULMONARY RESEARCH AND RESPIRATORY MEDICINE

ISSN 2377-1658

Open Journal

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Openventio PUBLISHERS

PULMONARY RESEARCH AND RESPIRATORY MEDICINE

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-4-e007

Editorial

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Volume 4 : Issue 2
Article Ref. #: 1000PRRMOJ4e007

Article History
Received: March 28th, 2017
Accepted: March 28th, 2017
Published: March 28th, 2017

Citation
Kohzuki M. Balloon pulmonary angioplasty (BPA) and rehabilitation for chronic thromboembolic pulmonary hypertension (CTEPH). *Pulm Res Respir Med Open J*. 2017; 4(2): e1-e2. doi: 10.17140/PRRMOJ-4-e007

Balloon Pulmonary Angioplasty (BPA) and Rehabilitation for Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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Chronic thromboembolic pulmonary hypertension (CTEPH) has a poor prognosis because of increased pulmonary arterial pressure (PAP) causing pulmonary hypertension and progressive right-sided heart failure.[1,2] Typical symptoms are dyspnea on exertion, fatigability, and reduced quality of life.[3] Balloon pulmonary angioplasty (BPA) has been reported to improve hemodynamics and functional capacity in patients with CTEPH who are not candidates for pulmonary endarterectomy.[4,5] However, the effect of BPA on respiratory function in patients with CTEPH is unclear.

Recently, Akizuki et al[3] investigated how BPA affects hemodynamics, ventilatory efficiency, and gas exchange in patients with CTEPH using right heart catheterization, respiratory function testing, and cardiopulmonary exercise testing (CPX).[3] They enrolled patients with inoperable CTEPH who underwent BPA primarily in lower lobe arteries and upper and middle lobe arteries. They compared changes in hemodynamics and respiratory function between different BPA fields.

They showed differences in the effect of BPA on respiratory function in different BPA fields in patients with CTEPH. Mean PAP and pulmonary vascular resistance significantly improved. Oxygenation at rest and during exercise improved regardless of the BPA field.

However, the time course of changes in the percent predicted diffusion capacity of lung for carbon monoxide (% D_{LCO}), The ventilation/CO_2 production (V_E/V_{CO2}) slope, and FET_{CO2} was significantly different between lower and upper/middle lung BPA fields. $\%DL_{CO}$ decreased after BPA in the lower lung field with no recovery. However, $\%DL_{CO}$ increased after BPA in the upper middle lung field and continued to improve during the follow-up. V_E/V_{CO2} slope significantly improved after BPA in the lower lung field and continued to improve during the follow-up. However, the V_E/V_{CO2} slope remained unchanged after BPA in the upper/middle lung field. Therefore, the effect of BPA on respiratory function in patients with CTEPH differed depending on the lung field.[3]

Based on their results, they suggested that BPA in the lower lung field improves oxygenation and respiratory function parameters during exercise, such as $V_{E/}V_{CO2}$ slope and $FET_{CO2,}$ because of remarkable improvement in hemodynamics. They also suggested that BPA in the upper/middle lung field may improve oxygenation and respiratory function parameters at rest, such as $\%DL_{CO}$, caused by improvement in V/Q mismatch.[3]

However, reduced D_{LCO} in CTEPH reflects not only the effect of low V/Q but also dead space ventilation (deadspace/tidal volume [V_D/V_T]) in regions with high V/Q.[6] Further, one hypothesis suggests that in patients with CTEPH, a decrease in D_{LCO} also indicates microvascular remodeling.[6] Results of previous reports that D_{LCO} remained unchanged even after successful pulmonary endarterectomy and BPA supported the hypothesis.[7,8]

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-e007

These points of view suggest that reduced D_{LCO} in patients with CTEPH may be caused by low V/Q, high V/Q and microvascular remodeling.[6] Therefore, it is important to distinguish the effects of these three components when discussing D_{LCO} in CTEPH. To obtain further evidence to support their hypothesis, Takei et al[6] suggest analyzing the V_D/V_T and shunt fraction (Qs/Qt) to distinguish the amelioration of high V/Q and deterioration of low V/Q in different lung lobes.[6]

The goal of effective CTEPH management is to relieve symptoms, slow disease progression, improve exercise tolerance, prevent and treat complications, and improve prognosis and overall quality of life. The clinical presentation of CTEPH is similar to pulmonary arterial hypertension (PAH) with nonspecific symptoms. Further studies are required to elucidate to noninvasively examine the severity of CTEPH and to noninvasively distinguish CTEPH from PAH, for example, by respiratory function or ventilator gas analysis in different postures.

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Openventio PUBLISHERS

PULMONARY RESEARCH AND RESPIRATORY MEDICINE

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-4-e008

Editorial

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Volume 4 : Issue 2
Article Ref. #: 1000PRRMOJ4e008

Article History
Received: September 5th, 2017
Accepted: September 5th, 2017
Published: September 5th, 2017

Citation
Kohzuki M, Izoe Y, Harada T. The importance of rehabilitation before and after lung transplantation. *Pulm Res Respir Med Open J*. 2017; 4(2): e3-e5. doi: 10.17140/PRRMOJ-4-e008

The Importance of Rehabilitation before and after Lung Transplantation

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Lung transplantation (LTx) has gained widespread acceptance as a therapeutic option for end-stage pulmonary disease. LTx has been shown to improve quality of life (QoL) and survival in individuals with various end-stage lung diseases.

However, numerous studies have been demonstrated that LTx recipients experience persistent impairments in exercise capacity and skeletal muscle function despite a vast improvement in lung function after LTx.[1-7] Persistent limitations in exercise capacity and skeletal muscle function have been observed for more than 1 year after transplantation.[8]

Investigations of muscle function in LTx recipients reveal decreased muscle mass and strength, reductions in type 1 fiber proportion, decreased calcium uptake and release, decreased mitochondrial enzyme activity, and impaired oxidative capacity of the peripheral muscles.[1]

Similarly, poor daily physical activity has been studied in heart and kidney recipients. Heart recipients were classified as very sedentary, based on accelerometer measurements.[9] Children and adolescents with renal tranplants have severely impaired cardiorespiratory fitness and physical activity compared with their healthy counterparts.[10,11]

In these patients, inactivity prior to transplantation and resulting pre-transplant deconditioning are likely to influence functional recovery after surgery. Repeated episodes of infection and rejection, use of anti-inflammatory and immunosuppressive drugs and a sedentary life style are possible post-transplant contributing to limitations in the physical fitness.

In LTx patients, pulmonary function is only patially related to participation in daily physical activities. For a given limitation in pulmonary function a considerable variability in daily physical activity was found. Of all measured variables the six minutes walking distance (6MWD) showed the strongest association with participation in daily physical activity. Good correlations between 6MWD and both minutes in activities 2 METs and number of steps were observed.[12]

A systematic review was undertaken to examine the evidence for exercise training on functional outcomes in LTx recipients.[1] Some evidence was found to support that a period of structured exercise training could improve maximal and functional exercise capacity, skeletal muscle strength, and lumbar bone mineral density in LTx recipients.[1]

Rehabilitation is also important in the pre-operative management of patients.[13] The importance of pre-transplant rehabilitation has been shown in the latest joint American Thoracic Society (ATS)/European Respiratory Society (ERS) official statement on pulmonary rehabilitation.[14] Before LTx, while patients wait for surgery, rehabilitation was found to improve exercise tolerance and activities of living, without any significant change in respiratory function.[15] Pulmonary rehabilitation improves physical fitness of pulmonary failure patients who are on waiting list for lung transplantation, meanwhile some of the candidates could deviate from the LTx waiting patients list.[15] Moreover, reduced cardiorespiratory fitness was associated with the clustering of cardiovascular risk factors. Routine counseling for increased physical

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-e008

activities is strongly recommended.

Further studies are needed to determine the potential for exercise training to optimize these functional outcomes and to develop optimal guidelines for exercise prescription in the LTxs population.[16]

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-e008

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PULMONARY RESEARCH AND RESPIRATORY MEDICINE

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-4-e009

Editorial

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Volume 4 : Issue 2
Article Ref. #: 1000PRRMOJ4e009

Article History
Received: September 20th, 2017
Accepted: September 21st, 2017
Published: September 21st, 2017

Citation
Saraya T. Paraneoplastic syndrome: What should pulmonologists know? *Pulm Res Respir Med Open J*. 2017; 4(2): e6-e8. doi: 10.17140/PRRMOJ-4-e009

Paraneoplastic Syndrome: What should Pulmonologists know?

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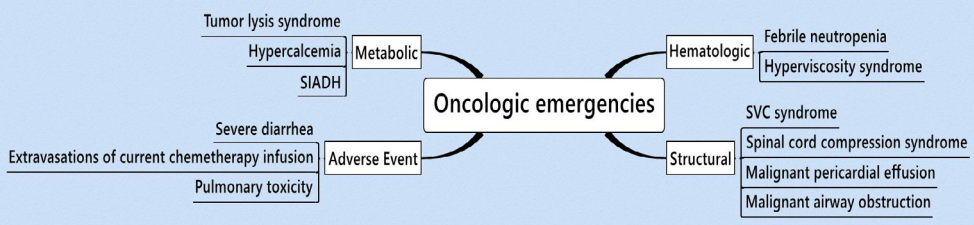
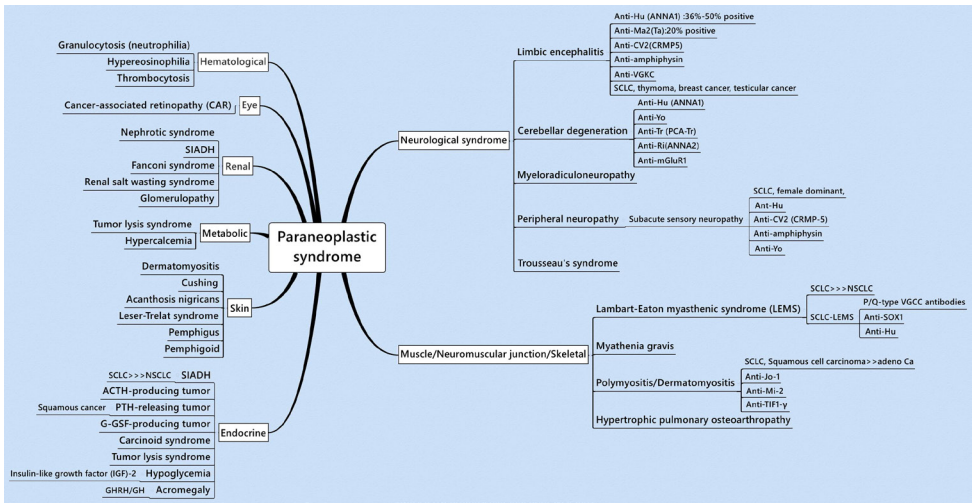
Pulmonologists often encounter patients with oncologic emergencies (Figure 1) such as metabolic syndrome (tumor lysis syndrome),[1] hypercalcemia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hematologic (febrile neutropenia and hyperviscosity syndrome) and structural disorders (superior vena cava syndrome,[2] spinal cord compression syndrome, malignant pericardial effusion,[3] and malignant airway obstruction[4]), alongwith drug-related adverse eventsin already-known malignancies including liver[5] or pulmonary toxicity[6,7] and renal disease.[8,9] Additionally, pulmonologists occasionally encounter paraneoplastic syndrome (PNS), which partially overlaps with oncologic emergencies (Figure 1). In this regard, pulmonologists should be aware of PNS, involving organ-based classification (Figure 2).

Figure 1: Schema of the Common Oncologic Emergencies.



SIADH: Syndrome of Inappropriate Secretion of Antidiuretic Hormone; SVC: Superior Vena Cava Syndrome.

Figure 2: Organ-based Classification of Paraneoplastic Syndrome.



ACTH: Adrenocorticotropic Hormone; ANNA1: Type I Anti-Neuronal Nuclear Antibody; Anti-SOX1: Anti-Sry-related HMG; Anti-TIF1: Anti-transcriptional intermediary factor 1-gamma; Anti-VGCC: Anti-Voltage-Gated Calcium Channel; Anti-VGKC: Anti-VoltAge-Gated Potassium Channel, G-CSF: Granulocyte-Colony Stimulating Factor, GHRH/GH: Growth Hormone Releasing Hormone/Glucose Hormone, PTH: Parathyroid Hormone, SCLC: Small Cell Lung Cancer.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-e009

PNS has diverse symptoms and signs in neurologic,[10,11] muscle/neuromuscular junction/skeletal,[10] hematological,[12] eye,[13] renal,[14] metabolic,[1] skin,[15,16] and endocrine systems,[17] which often present as antecedent problems of lung cancer or other malignancies. In some cases, physicians might have difficulty in discriminating PNS from malignant independent conditions due to clinical similarity but they are pathologically different.[18] PNS occurs in approximately 10% of patients with lung cancer,[19] and the histology of lung cancer influences the type of associated PNS. The most common forms of PNS are hypercalcemia fromsquamous carcinoma and SIADH in small cell lung cancer.

Nowadays, various onconeural antibodies have been detected, and well-characterized autoantibodies such as anti-Hu (ANNA1), anti-Yo (PCA1), anti-CV2 (CRMP5), anti-Ri, anti-Ma2 (Ta), and anti-amphiphysin have been described. Other partially characterized onconeural antibodies and other antibodies were also identified.[17] These antibodies seem to be directly involved in cell surface or synaptic proteins or disrupt function of receptors by cross-linking and internalization, which leads to PNS.[20]

Of note, a high frequency of anti-Hu antibody has been reported in PNS such as limbic encephalitis, cerebellar degeneration, and peripheral neuropathy (Figure 2), which resulted in "anti-Hu syndrome" being considered an independent entity.[21] Moreover, although identification of onconeural antibodies can be a useful marker for early diagnosis of PNS and/or malignancies, multidisciplinary assessment for PNS is needed along with long-term observation.

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ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-e009

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Openventio PUBLISHERS

PULMONARY RESEARCH AND RESPIRATORY MEDICINE

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-4-135

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Volume 4 : Issue 2
Article Ref. #: 1000PRRMOJ4135

Article History
Received: February 8th, 2017
Accepted: March 3rd, 2017
Published: March 3rd, 2017

Citation
Yokoo K, Shiratori M, Ikeda K, et al. Significance of combined emphysema in idiopathic pulmonary fibrosis and serum surfactant protein-D as a prognostic factor. *Pulm Res Respir Med Open J*. 2017; 4(2): 24-32. doi: 10.17140/PRRMOJ-4-135

Significance of Combined Emphysema in Idiopathic Pulmonary Fibrosis and Serum Surfactant Protein-D as a Prognostic Factor

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ABSTRACT

Background and Objectives: Idiopathic pulmonary fibrosis (IPF) is a chronic disease of unknown aetiology and is often associated with a syndrome called combined pulmonary fibrosis and emphysema (CPFE). This study aimed to identify practical predictors of prognosis in IPF patients associated with CPFE.
Subjects and Methods: We retrospectively studied 72 patients with IPF and evaluated the threshold of emphysematous area affecting prognosis on high-resolution computed tomography (HRCT) scans. As predictor candidates, various pulmonary function tests (PFTs) and biomarkers, e.g. surfactant protein (SP)-A and SP-D, were assessed.
Results: The survival rate of the CPFE group, defined as having an emphysematous area greater than 25% on HRCT, was significantly worse than that of the non-CPFE group, despite no significant difference in fibrosis scores. An annual percent decline of diffusing capacity of the lung for carbon monoxide (% DLCO) of more than 5% was a significant prognostic factor in the CPFE group. High concentration of serum SP-D was a significant prognostic factor in both the CPFE and non-CPFE groups. However, cut-off levels in the CPFE group were lower than those in the non-CPFE group.
Conclusions: We demonstrated worse prognosis in IPF associated with CPFE syndrome compared to the other subset of IPF, and showed that % DLCO and SP-D are useful predictors of poor prognosis.

KEY WORDS: Emphysema; Idiopathic pulmonary fibrosis; Prognosis, Pulmonary function test; Surfactant protein-D.

ABBREVIATIONS: ALAT: The Latin American Thoracic Association; ATS: The American Thoracic Society; CI: Confidence Interval; CPFE: Combined Pulmonary Fibrosis and Emphysema; DLCO: Diffusing capacity of the Lung for carbon monoxide; ERS: The European Respiratory Society; eSPAP: Estimated Systolic Pulmonary Arterial Pressure; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; HR: Hazard Ratio; HRCT: High-Resolution Computed Tomography; IIPs: Idiopathic Interstitial Pneumonias; IPF: Idiopathic Pulmonary Fibrosis; JRS: The Japanese Respiratory Society; KCO: DLCO divided by the alveolar volume (DLCO/V_A); KL-6: Krebs van den lungen-6; PFT: Pulmonary Function Test; PH: Pulmonary Hypertension; SD: Standard Deviation; SP: Surfactant Protein; TLC: Total Lung Capacity; UIP: Usual Interstitial Pneumonia; V_A: Alveolar Volume.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-135

INTRODUCTION

The concept of combined pulmonary fibrosis and emphysema (CPFE) has been recently proposed as a syndrome characterized by the coexistence of emphysematous and fibrotic lesions within the same lobe of the lung[1-3]; this concept is also applicable to patients with idiopathic pulmonary fibrosis (IPF). IPF is a disease with poor prognosis and diverse causes of death,[4-7] and it has not yet been determined whether features of CPFE in IPF patients have an effect on its prognosis and/or causes of death.

Past reports, in which CPFE was defined as having an emphysematous area of 10% or more of the whole lung, showed uncertain prognoses[8-10]; another report suggested that the prognosis of CPFE was poor when it was defined as having an emphysematous area of 25% or greater.[11] Therefore, we considered it necessary to define CPFE based on the emphysematous area reflecting prognosis.

Although the evaluation of restrictive disturbance in pulmonary function tests (PFTs) (which is represented by forced vital capacity; FVC) is reported as a useful predictor of prognosis,[7,12-14] its meaning is uncertain in cases where emphysematous lesions are involved. Therefore, the evaluation of restrictive disturbance seems inappropriate for the prediction of prognosis in IPF patients with features of CPFE.

Various predictors have been reported for the prognosis of IPF.[15] For example, measurements of concentrations of serum markers such as surfactant protein (SP)-A, SP-D and Krebs van den Lungen-6 (KL-6) have been reported as useful for predicting prognosis.[16-19]

In this paper, we elucidate the prognosis of IPF patients with features of CPFE and investigate whether the serum markers including SP-D are useful to predict prognosis, even when restricted to IPF patients with features of CPFE.

SUBJECTS AND METHODS

Subjects

Seventy-two consecutive patients with IPF who visited Sapporo Medical University Hospital or Teine Keijinkai Hospital from 1st January 2007 to 30th September 2012 were enrolled in this retrospective cohort study. Patients were diagnosed with IPF in accordance with the American Thoracic Society (ATS)/The European Respiratory Society (ERS)/ The Japanese Respiratory Society (JRS)/The Latin American Thoracic Association (ALAT) statement.[20] Exclusion criteria included the presence of connective tissue disease or any other interstitial lung disease, such as other subtypes of idiopathic interstitial pneumonias (IIPs), pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, pulmonary lymphangioleiomyomatosis, eosinophilic pneumonia and drug-induced interstitial pneumonia. IPF patients with malignant tumours (e.g., lung cancer) at enrolment were also excluded. All patients were clinically stable at the initial visit. This study was approved by the Sapporo Medical University Hospital Institutional Review Board and the Teine Keijinkai Hospital Ethics Committee.

Methods

A high-resolution computed tomography (HRCT) scan was performed within a month after enrolment. In accordance with the ATS/ERS/JRS/ALAT statement,[20] patients were enrolled if they had presence of a "usual interstitial pneumonia (UIP) pattern" on HRCT or both "possible UIP pattern" on HRCT and "UIP" on pathological criteria. For evaluating emphysema, low attenuation areas on three scans (upper: near the superior margin of the aortic arch; middle: at the level of bifurcation of trachea and lower: level of the inferior pulmonary veins) in both lungs were calculated. To identify the CPFE criteria that reflect prognosis of IPF, we evaluated two thresholds: 10% and 25% emphysematous area in the total lung area. The case in which the sum of emphysema areas in all lung fields was at or above the threshold was defined as CPFE. HRCT findings were evaluated with the consensus of two pulmonologists who are experts in radiographic diagnosis and were blinded to patients' clinical information. We evaluated inter-observer agreement with a senior pulmonologist who was blinded to the first diagnosis and had previously studied the definitions we used to classify the patients as having CPFE. Final conclusions were reached through consensus. Fibrosis was defined as the presence of irregular linear opacities, traction bronchiectasis and honeycombing in HRCT, as described by Hanak et al.[21] To determine fibrosis score, the extent of fibrosis was calculated using HRCT scans as described above and patients were divided into three subsets: <10%, 10-40% and >40%.

PFTs were performed with a Chestac-9800 (Chest M.I. Inc., Tokyo, Japan) several times during the study period. The number of PFTs and their testing intervals differed across patients due to the retrospective cohort design of the study. To simplify the study design, we analyzed only two values: The initial and final PFT values for each patient. Initial values were obtained within a month after enrolment, and final values were the final PFT values collected in the follow-up period. The percentage change in each index of a PFT was calculated according to the following formula:

$$\Delta\%\text{Value}=[(\%\text{Value}_{\text{final}}-\%\text{Value}_{\text{initial}})/\%\text{Value}_{\text{initial}})\times 100].$$

Moreover, the percentage of change per year in each index was calculated as Δ% Value/year=(Δ% Value/the number of follow-up months)×12.

Concentrations of biomarkers KL-6, SP-A and SP-D were measured *in sera* using the commercialized enzyme-linked

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-135

immunosorbent assay developed for each protein.[16,19] All patients underwent semi-ordinal blood examination of KL-6, SP-A and SP-D once every 1-3 months. For analyses, we used data from blood collection within a month of enrolment.

Forty-eight patients underwent echocardiography to identify complications of pulmonary hypertension (PH), which were defined as >45 mmHg estimated systolic pulmonary arterial pressure (eSPAP), based on tricuspid regurgitant pressure gradient, as reported by Mejía et al.[8] In patients undergoing surgical biopsy, we confirmed diagnoses in accordance with the ATS/ERS/JRS/ALAT statement.[20]

Statistical Analysis

Clinical data are presented as mean±standard deviation (SD). Comparison between the groups was performed using the Student's unpaired *t*-tests, the Mann-Whitney *U*-test (Wilcoxon rank-sum test), chi-square statistics and Fisher's exact test, as appropriate. A Cox proportional hazards model analysis was performed to determine the relationships between clinical data-including PFTs and laboratory data and survival. Survival analysis was performed *via* the Kaplan-Meier method, with end-points of death or censoring. JMP10 software (SAS Institute Inc. Cary, NC, USA) was used for statistical analysis, and a $p<0.05$ was considered significant.

RESULTS

Baseline Characteristics

The study period for each patient lasted from enrolment until the last day before study commencement (range: 4.5-64.7 months; median: 38.3 months). For patients with an emphysema area of <10%, 40 and 32 (56% and 44%) out of 72 patients were classified as CPFE and non-CPFE, respectively. For patients with an emphysema area of 25%, 34 and 38 (47% and 53%) out of 72 patients were classified as CPFE and non-CPFE, respectively. We consequently adopted 25%, and not 10%, as a threshold for CPFE so that the survival analysis could distinguish (i.e., find a significant difference) between the CPFE and non-CPFE groups, as described in the following section ("Prognosis").

Patient's background characteristics and clinical manifestations at enrolment are shown in Table 1. Significant differences in gender and smoking history were found between the CPFE and non-CPFE groups. The smoking history of the two groups was 50.2±27.1 pack/year and 33.9±32.1 (p=0.021), respectively. Ten patients in the CPFE group and nine in the non-CPFE group were surgically proven to have UIP. Honeycombing

Table 1: Demographic Characteristics, Fibrosis Score and Serum Markers at Enrolment.

Characteristics	Threshold; 25% area of emphysema		Threshold; 10% area of emphysema	
	CPFE group	non-CPFE group	CPFE group	non-CPFE group
	n=34	n=38	n=40	n=32
Gender (male/female)	32/2#	25/13	37/3#	20/12
Age at enrolment (years)	70.8±7.1	72.2±8.6	71.5±7.3	71.6±8.9
Smoking status				
Current or former/never	34/0#	27/11	38/2#	31/1
Pack-years	50.2±27.1*	33.9±32.1	50.1±27.0*	30.9±32.3
Surgical lung biopsy (yes/no)	10/24 (29)	9/29 (24)	11/40 (27.5)	8/32 (25)
Previous treatment (yes/no)	21/13	17/21	23/17	14/18
CS + IS	8	6	9	5
CS + IS +PFD	3	4	3	4
PFD alone	10	7	11	5
Fibrosis score				
less than 10%	6	7	12	9
10%-40%	22	28	22	20
more than 40%	6	3	6	3
Echocardiography				
eSPAP (mmHg)	32.5±11.0	33.1±9.9	32.7±10.5	33.0±10.6
eSPAP>45 mmHg (yes/no)	1/24	1/22	1/28	1/18
Serum biomarkers				
KL-6 (U/mL)	1242.5±881.0	1142.0±749.3	1245.7±914.5	1120.3±664.1
SP-A (ng/mL)	92.7±45.8	82.1±39.3	92.4±44.3	80.4±39.9
SP-D (ng/mL)	277.7±195.1	250.2±176.2	260.7±191.6	266.2±178.2

We defined the CPFE group using two thresholds of emphysematous area on HRCT: >25% and >10%. Values are expressed as mean±SD or n (%). CPFE: combined pulmonary fibrosis and emphysema; CS: corticosteroids; IS: immunosuppressants; PFD: pirfenidone; eSPAP: estimated systolic pulmonary arterial pressure; KL-6: Krebs von den Lungen-6; SP: Surfactant protein. *$p<0.05$, #$p<0.01$, using Mann–Whitney *U*-test or chi-square test.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-135

was not recognized in four out of the 72 patients in HRCT, two in the CPFE and two in the non-CPFE group who were diagnosed with UIP by surgical biopsy. There were no significant differences in treatment between the groups. Twenty-six patients in CPFE and 22 in non-CPFE underwent echocardiography during the study period. In each group, only one patient was defined with PH, and mean eSPAP was extremely low compared to that in past reports.[8]

Regarding lung cancer as a complication observed after enrolment, one patient had adenocarcinoma and two patients had squamous cell carcinoma in the CPFE group. On the other hand, one patient had squamous cell carcinoma in the non-CPFE group. The two groups showed no significant difference in fibrosis scores on HRCT or levels of serum biomarkers (e.g., KL-6, SP-A and SP-D) at enrolment.

PFTs

Indices of PFTs at enrolment are shown in Table 2 with significantly lower diffusing capacity of the lung for carbon monoxide (DLCO) and KCO (DLCO divided by the alveolar volume; $DLCO/V_A$). Thus, the CPFE group showed the tendency towards preservation of lung volume and decreased diffusing capacity. The mean FEV_1/FVC did not significantly differ between the groups. Similar PFT results were also observed when the <10% threshold for emphysema area was analyzed.

Prognosis

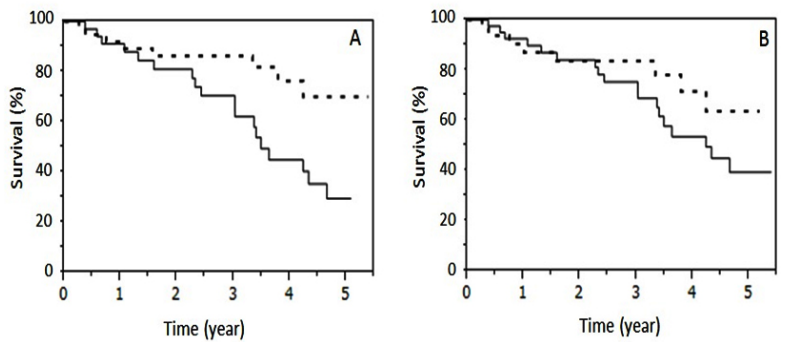
To identify appropriate CPFE criteria for IPF prognosis, we evaluated the utility of two threshold proportions: 10% and 25% emphysema area out of the total lung area in HRCT. Survival rate of the CPFE group was significantly worse (p=0.012, log-rank test) than that of the non-CPFE group when the threshold was set at 25% (Figure 1, panel A), while the 10% threshold did not show a significant difference (Figure 1, panel B). These results demonstrate that IPF patients with severe emphysema have poor prognoses in CPFE. Therefore, we set the threshold for the area of emphysema affecting the prognosis of CPFE at

Table 2: Comparison of Pulmonary Function Indices at Enrolment.

Indices	Threshold; 25% area of emphysema			Threshold; 10% area of emphysema		
	CPFE group n=34	non-CPFE group n=38	*p*-value	CPFE group n=40	non-CPFE group n=32	*p*-value
FVC (% pred)	88.0±17.6	84.3±19.7	0.2217	87.8±17.4	83.8±19.9	0.1782
FEV_1 (% pred)	98.3±15.2	94.8±20.9	0.1596	98.3±15.3	94.1±21.8	0.1257
FEV_1/FVC (%)	81.9±8.1	82.9±8.3	0.3300	81.6±8.3	83.5±8.0	0.1820
TLC (% pred)	78.0±14.8	79.1±15.7	0.9090	78.9±14.8	78.3±15.9	0.7446
DLCO (% pred)	44.7±14.0#	56.8±17.7	0.0083	47.1±15.9*	56.3±17.4	0.0288
KCO (% pred)	65.3±20.4#	83.5±18.7	0.0018	67.7±20.4#	84.2±19.3	0.0056

We defined the CPFE group using two thresholds of emphysematous area on HRCT: >25% and >10%. Values are expressed as mean±SD. CPFE: combined pulmonary fibrosis and emphysema; FVC: forced vital capacity; % pred: % predicted; TLC: total lung capacity; FEV_1: forced expired volume in 1 s; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: DLCO per alveolar volume. *p-values are reported for the difference between groups using Mann–Whitney U-test. *p<0.05, #p<0.01

Figure 1: Survival Compared between CPFE Group and non-CPFE Group.



The solid and dotted lines indicate survival of the CPFE group and non-CPFE group, respectively. Although survival of the CPFE group (n=34), when defined as >25% emphysematous area in lung fields, was worse than that of the non-CPFE group (n=38) (p=0.0122, log-rank test; Panel A), survival of the CPFE group (n=40), when defined as >10% emphysematous area in lung fields on HRCT, was not significantly different from that of the non-CPFE group (n=32) (Panel B).

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-135

25% in this study.

Total number of deaths were 20 (58.8%) in the CPFE group and 8 (21.1%) in the non-CPFE group (Table 3). There were no changes in the number of deaths between the two thresholds for the area of emphysema. The causes of death in the CPFE group were 12 chronic respiratory failures with occasionally repeated infection in the respiratory tract, 5 acute exacerbations of IPF, 1 lung cancer and 2 'others'. In the non-CPFE group, five were chronic respiratory failures and three were acute exacerbations. We evaluated the relationships among values at enrolment, longitudinal change in PFTs and prognosis using a Cox proportional hazard model. The initial values of % FVC, FEV_1/FVC, % FEV_1 and % TLC were predictors of mortality in both groups (Table 4). In the analysis of longitudinal change in PFTs, the cut-off value of percentage change in each index of PFTs (Δ%Value) was set at 5% or 10% to conform with previous studies. [13,14,22] As a result, Δ% DLCO/year (declining more than 5%) and Δ% FVC/year (declining more than 10%) were independent predictors of poor prognosis in the CPFE and non-CPFE groups, respectively (Table 5).

We evaluated the relationship between prognosis and values of serum biomarkers at enrolment. Unlike CPFE, non-CPFE patients with higher serum SP-D levels revealed worse prognosis (hazard ratio (HR): 1.007; 95% confidence interval (CI): 1.003-1.011; $p<0.001$), as shown in Table 6. We then performed further evaluation focusing on SP-D. The cut-off values for serum SP-D were set at 150, 200 and 250 ng/mL to determine the most appropriate value, in conformity with previous studies.[16-18] As a result, CPFE patients with higher SP-D (threshold 150 ng/mL) revealed poor prognosis (HR 11.417; 95% CI: 2.275-207.785; $p=0.001$) (Table 7). In contrast, non-CPFE patients with SP-D>250 ng/mL revealed the worst prognosis (HR 15.237; 95% CI: 2.695-285.409; $p=0.001$).

DISCUSSION

The recent conception of CPFE defines it as a syndrome rather than a single disease, as it is characterized by an overlapping series of interstitial pneumonias, such as IPF.[2] Thus, some patients with IPF may demonstrate clinical characteristics of CPFE. Because CPFE is characterized by the combination of emphysema and pulmonary fibrosis, the presence of differing proportions of the two elements is thought to affect clinical analyses of IPF. In the current study, we evaluated the clinical

Table 3: Patient Outcomes During the Follow-up Period.

	CPFE group n=34	non-CPFE group n=38
Follow-up period years	2.80±1.53	3.11±1.56
Dead/Alive (Dead %)	20/14 (58.8)	8/30 (21.1)
Cause of death		
Acute exacerbation of interstitial pneumonia	5 (25.0)	3 (37.5)
Chronic respiratory failure including infection	12 (60.0)	5 (62.5)
Lung cancer	1 (5.0)	0 (0)
Others	2 (10.0)	0 (0)

CPFE was defined as >25% of emphysematous area on HRCT. Values are expressed as mean±SD or n (%). CPFE: combined pulmonary fibrosis and emphysema.

Table 4: Univariate Hazard Ratios for Mortality According to Values of Pulmonary Function Tests at Enrolment.

	CPFE group HR (95% CI)	non-CPFE group HR (95% CI)
Initial FVC (% pred)	0.959 (0.933-0.985)#	0.901 (0.840-0.953)#
Initial FEV_1/FVC (%)	1.083 (1.016-1.158)*	1.379 (1.125-1.796)#
Initial FEV_1 (% pred)	0.967 (0.942-0.995)*	0.927 (0.876-0.975)#
Initial TLC (% pred)	0.957 (0.925-0.988)#	0.905 (0.847-0.957)#
Initial DLCO (% pred)	0.978 (0.944-1.014)	0.952 (0.889-1.002)
Initial KCO (% pred)	0.997 (0.975-1.021)	0.995 (0.951-1.034)

CPFE was defined as >25% of emphysematous area on HRCT. CPFE: combined pulmonary fibrosis and emphysema; HR: hazard ratio; CI: confidence interval; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expired volume in 1 s; TLC: total lung capacity; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: DLCO per alveolar volume. *$p<0.05$, #$p<0.01$; using univariate Cox hazard analysis.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-135

Table 5: Univariate Hazard Ratios for Mortality According to Annual Changes in Pulmonary Function Tests.

	CPFE group		non-CPFE group	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Annual decline in FVC % pred				
<10% decline or increase	22 (84.6)	1	25 (78.1)	1
>10% decline	4 (15.4)	1.76 (0.267-6.900)	7 (21.9)	10.716 (1.689-84.756)*
Annual decline in DLCO % pred				
<5% decline or increase	8 (33.3)	1	19 (65.5)	1
>5% decline	16 (66.7)	8.185 (1.459-153.974)*	10 (34.5)	0.698 (0.034-5.482)

CPFE was defined as >25% of emphysematous area on HRCT. CPFE: combined pulmonary fibrosis and emphysema; HR: hazard ratio; CI: confidence interval; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide. The percentage of change per year, named annual decline, in each index was calculated as Δ%Value/year = (Δ%Value/number of follow-up months) × 12 (see Subjects and Methods). *p<0.05; using univariate Cox hazard analysis.

Table 6: Univariate Hazard Ratios for Mortality According to Serum Biomarkers.

	CPFE group	non-CPFE group
	HR (95% CI)	HR (95% CI)
Initial KL-6	1.000 (0.999-1.001)	1.000 (0.999-1.001)
Initial SP-A	1.002 (0.990-1.012)	1.003 (0.980-1.021)
Initial SP-D	1.002 (0.999-1.003)	1.007 (1.003-1.011)#

CPFE was defined as >25% of emphysematous area on HRCT. CPFE: combined pulmonary fibrosis and emphysema; HR: hazard ratio; CI: confidence interval; KL-6: Krebs von den Lungen-6; SP: surfactant protein. #p<0.01; using univariate Cox hazard analysis.

Table 7: Univariate Hazard Ratios for Mortality According to Concentration of SP-D.

	CPFE group		non-CPFE group	
Initial SP-D	n (%)	HR (95% CI)	n (%)	HR (95% CI)
<150 ng/mL	9 (26.5)	1	14 (36.8)	1
>150 ng/mL	25 (73.5)	11.417 (2.275-207.785)#	24 (63.2)	6.395 (1.115-120.455)*
<200 ng/mL	14 (41.2)	1	19 (50.0)	1
>200 ng/mL	20 (58.8)	3.977 (1.376-14.486)#	19 (50.0)	9.600 (1.689-180.222)#
<250 ng/mL	18 (53.0)	1	24 (63.2)	1
>250 ng/mL	16 (47.0)	2.117 (0.825-5.621)	14 (36.8)	15.237 (2.695-285.409)#

CPFE was defined as >25% of emphysematous area on HRCT. CPFE: combined pulmonary fibrosis and emphysema; HR: hazard ratio; CI: confidence interval; SP: surfactant protein. *p < 0.05, #p < 0.01; using univariate Cox hazard analysis.

features of 34 patients with IPF having an emphysema area of more than 25% in the entire lung field in comparison to 38 patients with IPF outside of this range (CPFE group and non-CPFE group, respectively). The threshold of 25% emphysema area was selected on the basis of our survival analysis. In addition, there was no significant difference in the degree of fibrotic change between the two groups.

It is evident that CPFE is closely associated with smoking tobacco.[23,24] IPF with CPFE syndrome is also associated with a heavy smoking history, as demonstrated in Table 1 of the current study. In general, clinical features of CPFE are characterized as follows: 1) % FVC and FEV_1/FVC are preserved, 2) DLCO is markedly decreased and 3) CPFE is complicated with PH and lung cancer.[9,23-25] However, it was previously clear whether these features hold true when patients are restricted to those with IPF. Our study showed that FVC values were preserved in both the CPFE and the non-CPFE groups, while diffusing capacity (including % DLCO and % KCO) were significantly lower in the CPFE than the non-CPFE

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-135

group. These results suggest that functional profiles of IPF with CPFE in this study are similar to those in other reports.

Prevalence of PH has been reported as 32-85% in IPF and 36% in COPD.[26,27] A study by Mejía et al[8] showed high prevalence of severe PH and poor prognosis in IPF patients with emphysema in an echocardiography evaluation in Mexican patients. This study also found high eSPAP, on average in patients with IPF and emphysema. In comparison, our study showed an extremely low prevalence of PH and lower eSPAP in both groups. Sugino et al[10] used echocardiography and reported an average eSPAP similar to our own in Japanese patients with IPF alone or IPF and emphysema. Although the threshold of emphysematous area was 10% <on HRCT in the report by Mejía et al[8] and the difference in prevalence of PH between Mexican and Japanese CPFE patients might be due to racial differences, it is suggested that their patients were more severe than our patients according to PFT features.

There has been controversy regarding whether the co-existence of emphysema affects outcomes for patients with IPF.[8-11] Our results showed that the CPFE group revealed a significantly worse prognosis than did the non-CPFE group when the threshold of ratio of emphysematous area on HRCT was set at 25%, but no significant difference was found at 10% (Figure 1). Regarding PFTs, a large cohort study of patients with IPF suggested that a decline in FVC of more than 10% in IPF[13] and that in FEV_1 of more than 10% in moderate-to-severe CPFE[28] during a 6-month observation are the best physiological predictors of mortality. On the other hand, the present study suggested that an annual decline of more than 5% in % DLCO was a good predictor in the CPFE group, but that FVC and FEV_1 were not. Thus, DLCO might be a key predictor of the prognosis of IPF patients with CPFE syndrome.

KL-6, SP-A and SP-D are known to be useful diagnostic serum biomarkers of interstitial pneumonia including IPF and are potential predictors for IPF.[16,17,19] Unlike PFTs, these biomarkers are capable of performing measurements repeatedly even in the severe conditions of pulmonary diseases. For this reason, we evaluated the potential of these biomarkers to predict the survival of IPF with CPFE syndrome. Results indicated that patients with higher SP-D revealed poor prognosis in not only the non-CPFE but also the CPFE group. In addition, these groups showed different cut-off levels for survival: 250 ng/mL and 150 ng/mL, respectively. Thus, serum SP-D may be a good predictor for survival of IPF either with or without emphysematous changes, and each cut-off level should be defined in the distinct group. This is especially the case for CPFE patients with lower cut-off levels for SP-D (>150 ng/mL), which is considered a poor prognosis and requires careful management. SP-D might be a better prognostic predictor, especially for severe CPFE patients, because it is possible to measure SP-D repeatedly by blood collection; in contrast, DLCO cannot be measured in severe IPF patients with small VC.

Prevalence of CPFE syndrome in IPF showed varying rates (8-44%) in previous studies.[8,9,28-31] There seem to be two explanations for this: differences in the assessment of emphysema area on HRCT and race differences. Standardization of diagnosis criteria and a large-scale study that takes race into consideration are areas for future research.

CONCLUSION

We demonstrated poorer prognosis in IPF with an emphysematous area of more than 25%, but not 10%, when compared to the other subset of IPF (i.e., non-CPFE). Analyses of PFTs and biomarkers demonstrated that DLCO and SP-D are useful predictors of poor prognosis. SP-D might be a better prognostic predictor than DLCO, especially in cases of severe CPFE, due to the invasiveness of examination.

AUTHOR'S CONTRIBUTIONS

KY, MS, KI and HT designed the study. KY, MS, KI, YU, MO, HN, HC, HK and HT checked the diagnosis and eligibility of study subjects. KY, MS, KI and HT analyzed and interpreted the data. All authors read and approved the final manuscript.

STATEMENT OF SUPPORT

This work was supported partly by a grant-in-aid for the Japanese Ministry of Health, Labour and Welfare.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-135

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ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-4-136

Case Report

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Volume 4 : Issue 2
Article Ref. #: 1000PRRMOJ4136

Article History
Received: June 23rd, 2017
Accepted: July 10th, 2017
Published: July 10th, 2017

Citation
Kim C, Debesa O, Nicolato P, Fisher B, Natarajan R, Fowler AA. Vitamin C infusion for gastric acid aspiration-induced acute respiratory distress syndrome (ARDS). *Pulm Res Respir Med Open J*. 2017; 4(2): 33-37. doi: 10.17140/PRRMOJ-4-136

Vitamin C Infusion for Gastric Acid Aspiration-Induced Acute Respiratory Distress Syndrome (ARDS)

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ABSTRACT

Introduction: Gastric acid aspiration into the lung has long been established as a direct cause of acute lung injury that rapidly leads to a clinical diagnosis of acute respiratory distress syndrome (ARDS). Gastric juices contain a low pH liquid and frequently mouth organisms. When aspiration of gastric liquid into the lower airway occurs, a caustic injury to the lower airway and distal airspaces occurs. The acute inflammatory events that occur following gastric acid aspiration induce injury by direct lung tissue toxicity.[1] As well, acute adhesion of activated blood neutrophils throughout the pulmonary microcirculation and the subsequent migration of activated cells into the alveolar space rapidly induces acute injury to the alveolar capillary membrane with subsequent rapid loss of lung barrier function. Virtually always acute lung injury of the magnitude described in the case we report here occurs, producing ARDS. Thus far, no therapy has reliably proven effective for gastric acid-induced ARDS.
Case Presentation: In this report, we describe the onset of acute respiratory failure with rapid onset ARDS in a 34-year-old patient who experienced a generalized tonic-clonic seizure followed by witnessed vomiting and aspiration of gastric contents following a morning meal. The patient rapidly developed acute respiratory failure, necessitating mechanical ventilation. Ventilatory support failed to oxygenate or ventilate the patient. Extracorporeal membrane oxygenation was instituted. Vitamin C was infused intravenously at 50 mg/kg every 6 hours starting on hospital day 2 with subsequent significant improvement in lung function and lung imaging.
Conclusion: This report adds to the increasing clinical experience employing high dosages of intravenous vitamin C to attenuate the acute inflammatory lung injury. If further adds to the experience of using extracorporeal membrane oxygenation to support lung injured patients.

KEY WORDS: Intravenous vitamin C; Acute respiratory distress syndrome; Extracorporeal membrane oxygenation; Acute respiratory failure; Gastric acid aspiration.

ABBREVIATIONS: ARDS: Acute Respiratory Distress Syndrome; ECMO: Extracorporeal Membrane Oxygenation; MRSA: Methicillin-resistant *Staphylococcus aureus*; iNO: Inhaled Nitric Oxide; CT: Computed Tomography; PEEP: Positive End Expiratory Pressure; NIH: National Institutes of Health.

INTRODUCTION

Massive pulmonary gastric acid aspiration uniformly produces very severe, acute lung injury. At present there is no know interventional therapy for aspiration-induced acute lung injury. Emergent therapeutic approaches in the past have included careful volume limited mechanical ventilatory support along with appropriate critical care measures such as careful fluid man-

ISSN 2377-1658
http://dx.doi.org/10.17140/PRRMOJ-4-136

agement, vasopressor support, and broad spectrum antibiotics. Increasingly, extracorporeal membrane oxygenation (ECMO) is being employed to support patients following the onset of acute respiratory distress syndrome (ARDS) induced by a number of acute illnesses (e.g., sepsis, pneumonia, toxic inhalation, viral illnesses, etc). Here we describe the first use of high dosage intravenous vitamin C as an adjunctive measure to decrease the intensity of lung injury suffered in a patient following high volume gastric acid aspiration that rapidly led to ARDS.

CASE PRESENTATION

A 34-year-old male experienced a witnessed generalized tonic clonic seizure and gastric aspiration followed by 3 minutes of cardiopulmonary resuscitation for pulseless electrical activity arrest. The patient's past medical history was significant for attention deficit/hyperactivity disorder, gastro-esophageal reflux disease, hypothyroidism and chronic lower back pain. There was no known history of seizure disorder. Postictal and post-return of spontaneous circulation, the patient was restless but following commands. The patient was normotensive. The cardiac exam revealed a regular tachycardia with no murmurs, gallops or rubs. No jugular venous distension was present. Chest exam revealed diffuse rhonchi bilaterally with diminished air movement. Blood was present in the mouth and nares. Upon arrival at an outside hospital, tracheal intubation and volume-limited mechanical ventilation was begun. Oxygenation failed to improve despite multiple attempts to optimize ventilatory support with a positive end expiratory pressure (PEEP) of 18 cm of water, F_iO_2 of 1.0, and inhaled nitric oxide (iNO) at 20 parts per million (ppm). The patient was subsequently transferred to Virginia Commonwealth University Medical Center for ECMO support. Upon arrival, assist-control, pressure-control ventilation was continued. Delivered PEEP, oxygen fraction and iNO were unchanged. Anterior-posterior chest X-ray imaging revealed diffuse bilateral opacification consistent with acute respiratory distress syndrome (Figure 1). Subsequent computed tomographic (CT) imaging of the brain was found to be within normal limits.

With ongoing hypoxemic respiratory failure in the setting of severe ARDS, veno-venous ECMO was instituted, employing a 31 French Avalon Elite® Bi-Caval Dual Lumen Catheter *via* the right internal jugular vein. Rotational frequency was set to maintain a flow of 5 liters per minute. Bilvalirudin was initiated for device anticoagulation, maintaining a partial thromboplastin time of 60-80 seconds. Hydromorphone and propofol infusions were administered for analgesia and sedation. Volume limited mechanical ventilation (tidal volume, 3-4 ml/kg) was continued. Vancomycin and pipercillin-tazobactam were selected as antibiotic therapy. CT angiography of the chest was negative for pulmonary emboli but revealed near-complete opacification of bilateral hemi-thoraces with modest preservation of aeration of the middle lobe, lingula and apical upper lobe segments (Figure 2). Bronchoscopy revealed the presence of extensive blood clots throughout the tracheobronchial tree with severe mucosal hyperemia. Active bleeding was not identified.

On hospital day 2 (ECMO day 2), high dose intravenous ascorbic acid was initiated at 50 mg/kg every 6 hours. Methylprednisolone (2 mg/kg every 6 hours) was initiated. Also this day, furosemide was infused to maintain a negative fluid balance. Repeat bronchoscopy was performed on ECMO day 3 which demonstrated decreased mucosal hyperemia, and the absence of active bleeding.

Over subsequent days, lung compliance, oxygenation and ventilation improved significantly as did chest imaging. Repeat non-contrast CT imaging of the chest on ECMO day 6 revealed significantly less opacification with improved lung aeration (Figure 3). A methylprednisolone taper was initiated. Hospital day 6, ECMO was successfully trialed on a sweep flow of 0 liters/minute. Ascorbic acid dosing was decreased to 25 mg/kg every 6 hours. A respiratory culture obtained this day revealed gram negative rods and gram positive cocci, ultimately speciated

Figure 1: Hospital Day 1, Anterior-Posterior Chest x-ray Demonstrating Widespread Pulmonary Edema. ECMO Support Initiated.

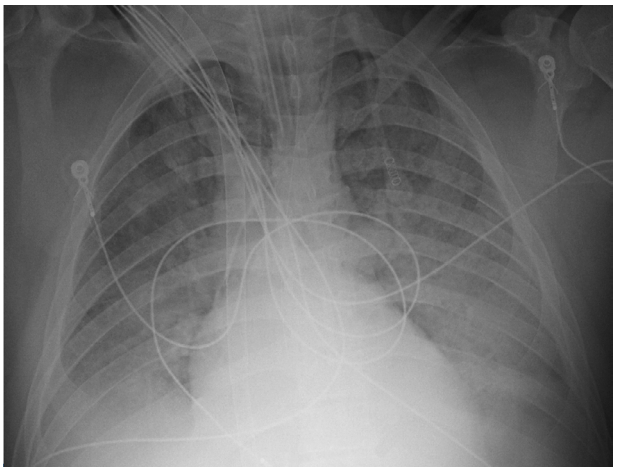
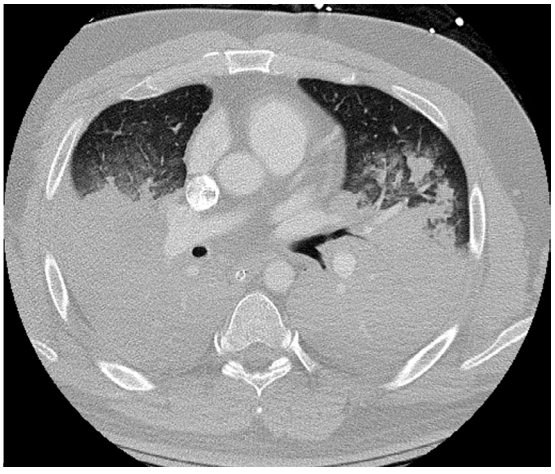


Figure 2: Hospital Day 1: Chest CT Imaging Demonstrating Widespread Consolidation of Lung Consistent with ARDS.



ISSN 2377-1658
http://dx.doi.org/10.17140/PRRMOJ-4-136

as *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA). The patient was liberated from ECMO on hospital day 7. Chest imaging with anterior-posterior chest X-ray on the day ECMO was stopped continued to reveal substantial radiographic improvement (Figure 4).

On hospital day 8, ascorbic acid infusions were discontinued. Repeat respiratory cultures on hospital day 11 continued to demonstrate MRSA and ceftaroline was initiated. The patient was liberated from mechanical ventilation on hospital day 13 (Figure 5). He was discharged to home on hospital day 19.

DISCUSSION

No effective therapy has previously been described for gastric acid-induced ARDS. High dosage intravenous vitamin C as described in this report and other reports from Virginia Commonwealth University Richmond, VA, USA, have proven to be effective adjunctive anti-inflammatory therapies. We report here the first application of high dose intravenous vitamin C employed as an interventional drug therapy for gastric acid-induced ARDS.

The use of intravenous vitamin C to treat acute lung injury is still investigational and is the subject of an ongoing NIH-funded double-blinded placebo-controlled multicenter trial, examining its use in sepsis-induced ARDS. Few studies have reported the use of intravenous vitamin C in critically ill patients with ARDS. Sawyer et al[2] reported that large intravenous doses of ascorbic acid plus other antioxidants (i.e., tocopherol, N-acetyl-cysteine, selenium), in patients with ARDS reduced mortality by 50%. Nathens and colleagues infused ascorbic acid intravenously at 1 gram every 8 hours co-administered with oral vitamin E for 28 days in 594 surgically critically ill patients.[3] They found a lower incidence of multiple organ failure and acute lung injury. Tanaka and colleagues infused ascorbic acid at a dosage of 66 mg/kg/hour for the first 24 hours in patients suffering greater than 50% surface area burns and showed significantly reduced thermal injury-induced capillary permeability with significantly lower intravenous volume required for resuscitation.[4] Increasing plasma ascorbic acid levels in hospitalized patients following gastric acid-induced ARDS is not part of current critical care practice. Vitamin C dosages utilized in the treatment of the patient we describe in this case report of gastric acid-induced ARDS arose

Figure 3: Computed Tomographic Imaging of the Chest Hospital Day 6, ECMO Day 6 Reveals Significant Resolution of Pulmonary Edema and Airspace Opacities.

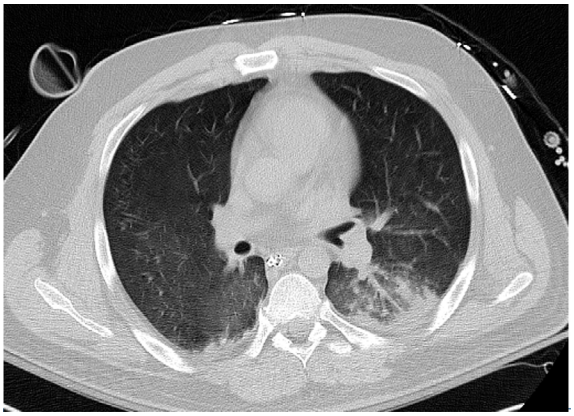


Figure 4: Anterior-Posterior Chest X-ray Hospital Day 7 Continues to Reveal Substantial Improvement.

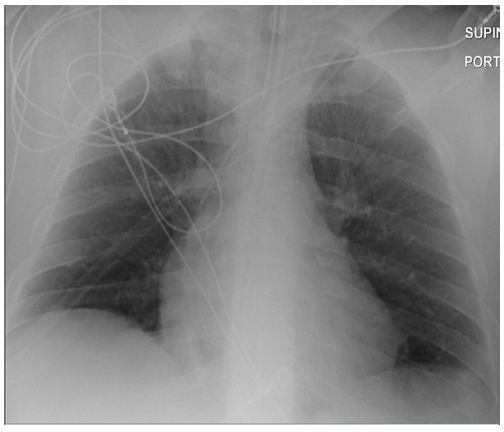
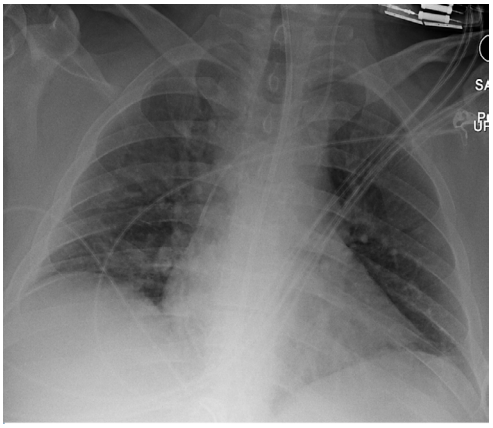


Figure 5: Hospital Day 13 Mechanical Ventilation was Discontinued. AP Chest X-ray Following Extubation Reveals Continued Resolution of ARDS.



ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-136

from our previous human studies where we infused high doses intravenous vitamin C into critically ill patients with severe sepsis[5] and in our preclinical animal studies.[6-8] Our preclinical studies clearly show that vitamin C exerts robust "pleiotropic effects" when utilized as reported in the care of this patient with gastric acid-induced ARDS. In a recent study in critically ill patients with severe sepsis, we infused vitamin C at 50 mg/kg every 6 hours and found a marked reduction in multiple organ injury with reduced inflammatory biomarker levels in plasma.[5] Our preclinical work in septic, lung-injured animals, shows that vitamin C down-regulates pro-inflammatory genes driven by transcription factor NF-κB.[7] Early work by Kennedy et al and Goldman et al previously established that pulmonary gastric acid aspiration promotes an "acid burn" in lung, leading to rapid loss of lung barrier function as activated neutrophils migrate into the airspaces, producing tissue injury by liberating reactive oxygen species and proteolytic enzymes.[9,10] As a consequence, following acid aspiration, pulmonary edema forms rapidly as we report here with the acute onset of respiratory failure. Our prior research with vitamin C has revealed that parenteral infusion of vitamin C significantly increases alveolar fluid clearance in septic lung-injured animals.[8] Further, our research shows that vitamin C down-regulates neutrophil extracellular trap formation, a newly described phenomenon where circulating blood neutrophils exposed to certain pro-inflammatory stimuli disgorge their genomic DNA into their peri-cellular space.[11] Extracellular DNA from the neutrophil contains adherent lysosomal enzymes which remain active and capable of damaging lung microcirculation, thus leading to pulmonary capillary damage.[12] Infused vitamin C is also capable of dismuting liberated reactive oxygen and nitrogen species which also appears necessary for attenuating lung injury.[13]

Prior reports have described ARDS with such severity that ECMO was required. Wetsch et al described a 39-year-old man who sustained massive gastric acid aspiration with resultant ARDS who was supported with ECMO.[14] During the hospital course of the patient we report here, short-term methyl prednisolone was also infused and likely played an undetermined role in promoting resolution of the patient's lung injury. Zhao et al[15] recently reported a retrospective analysis of 73 acute stroke patients who were diagnosed with aspiration-related ARDS and in whom the hospital mortality rate was 39.7%. Short-term corticosteroids reported in Zhao's study were administered in 47 patients (64.4 %) at a mean dosage of 1.14 mg/kg per day of methylprednisolone *via* intravenous infusion for a period of 7.3 days. Ground glass opacities reported in chest computed tomography images in Zhao's study improved when corticosteroids were administered. However, none of the ARDS patients Zhao reported sustained the extent of lung injury similar to the patient we describe here and none were treated with extracorporeal membrane oxygenation.

CONCLUSIONS

In summary, we describe the first utilization of high dose, intravenously infused, vitamin C in the treatment of severe gastric acid-induced ARDS. Both extensive preclinical work and as well as human studies thus far, examining *parenterally administered vitamin C*, leads us to conclude that this new form of therapy may become a useful adjunct in the care of patients with acute lung injury. The use of intravenous vitamin C is slowly emerging as a potentially effective adjunctive therapy for ARDS secondary to multiple etiologies (i.e., bacterial and viral infection). Bharara et al previously described the use of intravenous vitamin C as adjunctive therapy in a young woman with recurrent sepsis-induced ARDS,[16] while Fowler et al reported intravenous vitamin C infusion in a patient who developed ARDS secondary to enterovirus/rhinovirus-induced ARDS.[17] The current case report and the two reports cited here[16,17] along with the phase II NIH-supported multi-center trial, examining intravenous vitamin C's role as therapy in sepsis-induced ARDS will begin to shape the usage of vitamin C as a new standard of care therapy. As has been established for decades now, ARDS can occur secondary to many lung insults. In the current report, intravenous vitamin C was employed in a patient with who developed ARDS secondary to massive gastric acid aspiration.

DECLARATIONS

Ethics approval and consent to participate: This study was approved by the Virginia Commonwealth University Institutional Review Board (IRB). The IRB approval number assigned to this trial was: HM12903.

Consent for publication: Consent for publication was given by the patient. Data for this report was de-identified and confidentiality maintained.

ACKNOWLEDGEMENTS

The authors acknowledge the superior care provided by the VCU Cardiothoracic Nursing service for their amazing nursing care which assured a good outcome to this patient's care.

COMPETING INTERESTS

The authors declare no financial or non-financial competing interests.

Availability of Data and Materials

Data for this case report was extracted from the patient's electronic medical record and the VCU Radiology Imaging Service. The dataset generated and analyzed during the current study are not publicly available due to the fact that individual privacy could be compromised. The authors feel it essential that privacy not be compromised. We assure the material reported here be kept confidential to maintain that privacy. Thus, the data is NOT publically available due to confidentiality reasons.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-136

AUTHORS' CONTRIBUTIONS

- Christin Kim, MD: Clinical Critical Care of the patient, ECMO clinician, manuscript drafting, editing;
- Orlando Debesa, DO: Clinical Critical Care of the patient, ECMO clinician, manuscript drafting, editing;
- Patricia Nicolato, DO: Clinical Critical Care of the patient, Thoracic Surgeon who inserted ECMO, manuscript drafting, editing
- Bernard Fisher, MS: Vitamin C scientist, manuscript drafting, editing;
- Ramesh Natarajan, PhD: Vitamin C scientist, manuscript drafting, editing;
- Alpha A. Fowler, III, MD: Vitamin C scientist, manuscript Author.

FUNDING

National Institutes of Health, 5UM1HL116885-02, The Aubrey Sage Macfarlane Lung Injury Research Fund (a philanthropic fund gifted to the VCU Johnson Center for Critical Care and Pulmonary Research).

We additionally acknowledge the amazing care provided by the intensive care unit Nursing staff who cared for the patient in the Cardiac Surgery Intensive Care Unit at Virginia Commonwealth University.

TRIAL REGISTRATION

Trial registry: Clinical Trials.gov; https://clinicaltrials.gov/ct2/show/NCT02106975?term=citris-ali&rank=1, Trial Registration Number: NCT02106975, Date of Registration: March 27, 2014, Date of 1st enrollment: 9-15-14.

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PULMONARY RESEARCH AND RESPIRATORY MEDICINE

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-4-137

Brief Research

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Volume 4 : Issue 2
Article Ref. #: 1000PRRMOJ4137

Article History
Received: August 18th, 2017
Accepted: September 22nd, 2017
Published: September 25th, 2017

Citation
Kandi S, Reddy V, Nagaraja SB. Diagnosis of pulmonary and extra pulmonary tuberculosis: How best is CBNAAT when compared to conventional methods of TB detection? *Pulm Res Respir Med Open J*. 2017; 4(2): 38-41. doi: 10.17140/PRRMOJ-4-137

Diagnosis of Pulmonary and Extra Pulmonary Tuberculosis: How Best is CBNAAT when Compared to Conventional Methods of TB Detection?

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ABSTRACT

Background: Globally, India is a home for more than 25% of global Tuberculosis (TB) burden. The sensitivity of smear microscopy and its inability to detect drug resistance limits its impact on TB control. We compared the cartridge-based nucleic acid amplification test (CBNAAT) results for diagnosis of pulmonary and extrapulmonary tuberculosis with the conventional methods like sputum smear and solid culture examination.
Methods: A descriptive study was conducted at Government General and Chest Hosptial, Hyderabad, India during 2014 to 2016. The study population included all the pulmonary and extrapulmonary presumptive TB cases who were subjected for further investigations.
Results: Of the two hundred samples received, 110 (55%) were sputum samples and 90 (45%) were extrapulmonary samples. For pulmonary samples, the sensitivity and specificity for CBNAAT samples were 79.2% and 89.5% respectively; while that for sputum smear were 41.5% and 98.2% respectively. For extrapulmonary samples, the sensitivity and specificity for CBNAAT samples were 85.7% and 93.5% respectively; while that for sputum smear were 60.7% and 100% respectively.
Conclusion: CBNAAT is one of the rapid diagnostic tests available in the country and it should be routinely used under the public and private health sector effectively to detect a tuberculosis case.

KEY WORDS: Cartridge-based nucleic acid amplification test (CBNAAT); Tuberculosis; Sputum smear.

ABBREVIATIONS: TB: Tuberculosis; CBNAAT: Cartridge-Based Nucleic Acid Amplification Test; PCR: Polymerase Chain Reaction; DNA: Deoxyribonucleic acid; LED: Light Emitting Diode; FM: Fluorescent Microscopy; LJ: Lowenstein-Jensen; FNAC: Fine Needle Aspiration Cytology; ATT: Anti-Tuberculosis Treatment; RNTCP: Revised National TB control Programme; BAL: Bronchoalveolar Lavage; MDR-TB: Multi-drug resistant TB; MTB: Mycobacterium Tuberculosis; RIF: Resistance to Rifampicin.

INTRODUCTION

India has the highest number of Tuberculosis (TB) cases in the world, with over two million TB cases every year.[1] Annually, one fourth of the global incident TB cases occur in India. Early and accurate diagnosis is the first critical step in controlling TB. The control of TB is hampered by diagnostic methods with sub-optimal sensitivity, particularly for the detection of drug resistant forms and in patients with human immunodeficiency virus (HIV) infection. Early detection is essential to interrupt transmission and reduce the death rate, but the complexity and infrastructure needs sensitive methods which limit their accessibility and effect.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-137

According to WHO global TB report, the estimated incidence of TB (including TB with HIV) is 2.2 million and prevalence is 2.5 million with mortality (excluding TB with HIV) of 0.22 million.[1] There were 580,000 estimated new cases of MDR-TB (Multi-drug resistant TB) and Rifampicin resistant TB (RR-TB); among them 125,000 (20%) were enrolled. India, China and the Russian Federation accounted for 45% of all estimated MDR/RR-TB cases (henceforth to be called as MDR-TB). India, one of the countries with high burden of TB, has an estimated 79,000 MDR-TB cases among notified pulmonary TB cases. The estimated incidence of MDR-TB is 2% among new cases and 15% among re-treatment cases.

The sensitivity of smear microscopy and its inability to detect drug resistance limits its impact on TB control. Culture methods and drug susceptibility testing is complex, time consuming, and takes around 6-8 weeks. While patients await diagnosis, they are likely to receive inappropriate or in effective treatment and consequently disease may progress. This results in an increased chance of morbidity from tuberculosis. They continue to transmit drug-resistant TB to others; especially for family members and the resistance might have amplified.

To address this issue there was a need for a simple and rapid diagnostic tool at least for high-burden countries and a new diagnostic test cartridge based nucleic acid amplification test (CBNAAT) was developed which was rapid, fully automated and was based on polymerase chain reaction (PCR) that detects deoxyribonucleic acid (DNA) directly from the clinical specimens and also detects rifampicin resistance.[2] This diagnostic test was designed to purify, concentrate, amplify and identify targeted *rpoB* nucleic acid sequences, and delivered the results in about 120 minutes.

In this study, we compared the CBNAAT results for diagnosis of pulmonary and extrapulmonary tuberculosis with the conventional methods like sputum smear and solid culture examination.

METHODS

A descriptive study was conducted in Department of Pulmonary Medicine, Government General and Chest Hosptial, Hyderabad, Telangana, India during January 2014 to January 2016. The study population included all the pulmonary and extrapulmonary presumptive TB cases who were subjected for further investigations. To diagnose tuberculosis the investigations included sputum smear microscopy by light emitting diode (LED) fluorescent microscopy (FM), solid culture and liquid culture examination, CBNAAT and Fine needle aspiration cytology (FNAC) depending upon the type of specimen.

Non-sterile clinical specimens were processed by conventional N-acetyl-l-cysteine–NaOH method. After decontamination, the smears were prepared by the auramine-rhodamine acid-fast staining method. The decontaminated specimens were inoculated into Lowenstein-Jensen (LJ) solid medium and MB/BacT liquid culture medium for growth detection. The smear-positive specimens were evaluated within two weeks at the latest, while the smear-negative specimens were studied immediately after the growth of culture.

For CBNAAT examination the sample reagent were added at a 3:1 ratio to clinical specimens. The closed specimen container was manually agitated twice during a 15 minute period at room temperature, before 2 ml of the inactivated material (equivalent to 0.5 ml of decontaminated pellet) was transferred to the test cartridge. All the specimens which were culture positive and mycobacterium tuberculosis/resistance to rifampicin (MTB/RIF) assay negative and specimens that were culture negative and MTB/RIF assay positive were retested twice. The last result was included for the analysis.

All the data were entered in Microsoft excel and the statistical analysis was performed using Epi-data analysis software (version V2.2.2.178).

Ethics

The Institutional Ethics Committee (IEC) of Osmania Medical College, Hyderabad had approved the conduct of the study.

RESULTS

There were 200 specimens collected during the study period. Of which 110 (55%) samples were sputum samples while the remaining 90 (45%) were extrapulmonary samples. Among the samples provided 120 (60%) were males and 12 (6%) were found to be reactive for HIV. The comparison of CBNAAT, sputum smear against solid culture is shown in Table 1.

Pulmonary Samples

The sensitivity and specificity for CBNAAT samples were 79.2% and 89.5% respectively; while that for sputum smear were 41.5% and 98.2% respectively. The positive and negative predictive value for CBNAAT was 79.2% and 89.5% respectively. The positive and negative predictive value for sputum smear was 41.5% and 98.2% respectively.

Extrapulmonary Samples

The proportion of the samples received from different anatomical sites were: lymph node 38 (19%), pleural fluid and bronchoalveolar lavage (BAL) 20 (10%) and cerebrospinal fluid 5 (2.5%). The sensitivity and specificity for CBNAAT samples were 85.7% and 93.5% respectively; while that for sputum smear were 60.7% and 100% respectively. The positive and negative predictive value for CBNAAT was 85.7% and 93.5% respectively. The positive and negative predictive value for sputum smear was 100% and 84.9% respectively.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-137

Table 1: Comparative Table Showing the Results for Culture, CBNAAT and Smear Examination for Pulmonary and Extra-Pulmonary Samples (N=200).

Type of samples →		Pulmonary (n=110)		Extra-pulmonary (n=90)	
Type of tests		Culture		Culture	
	Results	Negative n (%)	Positive n (%)	Negative n (%)	Positive n (%)
CBNAAT	Negative	51(89.5)	11(20.8)	58(93.5)	4(14.3)
	Positive	6(10.5)	42(79.2)	4(6.5)	24(85.7)
Sputum smear	Negative	56(98.2)	31(58.5)	62 (100)	11 (39.3)
	Positive	1(1.8)	22(41.5)	0 (0)	17 (60.7)

DISCUSSION

Our study findings suggest that CBNAAT has higher sensitivity for detection of pulmonary and extrapulmonary tuberculosis cases. The WHO 2012 has also recommended the CBNAAT for routine use under programmatic conditions.[3]

In the present study, only 200 specimens were included; among them 110 were pulmonary and 90 were extrapulmonary. Among the 110 pulmonary presumptive TB cases, 15 were unable to produce adequate amount of quality sputum and hence were subjected to bronchoscopy and BAL was performed for collection of the sputum. The sensitivity of CBNAAT for pulmonary samples was 79% when compared to sputum smear which was 42%. The sensitivity of CBNAAT for extrapulmonary samples was 86% when compared to sputum smear which was 61%. The sensitivity of CBNAAT in smear-positive, culture-positive and smear-negative, culture-positive pulmonary samples were 100% and 66.67% respectively. Sensitivity of smear negative pulmonary samples can be increased by including more than one sample for diagnosis.

In a study done by Panayotis et al,[4] the sensitivity and specificity of CBNAAT in 80 pulmonary samples were 90.6% and 94.3% respectively. In a study done by Armand et al[5] the sensitivity of CBNAAT in 60 pulmonary samples which included sputum, BAL, bronchial aspirate and gastric aspirate was 79%. Among individual extrapulmonary samples, the sensitivity of CBNAAT was highest among lymph nodes (94.74%) when compared to sputum smear (73.68%). Inclusion of CBNAAT in the initial diagnosis of tubercular lymphadenopathy in addition to the FNAC would decrease the over diagnosis of tuberculosis and injudicious use of anti-tuberculosis treatment (ATT).

Various studies conducted across India has suggested the usage of CBNAAT up-front for people living with HIV (PLHIV).[6] The operational feasibility studies conducted under the Revised National TB Control Programme (RNTCP) have demonstrated the feasibility of the machine to efficiently work under Indian settings.[7]

The study has following limitations (a) it was an experimental study and it did not adapt a rigorous study design while the samples included were also small to make a generalised statements (b) the culture is known to be a suboptimal standard for extrapulmonary TB and the same was used as standard to compare with CBNAAT and sputum smear.

To conclude, CBNAAT is one of the rapid diagnostic tests available in the country and it should be routinely used under the public and private health sectors efficiently to detect a tuberculosis case.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-137

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PULMONARY RESEARCH AND RESPIRATORY MEDICINE

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-4-138

Research

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Volume 4 : Issue 2
Article Ref. #: 1000PRRMOJ4138

Article History
Received: December 10th, 2017
Accepted: December 28th, 2017
Published: December 28th, 2017

Citation
Murray TS, Metzger NL, Chesson MM, Walker SD. Refusal of venous thromboembolism prophylaxis and incidence of thrombosis in patients with cystic fibrosis. *Pulm Res Respir Med Open J*. 2017; 4(2): 42-47. doi: 10.17140/PRRMOJ-4-138

Refusal of Venous Thromboembolism Prophylaxis and Incidence of Thrombosis in Patients with Cystic Fibrosis

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ABSTRACT

Background: Patients with cystic fibrosis (CF) are at risk of venous thromboembolism (VTE) during hospitalization but many refuse VTE prophylaxis.
Methods: A single-center, retrospective medical record review was conducted to determine the refusal rate of pharmacologic VTE prophylaxis in adult patients with CF and to identify any correlation between patients who refused prophylaxis and the incidence of VTE.
Results: Of the 426 patient encounters screened, 307 were included, representing 144 unique patients, with a mean age of 28.4±8.9 years. Venous thromboembolism prophylaxis was refused in 77.5% of the patient encounters. Refusal rates were similar for both unfractionated heparin and enoxaparin (78.8% *vs*. 75.0%). Five patients (1.63%) developed a VTE during hospitalization or within 30 days of discharge; all five patients refused VTE prophylaxis.
Conclusions: The majority of hospitalized patients with CF refused pharmacologic prophylaxis with no difference in refusal between pharmacologic agents, and the combined incidence of VTE was low.

KEY WORDS: Cystic fibrosis; Prophylaxis; Pulmonary; Anticoagulation; Clinical pharmacy.

ABBREVIATIONS: CF: Cystic Fibrosis; VTE: Venous Thromboembolism; BCC: *Burkholderia Cepacia* Complex; ppFEV1: percent predicted forced expiratory volume in the first second; ICD-9: International Classification of Diseases, Ninth Revision; BMI: Body Mass Index.

BACKGROUND

Patients in the hospital are at an increased risk of developing a deep vein thrombosis or pulmonary embolism. Some risk factors including recent surgery, vascular injury, or hypercoagulability increase a patient's risk for a venous thromboembolism (VTE); however, these events can occur in patients without risk factors, as well. The reported rate of VTE in medically ill patients is 10-26%.[1-2] Due to this risk, it is important for all acutely ill, hospitalized patients to receive pharmacologic or mechanical prophylaxis, to avoid a preventable VTE from occurring. Venous thromboembolism prophylaxis is considered a core measure by The Joint Commission and Centers for Medicare and Medicaid Services for all patients older than 18 years of age and with a hospitalization length of stay at least 2 days.[3-4] Pharmacologic prophylaxis has demonstrated the potential to reduce VTE events by 50-65% in acutely ill patients with a favorable safety profile.[5]

Patients with cystic fibrosis (CF) are frequently hospitalized for intravenous antibiotics due to persistent pulmonary infections and difficulty in eradicating pulmonary bacterial

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-138

colonization. These patients, similar to other acutely ill medical patients, have an 8-fold increased risk of VTE.[3] Some common risk factors among acute medically ill patients and those with CF include decreased respiratory function and decreased mobility.[6-8] Additional VTE risk factors identified for patients with CF include the presence of central venous catheters, colonization with *Burkholderia cepacia* complex (BCC), ongoing inflammation, liver dysfunction, platelet hyper-reactivity and vitamin K deficiency.[9-13] Several studies have evaluated the rates of VTE in patients with CF, but these studies vary in design and length, ranging from 2-13 years. The rate of VTE in adults and children with CF is reported between 3.5% and 16.1%.[11,14-17]

Venous thromboembolism in patients with CF has the potential to increase morbidity, mortality and health care costs. Development of a pulmonary embolism will further decrease an already limited pulmonary reserve, as well as introduce potential complications from long-term anticoagulation, such as hemoptysis or other bleeding and the potential need for therapeutic drug monitoring. This study characterizes refusal rates of pharmacologic VTE prophylaxis in adult patients with CF at a large CF-accredited center. Furthermore, the study assesses the resulting incidence of VTE of patients during their admission as well as within 30 days of hospital discharge during a two-year study period.

METHODS

The study is a retrospective, single-center medical record cohort review of adult patients (≥18 years) with CF (based on International Classification of Diseases, Ninth Revision (ICD-9) billing code 277) admitted to the hospital between September 1, 2013 and August 30, 2015. Patients who were receiving therapeutic anticoagulation, who were pregnant, had an active VTE, or who had previously received a lung transplant were excluded. The Institutional Review Boards at both Mercer University and Emory University approved the study procedures.

Medical and laboratory data were collected from the electronic medical record. Patient demographics and clinical data including age, sex, height, weight, serum creatinine at baseline, percent predicted forced expiratory volume in the first second (ppFEV1) at admission, ppFEV1 at baseline, liver function tests, length of stay, past medical history, and history of VTE were collected. Creatinine clearance and body mass index (BMI) were calculated from the collected data.

The primary endpoint for the study was to determine the rate of refusal of pharmacologic VTE prophylaxis in adult patients with cystic fibrosis. Secondary endpoints include the incidence of VTE during hospitalization, the incidence of VTE within 30 days following the date of discharge, the combined incidence of VTE during hospitalization and within 30 days following the date of discharge, the difference in refusal rate between pharmacologic agents, a comparison between patients who refused prophylaxis and those who did not refuse prophylaxis, and the incidence of VTE in patients with BCC.

Patients were divided into two categories: refused prophylaxis and did not refuse prophylaxis. Patients were defined as refusing their pharmacologic prophylaxis if 50% or more of the scheduled administrations were refused during the first 48 hours of admission.

Statistical analysis was performed with IBM Statistical Package for the Social Sciences (SPSS) Software. Descriptive statistics were calculated for baseline characteristics along with primary and secondary endpoints. Chi-square tests were used to assess difference in categorical variables and student *t*-tests were used to assess the differences in continuous variables. An α of ≤ 0.05 was considered to be statistically significant.

RESULTS

Four hundred and twenty-six patient encounters were identified based on the ICD-9 billing code for CF and admission to the hospital during the defined study period. Of these, 307 patient encounters of 144 unique patients were included in the study (Figure 1). One hundred and nineteen patient encounters were excluded because they did not have a pharmacologic prophylaxis agent ordered (n=49), had previously received a lung transplant (n=36), were receiving treatment for VTE (n=10), were pregnant (n=4) or did not meet other inclusion criteria (n=20).

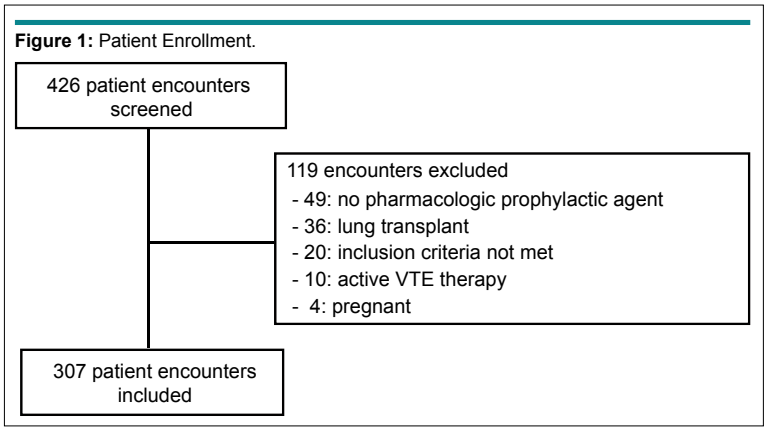


Figure 1: Patient Enrollment.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-138

Characteristics of the patients included in the study are described in Table 1. Patients were approximately 28 years of age with a body mass index of 21 kg/m^2. The mean ppFEV1 at admission, an important measure of pulmonary function, was just under 48%, which was reduced from the patients' mean baseline ppFEV1 of around 60%. Unfractionated heparin 5000 units administered subcutaneously every eight hours was the most common regimen used for VTE prophylaxis, ordered in 62.5% of patients.

Pharmacologic VTE prophylaxis was refused during 238 (77.5%) patient encounters. Over 22% of patients had pharmacologic prophylaxis administered during their encounters (Figure 2). No differences were seen in the rates of refusal based on pharmacologic agent or dosing interval. Unfractionated heparin was refused by 77.8% of patients and enoxaparin was refused by 75.0% of patients (p-value = 0.84).

The characteristics of the patients who refused pharmacologic prophylaxis were compared with patients who did not refuse and are shown in Table 2. Patients who were younger (p=0.003), weighed less (p=0.017) and had a lower BMI (p=0.008) were significantly more likely to refuse pharmacologic prophylaxis compared to those who did not refuse.

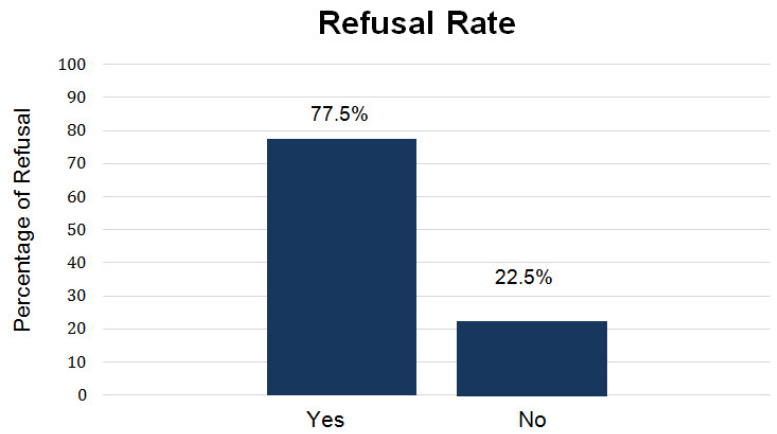
A VTE event occurred in five patients total with three events during the hospitalization and two different patients within 30 days of discharge. The combined incidence of VTE per hospitalization was 1.63%. Three of the patients developed a pulmonary embolism and the two patients developed an upper extremity deep vein thrombosis. All of the patients who developed a VTE refused their pharmacologic prophylaxis agent, with 80% of these patient encounters having an order for enoxaparin 40 mg subcutaneous every 24 hours. No differences were observed between patients who refused and did not refuse prophylaxis with respect to developing a VTE during hospitalization, within 30 days or as a combined incidence, likely due to the small number of VTE events. None of the patients who developed a VTE during the study period had a microbiological history of colonization with BCC.

Table 1: Characteristics of the Study Population (n=307).

Characteristic	Study Population[a]
Age [years]	28.4±8.9
Male [%]	50
Height [cm]	166.1±10.2
Weight [kg]	58.4±13.7
Body Mass Index [kg/m^2]	21.0±3.8
Serum Creatinine [mg/dL]	0.9±0.3
Creatinine Clearance [mL/min]	105.6±32.5
ppFEV1 Admission[b]	47.9±22.5
ppFEV1 Baseline[b]	59.9±24.3
Length of Stay	4.9±3.3
History of VTE [%]	3.3

[a]Mean ± standard deviation.
[b]ppFEV1: Percent predicted forced expiratory volume in the first second.

Figure 2: Primary Outcome: Refusal Rate of Pharmacologic VTE Prophylaxis.



ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-138

Table 2: Comparison of Baseline Characteristics for Patients who Refused and did not Refuse Pharmacologic Prophylaxis.

Characteristic	Refused	Did not refuse	*p*-value
Age [years][a]	27.5±8.2	31.6±10.4	0.003
Sex[b]			0.221
Male	114 (47.9)	39 (56.5)	
Female	124 (52.1)	30 (43.5)	
Height [cm][a]	165.9±10.2	166.6±10.1	0.648
Weight [kg][a]	57.2±12.6	62.4±16.4	0.017
Body Mass Index [kg/m^2][a]	20.7±3.4	22.3±4.8	0.008
Serum Creatinine [mg/dL][a]	0.8±0.3	0.9±0.4	0.222
Creatinine Clearance [mL/min][a]	105.5±32.3	105.7±33.6	0.973
ppFEV1 Admission[a,c]	47.3±21.6	50.3±25.5	0.404
ppFEV1 Baseline[a,c]	58.8±23.7	63.9±25.9	0.123
Length of Stay [days][a]	4.9±3.1	5.3±4.2	0.410
History of VTE[b]			0.240
No	232 (97.5)	65 (94.2%)	
Yes	6 (2.5)	4 (5.8%)	
VTE Order[b]			0.844
Heparin 5000 units q12h	8 (3.4)	3 (4.3)	
Heparin 5000 units q8h	152 (63.9)	40 (58.0)	
Enoxaparin 30 mg daily	9 (3.8)	3 (4.3)	
Enoxaparin 40mg daily	69 (29.0)	23 (33.3)	

[a]Mean±standard deviation.
[b]n(%).
[c]ppFEV1: Percent predicted forced expiratory volume in the first second.

DISCUSSION

Refusal of pharmacologic VTE prophylaxis is high among adult patients with CF and occurred in three-fourths of the study patients. Refusal was similar between all pharmacologic agents and was not dependent on the number of administrations per day. Refusal of pharmacologic prophylaxis was chosen as the primary endpoint since there was a concern at the study institution about an increased number of VTE events and no previous available literature characterizing the role of pharmacologic prophylaxis refusal in this patient population.

The combined incidence of VTE observed in this study (1.63%) was lower than previously reported. The previous studies that have quantified the rates of VTE in patients with CF have varied in duration from 2 years to 13 years[14-16] with two of the studies being prospective observations.[11,17] The three retrospective reviews that are most similar to our patient population included adults with CF who had central venous catheters and reported VTE rates from 3.5% to 16.1%.[14-16] Nash et al also evaluated the rate of VTE in patients with a positive culture for BCC. The rate of VTE was significantly higher at 20.9% (p=0.02) compared to those with negative cultures.[16]

Two studies reported their findings from prospective studies evaluating both children and adult patients with CF, all with central venous catheters and found the rate of VTE to be 3.7-6.6%.[11,17] Similarly, Raffini et al reported a high incidence of VTE (27%) in patients with a history of BCC.[11]

This study evaluated patient encounters, as many patients were admitted to the hospital multiple times during the study period and had the opportunity to refuse or accept pharmacologic prophylaxis at each admission. Of the combined incidence of VTE observed, five different patients developed a venous thromboembolism. It could be argued the combined incidence based on individual patients (n=144) was higher at 3.8%; however, this is still on the lower end of the rates reported previously.

The statistical findings from the post-hoc analysis did identify younger age, lower body weight, and lower body mass index as factors associated with increased refusal of pharmacologic prophylaxis. Younger patients might be more likely to refuse their prophylaxis as they may have had fewer hospital admissions and be less familiar with the purpose of VTE prophylaxis, particularly if they were more recently treated in a pediatric hospital where VTE prophylaxis is less routine, or they may be more ambulatory in the hospital. Additionally, patients with lower body weight or body mass index may have more severe disease and frequent hospital admissions, or be concerned about injection site pain due to their small body size. These associations may be due to chance and may not represent risk factors for refusal.

The findings of this study illustrate a high rate of VTE prophylaxis refusal with a low rate of resulting venous thromboembolism. Although, pharmacologic prophylaxis is more effective and the preferred strategy for preventing VTE, it may be reasonable to calculate the VTE risk for each patient to determine if pharmacologic prophylaxis is necessary and to educate high-risk patients about the benefits of VTE prophylaxis.

ISSN 2377-1658 http://dx.doi.org/10.17140/PRRMOJ-4-138

LIMITATIONS

This study is limited by its single-center, retrospective design; however, the large number of patient encounters included in this evaluation and the continuity of care between inpatient admissions and the outpatient clinic visits abrogates this limitation. The low number of VTE events is an additional limitation since the small numbers did not allow for comparisons between those who developed VTE *versus* those who did not. Third, a bias of inclusion can be considered a limitation, as patient encounters were included in the study and not individual patients. Patients were admitted multiple times during the two-year time period and are more likely to refuse their prophylactic agents if they have refused in the past. It is possible that although most of these patients follow-up at the CF clinic, some may have been admitted to other hospitals with VTE events or seen at other medical clinics. Lastly, the presence or type of central venous catheter was not assessed in this study.

CONCLUSIONS

The majority of adult patients with CF admitted to the hospital over a two-year period refused pharmacologic VTE prophylaxis with no difference in refusal between pharmacologic agents, and the combined incidence of VTE was low.

ACKNOWLEDGEMENTS

Kathryn M. Momary, PharmD, BCPS assisted with statistical analysis and is a Vice Chair and Associate Professor in the Department of Pharmacy Practice at Mercer University College of Pharmacy.

FINANCIAL SUPPORT: None.

CONFLICTS OF INTEREST

The author(s) declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

PRESENTATIONS

An abstract from this study was presented at the United Health Consortium poster session in New Orleans, LA on December 5, 2015, and the Southeastern Residency Conference in Athens, GA on April 28, 2016.

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