ACUTE EFFECTS OF ORAL CAPTOPRIL ON HEMODYNAMICS
IN PATIENTS WITH COR PULMONALE

KAZUO TAKADA, M.D., MASATO HAYASHI, M.D., KEIJI TAKAHASHI, M.D.
AND SHOJI YASUI, M.D.

The cause of pulmonary hypertension in chronic obstructive pulmonary
disease (COPD) is considered to be hypoxic pulmonary vasoconstriction,
which may be mediated in part by angiotensin II. We administered captopril
(25 mg, orally) to seven patients with COPD and complicating cor pulmonale
in stable state. Hemodynamic responses were recorded before and one hour
after the administration of the drug.

Captopril increased cardiac output by 23% (p < 0.025) and reduced mean
systemic pressure by 12% (p < 0.004), but did not alter mean pulmonary
arterial pressure. Pulmonary and systemic vascular resistance fell, respectively,
by 14% (p < 0.035) and 31% (p < 0.03). There was an increase in pulmonary
systemic vascular resistance ratio (p < 0.007). Heart rate, mean right atrial,
pulmonary capillary wedge pressure, arterial oxygen tension and dioxide
tension, and alveolar-arterial oxygen tension difference remained unchanged.

These results suggest that captopril is successful in reducing pulmonary
vascular resistance without affecting arterial blood gases, but does not change
mean pulmonary arterial pressure probably because of the concurrent increase
in pulmonary blood flow. In addition, results indicate that captopril has
more effects on the systemic vasculature than on the pulmonary circulation.

A serious complication in patient with chronic obstructive pulmonary disease (COPD) is
the development of cor pulmonale characterized by right ventricular hypertrophy and pulmonary
hypertension. The presence of pulmonary hypertension in COPD has been associated with a signi-
ificantly poor prognosis. Therefore, a reduction in pulmonary vascular resistance can be
therapeutic.

Recently attention has been paid to the use of some vasodilators, such as phenolamine.

**Key Words:**
- Cor pulmonale
- Chronic obstructive pulmonary disease
- Captopril
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- Hypoxic pulmonary vasoconstriction

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The First Department of Internal Medicine, Yamagata University School of Medicine, Yamagata; *The Second
Department of Internal Medicine, Hiraka General Hospital, Yokote, Japan
Mailing address: Kazuo Takada, M.D., The First Department of Internal Medicine, Yamagata University
School of Medicine, Zao-ida, Yamagata 990-23, Japan

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this agent in treating cor pulmonale of COPD.
Therefore, we studied the effect of oral captopril on the hemodynamic status in patients with clinically stable cor pulmonale.

MATERIALS AND METHODS
Seven patients with COPD, 5 men and 2 women with a mean age of 59 yr (range, 52 to 66 yr), were investigated. They showed a forced vital capacity (FVC) of $2.02 \pm 0.31$ L (mean $\pm$ standard deviation), a forced expiratory volume in one second ($FEV_1$) of $0.79 \pm 0.17$ L, and $FEV_1/FVC$ of $40.6 \pm 12.0\%$. Two of 5 men had undergone tracheostomy. The diagnosis of cor pulmonale was based on chest X-ray film, electrocardiogram findings, and was confirmed by right heart catheterization in all patients. All patients were clinically stable and without a history of left ventricular failure. They ate a regular diet without salt restriction until the day before the hemodynamic study.

After informed consent was obtained, other vasodilators and bronchodilators were discontinued for at least 24 hours, and supplemental oxygen therapy was stopped for at least one hour.
Fig. 3. Changes in right atrial pressure, pulmonary capillary wedge pressure, and right ventricular end-diastolic pressure in response to captopril.

Fig. 4. Effect of captopril on systemic and pulmonary vascular resistance. Pulmonary/systemic vascular resistance ratio (PVR/SVR) increases at one hour after administration of the drug.

All patients were in the fasting state and lying supine. A triple-lumen thermodilution catheter (Model SP 5108, Gould H.B.) was inserted into a femoral vein, and placed into the pulmonary artery. The patients were allowed to rest 10 minutes after insertion of the catheters, then simultaneous arterial and mixed venous blood samples were collected anaerobically in order to measure blood gases on a Radiometer Model ABL 2 blood gas analyzer (Radiometer Corp., Copenhagen, Denmark). Cardiac output was measured in triplicate by the thermodilution method, using the EH-11 cardiac output computer (Fukuda Denshi Corp., Tokyo, Japan). Then measurements of pulmonary capillary wedge pressures, pulmonary arterial, right ventricular, and right atrial pressures were sequentially made by averaging the values over at least three respiratory cycles. The pressures were measured using Statham P 23 ID transducers (Gould-Statham Instruments Inc., Hato Rey, Puerto Rico) coupled to Meddars Series 300 system (Honeywell Corp., Denver, Colorado). Systemic arterial pressure was measured by using cuff sphygmomanometry,
and mean pressures were calculated by adding one-third of the pulse pressure to the diastolic pressure. Heart rate was determined from an electrocardiographic lead, which was monitored continuously at the time of cardiac output measurements.

The same measurements were performed at one hour after oral administration of 25 mg of captopril. Mixed venous blood gas analysis and right ventricular end-diastolic pressure measurement were made in 6 patients. Hemodynamic parameters were calculated using standard formulas. Values are expressed as a mean ± standard deviation. Statistical analysis of the data was performed with use of Student’s paired t test. For all tests a p value less than 0.05 was considered significant.

RESULTS

One hour after captopril, mean systemic arterial pressure fell from 97 ± 11 to 86 ± 11 mmHg (p < 0.004), whereas mean pulmonary arterial pressure was unchanged from 38 ± 10 to 39 ± 9 mmHg (Fig. 1). Heart rate did not change significantly (84 ± 10 → 85 ± 8 beats/min). Cardiac output was increased from 4.46 ± 0.86 to 5.51 ± 0.61 L/min (p < 0.025), and stroke volume was increased from 52.6 ± 7.3 to 65.6 ± 9.8 mL/beat (p < 0.03) (Fig. 2). There were no significant changes in the mean right atrial pressure (3.9 ± 2.0 → 3.1 ± 1.6 mmHg), pulmonary capillary wedge pressure (8.0 ± 2.4 → 7.7 ± 1.7 mmHg) (Fig. 3). Right ventricular end-diastolic pressure was decreased from 6.7 ± 2.1 to 5.3 ± 1.5 mmHg (p < 0.05) (Fig. 3). Systemic vascular resistance

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Fig. 7 Changes in arterial oxygen transport and oxygen consumption after captopril.

(SVR) was decreased from 1762 ± 517 to 1210 ± 250 dyne·sec·cm⁻⁵ (p < 0.03), and pulmonary vascular resistance (PVR) was decreased from 538 ± 139 to 464 ± 151 dyne·sec·cm⁻⁵ (p < 0.035). The mean ratio of pulmonary-to-systemic vascular resistance was increased from 0.32 ± 0.11 to 0.39 ± 0.13 (p < 0.007) (Fig. 4). The magnitude of fall in SVR and that in PVR did not correlate with the baseline level of plasma renin activity (PRA) as shown in Fig. 5.

There were no significant changes in blood gases, alveolar-arterial oxygen tension difference (Fig. 6), and oxygen consumption (Fig. 7). Oxygen transport was increased from 493 ± 89 to 617 ± 115 mL/min/m² (p < 0.05) (Fig. 7).

No side effect was recorded.

DISCUSSION

A serious complication of COPD is the development of cor pulmonale with pulmonary hypertension. The cause for pulmonary hypertension has been considered to be hypoxic pulmonary vasoconstriction (HPV) in addition to the diminished pulmonary vascular bed, since oxygen therapy causes a reduction in pulmonary arterial pressure and pulmonary vascular resistance.⁸,¹⁹ Although it is not clear whether HPV is due to a direct effect of hypoxia on smooth-muscle cells or to local release of mediators, the role of chemical mediators may be very significant.¹¹

Angiotensin II, a potent vasoconstrictive agent, may be produced in the lung because ACE is found predominantly in the pulmonary endothelium.²⁰ Animal studies indicate that angiotensin II augments HPV¹¹ and the pulmonary hypertension and right ventricular hypertrophy caused by chronic hypoxia can be decreased by ACE inhibitors (captopril, teprotide). Mice exposed to chronic alveolar hypoxia showed elevations of serum and lung ACE activity.²⁴ These studies suggest that angiotensin II may be involved in eliciting HPV, although the reactivity of the pulmonary vessels is not quite comparable in human and in animals.

Maximal concentration of captopril in blood was observed between 0.5 and 1.5 hours after oral administration in normal subjects,²⁵ and the nadir of blood pressure occurred 60 to 90 minutes after dosing in hypertensive patients.²⁶ Moreover, the reduction in plasma angiotensin II concentration 60 to 90 minutes after 25 mg oral captopril was reported.²⁷ Therefore, it is thought that a single dose of this drug (25 mg, orally) is sufficient to inhibit the local generation of angiotensin II and to have an anti-hypertensive effect one hour after dosing.

In our patients, cardiac output increased significantly because of the increase in stroke volume. On the contrary, in previous studies, cardiac output did not change after a single dose of 25 mg captopril in hypertensive patients.²⁷-²⁹ An interaction between withdrawal of endogenous angiotensin II-mediated inotropic effect on the heart and its SVR-lowering effect might explain the lack of increase in cardiac output.²⁷
This discrepancy seems to be based on the difference of patients that have been studied. We studied normotensive patients with pulmonary hypertension secondary to COPD. In fact, the rise in cardiac output has been observed after oral captopril in patients with secondary form of pulmonary hypertension.\(^{30}\) The increase in stroke volume may not be due to a direct inotropic effect of captopril on heart muscle but possibly due to a reduction in right ventricular afterload, since right ventricular end-diastolic pressure decreased. In our patients, captopril reduced in PVR, but pulmonary arterial pressure was unchanged. It is probably because of the concurrent increase in cardiac output that pulmonary arterial pressure was unchanged in spite of a decrease in PVR. It is uncertain whether the decrease in PVR is secondary to the increase in cardiac output or because of vasodilation in pulmonary vasculature. As pulmonary blood flow increases, however, pulmonary arterial pressure almost linearly increases in patients with COPD.\(^{31}\) Therefore, PVR reduction after captopril is more probably due to pulmonary vasodilation than to recruitment or distention of pulmonary vasculature.

No significant correlation between the level of baseline PRA and acute reduction of SVR and that of PVR was noted in our patients, although the magnitude of fall in SVR and that in PVR tended to increase in proportion to the baseline level of PRA. Some investigators observed the correlation between the fall in mean systemic pressure and baseline PRA in hypertensive patients\(^{27,28}\) others did not\(^{32,33}\) Such differences might result from variation in the state of hydration and the sodium balance among the various groups of patients.\(^{27}\)

Although we considered captopril to be a relatively selective pulmonary vasodilator, this agent affected the systemic vasculature more remarkably than the pulmonary circulation in our patients. The mean ratio of pulmonary-to-systemic vascular resistance was significantly increased. These findings suggest that angiotensin II does play a minor role in the development and maintenance of HPV in humans.

It is generally believed that vasodilators worsen the hypoxemia by exaggerating the existing ventilation/perfusion imbalance by inhibition of HPV. This phenomenon was observed in patients receiving nitroglycerin\(^{34}\) or nitroprusside\(^{35}\) In our patients, however, arterial oxygenation was not decreased after oral captopril. This is due to an increased oxygen delivery to the tissue by the concurrent increase in cardiac output.

An ideal drug in treating pulmonary hypertension would dilate pulmonary vasculature alone, without inhibiting HPV. From this point of view, oxygen administration may be favorable. However, oxygen therapy is expensive and inconvenient and the responsiveness of the pulmonary vascular bed to inspired oxygen tends to diminish with prolonged use.\(^{36}\) Further studies are needed in order to find the ideal vasodilating agents.

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