A Study of Patients with "Interface Respiratory Failure" Due to Chronic Obstructive Pulmonary Diseases

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ABSTRACT

Objective: *To explain a definition of "interface respiratory failure" as arterial blood gas assay with arterial oxygen partial pressure in the range of 60–75 mmHg.*

Subjects and Methods: *We compared arterial blood gases (ABGs), resting respiratory drive and its derivatives, mechanics of respiratory muscles, resistance and compliance of the respiratory tract and some important cytokines (interleukin-4 and interferon-γ) of stable chronic obstructive pulmonary diseases (COPD) subgroups (total 50 cases) and control group (25 cases).*

Results: *The patients attaining the "interface respiratory failure" stage developed great changes in respiratory mechanics parameters and inflammatory mediator, which might cause the exacerbation of COPD and the inclination to generate "real respiratory failure" and COPD progression.*

Conclusions: *The definition of interface respiratory failure is scientific, direct and its width is appropriate. We should intervene appropriately and positively to avoid progression from "interface respiratory failure" to the "real respiratory failure" stage, and this avoidance means a higher survival rate and a lower medical expense. Interventions should focus on oxygen therapy, bronchodilators, improving respiratory compliance, cytokines and anti-infective agents, respectively.*

Keywords: Chronic obstructive pulmonary disease (COPD), forced expiratory volume in first second (FEV1), forced oscillation technology (FOT), phase angles of respiratory resistance-Phi, resistance of airway, respiratory drive

Estudio de Pacientes con "Insuficiencia Respiratoria de Interfaz" Debido a Enfermedades Pulmonares Obstructivas Crónicas

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RESUMEN

Objetivo: *Explicar una definición de "insuficiencia respiratoria de interfaz" como análisis de gasometría arterial con presión parcial de oxígeno arterial en el rango de 60–75 mmHg.*

Sujetos y métodos: *Comparamos la gasometría arterial (ABG, por sus siglas en inglés), la dinámica respiratoria de descanso y sus derivados, la mecánica de los músculos respiratorios, la resistencia y compliancia (distensibilidad) de las vías respiratorias y algunas importantes citoquinas (Interleuquina-4 y el interferón-γ) de subgrupos estables de enfermedad pulmonar obstructiva crónica (EPOC) (total 50 casos) y grupo control (25 casos).*

Resultados: *Los pacientes que alcanzaron la etapa de "insuficiencia respiratoria de interfaz" desarrollaron grandes cambios en los parámetros de mecánica respiratoria y mediador inflamatorio, que podrían causar la exacerbación de la EPOC y la inclinación a generar "insuficiencia respiratoria real" así como la progresión de la EPOC.*

Conclusiones: *La definición de insuficiencia respiratoria de interfaz es científica, directa y su amplitud es apropiada. Debemos intervenir adecuadamente y positivamente para evitar la progresión de la "insuficiencia respiratoria de interfaz" a la etapa de "insuficiencia respiratoria real". El hacerlo significa una mayor tasa de supervivencia y un menor gasto médico. Las intervenciones deben centrarse en la terapia de oxígeno, los broncodilatadores, el mejoramiento de la compliancia respiratoria, las citoquinas y los agentes antiinfecciosos, respectivamente.*

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Palabras claves: Enfermedad pulmonar obstructiva crónica (EPOC), volumen espiratorio forzado en el primer segundo (VEF1), tecnología de oscilación forzada (TOF), ángulos de fase Phi de resistencia respiratoria, resistencia de la vía respiratoria, dinámica respiratoria

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disorder that causes considerable morbidity and mortality. Currently, it represents the fourth leading cause of death in the world, and it is expected to increase both in prevalence and in mortality over the next decades (1). Since the progression of COPD is irreversible, prevention, early detection and prompt treatment are vital to improve the symptoms and health status and reduce mortality and the burden of COPD patients. However, many patients with COPD in many developing countries including China will not get treatment until they have an exacerbation and reach the status of respiratory failure, because they know little about this disease. Then, the treatment is complicated, difficult and costly.

Respiratory failure (RF) is an important and critical status in the course of COPD because it is related to severity of the disease. The traditional term "respiratory failure" describes blood gas abnormalities of low systemic arterial oxygen tension (hypoxaemia) [PaO_2 under 60 mmHg] and/or a high systemic arterial carbon dioxide tension (hypercapnia) [$PaCO_2$ over 50 mmHg]. In this study, we used a definition of "interface respiratory failure" as arterial blood gas assay with arterial oxygen partial pressure in the range of $\geq$ 60 mmHg and $<$ 75 mmHg and aimed to prove that the definition is scientific, direct and its spectrum is appropriate.

SUBJECTS AND METHODS

All subjects were admitted between February 2011 and September 2012. Twenty-five healthy volunteers from the medical examination centre of Tianjin Medical University General Hospital were enrolled in this study and they comprised the normal control group (Group A). A total of 50 consecutive outpatients diagnosed with COPD (2) from the respiratory department of Tianjin Medical University General Hospital were recruited and divided into two groups of 25 each (Group B and Group C), based on arterial oxygen partial pressure (PaO_2) and arterial carbon dioxide partial pressure ($PaCO_2$). Twenty-five COPD patients in Group B had not attained interface respiratory failure (IRF) status, and met the following criteria: [i] stable COPD patients who had no recurrent exacerbation over the last three months and [ii] $PaO_2 \geq 75$ mmHg and $PaCO_2 < 50$ mmHg. All patients in Group C had attained IRF status, and were stable COPD patients who had no recurrent exacerbation during the last three months and their $PaO_2 \geq 60$ mmHg and < 75 mmHg and $PaCO_2 < 50$ mmHg. The study was approved by the ethics committee of the General Hospital of Tianjin Medical University, and written informed consent was obtained from all patients or the authorized persons.

Measurements

All subjects performed the pulmonary function tests according to the American Thoracic Society guidelines by spirometry [CUSTO vit m, German] (3). Measurements of lung function included the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV1) before and at least 15 minutes after bronchodilation with 200 mg of salbutamol. The best of a minimum of three acceptable retained flow volume curves was used to determine the postbronchodilator FEV1:FVC ratio [FEV1/FVC] (2). Resistance of airway (RAW) [with forced oscillation technology (FOT)] was measured by German "CUSTO vit m" spirometry. Respiratory drive (mouth occlusion pressure 100 milliseconds after initiation of breath; $P_{0.1}$) and its derivative parameters including maximal inspiratory pressure (PIMAX), maximal expiratory pressure (PEMAX), mouth occlusion pressure during maximum ventilation ($P_{0.1}$MAX), $P_{0.1}$/PIMAX, $P_{0.1}/P_{0.1}$MAX, inspiration time/total time (TIN/TTOT), $P_{0.1}$/minute volume ($P_{0.1}$/MV) and $P_{0.1}$/mean inspiratory flow ($P_{0.1}$/MIF) were collected by German JAEGER spirometry. Radial arterial blood was collected for blood gas assay (AVL-995, Switzerland).

We used ficoll-hypaque density gradient centrifugation technology to get peripheral blood mononuclear cell (PBMC), cultured (10%FCS RPMI-1640 culture medium, American GIBCO Company) and then measured interleukin (IL)-4 and interferon gamma (IFN-γ) level by enzyme-linked immunosorbent assay (ELISA) [American GIBCO Company test kit].

Statistical analysis

The statistical analysis and chart were got from SPSS 11.5 for Windows. All values are reported as mean ± standard deviation ($\overline{x} \pm s$) . The mean differences between different groups were listed in comparison analysis. Statistical comparisons between different groups were performed by a general linear model one-way analysis of variance (ANOVA). Pearson correlations were used to determine the relationships between different parameters. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 75 cases were admitted and their ages ranged from 60 to 84 years. There were no statistical differences in weight, height, gender and age between these three groups. The measurements of all subjects are shown in Table 1. The mean differences of measurements between different groups are listed in Table 2.

The patients that attained the "interface respiratory failure" stage (Group C), developed greater changes in respiratory

Table 1: Descriptive analysis of all measured items ($\overline{x} \pm s$)

Items	All subjects	Group A	Group B	Group C
PIMAX (Kpa)	5.29 ± 2.39	6.09 ± 2.729	6.05 ± 1.71	3.74 ± 1.86
PEMAX (Kpa)	7.80 ± 3.49	9.11 ± 3.12	9.10 ± 3.04	5.18 ± 2.79
$P_{0.1}$MAX (Kpa)	1.60 ± 0.85	1.578 ± 0.80	1.65 ± 0.68	1.57 ± 1.05
$P_{0.1}$ (Kpa)	0.19 ± 0.11	0.14 ± 0.03	0.18 ± 0.09	0.27 ± 0.14
$P_{0.1}$/PI MAX	0.05 ± 0.04	0.03 ± 0.02	0.04 ± 0.02	0.08 ± 0.04
$P_{0.1}$/$P_{0.1}$ MAX	0.16 ± 0.12	0.11 ± 0.06	0.14 ± 0.09	0.22 ± 0.16
TIN/TTOT	0.43 ± 0.06	0.42 ± 0.08	0.42 ± 0.05	0.43 ± 0.05
$P_{0.1}$/MV (Kpa*min/L)	0.02 ± 0.01	0.02 ± 0.06	0.02 ± 0.01	0.03 ± 0.01
$P_{0.1}$/MIF (Kpa*s/L)	0.36 ± 0.21	0.26 ± 0.08	0.29 ± 0.16	0.53 ± 0.23
FEV1%FVC	76.43 ± 17.80	88.12 ± 6.17	82.20 ± 8.74	58.96 ± 19.16
R4Hz RFO (10^{-1}Kpa*s/L)	3.78 ± 1.76	3.34 ± 0.92	3.09 ± 1.69	4.89 ± 1.98
R8Hz RFO (10^{-1}Kpa*s/L)	3.46 ± 1.45	3.10 ± 0.98	3.11 ± 1.72	4.17 ± 1.32
R16Hz RFO (10^{-1}Kpa*s/L)	2.82 ± 1.16	2.52 ± 0.84	2.73 ± 1.55	3.21 ± 0.87
PaO_2 (mmHg)	79.24 ± 10.18	88.78 ± 6.44	81.44 ± 4.21	67.50 ± 4.06
$PaCO_2$ (mmHg)	40.28 ± 8.73	39.08 ± 4.98	41.26 ± 10.18	40.49 ± 10.20
IL-4 (ng/L)	14.23 ± 5.60	12.94 ± 2.66	16.10 ± 7.47	13.64 ± 5.31
IFN-γ (ng/L)	2132.15 ± 806.83	1646.74 ± 89.16	2330.46 ± 1223.70	2419.25 ± 359.87
R (8Hz-16Hz)	0.64 ± 0.70	0.58 ± 0.42	0.38 ± 0.91	0.96 ± 0.59

PIMAX: maximal inspiratory pressure; PEMAX: maximal expiratory pressure; $P_{0.1}$MAX: mouth occlusion pressure during maximum ventilation; TIN/TTOT: inspiration time/total time; $P_{0.1}$/MV: $P_{0.1}$/minute volume; $P_{0.1}$/MIF: $P_{0.1}$/mean inspiratory flow; FEV1% FVC: percentage forced expiratory volume in 1 second/forced vital capacity; PaO_2: oxygen partial pressure; $PaCO_2$: carbon dioxide partial pressure; IL-4: interleukin-4; IFN-γ: interferon gamma

Table 2: Comparison of the three different groups in the study

Items	*F* value	Mean difference between B and A	Mean difference between C and A	Mean difference between C and B
PI MAX (Kpa)	9.833**	-0.0384	-2.3500**	-2.3116**
PE MAX (Kpa)	14.357**	-0.0120	-3.9280**	-3.9160**
$P_{0.1}$ MAX (Kpa)	0.067			
$P_{0.1}$ (Kpa)	11.440**	0.0432	0.1308**	0.0876**
$P_{0.1}$/PIMAX	32.434**	0.0056	0.0508**	0.0452**
$P_{0.1}$/$P_{0.1}$MAX	12.352**	0.0244	0.1092**	0.0848*
TIN/TTOT	0.048			
$P_{0.1}$/MV (Kpa*min/L)	9.019*	-0.0016	0.0084*	0.0100*
$P_{0.1}$/MIF (Kpa*s/L)	19.808**	0.0384	0.2756**	0.2372**
FEV1%FVC	37.007**	-5.9200*	-29.1600**	-23.2400**
R4Hz RFO (10^{-1}Kpa*s/L)	9.382**	-0.2576	1.5456**	1.8032**
R8Hz RFO (10^{-1}Kpa*s/L)	4.989**	0.0044	1.0656*	1.0612**
R16Hz RFO (10^{-1}Kpa*s/L)	10.780**	0.2088	0.6936**	0.4848*
PaO_2 (mmHg)	115.709**	-7.3400**	-21.2840**	-13.9440**
$PaCO_2$ (mmHg)	0.395			
IL-4 (ng/L)	6.730*	3.1560	0.7000	-2.4560**
IFN-γ (ng/L)	51.495**	683.7200**	772.5160**	88.7960**
R (8Hz-16Hz)	4.766*	-0.2044	0.3720*	0.5764*

*p value < 0.05, **p value < 0.01

PIMAX: maximal inspiratory pressure; PEMAX: maximal expiratory pressure; $P_{0.1}$MAX: mouth occlusion pressure during maximum ventilation; TIN/TTOT: inspiration time/total time; $P_{0.1}$/MV: $P_{0.1}$/minute volume; $P_{0.1}$/MIF: $P_{0.1}$/mean inspiratory flow; FEV1%FVC: percentage forced expiratory volume in 1 second/forced vital capacity; PaO_2: oxygen partial pressure; $PaCO_2$: carbon dioxide partial pressure; IL-4: interleukin-4; IFN-γ: interferon gamma

mechanics parameters and inflammatory medium based on the data in Table 2. There was no difference with $PaCO_2$ between these three groups. This means that remission stage patients with COPD seldom demonstrate high $PaCO_2$ and shows that PaO_2 is a relatively objective index in COPD progression. Respiratory drive ($P_{0.1}$) was negatively correlated with PaO_2 and FEV1%FVC, respectively (Tables 3 and 4). Linear regression of $P_{0.1}$ to PaO_2 showed the same result [$P_{0.1} = 0.6189\text{-}0.0054 \times PaO_2$, (Rsq = 0.23800)] (Figure).

Table 3: Analysis of correlation (1)

Items	$P_{0.1}$	$P_{0.1}/P_{0.1}MAX$	TIN/TTOT	$P_{0.1}/MV$	$P_{0.1}/MIF$	FEV1%FVC
$P_{0.1}$						
$P_{0.1}/P_{0.1}MAX$	0.570**					
TIN/TTOT	-0.148	-0.376**				
$P_{0.1}/MV$	0.781**	0.534**	-0.240*			
$P_{0.1}/MIF$	0.91**	0.662**	-0.285*	0.817**		
FEV1%FVC	-0.674**	-0.473**	0.020	-0.498**	-0.660**	

* p value < 0.05, ** p value < 0.01

$P_{0.1}MAX$: mouth occlusion pressure during maximum ventilation; TIN/TTOT: inspiration time/total time; $P_{0.1}/MV$: $P_{0.1}$/minute volume; $P_{0.1}/MIF$: $P_{0.1}$/mean inspiratory flow; FEV1%FVC: percentage forced expiratory volume in 1 second/forced vital capacity;

Table 4: Analysis of correlation (2)

Items	$P_{0.1}$	FEV1%FVC	PaO_2	IL-4	IFN-γ
$P_{0.1}$					
FEV1%FVC	-0.674**				
PaO_2	-0.488**	0.610 **			
IL-4	-0.110	0.001	0.178		
IFN-γ	0.300**	-0.655**	-0.718**	0.027	

** p value < 0.01

$P_{0.1}$: mouth occlusion pressure; FEV1%FVC: percentage forced expiratory volume in 1 second/forced vital capacity; PaO_2: oxygen partial pressure; IL-4: interleukin-4; IFN-γ: interferon gamma

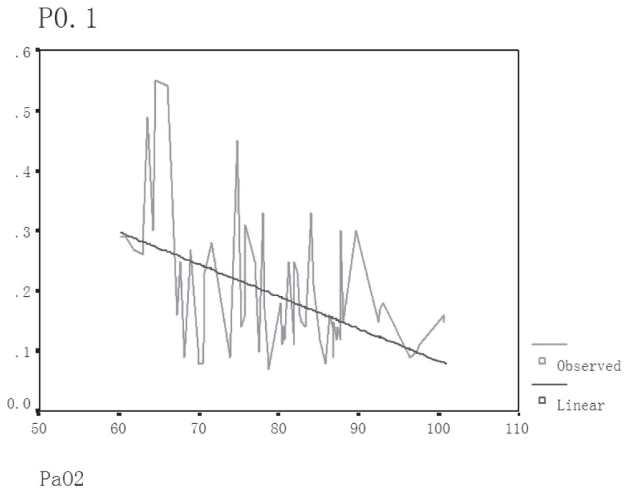

Figure: Linear regression of mouth occlusion pressure ($P_{0.1}$) to oxygen partial pressure (PaO_2). Linear regression of $P_{0.1}$ to PaO_2 showed $P_{0.1}$ was negatively correlated with PaO_2 [$P_{0.1} = 0.6189\text{-}0.0054 \times PaO_2$, (Rsq = 0.23800)].

DISCUSSION

The results of this study showed that there was no difference with $PaCO_2$ among the three groups. This means remission stage patients with COPD seldom demonstrate high $PaCO_2$, which appears only if these stable COPD patients develop acute exacerbation and shows that PaO_2 is a relatively objective index in COPD progression. PIMAX was used to evaluate inspiratory function of respiratory muscles, and a low PIMAX means the patients are inclined to develop hypoxaemia and the use of aminophylline can increase diaphragm contractility so as to improve this status (4–6). Table 2 shows that with PIMAX, there was no difference between Group A and Group B but obvious difference between Group C and Group A and obvious difference between Group C and Group B. This indicates that if patients attain interface respiratory failure status, then these patients will develop impaired inspiratory function and hypoxaemia. Meanwhile, PIMAX represents inspiratory muscle function (7), is an important parameter to measure motor capacity of COPD patients (8), and its deduc-

tion suggests a low exercise tolerance. The activity of expiratory muscles increases in proportion to ventilatory demands (9). PEMAX was used to evaluate function of expiratory muscles, so it would certainly be useful for evaluating some of their roles, such as those related to the efficiency of cough efforts (10). Given Table 2, we can recognize the decrease of secretion drainage which can cause recurrent infection and could accelerate the exacerbation of COPD.

Mouth occlusion pressure 100 milliseconds after initiation of breath ($P_{0.1}$) was used to assess the central respiratory drive. It is generally recognized that $P_{0.1}$ is the best non-invasive technical index that could exclude influences generated by breathing mechanics and by consciousness in the measurement of central efferent function (11). From Table 2, maybe a higher central respiratory drive must be operated by the patients to maintain a normal breathing physiology status and regular daily activities because of hypoxaemia and/or increased respiratory resistance in Group C. This result was consistent with the information from Table 3 and Table 4 and there were negative correlations between $P_{0.1}$ and FEV1%FVC and between $P_{0.1}$ and PaO_2, respectively (Tables 3 and 4). Linear regression of $P_{0.1}$ to PaO_2 showed the same result [$P_{0.1} = 0.6189 - 0.0054 \times PaO_2$, (Rsq = 0.23800)] (Figure).

We did partial correlation analysis between $P_{0.1}$ and PaO_2, with $PaCO_2$ as controlled variance, and got that r = -0.4665 ($p = 0.000$) which seemed that the correlation between $P_{0.1}$ and PaO_2 would not be changed with $PaCO_2$ change. Prolonged higher respiratory drive can cause severe fatigue in the respiratory centre and in respiratory muscles (12), and the inclination to generate respiratory failure and COPD progression. A little internal and external environment change could mean recurrent respiratory failure and respiratory tract infections. However, several studies showed that bronchodilators could reduce $P_{0.1}$ and improve ventilation mechanism (13–15). Using $P_{0.1}$/PIMAX could preclude the influence in $P_{0.1}$ measurement from respiratory muscles' contraction capability (16), and we got the same results in $P_{0.1}$/PIMAX parameter appraisal.

$P_{0.1}/P_{0.1}$MAX is negatively correlated with central respiratory drive backlog, and in Group C its decrease indicated a lower compensation capability in the respiratory system, worsened function for stress status and tendency to respiratory failure. $P_{0.1}$/MV reflects the relationship between length (ventilation volume) and tension (neuromuscular efferent) in inspiratory mechanism (13), and its diminution showed a decreased respiratory efficiency in Group C. Consistent with reduction of FEV1%FVC, increase of $P_{0.1}$/MIF indicated high inspiratory impedance with patients in Group C (14), and this result is also obtained from correlation analysis in Table 3. Meanwhile, no statistical difference between $P_{0.1}$MAX and TIN/TTOT showed no radical change in respiratory pattern (14) and so interface respiratory failure stage is an appropriate time for intervention.

CD4+ Th cells can be categorized into Th1 and Th2 with unique cellular characteristics based on the cytokines primarily produced by them. These cell subsets have distinctive roles in defending hosts against pathogens. Th1 cells are essential for controlling intracellular micro-organisms such as mycobacteria by activating macrophages with IFN-γ (17). Parasites are effectively controlled by Th2 cells (17). Th1 and Th2 cells predominantly produce IFN-γ and IL-4, respectively. Interferon gamma is a biological multifunctional cytokine, which is an important immunoregulator and an important activator for macrophage. Some studies showed that IFN-γ had critical synergism in the elimination of respiratory tract pathogens. Interferon gamma could be generated by the stimulation of bacteria and virus to the T lymphocyte, and facilitate the change from $CD4^+$ to Th1, and then the formation of Th1 could generate more IFN-γ for immunoregulation. *In vitro* experiments suggested that IFN-γ could prevent the formation of Th2.

Our study demonstrated Th1 preponderance in Group C, and this result could develop because of recurrent infection which facilitated Th1, suppressed Th2, and produced a higher IFN-γ and a lower IL-4. Proper cytokine intensity and inflammation cell infiltration are important body defence mechanisms that participate in repair effect, but overdose of cell infiltration and inflammatory mediator (IFN-γ for instance) release can generate tissue damage, increased airway resistance, hypoxaemia, higher respiratory drive [Table 4], exacerbation of COPD and finally, respiratory failure. All these findings indicate a broad prospect of cytokine therapy.

Forced oscillation technology (FOT) adds oscillatory signals to the respiratory tract, forces airway and lung tissue to develop corresponding oscillation reaction, through spectrum analysis, and we can get resistance parameters of this respiratory system, by including airway resistance on 4Hz oscillatory frequency (R4HZ RFO), 8Hz (R8HZ RFO) and 16Hz (R16HZ RFO), among them R8HZ RFO the most significant in CUSTO machine. In normal subjects, airway resistance changes little with the change of oscillatory frequency, but according to mechanical rationale, if respiratory tract compliance decreases, airway resistance will decrease more significantly with the raise of oscillatory frequency, and this "frequency reliance" can be fully perceived by FOT and has a good correlation with system impedance and compliance (18), and is the result of damaged small airway function, lower compliance, decreased alveolar elasticity.

Pride reported that COPD patients had characteristics of "frequency reliance" and resonance frequency augmentation (19), and we used ΔR [8~16Hz] (R8HZ RFO value minus R16HZ RFO value) to reflect the characteristics (20). From Table 2, we had gotten that, on all three different frequencies of Group C, airway resistance increased significantly and ΔR(8~16Hz) also increased; these demonstrated occluded small airways, higher respiratory tract resistance, lower airway compliance, rigid airway and more seriously damaged small airway walls and alveoli in Group C.

So, in this study, these findings suggested that when COPD patients attained the "interface respiratory failure"

stage, great changes had appeared in respiratory drive, airway resistance, respiratory tract compliance and inflammatory medium. At this stage, we should intervene appropriately and positively to avoid progression to "real respiratory failure" stage, and this avoidance means a higher survival rate and a lower expense of medical resource which has great practical significance. Apparently, based on our study, interventions should focus on oxygen therapy, bronchodilators, improving respiratory compliance, cytokines and anti-infective agents, respectively.

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