ISSN 2218-6255 (online)

World Journal of *Respirology*

World J Respirol 2012 February 28; 2(1): 1-5

Baishideng Publishing Group
www.wjgnet.com

WJR World Journal of Respirology

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WJR

World Journal of Respirology

Contents

Bimonthly Volume 2 Number 1 February 28, 2012

World Journal of Respirology
Volume 2 Number 1 February 28, 2012

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NAME OF JOURNAL
World Journal of Respirology

ISSN
ISSN 2218-6255 (online)

LAUNCH DATE
December 30, 2011

FREQUENCY
Bimonthly

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PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpg@baishideng.com
http://www.wjgnet.com

PUBLICATION DATE
February 28, 2012

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-6255/g_info_20100722180607.htm

ONLINE SUBMISSION
http://www.wjgnet.com/2218-6255/esps/

World Journal of Respirology

Online Submissions: http://www.wjgnet.com/esps/
wjrespirol@wjgnet.com
doi:10.5320/wjr.v2.i1.1

World J Respirol 2012 February 28; 2(1): 1-5
ISSN 2218-6255 (online)

BRIEF ARTICLE

Effect of oxidative stress on development of silicosis

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Received: December 10, 2011 Revised: February 10, 2012
Accepted: February 18, 2012
Published online: February 28, 2012

Abstract

AIM: To investigate the changes of oxidative stress indicators in the serum of silicosis patients and explore the mechanism of silicosis development.

METHODS: Two hundred workers who were exposed to silica dust for more than one year were recruited as dust-exposed group, 100 non-dust-exposed subjects served as control group, 32 patients with suspected 0^+ silicosis as observation group, and 130 silicosis patients were taken as the silicosis group. Indicators of oxidative stress, including superoxide dismutase (SOD), nitric oxide (NO), serum glutathione peroxidase (GSH-Px), total antioxidant capacity (T-AOC), nitric oxide synthase (NOS), and lipid malondialdehyde (MDA), were determined in all the groups.

RESULTS: Compared with the control group, NO and GSH-Px in dust-exposed group and silicosis group increased, and SOD decreased significantly (81.162 ± 35.176, 270.469 ± 39.228 and 68.209 ± 21.528, respectively, $P = 0.004$, $P = 0.002$, $P = 0.005$). Compared with the control and dust-exposed group, T-AOC, NOS and MDA in silicosis group increased significantly (13.048 ± 4.153, 36.201 ± 7.782 and 5.054 ± 1.204, respectively, $P = 0.018$, $P = 0.022$, $P = 0.011$). Compared with dust-exposed group, GSH-Px in the silicosis group increased significantly (270.469 ± 39.228, $P = 0.002$). GSH-Px in phase Ⅲ silicosis was significantly higher than in phase Ⅰ silicosis (290.750 ± 39.129, $P = 0.021$). Pearson correlation analysis showed that serum GSH-Px was positively correlated with silicosis staging, length of dust exposure and type of occupation (47.109 ± 8.015, $P = 0.001$).

CONCLUSION: The imbalance of oxidative and anti-oxidation system is associated with the development of silicosis. The surveillance of oxidative stress indicators will benefit the prognosis of silicosis patients.

Key words: Silicosis; Oxidative stress; Superoxide dismutase; Glutathione peroxidase; Total antioxidant capacity; Nitric oxide synthase; Malondialdehyde

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Miao RM, Zhang XT, Guo P, He EQ, Zhou F, Zhao DK, Zhang YY. Effect of oxidative stress on development of silicosis. *World J Respirol* 2012; 2(1): 1-5 Available from: URL: http://www.wjgnet.com/2218-6255/full/v2/i1/1.htm DOI: http://dx.doi.org/10.5320/wjr.v2.i1.1

INTRODUCTION

Silicosis is the most destructive form of pneumoconiosis caused by the inhalation of SiO_2. Exposure to silica par-

ticles smaller than 10 micrometers is considered a major cause of silicosis. According to the United States National Institute for Occupational Safety and Health, the most important factor in the development of silicosis is "the product of the concentrations of dust containing respirable silica in workplace air and the percentage of respirable silica in the total dust[1]. The disease is associated with inflammation of the respiratory system that eventually results in fibrosis, the hardening of the lungs, reducing the ability of the patients to breathe efficiently[2].The pathological manifestation includes macrophages alveolitis, silicotic nodule and dust fibration[3]. The role of macrophages has been investigated[4], but the pathogenesis remains unclear. The imbalance of oxidation and anti-oxidation due to long-term exposure to silica dusts may be one of the causative factors for silicosis[5]. This study aims at clarifying the pathogenesis of silicosis by observing oxidative stress indicators in peripheral blood of silicosis patients in an attempt to search for new strategies for the prevention and treatment of silicosis.

MATERIALS AND METHODS

Subjects

This research was approved by the Ethics Committee of Wuxi Hospital for Prevention and Treatment of Occupational Disease, Wuxi, China. All subjects were male and they were divided into control group, dust-exposed group, and silicosis patient group. The control group was composed of hotel staff who had no silica dust exposure (age 48.7± 8.0 years, n = 100). The dust-exposed group consisted of workers from a local casting factory who had more than one year dust-exposure (age 50.78 ± 9.4 years, n = 200). The silicosis patient group was composed of in-patients and out-patients who have been admitted to our hospital since 2008 (age 52.0 ± 10.4 years, n = 130). There were 64 phase Ⅰ, 46 phase Ⅱ, and 20 phase Ⅲ silicosis patients in this group. Besides, the cases of suspected 0^+ silicosis were chosen as observation group (age 53.0 ± 9.12 years, n = 32). There was no significant difference in the age among the groups (P > 0.05). None of the subjects had working experience with radiation and toxic substance, and digestive disorders. No one had taken anti-oxidants, such as Vitamin C, Ginggo leaf or Teapol, one month before the test.

Methods

A questionnaire was designed and used to collect the general information of the subjects, including age, history of dust exposure and smoking, and past and family histories[6]. Physical examination, electrocardiogram, high-kilovolt X-ray, pulmonary function tests including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC and maximal voluntary ventilation, and abdominal ultrasonography were performed and serum fasting glucose, lipids, liver and kidney functions were examined.

Silicosis diagnosis

All the subjects were diagnosed and categorized based on the "Diagnostic Criteria of Pneumoconiosis"[7].

Blood sample collection

Five milliliter peripheral blood was taken before breakfast, then centrifuged and preserved under -80 ℃.

Reagents and instruments

Superoxide dismutase (SOD), nitric oxide (NO) enzyme-linked immunosorbent assay kit (Biosource Corporation, United States). Serum glutathione peroxidase (GSH-Px), total antioxidant capacity (T-AOC), nitric oxide synthase (NOS), malondialdehyde (MDA) test kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China), automatic biochemical analyzer (Beckman Inc., United States), Spiro lab Ⅱ portable spirometer (MIR Company, Italia), 550 microplate reader (BIORAD, United States), and New Century T6 ultraviolet (UV)-visible spectrophotometer (Beijing Puxi General, Beijing, China).

Test of oxidative stress indicators

SOD activity and NO levels were detected by enzyme-linked immunosorbent assay. GSH-Px activity, T-AOC and NOS were detected by chemical colorimetric assay. MDA was detected by dithiobisnitro-benzoate colorimetric assay and UV spectrophotometer was used for colorimetric assay. All the detections were performed manually according to the manufacturers' instructions.

Statistical analysis

All the data were expressed as mean ± SD. SPSS11.5 was used for statistical analysis. Univariate analysis of variance and Pearson correlation analysis were used for the significance comparison between each group. P < 0.05 was considered statistically significant.

RESULTS

Comparison of general indicators between each group

There was no significant difference in the blood pressure, blood glucose, blood lipids, creatinine, urea nitrogen, and alanine aminotransferase between groups (P > 0.05) (Table 1).

Comparison of serum NO, SOD, MDA, T-AOC, NOS and GSH-Px between each group

NO in dust-exposed and silicosis groups was significantly higher than in the control group (P < 0.01), while there was no difference between dust-exposed group and silicosis patient group (P > 0.05). SOD in dust-exposed and silicosis group was lower than in the control group (P < 0.01), whereas there was no difference between silicosis and dust-exposed group (P > 0.05). T-AOC, NOS and MDA in silicosis group were obviously higher than in the control group and dust-exposed group (P < 0.05, P < 0.01), but there was no difference between the

Table 1 Comparison of general indicators between control group, dust-exposed group and silicosis patient group

Group	*n*	Age (yr)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Blood glucose (mmol/L)	Triglyceride (mmol/L)	Cholesterol (mmol/L)	Creatinine (μmol/L)	Urea nitrogen (mmol/L)	Alanine transarninase (mmol/L)
Control	100	48.7 ± 8.0	130.42 ± 8.65	82.65 ± 7.68	4.93 ± 0.94	1.45 ± 0.94	5.15 ± 1.03	71.80 ± 16.50	5.53 ± 1.20	24.31 ± 17.44
Dust-exposed	200	50.8 ± 9.4	129.53 ± 9.45	84.72 ± 8.96	4.95 ± 0.79	1.52 ± 0.42	4.24 ± 0.89	69.97 ± 18.96	6.37 ± 1.16	29.16 ± 16.68
Silicosis	130	52.0 ± 10.4	131.42 ± 10.23	84.52 ± 8.14	5.06 ± 0.94	1.53 ± 0.90	4.75 ± 0.92	80.12 ± 19.10	6.47 ± 1.87	27.10 ± 16.83

Table 2 Comparison of nitric oxide, superoxide dismutase, malondialdehyde, total antioxidant capacity, nitric oxide synthase and serum glutathione peroxidase between control, dust-exposed group and silicosis patient group

Group	*n*	NO (μmol/L)	SOD (U/mL)	MDA (μmol/L)	T-AOC (U/mL)	NOS (μmol/L)	GSH-Px (U/mL)
Control	100	45.622 ± 24.081	75.239 ± 24.020	4.027 ± 0.822	11.639 ± 3.707	33.812 ± 6.398	223.360 ± 46.838
Dust-exposed	200	77.148 ± 30.188[b]	70.515 ± 20.034[b]	4.240 ± 1.167	11.814 ± 4.758	35.598 ± 5.664	231.164 ± 36.484[a]
Silicosis	130	81.162 ± 35.176[b]	68.209 ± 21.528[b]	5.054 ± 1.204[a,d]	13.048 ± 4.153[a,c]	36.201 ± 7.782[a,c]	270.469 ± 39.228[b,d]

[a]$P < 0.05$, [b]$P < 0.01$ *vs* control group; [c]$P < 0.05$, [d]$P < 0.01$ *vs* dust-exposed group. NO: Nitric oxide; SOD: Superoxide dismutase; MDA: Malondialdehyde; T-AOC: Total antioxidant capacity; NOS: Nitric oxide synthase; GSH-Px: Serum glutathione peroxidase.

Table 3 Comparison of nitric oxide, superoxide dismutase, malondialdehyde, total antioxidant capacity, nitric oxide synthase and serum glutathione peroxidase between observation group and silicosis at different stages

Group	*n*	NO (μmol/L)	SOD (U/mL)	MDA (μmol/L)	T-AOC (U/mL)	NOS (μmol/L)	GSH-Px (U/mL)
Observation	32	74.130 ± 38.049	70.414 ± 20.036	4.489 ± 1.154	12.903 ± 3.790	35.379 ± 5.504	256.906 ± 21.418
Silicosis							
Phase Ⅰ	64	79.145 ± 36.149	69.215 ± 25.033	4.994 ± 1.237	12.905 ± 4.448	35.626 ± 7.234	259.594 ± 34.79
Phase Ⅱ	46	80.173 ± 36.215	67.896 ± 26.018	5.038 ± 1.208	12.834 ± 3.481	36.078 ± 5.911	276.783 ± 40.969
Phase Ⅲ	20	83.176 ± 34.131	67.201 ± 30.030	5.244 ± 1.127	13.993 ± 4.662	36.899 ± 4.162	290.750 ± 39.129[a,c]

[a]$P < 0.05$ *vs* observation group; [c]$P < 0.05$ *vs* phase Ⅰ silicosis. NO: Nitric oxide; SOD: Superoxide dismutase; MDA: Malondialdehyde; T-AOC: Total antioxidant capacity; NOS: Nitric oxide synthase; GSH-Px: Serum glutathione peroxidase.

Table 4 Serum glutathione peroxidase Pearson correlation test

	Silicosis stage	Category	Length of dust exposure	Type of occupation
r value	0.507	0.456	0.365	0.341
P value	0.000	0.000	0.000	0.000

control group and dust-exposed group ($P > 0.05$). GSH-Px in dust-exposed group and silicosis group was higher ($P < 0.05$, $P < 0.01$) than in the control group, but it was even higher in silicosis group, and the difference was statistically significant ($P < 0.01$) (Table 2).

Comparison of NO, SOD, MDA, T-AOC, NOS and GSH-Px between observation group and silicosis group at different stages

Compared with observation group and phase Ⅰ silicosis, GSH-Px in phase Ⅲ silicosis increased, and the difference was statistically significant ($P < 0.05$). There was no significant difference in the NO, SOD, MDA, T-AOC, NOS and GSH-PX between observation group and different stages of silicosis ($P > 0.05$) (Table 3).

Pearson correlation test

Serum GSH-Px was positively correlated with the silicosis stage, category, length of dust exposure and type of occupation (based on the exposure concentration of dust), and the differences were statistically significant ($P < 0.01$) (Table 4).

DISCUSSION

Pathogenesis of silicosis mainly involves oxidative stress, cytokines, cell apoptosis and immunity doctrine[8-12]. Although the pathogenesis varies, the mechanism that the SiO_2 stimulates the body to secrete a variety of cytokines and other biological activity substances resulting in the fibrosis of lung tissue, is affirmative[13-16]. The clinical diagnosis of silicosis rely mainly on the chest radiograph, but a definite diagnosis is often established when the lesion is irreversible, imposing heavy economic burdens on both the patient and society[17,18]. If the quantitative and qualitative changes of these cytokines can be detected earlier and one or more cytokines as a relatively specific indicator can be found, it will be of great significance for the early diagnosis of silicosis and the dust-exposed population census. Many early stage biomarkers have been found in the sera of human and animals. Reactive oxygen species/reactive nitrogen species (ROS/RNS)[5,19], cytokines[20,21] and apoptosis-related factors[22] are indicators related to the early biological indicators of silicosis. Clara cell protein CC16[23,24], the lung surface ac-

tive substances D and heme monooxygenase-1 are early specific indicators for silicosis[23,25,26]. With the progress made in the pathogenesis studies of silicosis, a variety of theories have become available. Free radical is one of the most important theories. Under physiological circumstances, the normal metabolic process continuously generates free radicals meanwhile they are eliminated by the antioxidant mechanisms in order to maintain homeostasis. When the body is subjected to different kinds of harmful stimuli, oxidative stress occurs and more bioactive molecules such as ROS and RNS are produced that exceeds the removal of oxide, resulting in the imbalance of oxidation and anti-oxidation system[27,28]. This research shows that the imbalance of oxidation and anti-oxidation system existed in both the dust-exposed group and silicosis group, which was particularly remarkable in silicosis group. The increase of NO, NOS, T-AOC and MDA and the decrease of SOD are the prime manifestations. It suggests that silica dust can induce the occurrence of oxidative stress and increase lipid peroxidation, and then cause lung tissue damage. Since serum GSH-Px increases with stages of silicosis, it may be related to the severity of silicosis. Silicosis patients have a higher level of oxidant and anti-oxidant molecules. It may be caused by the continuous production of free radicals and lipid peroxidation with the development of silicosis[29,30]. As the illness progresses, oxidative stress becomes more severe. Therefore, the abnormality of oxidative stress indicators not only suggests the existence of silicosis, but also the inevitable outcome of silicosis. These indicators can be used to predict the occurrence, development, severity and prognosis of silicosis in clinical practice. Due to the known effects of oxidative damage in the development of silicosis, administration of antioxidant agents is a potential strategy for the prevention and treatment of silicosis.

COMMENTS

Background

Silicosis is the most destructive form of pneumoconiosis caused by the inhalation of SiO_2.The pathological manifestation includes macrophages alveolitis, silicotic nodule and dust fibration. But the pathogenesis is still unclear.

Research frontiers

The imbalance of oxidation and anti-oxidation induced by long-term exposure to silica dusts may be one of the causes for silicosis. The authors investigated the pathogenesis of silicosis by observing oxidative stress indicators in the peripheral blood of silicosis patients in an effort to search for new therapies for the disease.

Innovations and breakthroughs

The authors concluded that the imbalance of oxidation and anti-oxidation system exists in both the dust-exposed group and silicosis group, particularly evident in silicosis group. As the illness progresses, the oxidative stress becomes more severe. So, the abnormality of oxidative stress indicators suggests not only the existence of silicosis, but also the inevitable outcome of silicosis.

Applications

The oxidative stress indicators can be used to predict the occurrence, development, severity and prognosis of silicosis in clinical practice. Due to the important effects of oxidative damage in the development of silicosis, administration of antioxidant agents will be a potential strategy for the prevention and treatment of silicosis.

Terminology

Silicosis is the most destructive form of pneumoconiosis caused by the inhalation of SiO_2. When the body is subjected to different kinds of harmful stimuli, oxidative stress occurs and more bioactive molecules such as reactive oxygen species and reactive nitrogen species will be produced that exceeds the removal of oxide, resulting in the imbalance of oxidation and anti-oxidation system.

Peer review

The paper is a short epidemiological study about oxidative stress occurrence in healthy and dust-exposed subjects and silicosis patients and addresses an important issue about the plasma level of oxidative stress-related molecules and its correlation with silicosis.

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World J Respirol 2012 February 28; 2(1): I
ISSN 2218-6255 (online)

Acknowledgments to reviewers of *World Journal of Respirology*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

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World J Respirol 2012 February 28; 2(1): I
ISSN 2218-6255 (online)

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Events Calendar 2012

January 13-14, 2012
Innovation in Severe Acute Respiratory Infections
Sitges, Spain

January 22-26, 2012
50th WSAAI Annual Scientific Session Western Society of Allergy, Asthma and Immunology
Kauai, Hawaii

March 2-6, 2012
68th American Academy of Allergy Asthma and Immunology Annual Meeting
Orlando, FL, United States

March 14-17, 2012
Gulf Thoracic 2012
Dubai, United Arab Emirates

March 30-April 1, 2012
Lung Science Conference
Estoril, Portugal

April 18-21, 2012
3rd European Lung Cancer Conference
Geneva, Switzerland

April 21-24, 2012
5th World Asthma and Chronic Obstructive Pulmonary Disease Forum
New York, NY, United States

April 25-28, 2012
6th International Primary Care Respiratory Group World Conference 2012
Edinburgh, United Kingdom

April 28-29, 2012
Houston Lung Symposium
Houston, TX, United States

May 18-23, 2012
American Thoracic Society ATS 2012 International Conference
San Francisco, CA, United States

June 15-18, 2012
17th World Congress for Bronchology and Interventional Pulmonology joint with The 17th World Congress for Bronchoesophagology
Ohio, OH, United States

June 16-20, 2012
European Academy of Allergy and Clinical Immunology Congress 2012
Geneva, Switzerland

June 20-22, 2012
COPD8 International Conference on Chronic Obstructive Pulmonary Disease
Birmingham, United Kingdom

August 18-23, 2012
15th International Congress of Immunology
Rome, Italy

August 18-21, 2012
21st World Congress of Asthma 2012
Quebec, Canada

September 1-5, 2012
22nd Annual Congress of the European Respiratory Society
Vienna, Austria

October 11-13, 2012
26th Annual North American Cystic Fibrosis Conference
Orlando, FL, United States

October 20-25, 2012
CHEST 2012
Atlanta, Georgia

November 8-14, 2012
Asthma and Immunology
Anaheim, CA, United States

November 13-17, 2012
The 43rd Union World Conference on Lung Health
Kuala Lumpur, Malaysia

December 26-28, 2012
ICBIPRD 2012 International Conference on Bronchology, Interventional Pulmonology and Respiratory Diseases
Bangkok, Thailand

World Journal of Respirology

Online Submissions: http://www.wjgnet.com/esps/
wjrespirol@wjgnet.com
www.wjgnet.com

World J Respirol 2012 February 28; 2(1): I-V
ISSN 2218-6255 (online)

GENERAL INFORMATION

World Journal of Respirology (*World J Respirol, WJR,* online ISSN 2218-6255, DOI: 10.5320) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 84 experts in respirology from 30 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJR* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJR* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJR* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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The aim of *WJR* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of respirology. *WJR* covers diagnostic imaging, respiratory physiology, respiratory endoscopy, respiratory system tumors, chronic obstructive pulmonary disease, bronchial asthma, respiratory infections, critical respiratory illness, sleep-related respiratory disorders, interstitial lung disease, pulmonary vascular diseases, pulmonary embolism, traditional medicine, integrated Chinese and Western medicine, evidence-based medicine, epidemiology and nursing. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to respirology, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

Columns

The columns in the issues of *WJR* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in respirology; (8) Brief Articles: To briefly report the novel and innovative findings in respirology; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJR*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of respirology; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in respirology.

Name of journal

World Journal of Respirology

ISSN

ISSN 2218-6255 (online)

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Indexed and abstracted in
Digital Object Identifier

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Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

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Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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There are unstructured abstracts (no less than 256 words) and structured abstracts (no less than 480). The specific requirements for structured abstracts are as follows:

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2218-6255/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclu-

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REFERENCES

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pres-

sure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2218-6255/g_info_20100725065142.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/2218-6255/g_info_20100725063138.htm

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Observation: http://www.wjgnet.com/2218-6255/g_info_20100725063458.htm

Guidelines for basic research: http://www.wjgnet.com/2218-6255/g_info_20100725063622.htm

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Review: http://www.wjgnet.com/2218-6255/g_info_20100725063905.htm

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Brief articles: http://www.wjgnet.com/2218-6255/g_info_20100725064216.htm

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Letters to the editor: http://www.wjgnet.com/2218-6255/g_info_20100725064436.htm

Book reviews: http://www.wjgnet.com/2218-6255/g_info_20100725064518.htm

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