Strategy to Manage Pump Failure Due to Chronic Pulmonary Diseases
—Pathophysiology and Treatment of Right Ventricular Overload—

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The pathophysiology and treatment of pump failure with right ventricular overload due to chronic pulmonary diseases were discussed. When right ventricular overload occurs hypertrophy and dilatation of right ventricle follows and the heart as a whole, including left ventricle, is altered in morphology and function. Therapeutic measures for right ventricular overload are the key to management and treatment of pump failure.

Pulmonary hypertension, as an etiological factor, is discussed and is divided into two categories, that is, mild to moderate pulmonary hypertension with hypoxia due to chronic obstructive lung disease, and severe pulmonary hypertension due to pulmonary vascular disease. In each category, effects of oxygen inhalation and vaso-dilating agents were evaluated. Oxygen did not decrease pulmonary vascular resistance in the state of chronic hypoxia, though a vasodilating agent was effective. In pulmonary vascular disease, vaso-dilating agents were effective to decrease pulmonary vascular resistance and pulmonary artery pressure, though the effect was less than 30% down in resistance.

In clinical practice, heart failure due to pulmonary diseases is often seen as an acute circulatory failure caused by pulmonary embolism or chronic cor pulmonale with longstanding pulmonary diseases. Acute exacerbation with pulmonary infection often made diagnosis of chronic cor pulmonale poor. In this paper, we discuss management strategies for heart failure due to chronic pulmonary diseases. Emphasis is placed on pathophysiology and treatment of pump failure related to chronic right ventricular overload.

The natural history of chronic cor pulmonale is divided into three stages: pulmonary disease; right ventricular overload, hypertrophy and dilatation; and ventricular decompensation. Heart failure is the end-stage of the course and its prognosis is very poor. It is important to understand the process of disease, in terms of abnormalities in pulmonary hemodynamics and disorders of the pump function of heart.

The primary cause of heart failure in chronic pulmonary diseases is a marked increase in the afterload of the right ventricle, though there are many other attributable factors. Successful management requires a decrease be made in abnormally high pulmonary vascular resistance, there by increasing cardiac output. We examined measures to decrease pulmonary vascular resistance in patients with pulmonary hypertension when hypertension was due to chronic obstructive lung diseases and hypoxia, and/or chronic pulmonary vascular obstruction.

Key Words:
- Cor pulmonale
- Right ventricular overload
- Pump failure
- Vaso-dilating agent
- Pulmonary hypertension

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Fig. 1. Pulmonary hemodynamics in 3 stages of pulmonary heart disease.
NL = control subjects with normal hemodynamics and blood gas (NL group). Cardiac catheterization was performed in all the patients during the steady period of diseases. Of the 248, 55 patients were diagnosed as having chronic cor pulmonale, including 37 with right ventricular hypertrophy in EKG recordings (RVH group) and 18 with clinical right ventricular failure (RVF group). There were 193 patients with chronic pulmonary diseases without cor pulmonale (CPD group) in this series. Of these pulmonary diseases, one-third had chronic obstructive lung disease, one-fifth had diseases with pulmonary vascular obstruction, and the
The remainder had a variety of other diseases. The ejection fraction of right and left ventricles as an index of ventricular performance was measured in both subjects and controls using a cardiac pool-scan with 99m-technetium.

Analysis with two-dimensional echocardiography was performed and in the short axis view of the left ventricle at the level of papillary muscles.
Fig. 3. Hemodynamic parameters in right ventricle in 3 stages of pulmonary heart disease.

Pathophysiology

1) Abnormalities of pulmonary hemodynamics

Pulmonary circulatory parameters were compared among four groups in the natural course of pulmonary heart disease (Fig. 1). Blood gas analysis revealed significant hypoxia in all the groups with chronic pulmonary diseases. The pulmonary artery mean pressure increased as the disease progressed, while pulmonary capillary wedge pressure showed no change. Pulmonary artery mean pressure averaged 38 mmHg in RVH group and 51 mmHg in the RVF group. In the RVF group, heart rate was high and cardiac output was 2.1 L/min/M² in average and low, though the level of pulmonary artery pressure was higher than that of RVH group. Total pulmonary vascular resistance, and pulmonary arteriolar resistance increased in relation to the progress of pulmonary disease. Compared with NL group, pulmonary arteriolar resistance nearly doubled in the CPD group, was up to five times that in RVH group, and fourteen times that in RVF group. Systemic pressure was decreased when cardiac output decreased in RVF group. Among patients with chronic cor pulmonale, including the RVH and RVF groups, pulmonary circulatory parameters were compared between cases with chronic obstructive lung disease and with pulmonary vascular disease (Fig. 2). Blood oxygen inhalation on pulmonary circulation. In 10 of the 16 cases, the effects of isosorbide dinitrate 5 mg sublingual on pulmonary hemodynamics were tested.

In 14 patients with pulmonary vascular disease, we examined the effects of vasodilating agents, such as prostaglandin E1, nifedipine, hydralazine, prazosin, and isoproterenol, on pulmonary circulation, using a Swan-Ganz balloon-tipped catheter. Hemodynamic measurement was performed prior to medication and during the maximum pharmacological effect of medicine.

Prostaglandin E1 0.03 μg/kg/min was given intravenously using an infusion pump for at least 20 min in 6 patients. Nifedipine 10 mg was given sublingually in 4 patients. Hydralazine 100 mg bid was given orally for three days in 2 patients. Prazosin was given orally in one patient. Isoproterenol was given intravenously for at least 20 min in another patient.

RESULTS

Pharmacological treatment

In 16 patients with pulmonary hypertension due to chronic obstructive lung disease and hypoxia, we observed effects of 40-100%
Fig. 4. Right ventricular work, ejection fraction of right and left ventricle in 3 stages of pulmonary heart disease.

Fig. 5. Two-dimensional echocardiogram in short axis view. Upper panel is a normal case and lower panel is a case with right ventricular pressure overload.
RV systolic pressure and $D_{AP}/D_{SL}$ in end-systole

Fig. 6. Correlation between right ventricular pressure and $D_{AP}/D_{SL}$ in end-systole in patients with primary pulmonary hypertension. $D_{AP}/D_{SL}$: an index of left ventricular distorsion, see text. Dotted line is connecting 4 studies in different period in a case.

PERCENT SYSTOLIC SHORTENING in DIAMETER

![Graph showing percent systolic shortening in diameters, $D_{AP}$ and $D_{SL}$, in normals and patients with primary pulmonary hypertension.]

Fig. 7. Percent systolic shortening in diameters, $D_{AP}$ and $D_{SL}$, in normals and patients with primary pulmonary hypertension.

gas analysis revealed decreased oxygen saturation with elevated pressure of carbon dioxide in obstructive lung disease, and decreased pressure of carbon dioxide in pulmonary vascular disease. Pulmonary artery mean pressure in pulmonary vascular disease averaged 50 mmHg and was twice large of that found in chronic obstructive lung disease. Cardiac output was low normal in patients with pulmonary vascular disease and was lower than that in those with chronic obstructive lung disease. Calculated pulmonary arteriolar resistance, therefore, averaged 400 dynes/sec/cm$^5$ in chronic obstructive lung disease. In pulmonary vascular disease it was more than 1500
TABLE I HEMODYNAMIC RESPONSES TO VASO-DILATING AGENTS IN PULMONARY HYPERTENSION WITH CHRONIC OBSTRUCTIVE LUNG DISEASE AND HYPOXIA

a. Effects of O₂ inhalation

|                  | Room air mean SD | Hyperoxia mean SD | p <  
|------------------|------------------|-------------------|------
| **SaO₂** %       | 84.8 ± 8.9       | 97.8 ± 2.6        | 0.001|
| **PaCO₂** Torr   | 40.7 ± 12.9      | 42.5 ± 14.4       | ns   |
| **PH**           | 7.45 ± 0.06      | 7.44 ± 0.07       | ns   |
| **H.R.** /min    | 83.0 ± 14.7      | 78.2 ± 11.7       | 0.005|
| **MBP.** mmHg    | 94.1 ± 19.6      | 94.3 ± 16.3       | ns   |
| **PAMP** mmHg    | 28.4 ± 13.9      | 27.9 ± 14.1       | ns   |
| **PCWMP** mmHg   | 5.4 ± 3.0        | 5.3 ± 2.9         | ns   |
| **C.I.** L/min/M²| 3.5 ± 1.1        | 3.2 ± 1.1         | 0.05 |
| **PAR** dynes-sec·cm⁻⁵ | 439 ± 461       | 462 ± 516         | ns   |

Chronic pulmonary disease with hypoxia (n = 16)

b. Effects of isosorbide dinitrate, SL

|                  | Control mean SD | Isosorbide dinitrate mean SD | p <  
|------------------|-----------------|-------------------------------|------
| **SaO₂** %       | 87.2 ± 6.0      | 87.7 ± 5.7                    | ns   |
| **PaCO₂** Torr   | 51.4 ± 9.6      | 47.7 ± 10.7                   | ns   |
| **PH**           | 7.40 ± 0.03     | 7.41 ± 0.03                   | ns   |
| **H.R.** /min    | 78.6 ± 10.8     | 85.0 ± 8.7                    | 0.05 |
| **MBP.** mmHg    | 93.9 ± 16.6     | 81.2 ± 11.4                   | 0.005|
| **PAMP** mmHg    | 26.8 ± 12.2     | 19.8 ± 7.4                    | 0.001|
| **PCWMP** mmHg   | 7.1 ± 3.1       | 6.0 ± 2.5                     | ns   |
| **C.I.** L/min/M²| 2.8 ± 1.0       | 2.6 ± 1.3                     | ns   |
| **PAR** dynes-sec·cm⁻⁵ | 385 ± 201       | 318 ± 166                    | 0.005|

Chronic pulmonary disease with hypoxia (n = 10)

dynes/sec/cm⁵. Decreased cardiac output due to obstruction in the pulmonary circuit caused systemic arterial pressure to decrease.

2) Disorders of the pump function

Comparisons of the right ventricular parameters among 4 groups are shown in Fig.3-4. Right ventricular systolic and end-diastolic pressures were elevated as the disease progressed.

Right atrial pressure increased only in RVF group. Right ventricular work index and stroke work index also increased with the progress of disease, though they were lower in RVF group (Fig. 9). The mean right ventricular ejection fraction with pool-scan was 49% in the NL group, decreased to 41% in RVH group, and further decreased to 22% in the RVF group. Left ventricular ejection fraction was 61% in NL group and there was no difference with RVH group and RVF group.

In two-dimensional echocardiogram, however, the left ventricle was distorted and had uneven contraction. Dap/Dsl in NL was 1.0, though in patients with right ventricular pressure overload it took a larger value (Fig. 5). In 7 patients with primary pulmonary hypertension, there was a correlation between right ventricular systolic pressure and Dap/Dsl (Fig. 6). Right ventricular pressure overload made left ventricle distorted. Percent systolic shortening of Dap and Dsl was same value in NL, while in patients with pressure overload, Dap was decreased and Dsl was hyperdynamic in its motion (Fig. 7).

Pharmacological treatment

1) Response in chronic obstructive lung disease

Oxygen inhalation (Table I-a)

Arterial oxygen saturation was improved from
84.8% to 97.8% in average, while there was no change in pulmonary artery pressure. Cardiac output was rather decreased in relation to oxygenation of arterial blood. There was no change in pulmonary arteriolar resistance.

Isosorbide dinitrate (Table I-b)

Pulmonary artery mean pressure decreased from 26.8 mmHg to 19.8 mmHg in average, and was associated with a decrease in pulmonary arteriolar resistance.

2) Response in pulmonary vascular disease

Prostaglandin E1 (Fig. 8-a)

Pulmonary artery mean pressure as well as systemic arterial pressure showed a decrease consistent with an increase in cardiac output. Pulmonary arteriolar resistance decreased 250 dyne·sec/cm² in average.

Nifedipine (Fig. 8-b)

There were no change in pulmonary artery pressure and systemic arterial pressure, though cardiac output increased 0.5 L/min/M² with a decrease of 100 dyne/sec/cm² in pulmonary arteriolar resistance.

Others

Hydralazine, prazocin, and isoproterenol were tested, though cases were too small to be statistically useful. There was no improvement in pulmonary arteriolar resistance observed with hydralazine. Prazocin and isoproterenol appeared to decrease pulmonary arteriolar resistance.

DISCUSSION

Problems in pump failure due to chronic pulmonary diseases are caused by abnormal pulmonary hemodynamics as the disorder of pump function is the result. The interaction between pulmonary circulation and cardiac function is the key to heart disease. The main cause for pump failure, however, is a marked
increase in the afterload of the right ventricle; though changes in pulmonary hemodynamics are multifactorial. There are significant mismatches between high afterload due to abnormalities in pulmonary circulation and the contractility of right ventricle as a pump, though the compensatory mechanism of the heart as a whole is working. This condition is by a distorted left ventricle with bellows-like motion, in addition to well known hypertrrophy and dilatation of right ventricle. The main measures used to support pump failure of the right ventricle are to increase myocardial contractility and to decrease elevated pulmonary vascular resistance.

In this paper, we evaluated the effects of vasodilating agents on the elevated pulmonary vascular resistance as the causative factor of pump failure.

In patients with chronic pulmonary disease associated with pulmonary hypertension and chronic hypoxia, there was no decrease in pulmonary arteriolar resistance with oxygen inhalation. Cardiac output actually decreased with arterial oxygenation. Acute hypoxia induced constriction of small pulmonary arteries and increased its resistance to flow, which was reversible after reoxygenation to normal level, both in experiments and in clinical settings. Therefore, oxygen inhalation might be expected to improve pulmonary hemodynamics of patients with chronic hypoxia. There remained a discrepancy, however, between chronic and acute hypoxia in response to arterial oxygenation. The poor response in chronic patients might be explained by diffuse pathological changes in pulmonary vascular beds. There may be no smooth muscles in the vascular wall to respond to the change in oxygen level and to control vascular resistance. But it was clarified that in these patients, nitrate decreased pulmonary vascular resistance. The fact suggested that in the pulmonary vascular beds, the mechanism to control vascular resistance related to arterial oxygen level is not as sensitive as with normal subjects. In other words, in patients with pulmonary hypertension with chronic hypoxia, it is not enough to give oxygen, but it is better to combine some vasodilating agent with oxygen in order to decrease the pulmonary arteriolar resistance and right ventricular pressure overload.

In terms of pulmonary vascular disease, there are many studies that report various vasodilating agents to decrease pulmonary vascular resistance. From our experience, in patients with pulmonary vascular disease and pulmonary hypertension, the maximum effect of vasodilating agents in reducing resistance was less than 30%. During the time preceding a clinical diagnosis, both pathoanatomical and diffuse irreversible changes have developed, such as in the case of a plexiform lesion. Therefore, functional improvement with vasodilating agents is limited. When cardiac output is low and systemic hypotension due to abnormally high afterload of right ventricle is present, vasodilating agents might cause low perfusion in peripheral organs. An agent with specific efficacy on pulmonary vascular bed should be developed in the future.

Finally, the evaluation of the chronic effect of vasodilating agent should be quite prudent. We had a case of primary pulmonary hypertension with spontaneous regression of pulmonary hypertension twice within three years. The regression was confirmed with cardiac catheterization performed seven times during the clinical course.

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