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2. The Pathogenesis and Treatment of Right Heart Failure with Special Reference to Cor Pulmonale[†]

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THE TERM cor pulmonale is generally used to define the right heart enlargement secondary to lung disease with or without failure¹⁾. The mechanism of cor pulmonale, however, is not completely understood, except for the important role played by the pulmonary hypertension²⁾.

The present study is conducted to examine the anatomical and functional vascular factors, which are responsible for the development of pulmonary hypertension. The management of cor pulmonale is also discussed, based on these findings.

I. STRUCTURAL ALTERATIONS OF PULMONARY VASCULAR BED IN COR PULMONALE

1. Incidence of cor pulmonale among the aged
Out of 300 autopsied cases in Yokufuen during last 3 years, 26 cases (9%) were diagnosed pathologically as cor pulmonale. The primary lung diseases consisted of pulmonary emphysema in 20 cases and pulmonary tuberculosis with marked pleural scal in 6 cases.

The pulmonary arterial system of these 26 cases and other 3 cases of cor pulmonale due to pulmonary embolism, primary pulmonary hypertension and pulmonary scleroderma were studied morphologically.

2. Anatomical changes of the pulmonary ar-

terial wall in cor pulmonale

The thickness of intima and media of the arterioles, muscular arteries and elastic arteries of the pulmonary vessels were measured in addition to detailed histological observations.

Marked thickening of the intima and media of the pulmonary arterial walls were found in all cases of cor pulmonale, with a uniform distribution throughout the pulmonary vessels. Intimal fibrosis and the increase of elastica in media were also fairly common in the muscular pulmonary arteries in these cases.

These changes in the pulmonary arterial walls are considered to represent the results rather than the cause of the persistence of the pulmonary arterial hypertension^{3,4)}.

3. Anatomical factors in response to the pathogenesis of pulmonary hypertension in several pulmonary diseases

Cor pulmonale is generally divided into two major categories: (1) diseases of the pulmonary vascular bed, (2) disorders of the lung parenchyma. The anatomical factors which might be directly responsible for the production of pulmonary hypertension are sought by standard histological methods and by post-mortem pulmonary arteriography⁵⁾ on several lung diseases.

- 1) Diseases of the pulmonary vascular bed
- (1) Embolism of pulmonary tumor cells

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Twenty-six year old woman complained of cough with sputum for 11 months. The electrocardiogram showed right heart loading 1 week before death. At autopsy, the pulmonary arteries were filled with numerous tumor cells and thrombi in various of stages organization.

(2) Primary pulmonary hypertension

Thirty-two year old woman was admitted to the Toranomon Hospital because of progressive exertional dyspnea and palpitation. For the last one and a half year she had noted cyanosis and edema. Right heart enlargement was demonstrated in chest x-ray film and electrocardiogram. Cardiac catheterization showed a marked elevation of pulmonary arterial pressure. At necropsy, narrowing of the lumen due to reactive intimal proliferation was found throughout the pulmonary artery.

2) Disorders of lung parenchyma

(1) Pulmonary fibrosis

Thirty-four year old woman suffered from scleroderma for 3 and a half years. For the last 2 years she showed the signs of pulmonary insufficiency. Chest x-ray film showed fine nodular densities throughout both lungs, and right heart enlargement was suggested in the electrocardiogram. On postmortem study, marked perivascular fibrosis and intimal proliferation with narrowing of the pulmonary artery were extensively demonstrated.

(2) Pulmonary emphysema

Chronic obstructive pulmonary emphysema is the most important cause of cor pulmonale. Pulmonary emphysema was much more common in men than in women, it was found 47% in male and 17% in female in Yokufuen. However, no marked sex differences was observed in the incidence of cor pulmonale among patients with pulmonary emphysema; cor pulmonale occurred 26% in males and 23% in females.

As the pulmonary emphysema is a disease characterized by the destructive changes in the alveolar walls, injuries to the capillaries as well as some of the larger vessels also expected. A post-mortem pulmonary arteriography was therefore undertaken to clarify the vascular changes in pulmonary vasculature. As showed in Fig. 1, marked destruction and deformity of vascular bed are found both in centrilobular and

Fig. 1. Post-mortem pulmonary arteriogram. Narrowing and deformity of small branches of the pulmonary artery in an area of panacinal destructive emphysema.

panacinal types of emphysema.

4) Comment

These findings are summarized in Fig. 2. The loss of the pulmonary vascular bed seems to con-

Fig. 2. Anatomical factors in response to the pathogenesis of pulmonary hypertension

stitute the most important anatomical factor in raising the resistance to pulmonary blood flow. In addition to disorders of the primary disorders of the pulmonary vascular bed, diseases of the lung parenchyma such as pulmonary fibrosis and emphysema are also accompanied by such vascular changes. Extensive changes of this sort might raise the pulmonary arterial pressure.

The persistence of pulmonary hypertension for a prolonged period would produce further morphological changes on the pulmonary arterial wall, such as thickening of the intima and media, intimal fibrosis and the increase of elastica in the media of the pulmonary artery. These changes also play a role as a contributory factor in the production of hypertension.

II. FUNCTIONAL FACTORS IN PULMONARY CIRCULATION

In some cases of cor pulmonale with reversible disturbances of pulmonary circulation, the func-

tional factors have been said to play an important role in raising the pulmonary arterial pressure⁶⁾. However, the mechanism of this increase in the pulmonary artery pressure has not been satisfactorily explained.

In an attempt to solve these problems, the effects of several functional factors on the pulmonary circulation were studied in the thoracotomized dog, with particular emphasis on the measurement of the moment-to-moment flow through the lungs, simultaneously with the direct measurements of pressures in pulmonary artery, systemic artery and left atrium⁷⁾.

1. Comparison of the role of vessel tone between the regulation of pulmonary and bronchial circulation.

There is little doubt that the tone of the systemic arteries plays an important part in the regulation of the resistance to blood flow in the systemic circulation. It is less certain whether the small vessels of the lungs exercise similar control over the pulmonary vascular resistance⁸⁾.

The effects of several drugs on the pulmonary and bronchial vasculature are summarized in Fig. 3. Bronchial vasculature showed marked

Drugs	Pulmonary vascular resistance	Bronchial vascular resistance
Aminophylline	○	↘
Acetylcholine	○	↘
Tetraethylammonium chloride	○	↘
Histamine	○	↘
Adrenaline	↗	↗
Serotonin	↗	↘

Fig. 3. Comparative study of the effects of drugs on pulmonary and bronchial vasculature. Arrows show the changes observed. Discussed in the text.

vasoconstrictive or vasodilative changes upon administration of drugs into bronchial circulation.

On the other hand, weak reactions were observed in the pulmonary vasculature against intrapulmonary injection of drugs. These results

seems to challenge the concept of an important role played by the tone of the pulmonary vessel in the regulation of the pulmonary circulation^{8, 9, 10)}.

2. Functional factors contributing to the pathogenesis of pulmonary hypertension

(1) Hypoxia

In both experiments of breathing pure nitrogen or mixture of 10% oxygen and 90% nitrogen, an elevation of pulmonary arterial pressure accompanied by the increase of pulmonary blood flow was observed. However, no marked changes were found in the calculated pulmonary vascular resistance. Unilateral administration of hypoxic gas caused no significant differences in the distribution of flow between the two lungs.

(2) Hypercapnia

The administration of gas mixture of 10% carbon dioxide and 90% oxygen produced increases of the pulmonary arterial pressure and pulmonary blood flow. Pulmonary vascular resistance, however, showed no marked changes during the experiment of hypercapnia. These data challenge the concept that hypoxia and hypercapnia produce pulmonary vasoconstriction¹¹⁾.

(3) Ventilatory air pressure

The effect of various degrees of inspiratory air pressure on the pulmonary vascular resistance are tested. As inspiratory air pressure is raised from 8 to 30 mmHg, the blood flow through the lungs decreased, and the pulmonary arterial pressure increased, indicating an enhanced pulmonary vascular resistance.

3. Comment

From the experimental results described above, a serious doubt might be cast upon the

Fig. 4. Schema illustrating the cause of cor pulmonale

hypothesis that the tone of the pulmonary vessels is a dominant factor in the cause of pulmonary hypertension. In view of a marked effect of ventilatory air pressure on the pulmonary vascular bed, on the other hand, there remains a possibility that the pulmonary circulation is regulated by such extravascular factor as intrapulmonary air pressure¹²⁾.

III. MANAGEMENT OF COR PULMONALE

The cause of pulmonary hypertension in various lung diseases may be classified into two main categories; anatomic and functional (Fig. 4). Among a variety of changes in the anatomical factors described above, the loss of pulmonary vasculature is most important in the development of pulmonary hypertension. When these anatomical changes are extensive or progressive, an irreversible type of pulmonary hypertension is produced. Once the heart failure occurs, the reaction to the treatment is poor. These types are seen frequently in pulmonary embolism, primary pulmonary hypertension and pulmonary fibrosis.

The most satisfactory response to treatment is seen in cases in which a functional factor is the determinant of the pulmonary hypertension, one of the important examples being pulmonary emphysema.

A reduction of the pulmonary vascular bed is observed in all cases of pulmonary emphysema by the post-mortem arteriography, though not sufficiently pronounced to cause pulmonary hypertension. Increase in the pulmonary blood flow in such cases might readily cause the elevation of the pulmonary arterial pressure, resulting in right heart failure. Clinically the frequent circulatory complications precipitated by acute pulmonary infections are well recognized.

Whether the functional factors might influence directly the pulmonary vessels to produce vasoconstriction was less certain. In addition to hypoxia and hypercapnia which are generally believed to be the most important factors in lung diseases, attention should be directed towards the effect of intrapulmonary pressure on the disturbances of pulmonary circulation. However, a passive elevation of the arterial pressure through the increased pulmonary blood flow induced by

hypoxia and hypercapnia cannot be ruled out.

Most of the abnormal circulatory complications seen in chronic cor pulmonale due to pulmonary emphysema are reversible, once these functional factors are relieved²⁾. In these patients, all therapeutic efforts are directed not only at the treatment of the heart failure, but also towards the elimination of the results of pulmonary dysfunction. Digitalization, combined use of diuretics, intensive use of antibiotics, oxygen and vaporized bronchodilators with a intermittent positive pressure apparatus are beneficial in acute cardiopulmonary failure of cor pulmonale. Once the patients have recovered from the acute episode, all efforts are directed at maintaining him free of circulatory complications and in as optimal a state of pulmonary function as possible. These patients should be followed regularly at frequent intervals, even when they are doing well.

SUMMARY

(1) Out of 300 autopsy cases in Yokufuen (old people's home) during the last 3 years, 26 cases were diagnosed as cor pulmonale: 20 cases as pulmonary emphysema and 6 cases as pulmonary tuberculosis. Although the emphysema is much more common in men, no marked sex difference was noted in the rate of development of cor pulmonale from pulmonary emphysema.

(2) Histological examination showed a marked thickening of the intima and media throughout the arterioles, muscular arteries and elastic arteries of the pulmonary vessels. Intimal fibrosis and the increase of elastica were also found. These changes are secondary manifestations of the disturbances in pulmonary circulation.

(3) From the studies with post-mortem pulmonary arteriography, the morphological factor in the cause of pulmonary hypertension is considered to be loss of pulmonary vascular bed.

(4) Effects of hypoxia, hypercapnia, intrapulmonary air pressure and drugs on the pulmonary vascular resistance were tested in the thoracotomized dogs. The results challenge the concept that the tone of pulmonary vessel plays an important role in the cause of pulmonary hypertension. The data suggest that the regulation of

pulmonary circulation may be determined by intrapulmonary air pressure.

(5) There are many cases of cor pulmonale in which a physiological abnormality rather than the morphological changes of pulmonary vascular bed is the determinant of the pulmonary hypertension. Disability of the heart in these cases can be relieved by the treatment. Therapeutic efforts are directed not only at the treatment of the heart failure, but also toward the elimination the results of pulmonary dysfunction.

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3. Clinical Aspect of Digitalis Treatment in Congestive Heart Failure Due to Acquired Heart Disease.[†]

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DIGITALIS HAS BEEN in usage as the drug of first choice in the treatment of congestive heart failure, particularly in the cases of acquired heart disease. Not infrequently, however, do we encounter instances in which digitalis fail to bring about desired effect when these patients are in need of full digitalization. In the use of digitalis, it is desirable to know in advance whether digitalis treatment, especially rapid digitalization could be carried out successfully, to avoid unnecessary medication which might have to be changed due to ineffectiveness, or hazard caused by the overdosage of digitalis¹⁾. Since it

might not be easy to know which therapeutic benefits will be obtained by the administration of digitalis, observations on the patient's responses to rapid digitalization would provide the useful information as to whether the digitalis treatment is going on successfully. The present paper is to report of clinical trial on the demonstration of immediate effect of strophanthine to obtain therapeutic guide or to forecast the efficiency of rapid digitalization.

METHOD

To investigate therapeutic efficiency of digi-

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