Animal models of emphysema

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Abstract

Objective: Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease of human beings characterized by not fully reversible airflow limitation. Emphysema is the main pathological feature of COPD which causes high mortality worldwide every year and consumes a large amount of medical expenses. This paper was to review the establishment and evaluation methods of animal models of emphysema or COPD, and put forward some new ideas on animal selection, method of modeling, and model evaluation.

Data sources: The author retrieved information from the PubMed database up to July 2019, using various combinations of search terms, including emphysema, model, and animal.

Study selection: Original articles, reviews, and other articles were searched and reviewed for animal models of emphysema.

Results: This review summarized animal models of emphysema from the perspectives of animal selection, emphysema mechanism, modeling method and model evaluation, and found that passive smoking is the classic method for developing animal model of emphysema, mice are more suitable for experimental study on emphysema. Compared with pulmonary function indicators, airway inflammation indicators and oxidative stress indicators, pathomorphological indicators of lung tissue are the most important parameters for evaluating the establishment of the animal model of emphysema.

Conclusions: Mice model induced by passive smoking is the classic animal model of emphysema. Pathomorphological indicators are the most important parameters for evaluating the establishment of the animal model of emphysema.

Keywords: Animal; Chronic obstructive pulmonary disease; Emphysema; Model

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease of human beings characterized by not fully reversible airflow limitation. It is mainly caused by cigarette smoke and has a strong impact on human health, seriously affects the quality of patient’s daily life, causes high mortality, which brings a heavy economic burden to patients themselves, their families and society. COPD is the fourth leading cause of death worldwide and is expected to rise to third place by 2020. More than 3 million patients died of COPD in 2012, accounting for 6 percent of all deaths worldwide. Buist et al. found that the prevalence of stage II or higher COPD was 10.1% overall, 8.5% for women, and 11.8% for men. In China, a survey of 20,245 adults in seven regions showed that the prevalence of COPD in people over 40 years old was as high as 8.2%. Globally, the burden of COPD will increase gradually in the coming decades due to the continuing exposure to risk factors and the aging of the population. Although COPD is an important public health problem and the leading cause of chronic disability and death worldwide, it can be prevented and treated.

Significance of Establishing Animal Model of Emphysema

COPD can be induced by many factors, and its mechanisms are very complex including oxidative stress, inflammation, protease-antiprotease imbalance, apoptosis, and even immunosenescence. The mechanisms of COPD are not completely illuminated as the exact mechanism by which COPD occurs and progresses remains much of unknown. Regarding ethical issues about the research on COPD patient, COPD animal models is very important for researcher to investigate the mechanism of COPD and the use of COPD animal models is inevitable. Emphysema, as the main pathological feature of COPD, has always been the focus of research which focuses on the mechanism of COPD. Animal models of emphysema improve our understanding of the basic mechanisms of COPD physiology, pathophysiology and treatment. Therefore, to further elucidate the
etiology and pathogenesis of COPD, many scholars made relevant studies on animal model of emphysema. Although these models only mimic some of the characteristics of the COPD, they are valuable for further study of the mechanisms of human COPD. The establishment and standardization of animal COPD models according to clinical pathology are explored. The establishment of animal models of emphysema is the key to elucidate the etiology and pathogenesis of COPD. In fact, animal models have provided valuable insights into the cellular and molecular mechanisms involved in the pathogenesis of COPD.

Animal Selection for Modeling

Today, a variety of animal models of emphysema have been developed, including sheep, dogs, pigs, rabbits, monkeys, guinea pigs, mice, rats, and squirrels. Animal models can on some extent reflect the pathology and physiology of human diseases. Most features of COPD, such as inflammatory cell aggregation, oxidative stress, cytokine and protease production, small airway and vascular remodeling, emphysema, pulmonary hypertension, and decreased lung function, can be induced in different models. The development of models of acute exacerbation and complication of COPD can reflect the progress of COPD and provides a powerful tool for the study of the pathogenesis of COPD. However, animals are animals, not human beings. Anatomy, physiology, reactivity to damage, sensibility to cigarette smoke (CS), cytokines, or protease varies from species to species. Lopes et al. considered that, unlike human progressive COPD, animal exposure to CS only exhibited mild emphysema which did not progress after cessation of exposure.

Anatomy and physiology

Rat model of emphysema was considered to have many advantages, including small body size, low cost of breeding, short reproduction cycle, and similar genome to humans. But rat also has its own limitations. Rats rely on nasal breathing and the nasal cilia have low function on filtering smoke. Furthermore, rats have few branches of the bronchi thus with poor respiratory function. The distribution of intratracheal cilia is less, the glandular submucosal glands are immature, and there are no goblet cells under the tracheal mucosa. The mediators of bronchial inflammation in rats are also different from those in humans.

Pigs have more mature lung tissue than rats, rabbits and other animals, and the volume of lung is relatively large, the lung structure is similar to that of humans with three lobes on the right and two on the left. Even more, pigs, like humans, have respiratory bronchioles, and increased airway resistance of small airways is the main cause of increased airway resistance in patients with COPD. The submucosal glands in the airway of pigs are relatively developed. Compared to other animals, pigs are more prone to respiratory diseases; hence, it is relatively easy to induce COPD. Endotracheal intubation is required for endotracheal infusion drugs, respiratory function evaluation, and simulated assisted ventilation in animals. Compared with rats and guinea pigs, small pigs have larger tracheal diameter, which is convenient for intubation. However, disadvantages of pigs are also obvious, including large body size, high cost of breeding and drug, long reproduction cycle, and less reproduction number. D’Ambrosio et al. believed that mice were considered to be the best choice for animal model. Although the distribution of bronchial glands in non-human primates and dogs are roughly similar to that in humans, bronchial glands are limited to the closest part of the trachea. Similarly, primates and dogs have respiratory bronchioles, and their alveolar ducts develop from the membranous bronchioles located at the distal end. The mice have no bronchial circulation. Rodents have much more Clara cells in the small airways than humans. Lung development and maturation are different between different animal species. For example, rats and mice develop their alveoli after birth, while the guinea pig and the monkey are almost fully alveolated at birth. There are differences in the absorption, distribution, metabolism, and elimination of drugs between different species, and these differences may become obstacles in animal modeling.

Reactivity to damage

Most animal models of emphysema induced by passive smoking displayed enlarged alveolar space, although there are various degrees of enlargement from species to species. However, unlike humans, some animals do not develop into serious illnesses, thus narrowing the window by which researcher determines the effects of potential therapeutic interventions. In addition, although goblet cell metaplasia is a characteristic finding of small airways in patients with COPD, the metaplastic response of mice and rats are weaker than those of guinea pigs, dogs and non-human primates.

Sensibility to tobacco

Unlike humans, animal models are an inbred population. Within a species, different strains may respond differently to the same stimulus. In one study, NZW/Lac/J mice were not sensitive to CS, C57BL/6J and SJL mice were somewhat sensitive, and AKR/J mice were more sensitive to CS and exhibited CS-induced COPD. Likewise, DBA/2 mice developed faster emphysema during exposure to smoking, but airway goblet cell metaplasia and mucin 5AC (MUC5AC) expression decreased when compared with C57BL/6J mice.

Cytokines

Common animal models, except monkeys, do not fully replicate human cytokines, which are magnified when compared to rodents. For example, in rodents, the closest cytokines match to human interleukin (IL)-8 are chemokines KC (CCK) and cytokine-induced neutrophil chemo tactic factors (CINC), and CINC has better homology to human melanoma growth stimulatory activity (MGSA)/gro. Different strains within the same species may have different inflammatory cell and cytokine response profiles for the same stimulus.
**Proteases**

Matrix metalloproteinases (MMP)-12 is a major component of mice macrophage metalloproteinases, but for humans, MMP-7 appears to be more important in destroying elastic tissues.\[37\]

Among the animals described above, although mice emphysema model could not be the exact replica of human emphysema because of differences between human and mice in both physiological, immune and anatomical systems.\[38\] Mice genome is more similar to that of human than many other animals,\[39\] and offers the advantages of naturally occurring mouse strains for different responses to smoking. Hence, mice are considered to be more suitable for experimental study on emphysema.

**Mechanisms of Emphysema**

**Elastase-antielastase imbalance**

The destruction of large amounts of proteins in the pathogenesis of COPD attracted researchers’ attention since 1970s. There is an imbalance between elastases (MMP family) and anti-elastases, which break down proteins in lung tissue of COPD patients. Too much of elastases released by patient’s inflammatory cells can cause damage to lung parenchyma, resulting in emphysema. Direct evidence is that the lack of genetic alpha 1-antitrypsin (AT) causes the elastase-antielastase imbalance.\[40\] Some antioxidants, such as endostatin, carboxymethyl steam, n-acetylcysteine, and ambroxol can alleviate the acute exacerbation of COPD, slow down the decline of pulmonary function,\[41\] which indicate that antioxidant may play a role in the onset and progression of COPD. In addition, these antioxidants have been applied to animal studies to reduce emphysema.\[44\] At present, the issue how to develop more effective antioxidant becomes one of the research priorities for COPD prevention.

**Inflammatory mechanism**

Inflammation has been recognized as the most important mechanism both at the beginning of COPD and the progress of COPD. Under normal circumstances, the human respiratory tract, including the nose, pharynx, larynx, trachea, and bronchi, has appropriate defensive function. The structures that perform the defensive function include the nasal hair in nasal cavity, normal cough reflex in the throat, the cilia on the surface of the tracheo-bronchi and the mucus removal system composed of mucus. These structures are looked as the natural barriers which defend human body against foreign invaders. The normal reflex of guttur ministry can prevent foreign material entering airway instinctively and keep the lower airway bioclean. If these defense mechanisms fail to work, foreign particles (including dust particles, bacteria and other microorganisms) will enter the lower respiratory tract, activate macrophages, neutrophils and lymphocytes in lung tissue, release a variety of media, including leukotriene B4 (LTB4), IL-8, tumor necrosis factor (TNF)-α, intercellular adhesion molecule (ICAM) 1 and transforming growth factor (TGF)-β, etc.\[42\] These mediators can damage lung tissue, promote neutrophil inflammation, which activates neutrophil cells to migrate to inflammatory sites, causing ciliated bronchial epithelial cells to become mucous goblet cells, damaging lung septum, and enlarging the alveolar cavity.

**Hormone related mechanism**

Inflammatory mechanism exists in COPD patients. Except for the acute exacerbation stage, corticosteroid therapy in COPD patients is rarely effective, that is called “hormone resistance,” and the mechanism is unclear. Birrell et al found that the hormonal resistance in COPD may be related to the inactivation of kB pathway.\[46\] Other study\[47\] found that the activity of histone deacetylase in the lung of COPD patients was decreased and negatively correlated with the severity of the disease, suggesting that the respiratory hormone resistance of patients may be related to the decreased activity of histone deacetylase.

**Immunologic mechanism**

Macrophages are the major phagocytes and they can engulf foreign particles and pathogens, release cytokines which can not only enhance the phagocytosis of macrophages, but also do some harm to human body.\[47\] Lymphocytes are also involved in the pathogenesis of COPD. CD8+ lymphocyte family members play a very important role in the pathogenesis of COPD.\[48\] Even after smoking cessation, the inflammatory response in the lungs does not stop, but continues to progress.

**Vagus nerve stimulation**

Vagus nerve excitation is present in the pathogenesis of COPD. COPD patients have the characteristics of high
airway reactivity, abnormal increase of cholinergic nerve tension and enhanced cholinergic nerve reflex. The reasons may lie in that the nerve transmission in the cholinergic ganglion is enhanced, which makes the release of acetylcholine increased. At the same time, the airway is more responsive to endogenous acetylcholine, and the dysfunction of inhibitory feedback regulation caused by the low function of muscarinic (M) receptor is another reason for hypercholinergic function.[49] The increased vagus nerve tension leads to the contraction of bronchial smooth muscle, which is mainly due to the increased expression of various signal molecules in the M-receptor-mediated airway smooth muscle and the excessive release of neuroacetylcholine caused by inflammation related neurogenic mechanism. Meanwhile, the increased vagus nerve tension causes hypersecretion of glands under airway mucosa. Acetylcholine could come from parasympathetic nervous system, bronchial epithelial cells, inflammatory cells and other cells,[50] and a variety of inflammatory cells express functional M receptors, participating in the regulation of airway inflammation. In addition, acetylcholine can induce the proliferation of fibroblasts and myofibroblasts, playing a prominent role on airway remodeling. Therefore, the cholinergic mechanism is of great significance in the pathophysiology of COPD.

Modeling Methods of Animal Model of Emphysema

Elastase induced animal model of emphysema

Emphysema could be induced by one or more drops of elastase into the trachea.[51,52] This method is relatively simple to operate and can shorten the experiment period and save the cost. The instillation of elastase disrupts protease-antiprotease balance in lung tissue, which not only destroys the main factors that protect lung tissue from damage, but also produces a large number of inflammatory factors and accelerates the rupture and fusion of alveolar walls to induce emphysema.[53] Commonly used elastases are: papain,[54] pig pancreatic elastinase (PPE),[55] and human neutrophil elastase (HNE).[56]

Papain is a proteolytic enzyme from plants and the earliest elastase used to induce emphysema model.[57] In 1960s, papain was used to successfully set up an rat model of emphysema for the first time.[58] In 1980s, Boyd et al[59] discussed the dosage of papain used in rat model and set the dosage at 2 or 4 mg/kg, but the results showed that there was no significant difference in emphysema-like lesions between the two different dose groups. So it was considered that one-time infusion of papain with 2 mg/kg into the trachea was a relatively reasonable dose.[59] Sulkowski et al[60] also induced stable emphysema model by one-time infusion of 2 mg/kg papain into the trachea of rats. Thereafter, papain was used to induce rat model of emphysema at a dose of 2 mg/kg. Interestingly, emphysema could also be induced by exposure to aerosol of 10% papain for 8 h twice in a 2-week interval.[61]

The commonly used PPE for animal model of emphysema was derived from swine pancreas.[53] PPE can not only act as a protease to destroy protease-antiprotease imbalance, but also act as an oxidant to induce oxidative stress. With the double effect described above on the progress of emphysema, the alveoli in the experimental animal model were significantly enlarged. Therefore, PPE was often used to induce emphysema. PPE concentrations range from 6 to 24 U. The usage of PPE induction mainly includes intratracheal drip, tracheotomy injection, atomization inhalation. Generally, it usually takes about 4 to 6 weeks to induce emphysema-like changes.[60]

HNE is serine protease, which plays a major role in the COPD inflammatory process. The protease/anti-protease imbalance leads to an excess of extracellular HNE hydrolyzing elastin and structural protein that confers elasticity to the lung tissue.[62] Due to the weak ability of HNE[20] to enter the alveolar septum and degrade elastic fibers, HNE is seldom used at present to induce emphysema.

Raub et al[63] showed that the hamster with intratracheal injection of 6, 12, or 24 units of PPE exhibited a dose-related change in lung function after 4 weeks, suggesting that in hamsters, six units of elastase could produce mild emphysema. The method of using protease to replicate animal model of emphysema has the advantages of less infection, easy to grasp the dosage and short period. Therefore, direct intratracheal administration of protease is an effective way to induce animal model of emphysema.

Passive smoking induced animal model of emphysema

According to clinical statistics, about 90% of COPD patients were smokers.[64] One of the most important risk factors for emphysema is smoking.[65] In 1990, Wright et al[66] successfully set up guinea pig model of emphysema by means of CS exposure for the first time. He found that the long-term smoking will lead to the changes in the center of the human lobules, causing emphysema. Animal with long-term CS exposure could result in inflammatory response in lungs, which was mainly composed of macrophages.[67] As a result, the bronchial lumen narrowed and the bronchial cartilage tissue was impaired, leading to the rupture and fusion of alveoli and the formation of emphysema, which was similar to human beings’ response to smoking. Passive smoking induced emphysema can simulate the pathogenesis of human emphysema as much as possible, and provide a foundation for the basic and clinical research of human emphysema. The structure of the airway and lung of experimental animals are different from species to species, and from that of human beings. The guinea pig is the most sensitive animal to the smoke stimulation, and the rats show a certain resistance to the smoke stimulation, but the susceptibility to smoke is also different in different species of rats. The experimental period of passive smoking induced COPD animal model is relatively long and the stability is relatively poor.[66]

According to the literature review, the exposure to CS can be roughly divided into two types: one is the part exposure (nose or head only) method.[65] Van der Strate et al[67] studied on C57BL/6J mice which inhaled CS through their noses for 2 times/day, 2 cigarettes/time, 10 spray/cigarette, 5 days/week. The results showed that after 4 months of exposure, the pulmonary alveoli enlarged with the increase
of smoking time. At the same time, B lymphocyte in lung tissue of the smoked mice increased similar to what was seen in human emphysema. The other exposure method is the whole body exposure method,\textsuperscript{[71]} in which the experimental animal is placed in a smoking box (a box full of smoke) as a whole. Valenca et al\textsuperscript{[24]} exposed C57BL/6 mice to cigarette smoke for 3 cigarettes/time and 3 times/day. After 60 days, emphysema-like changes in lung were observed, which were accompanied by increased alveolar macrophages, extracellular matrix changes and increased expression of MMP-12. Our previous study established mice model of emphysema by exposing C57BL/6 mice to CS in a smoking box with some hole on it. In the box, a partition with the same size holes was placed in the middle of the box to divided it into two parts: the lower part was used for cigarette burning, and the upper part was used for animal exposure to CS. Mice were exposed for 2 cycles/day, 6 days/week for 12 weeks.\textsuperscript{[73]} The passive smoking method is quite popular due to its low cost, simple operation, high success and can eliminate the experimental differences in a more objective environment.\textsuperscript{[74]}

The length of CS exposure for animal model of emphysema might be due to the different kind of cigarette, different exposure mode, duration and frequency, different smoke density, different species and age of animals and so on.

**Chemicals induced animal model of emphysema**

Many chemicals, including NO\textsubscript{2}, lipopolysaccharides (LPS),\textsuperscript{[75]} O\textsubscript{3}, and cadmium chloride (CdCl\textsubscript{2}), intravenous injection of hyaluronidase,\textsuperscript{[76]} inhalation of ovalbumin dry powder,\textsuperscript{[77]} could cause inflammation and emphysema. NO\textsubscript{2}, which is common in air pollution, can induce the animal model of emphysema by controlling the concentration and inhalation time of NO\textsubscript{2}. Wegman et al found that animal emphysema models could also be set up by oxidative stress after long-term exposure of mice to NO\textsubscript{2} with a volume fraction of $20 \times 10^{-6}$, which lasts 14 h a day for 25 days.\textsuperscript{[78]} LPS caused airway and lung tissue inflammation mainly through stimulating neutrophils, macrophages and endothelial cells which released a series of inflammatory mediums including TNF-α, IL-1, etc, triggering protease-antiprotease imbalance, eventually emphysema occurred.\textsuperscript{[79]} Snider et al found that animal model of emphysema could be induced by one-time dropping 0.5 mL 0.025% CdCl\textsubscript{2} solution into the trachea of golden ground squirrels.\textsuperscript{[23]}

**Cigarette smoke extract induced animal model of emphysema**

In 2006, Tarasewiciene-Stewart and coworkers\textsuperscript{[80]} reported that intraperitoneal injection of cigarette smoke extract (CSE) produced significant emphysema in mice. They hypothesized that CSE could act as an antigen to trigger an immune response, leading to emphysema. It took only 6 weeks to establish a model of emphysema. The problem whether CSE impairs lung tissue targeted making inflammatory cells homing in focus or the systemic inflammatory cells induced by CSE infiltrate in the lung tissue through the impaired endothelium is unclear and needs further study. Even more, in 2009, Chen et al\textsuperscript{[81]} reported that intraperitoneal injection of CSE in rats could induced emphysema-like injury within 3 weeks. Although it has been confirmed in these reports that intraperitoneal exposure to CSE was able to cause emphysema in animals, extrapulmonary effects were underestimated. Our research team established mice model of emphysema by intraperitoneal injection of CSE and fully evaluated the model.\textsuperscript{[79,82-85]} The total experimental period was four weeks. On day 29, the mice were disposed for lung function measurement, blood collection, bronchoalvolar lavage (BAL) and histomorphological detection of lung tissue. The results demonstrated that intraperitoneal injection of CSE could lead to pulmonary function decline, alveolar space increase, alveolar wall destruction, apoptosis of alveolar septum cells, chronic lung inflammation, decreased serum superoxide dismutate (SOD) concentration, and elevated IL-6 concentration in animal model. More importantly, the effectiveness of this modeling methods was equal to that of CS exposure.\textsuperscript{[73]} Our previous study described the preparation of CSE in details including the content of nicotine and carbon monoxide in the cigarette.\textsuperscript{[80]}

**Other exogenous factors induced animal model of emphysema**

It has also been reported that emphysema-like changes could be detected in the case of accelerated metabolism of elastic fibers and collagen fibers in lung tissues due to severe hunger. Sahebjami et al\textsuperscript{[81]} found that taking less food (for a third of control group) could induced emphysema, the number of alveoli, lung volume, alveolar lining area changed significantly, and the animal’s body weight decreased to 40% to 45% of normal, but there was no increased number of neutrophils in lung tissue. The authors believed that it may be because of long-term starvation that the growth and development of lung tissues in experimental animals were disturbed, which could not reflect the real destruction process of lung tissues in human emphysema. So this method is rarely used.

**Genetic manipulation in animal model of emphysema**

In recent years, with the development of human genome project and molecular biology technology, the relationship between diseases and genes has been deeply studied. Many scholars believed that the corresponding animal models of emphysema could be induced by regulating the emphysema-related genes which activates some new explorations in the research field.

**Natural variation in animal model of emphysema**

Spontaneous emphysema was first discovered in spotted mice in 1970s, and it was believed that spontaneous emphysema was mainly related to the abnormal mechanism of connective tissue, collagen and elastin cross-linking. In long-term animal experiments, it was found that the spontaneous emphysema of mice may be B6 thinly mice, Beige mice, Blotchy mice, Palliad mice, etc.\textsuperscript{[87]}

**Gene-knockout in animal model of emphysema**

With the development of molecular biology, the animal model of emphysema induced by gene knockout has been
widely used in the research of emphysema. In recent years, an increasing number of studies used gene knockout to copy animal model.\[88-90\] Baron et al outlined the major technological approaches to the utilization of gene-targeted and/or genetically modified mice to delineate the cellular and molecular basis of experimental lung disease.\[91\] Liang et al\[92\] found Abhd2 knockout mice exhibited emphysema-like changes in lung due to the excessive inflammatory cytokines and protease gene expression, increased macrophages, abnormal apoptosis, and resistance to the lack or loss of protease inhibitors. And the copies showed a gradual progress of emphysema in a similar way in occurrence, development process and clinical pathology. Therefore, it is of great significance to study the genetic susceptibility and environmental factors of emphysema.\[93\]

Other gene-associated animal model of emphysema

Platelet derived growth factor-β (PDGF-β), TNF-α, IL-6 and IL-11 could interfere the normal development of alveoli.\[94\] Previous study found that if the expression of some corresponding genes were extremely increased in the process of growth and development of mice, alveolar developmental disorders will happen, leading to the formation of emphysema because excessive expression of certain genes may disrupt the balance between alveolar damage and repair, leading to emphysema.\[93\] TNF-α is an immunomodulatory factor secreted by monocytes and macrophages, which could induce inflammatory cells.\[96\] It also plays a role in the synthesis of IL-6, IL-8, prostaglandin, leukotriene and other secondary inflammatory mediators. Appropriate expression of gene is necessary to maintain the homeostasis in human body, excessive expression will aggravate the inflammatory response.\[94\] In 1999, Hoyle et al\[97\] developed transgenic mice with the PDGF-β gene. The transgenic mice displayed many pathological changes in lung including dilation of alveolar cavity, rupture of alveolar wall, fusion of alveoli, inflammatory reaction. It was suggested that the replication of emphysema models in experimental animals could be achieved by overexpression of PDGF-β. Study on the lung tissue derived from homozygous mutant Klotho mice\[95\] showed that mice with Klotho gene disruption had enlarged alveolar cavity at 4 weeks of age accompanied by damaged alveolar wall and progressive aggravation with age, which was very similar to senile emphysema. Based on the study of emphysema-related gene, MMP-1 was found to be activated in the lungs of emphysema patients, and it was considered that transgenic mice with MMP-1 could also display emphysema-like lesions.\[98\] Many scholars believed that MMP-1, secreted by alveolar type II epithelial cells, may be the leading cause of continuous destruction of lung tissue.\[98,99\]

The advantages and disadvantages of animal models induced by the modeling methods described above were summarized in Table 1. Since the emphysema itself is a chronic progressive disease, short period of modeling is an advantage as well as a disadvantage.

| Models                                      | Advantages                                      | Disadvantages                                      |
|---------------------------------------------|-------------------------------------------------|----------------------------------------------------|
| Elastase induced animal model of emphysema  | Simple operation, short period of modeling and low costs. | 1. Not consistent with the process of human emphysema. |
| Passive smoking induced animal model of emphysema | Similar to smoking. Animal’s airflow obstruction and decreased compliance of respiratory system occur and progress slowly. Low costs. | 1. Not consistent with the process of human emphysema. 2. The acute effects of elastase instillation are different from the chronic progress of human emphysema. |
| Chemicals induced animal model of emphysema | Simple operation, short period of modeling and low costs. | 1. Not consistent with the process of human emphysema. 2. The short period of modeling is different from the chronic progress of human emphysema. |
| Cigarette smoke extract induced animal model of emphysema | Simple operation, short period of modeling and low costs. | 1. Not consistent with the process of human emphysema. 2. The short period of modeling is different from the chronic progress of human emphysema. |
| Other exogenous factors induced animal model of emphysema | Simple operation, short period of modeling and low costs. | 1. Not consistent with the process of human emphysema. 2. The long-term starvation induced emphysema cannot reflect the exact mechanisms of human emphysema. |
| Genetic manipulation in animal model of emphysema | Able to clarify the influence of various genes on emphysema. | 1. High requirement on technology. 2. High cost. |

Table 1: Advantages and disadvantages of each animal model.
Animal Model of Acute Exacerbation of COPD

An acute exacerbation of COPD (AECOPD) is defined as acute worsening of respiratory symptoms and requiring additional treatment.\(^{100}\) AECOPD can directly lower the quality of patient’s daily life, lead to high mortality. So, animal model of COPD Exacerbation is of great value in investigating the pathogenesis of AECOPD.

AECOPD animal models can be roughly divided into three types, including LPS, bacterial,\(^{102}\) and virus.\(^{103}\) A single large dose of LPS can cause an inflammatory response accompanied by fever, excessive mucus secretion, and bronchoconstriction, resulting in an AECOPD animal model. Animal model of LPS-induced exacerbation has been established in hamsters. Basic emphysema was established through elastase administration and subsequently LPS was applied twice a week for 5 weeks to evoke exacerbation. After 6 months, the AECOPD animal model exhibited severe mucus cell hyperplasia and serious alveolar enlargement which measured by mean linear intercept (MLI) and bronchial mucus cell hyperplasia (BMCH), scored in tissue slice stained with periodic acid-Schiff.\(^{104}\)

More than half of the acute exacerbations of COPD are caused by bacterial infections. The more severe the patient is, the more species of bacteria could be derived from the patient. Few study used bacteria induced animal model of AECOPD to study human’s AECOPD, although the animal model may display obviously increased inflammatory responses. Compared with mice exposed to normal air, mice infected with Haemophilus influenzae after 8 weeks of exposure to CS had an increased inflammatory response and worsened lung injury.\(^{102}\) Huvanne \textit{et al.}\(^{105}\) studied on the animal model which were exposed to CS for 4 weeks and with nasal administration of staphylococcus aureus enterotoxin B (SEB) for the next 2 weeks. The results demonstrated that the animal exposure to both CS and SEB exhibited increased inflammatory cells in the lung when compared with the animal exposure to either CS or SEB alone.

Patients with COPD have an increased susceptibility to influenza A virus (IAV) infection and an enhanced inflammatory immune response to infection. In the acute or chronic CS exposure induced animal models, an increased local and systemic inflammation were observed, which were followed by IAV infection. In some patients, viral proliferation increases or clearance decreases, and bronchodilator response decreases. Donovan \textit{et al.}\(^{103}\) placed mice in an 18 L perspex chamber and exposed them to CS which was generated from nine Winfield Red cigarettes (<16 mg tar, <1.2 mg nicotine and <15 mg of carbon monoxide) per day for 4 days. On day 5, mice were anaesthetized by inhalation of methoxyflurane and infected intranasally with 10 plaque forming units (PFU) of the mildly virulent influenza A virus Mem 71 (H3N1). On day 12, it was demonstrated that virus induced animal model of AECOPD was established.

Evaluation on Animal Model of Emphysema

After the establishment of the animal model of emphysema, corresponding evaluation methods are required to confirm the success of the model. There was global strategy for the diagnosis and classification of COPD in human,\(^{3}\) but no for animal emphysema or COPD. The commonly used parameters include pulmonary function indicators, airway inflammation indicators, oxidative stress indicators and pathomorphological indicators. Lung function indicators include recording airway resistance (Raw), lung dynamic compliance (Cdyn), peak expiratory flow (PEF), inspiratory time/expiratory time (Ti/Te),\(^{106-110}\) and blood gas analysis.\(^{111}\) Airway inflammation indicators include cell count and classification in alveolar lavage fluid, neutrophils, macrophages, eosinophils, TGF-\(\beta,\) IL-6, IL-8, TNF-\(\alpha,\) leukotriene B4 (LTB4), elastolytic enzymes such as MMP-1, MMP-2, MMP-9, MMP-12 and cathepsins K, L, S.\(^{122}\) and monocyte chemotactic protein 1 (MCP-1).\(^{122}\) Oxidative stress indicators include SOD, reactive oxygen species (ROS), and nuclear factor correlation factor 2.\(^ {124}\) Pathomorphological indicators include mean linear intercept (MLI), destructive index (DI), apoptotic index (AI), and pathologic score of airway.\(^{127}\) According to the American Thoracic Society, emphysema was defined as “abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls.”\(^ {128}\) Donaldson \textit{et al.}\(^ {129}\) considered the most important pathological and physiological changes of COPD are the obstruction of airway and the decline of lung function.\(^ {129}\) An ideal animal model of COPD should be in line with clinical practice, such as the injury factors consisted with the common causes of clinical COPD, airflow obstruction, decreased lung dynamic compliance, airway remodeling, and airway hyperreactivity. However, pulmonary function tests were considered to be less sensitive than morphometry and might detect only more severe degrees of airways remodeling or parenchymal destruction. Mild emphysema animal model might have normal lung function.\(^ {130}\) Ochs suggested that the quantitative assessment of micro-structure was the only way to reliably demonstrate the presence of emphysematous alterations.\(^ {131}\) So far, there is no uniform standard in the evaluation system. In consideration of the accessibility, objectivity, and stability of various parameter, we believe that the changes in pathomorphological indicators, including MLI, DI, AI, are the most important parameter for evaluating the establishment of the animal model of emphysema.

Summary and Prospect

Various animal models of emphysema have been developed, but there is no animal model which can simulate all the characteristics of human COPD. According to the mechanism of COPD, the evaluation method for emphysema animal model is based on pulmonary function, pathomorphism of lung tissue, airway inflammation.

Although several emphysema animal models have been established, exact comparisons of findings from various groups are difficult because different methods, different chemicals, different types of chemicals or cigarettes, different doses of cigarette smoke, different instruments, different exposure protocols, and a wide variety of animals are used. Cigarette smoking is by far the most important
risk factor for emphysema and COPD. CS exposure was regarded as the traditional method of long-term modeling of emphysema. CS exposure induced emphysema can simulate relatively complex pathological changes and is considered as the most reasonable animal model of COPD at present. Because of the long modeling time, inconsistency and unstability, researchers have constantly explored new modeling methods.

Up to now, there is no perfect experimental animal model of emphysema which is completely consistent with the pathogenesis and characteristics of human emphysema. Although mice and humans share many basic physiological processes, specific differences in lung structure, function and immunology between humans and mice have to be taken into consideration. Even within mice, different strains exhibit different sensitivities to the development of emphysema. With the continuous in-depth study of emphysema, there are more and more alternative induction methods. Therefore, we should not only induce corresponding experimental animal models of emphysema according to the requirements of experimental purposes, but also explore the pathogenesis of emphysema through multiple methods of modeling. We believe that with the development of science and technology, more reasonable and standardized animal models of emphysema will be applied to experimental research in the near future.

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**Conflicts of Interest**

None.

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