

Reexpansion Pulmonary Edema

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When a rapidly reexpanding lung has been in a state of collapse for more than several days, pulmonary edema sometimes occurs in it. This is called reexpansion pulmonary edema (RPE). In this article, I present my views on the history, clinical features, morphophysiological features, pathogenesis, and treatment of RPE. Histological abnormalities of the pulmonary microvessels in a chronically collapsed lung will cause RPE, as well as mechanical stress exerted during reexpansion. Although the most effective treatment method is to treat the histological abnormalities of the pulmonary microvessels formed in a chronically collapsed lung, the cause of these abnormalities is not clear, making it difficult to put forward a precise treatment method. However, reasonably good effects can be expected from a symptomatic therapy that reduces the level of mechanical stress during reexpansion. In the future, it is expected that the cause of histological changes of the pulmonary microvessels in a chronically collapsed lung will be revealed, and appropriate therapies will therefore be developed according to this cause. (Ann Thorac Cardiovasc Surg 2008; 14: 205–209)

Key words: reexpansion pulmonary edema, permeability pulmonary edema, chronic lung collapse, pulmonary microvascular injury, oxygen-derived free radical

When a lung that has collapsed for more than several days is rapidly reexpanded, pulmonary edema sometimes occurs in the reexpanded lung. This is called reexpansion pulmonary edema (RPE).

Because the protein concentration of sputum is extraordinarily high during the onset of pulmonary edema, it is believed that RPE belongs to the type of permeability pulmonary edema caused by an injury to the pulmonary microvessels.

RPE is unlikely to occur if the period of lung collapse is less than 3 days, nor does it always occur even when the collapse lasts for 3 days or more. RPE also has other remarkably interesting characteristics, such as the manner in which it occurs, even in regions where there is no visible collapse, and considerable research

has been conducted to explain its pathogenesis.

1. History of RPE

In 1853, Pinault reported that pulmonary edema occurred in a reexpanded lung after the removal of pleural effusion. It is believed that this was the first report of RPE.¹⁾ Since then, there have been many reports regarding the removal of pleural effusion and RPE.^{2–12)} In 1959, Carlson et al.¹³⁾ reported that pulmonary edema occurred when a lung that had collapsed as a result of pneumothorax was reexpanded by means of thoracocentesis. There have since been many reports regarding the evacuation of pneumothorax and RPE.^{14–30)}

Moreover, there are reports of RPE occurring in reexpanded lungs when large quantities of cystic fluid are removed from a giant hepatic cyst,³¹⁾ and reports also of RPE occurrences in reexpanded lungs after the excision of a giant mediastinal tumor,^{32–34)} in the contralateral lung of a reexpanded lung,^{35–38)} and in a reexpanded lung after decortication.³⁹⁾

As evidenced by these reports, it is possible for RPE to occur in every type of chronically collapsed lung that

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can be reexpanded.

2. Clinical Features of RPE

The most representative disorder that can cause RPE is pneumothorax. Mahfood et al. conducted a detailed investigation using 47 cases of RPE associated with pneumothorax that were reported from 1958 to 1987.²¹⁾ According to this report, RPE is more common among men in a ratio of 38:9, with an average age of 42 (ranging from 18 to 84), and 83% of the cases experienced periods of lung collapse lasting 3 days or more (39/47 patients). Of these cases, 64% (30/47 patients) experienced the onset of RPE within an hour after reexpansion, and in all cases the onset occurred within 24 h. Regarding the method of evacuation, 79% (37/47 patients) of cases underwent suction, and 17% underwent an underwater seal. RPE occurred in the reexpanded lung of 94% (44/47 patients) of the cases. Three patients also had RPE in the contralateral lung, and 2 of these 3 patients have died. The overall mortality was 19% (9/47 patients), with patients aged 50 and above accounting for 78% (7/9 patients) of those deaths.

The oldest report regarding RPE is of RPE associated with the removal of pleural effusion. In 9 reports regarding RPE that occurred after the removal of pleural effusion, among the diseases were mesothelioma, pleurisy, carcinomatous pleurisy, pancreatitis, lymphoma, hepatic hydrothorax, and similar. It is more common among women by a ratio of 4:5, with an average age of 40 (ranging from 8 to 60). The duration of symptoms associated with the pleural effusion was 4 days or more (4 to 120 days) for all cases. The aspirated volume averaged 2,483 mL (1,000 to 4,500 mL), and 89% (8/9 patients) of the cases experienced the onset of RPE within 2 h; all onsets occurred within 24 h. Overall mortality was 22%.^{2,4-6,8,9,35,36)}

The clinical progressions of RPE caused by disorders other than pneumothorax and pleural effusion are almost identical.³¹⁻³⁹⁾

From these facts, the clinical features of RPE are a lung collapse period of 3 days or more; an evacuation volume of 2,000 mL or more; a period of less than 1 h from reexpansion to the onset of RPE; and the type of pulmonary edema is permeability pulmonary edema.

On the other hand, there are also reports of pulmonary edema occurring in the contralateral lung.³⁵⁻³⁸⁾ Of these reports, 3 cases of edema were caused by pleural effusion and 1 by tension pneumothorax. In all, the me-

diastinum had shifted to the opposite side resulting from either effusion or pneumothorax. Although the involvement of aspiration pneumonia, barotrauma, and cytokine cannot be denied, compression atelectasis of the contralateral lung associated with the shift of the mediastinum is believed to be the main cause.

3. Morphophysiological Features of RPE

In 1978, Sewell et al. conducted the first experiment on RPE. Using the gravimetric method, he confirmed that when reexpanding the right lung of a goat after using a chest tube to collapse it for 24, 48, and 72 h, RPE occurred only in the lung that had been collapsed for 72 h.¹⁶⁾ Pavlin et al.⁴⁰⁾ and Doerschuk et al.⁴¹⁾ used both the gravimetric method and radioisotope method on rabbits to reveal that RPE is a form of permeability pulmonary edema. Koike et al.⁴²⁾ conducted a vital measurement of lung lymph flow using sheep and concluded from the flow volume and protein concentration that RPE does not occur in lungs collapsed for 24 h or less. In our vital observation of pulmonary microcirculation in rats, we confirmed that plasma albumin leaks from all the pulmonary microvessels immediately after reexpansion when reexpanding a lung that had been in a state of collapse for 3 days.⁴³⁾

In a histological examination of RPE, Doerschuk et al. noted the presence of alveolar fluid and interstitial edema and the remarkable increase in the number of alveolar macrophages.⁴¹⁾ Sewell et al. used an electron micrograph to confirm the remarkable thickening of the basement membrane.¹⁶⁾ We confirmed both the thickening of pulmonary capillary endothelium in a chronically collapsed lung and the interruption of endothelium during reexpansion.⁴³⁾

Based on these facts, it is believed that RPE is a permeability pulmonary edema associated with the injury of pulmonary microvessels.

4. Pathogenesis of RPE

There are 2 major causes of RPE. One is a histological abnormality of the pulmonary microvessels caused by chronic lung collapse, and the other is the mechanical stress that is added to the pulmonary microvessels by reexpansion.

A thickening of the pulmonary capillary endothelium and of the basement membrane, both caused by chronic lung collapse, harden the pulmonary microves-

sels and diminish their flexibility. Therefore these pulmonary microvessels are quite likely to be destroyed when they are stretched by the enlargement of the lung. Through a histological examination of the lung immediately after expansion, we confirmed that the pulmonary microvascular endothelium was destroyed.⁴³⁾

Why does chronic lung collapse present histological changes to the pulmonary microvascular endothelium? Anoxic stress, mechanical stress exerted on the endothelium by blood corpuscles, and changes of lung lymph flow associated with lung collapse are all believed to be causes; however, there is no clear evidence to prove this. Although there are reports of the superoxide dismutase (SOD) and cytochrome oxidase of mitochondria declining in a collapsed lung, it is unclear how these factors are involved in the histological abnormalities of the pulmonary microvessels.⁴⁴⁾

Sewell et al. points out the decrease of alveolar surfactant activity as an effect added by reexpansion to the pulmonary microvessels.¹⁶⁾ The decrease of alveolar surfactant activity is said to induce pulmonary edema by drastically lowering the intrapleural pressure and further lowering the perivascular pressure of pulmonary microvessels. However, it is difficult to believe that this alone can cause RPE.

McCord has pointed out that organ injuries were caused by the oxygen-derived free radicals produced during reperfusion.⁴⁵⁾ Saito et al. have reported that xanthine oxidase increased in a reexpanded lung.⁴⁶⁾ Jackson et al. have reported the increase of oxygen-derived free radicals and the increase of activity of its scavenger, catalase, in a reexpanded lung.⁴⁷⁾ As stated above, because the collapse and reexpansion of lung produce these oxygen-derived free radicals, it is very likely that these radicals injure the pulmonary microvessels. However, there are also reports of SOD, a free radical scavenger, being unable to prevent RPE, so it is difficult to explain RPE by looking only at the production of oxygen-derived free radicals.⁴⁴⁾

Nakamura et al. have reported on increases in leukocyte sequestration, as well as increases of interleukin (IL)-8, leukotriene (LT) B₄, and polymorphonuclear leukocyte (PMN) elastase levels in the sputum in a reexpanded lung.⁴⁸⁾ Sakao et al. have reported a sequestration of PMN and an increase of IL-8 and monocyte chemoattractant protein (MCP)-1.⁴⁹⁾ As stated above, leukocytes migrate to the lung associated with the reexpansion, so it is most likely that they injure the pulmonary microvessels. However, there are reports in

which the occurrence of RPE could not be prevented even in rabbits, whose leukocyte levels had been previously reduced; so it is difficult to explain RPE by looking only at leukocyte sequestration.⁵⁰⁾

Herein I state my theory on the pathogenesis of RPE. Chronic lung collapse thickens the pulmonary microvascular endothelium to harden it. The reexpansion of the chronically collapsed lung injures the pulmonary microvessels by stretching them. Alveolar surfactant activity decreases in the reexpanded lung; thus perivascular pressure decreases, and injury to the pulmonary microvessels further increases. Subsequently, when reperfusion occurs in the injured pulmonary microvessels, oxygen-derived free radicals are produced. The oxygen-derived free radicals and pulmonary microvascular injury induce leukocyte sequestration into the lung. Leukocytes that have migrated to the pulmonary microvessels further injure them. Biological injuries caused by oxygen-derived free radicals and leukocytes cause major damage to the pulmonary microvessels, and RPE is established.

When reexpanding a chronically collapsed lung, we find cases in which RPE occurs and others in which RPE does not occur. It is believed that the mechanical stress exerted during reexpansion is small in those where it does not. In this condition, biological injury is not induced, and therefore RPE is not established.⁴³⁾

5. Treatments for RPE

One of the treatments for RPE is of the histological abnormalities of the pulmonary microvessels that are formed in a chronically collapsed lung, and another is a response to the mechanical stress exerted on the pulmonary microvessels during reexpansion.

Although the treatment for histological changes of the pulmonary microvessels in a chronically collapsed lung is most effective, the cause of these abnormalities is currently unclear, making it difficult to present a precise treatment method. There have been reports that loxamide tromethamine inhibits leukocyte sequestration and plasma leakage in RPE.⁵¹⁾ It is possible that a steroid could work effectively to stabilize the pulmonary microvessel membrane.

On the other hand, various attempts are being made to respond to the mechanical stress exerted during reexpansion on the pulmonary microvessels. The most realistic response is to avoid rapid lung reexpansion. Extensive occurrences of pulmonary microvascular injury

can be avoided by expanding the lung at a moderate pace. The administration of diuretics and hyperosmotic colloidal solution can diminish the occurrence of pulmonary edema by raising the osmotic pressure and decreasing pulmonary blood flow. The most reliable method is to prepare for tracheal intubation and noninvasive positive pressure ventilation on the assumption that RPE will occur when reexpanding a chronically collapsed lung.

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