IMPROVEMENT OF RIGHT VENTRICULAR SYSTOLIC PERFORMANCE BY LONG-TERM DOMICILIARY OXYGEN THERAPY IN PATIENTS WITH CHRONIC RESPIRATORY FAILURE

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Eight patients with clinically stable chronic respiratory failure, hypoxemia ($\text{PaO}_2 \leq 60$ mmHg) and pulmonary hypertension (mean pulmonary arterial pressure ≥ 20 mmHg) were allocated to long-term domiciliary oxygen therapy, and were followed for three months. Oxygen was supplied for from 15 to 18 hours daily from an oxygen concentrator at a flow rate sufficient to raise the PaO_2 to 60 to 80 mmHg.

We examined the effects of this therapy on right ventricular performance both at rest and during exercise in these patients. Hemodynamic data were obtained by right heart catheterization. Right ventricular ejection fractions (RVEF) were ascertained using first-pass quantitative radionuclide $^{81\text{m}}\text{Kr}$ angiocardigraphy. Thirty minutes of oxygen inhalation at rest had no significant effect on cardiac function, both before therapy (T_0) and after 3 months of therapy (T_1). The mean pulmonary arterial pressure and the pulmonary vascular resistance during exercise were not significantly different between T_0 and T_1 . On the other hand, at T_0 , the RVEF tended to decrease from $51.6 \pm 4.9\%$ (during oxygen inhalation at rest) to $48.7 \pm 7.9\%$ (during exercise), whereas at T_1 it significantly ($p < 0.05$) increased from $48.8 \pm 6.8\%$ (during oxygen inhalation at rest) to $54.2 \pm 8.2\%$ (during exercise).

Thus, while 3 months of long-term domiciliary oxygen therapy did not reduce the right ventricular afterload either at rest or during exercise, it was found to improve the right ventricular systolic performance during exercise. This suggested that long-term oxygen therapy could be useful in improving the quality of daily life of patients with chronic respiratory failure.

IN patients with chronic respiratory failure, the major cardiovascular complication is the development of pulmonary hypertension because of chronic hypoxemia.^{1,2} Alveolar hypoxia induces pulmonary vasoconstriction, and if the

hypoxia persists, it leads to muscularization of the pulmonary arterioles.³ The resulting pulmonary hypertension causes right ventricular hypertrophy and, eventually, right ventricular dysfunction. Even if pulmonary hypertension is absent at rest in patient with chronic respiratory failure, pulmonary arterial pressure may increase during exercise. The resultant increase in the right ventricular afterload can then induce right ventricular dysfunction, which will restrict the daily activities of these patients.¹ Previous animal

Key words:

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TABLE I PULMONARY FUNCTION DATA BEFORE AND AFTER THREE MONTHS OF OXYGEN THERAPY

Case No.	Age	Sex	VC (L)		FEV ₁ (L)		RV (L)		PaO ₂ (mmHg)		PaCO ₂ (mmHg)	
			T ₀	T ₁	T ₀	T ₁	T ₀	T ₁	T ₀	T ₁	T ₀	T ₁
1	59	M	1.75	1.60	1.05	0.97			38	34	44	35
2	63	M	1.46	1.39	0.97	0.89	1.64	2.17	52	61	43	44
3	76	M	2.01	1.87	0.46	0.47	6.46	5.95	60	64	44	47
4	58	M	1.94	1.95	0.63	0.72	2.17	1.98	58	52	53	58
5	64	M	3.84	4.21	1.60	1.68	4.95	3.65	56	56	44	44
6	74	M	2.50	2.42	0.84	0.69	2.35	1.95	56	55	46	44
7	81	M	2.61	2.46	0.61	0.58	4.17	3.49	55	51	52	55
8	48	F	0.98	0.98	0.40	0.44		2.08	60	53	49	49
mean	65		2.14	2.18	0.76	0.81	3.62	3.04	54	53	47	47
± SD	± 11		± 0.88	± 0.98	± 0.39	± 0.40	± 1.89	± 1.47	± 7	± 9	± 4	± 7
			— NS —		— NS —		— NS —		— NS —		— NS —	

Definition of abbreviations: VC = vital capacity; FEV₁ = forced expiratory volume in one second; RV = residual volume; T₀ = before oxygen therapy; T₁ = after 3 months of oxygen therapy

experiments and clinical studies have reported that this chain of events can be reversed if pulmonary vasoconstriction is suppressed by continuous oxygen administration, i.e. that pulmonary hypertension is potentially reversible^{4,5}

Recently there have been reports of improvements in both the survival rate and the symptoms of patients with chronic obstructive lung disease who received long-term continuous oxygen therapy^{2,6,7}. However, there have been very few reports concerning the effects of long-term oxygen therapy on pulmonary hemodynamics during exercise². Also, the effects of such therapy on right ventricular systolic performance during exercise have not been clearly established.

The present study was carried out to evaluate the effects of long-term domiciliary oxygen therapy on right ventricular performance, both at rest and during exercise, in patients with chronic respiratory failure. It was based on pulmonary hemodynamics and right ventricular ejection fractions data, obtained both before and after 3 months of domiciliary oxygen therapy.

METHODS

Subjects

Eleven patients with clinically stable chronic respiratory failure, were selected as candidates for this study. The entry criteria were: (1) arterial oxygen pressure (PaO₂) below 60 mmHg,

(2) no history of acute respiratory failure for 3 months before the study, (3) no history of left ventricular failure, and (4) the absence of hypertension, valvular disease, angina pectoris and myocardial infarction. Of these 11 candidates, 8 patients were finally studied. These were patients in whom right heart catheterization could be performed both before and after oxygen therapy, and whose mean pulmonary arterial pressure was 20 mmHg or higher before oxygen therapy (Table I). They consisted of 7 males and 1 female, with a mean age of 65 years (range, 48 to 81 years). Five patients had obstructive ventilatory disturbance, 2 had restrictive ventilatory disturbance and 1 had combined ventilatory disturbance. These 8 patients were all receiving diuretic or bronchodilator therapy which was continued without changing the dose.

Oxygen supply

For domiciliary oxygen therapy, either 40% or 90% oxygen concentrators were employed. The patients were instructed to inhale oxygen for 15 to 18 hours a day through nasal prongs at a flow rate sufficient to keep PaO₂ at 60 to 80 mmHg.

Study protocol

Each patient was hospitalized for 1 week before the study commenced. Right heart catheterization and right ventricular ejection fraction measurement were carried out twice (before

TABLE II CHANGES IN HEMODYNAMICS IN EIGHT PATIENTS

	Rest (Room air)		Rest (Oxygen)		Legs up (Oxygen)	
	T ₀ [a]	T ₁ [b]	T ₀ [c]	T ₁ [d]	T ₀ [e]	T ₁ [f]
PCWP (mmHg)	13 ± 3 (8)	11 ± 5 (8)	13 ± 4 (8)	10 ± 4 (8)	16 ± 4 (8)	11 ± 3 (7)
mPAP (mmHg)	31 ± 6 (8)	29 ± 7 (8)	31 ± 5 (8)	28 ± 7 (8)	36 ± 5 (8)	31 ± 6 (7)
RAP (mmHg)	8 ± 3 (8)	4 ± 2 (8)	9 ± 3 (7)	4 ± 2 (8)	11 ± 3 (7)	6 ± 3 (7)
HR (beats/min)	75 ± 13 (8)	73 ± 9 (8)	70 ± 12 (8)	70 ± 11 (8)	74 ± 10 (8)	70 ± 12 (7)
CI (l/min/m ²)	2.87 ± 0.35 (8)	2.77 ± 0.42 (8)	2.69 ± 0.28 (8)	2.65 ± 0.56 (8)	3.14 ± 0.38 (8)	2.82 ± 0.50 (7)
SVI (ml/m ²)	38 ± 9 (8)	37 ± 10 (8)	39 ± 11 (8)	38 ± 10 (8)	42 ± 9 (8)	40 ± 11 (7)
mAP (mmHg)	87 ± 5 (8)	82 ± 14 (8)	87 ± 6 (8)	87 ± 9 (8)	95 ± 6 (8)	90 ± 11 (7)
PVR (dyne·sec·cm ⁻⁵)	370 ± 150 (8)	381 ± 209 (8)	378 ± 123 (8)	382 ± 214 (8)	395 ± 127 (8)	401 ± 238 (7)
SVR (dyne·sec·cm ⁻⁵)	1642 ± 286 (8)	1658 ± 357 (8)	1742 ± 348 (8)	1868 ± 352 (8)	1583 ± 283 (8)	1796 ± 410 (7)
RVSWI (g·m/best/m ²)	17.2 ± 3.4 (8)	20.3 ± 6.1 (8)	17.8 ± 5.2 (7)	18.6 ± 4.5 (8)	22.5 ± 6.4 (7)	23.0 ± 6.8 (7)
pHa	7.41 ± 0.02 (8)	7.41 ± 0.05 (8)	7.40 ± 0.02 (8)	7.40 ± 0.02 (8)	7.40 ± 0.02 (8)	7.39 ± 0.02 (7)
PaO ₂ (mmHg)	54 ± 7 (8)	54 ± 9 (8)	70 ± 8 (8)	79 ± 10 (8)	64 ± 7 (8)	71 ± 6 (7)
PaCO ₂ (mmHg)	46 ± 3 (8)	47 ± 7 (8)	47 ± 2 (8)	47 ± 4 (8)	47 ± 3 (8)	49 ± 4 (7)
PvO ₂ (mmHg)	33 ± 4 (8)	34 ± 3 (8)	37 ± 5 (8)	36 ± 2 (8)	33 ± 2 (8)	34 ± 1 (7)
PvCO ₂ (mmHg)	49 ± 5 (8)	49 ± 6 (8)	50 ± 2 (8)	53 ± 4 (8)	52 ± 3 (8)	54 ± 5 (7)
RVEF (%)	50.5 ± 7.4 (8)	48.9 ± 7.0 (8)	51.6 ± 4.9 (8)	48.8 ± 6.8 (8)	53.2 ± 4.2 (4)	53.7 ± 6.6 (7)
RVEDVI (ml/m ²)	75.3 ± 14.2 (8)	78.1 ± 28.2 (8)	74.3 ± 17.1 (8)	78.2 ± 24.3 (8)	84.8 ± 19.0 (4)	81.5 ± 29.4 (6)
RVESVI (ml/m ²)	37.3 ± 8.2 (8)	40.9 ± 19.8 (8)	35.8 ± 7.7 (8)	40.6 ± 15.6 (8)	39.5 ± 8.9 (4)	40.1 ± 18.8 (6)

Values are mean ± SD. Numbers in parentheses are the number of patients in whom measurements were available.

****p* < 0.01; ***p* < 0.02; **p* < 0.05.

Definition of abbreviations: PCWP = pulmonary capillary wedge pressure; mPAP = mean pulmonary arterial pressure; RAP = right atrial pressure; HR = heart rate; CI = cardiac index; SVI = stroke volume index; mAP = mean

oxygen therapy, T₀, and after 3 months of oxygen therapy, T₁). Drug therapy was discontinued for 24 hours, and oxygen inhalation was discontinued for 4 hours before the measurements were performed.

Right heart catheterization

In the supine position, a teflon catheter was inserted into the radial artery, and a Swan-Ganz catheter was inserted via the antecubital vein into the pulmonary artery. After the patients

had rested for 30 min, the following hemodynamic parameters were measured: pulmonary capillary wedge pressure (PCWP), pulmonary arterial pressure (PAP), right atrial pressure (RAP), heart rate (HR), radial arterial pressure (AP) and cardiac output (CO). At the same time, arterial and mixed venous samples for blood gas analysis were obtained from the radial artery and the pulmonary artery. Pressures were measured with a Statham P-23ID transducer (Gould-Statham) and recorded with a VR-12

AFTER THREE MONTHS OF OXYGEN THERAPY

Exercise (Oxygen)		p-values									
T_0 [g]	T_1 [h]	a-b	c-d	e-f	g-h	a-c	c-e	c-g	b-d	d-f	d-h
18 ± 6 (8)	17 ± 4 (5)	NS	***	*	NS	NS	NS	NS	NS	NS	**
54 ± 9 (8)	53 ± 9 (7)	NS	NS	**	NS	NS	***	***	NS	NS	***
15 ± 5 (7)	10 ± 6 (7)	**	***	**	NS	NS	***	***	NS	NS	**
102 ± 11 (7)	109 ± 13 (7)	NS	NS	NS	NS	***	NS	***	**	NS	***
4.62 ± 1.04 (7)	4.57 ± 1.42 (7)	NS	NS	NS	NS	**	***	***	NS	NS	***
45 ± 13 (7)	41 ± 13 (7)	NS	NS	NS	*	NS	NS	**	NS	*	NS
112 ± 12 (8)	111 ± 23 (7)	NS	NS	NS	NS	NS	***	***	NS	**	***
418 ± 127 (7)	422 ± 199 (5)	NS	NS	NS	NS	NS	NS	NS	NS	NS	*
1282 ± 385 (7)	1368 ± 397 (7)	NS	NS	NS	*	NS	**	***	*	NS	***
37.4 ± 13.1 (6)	38.0 ± 12.0 (7)	NS	NS	NS	NS	NS	*	***	NS	**	***
7.38 ± 0.03 (6)	7.35 ± 0.03 (7)	NS	NS	***	**	**	NS	*	NS	*	***
55 ± 9 (8)	55 ± 8 (7)	NS	NS	NS	NS	***	*	***	***	*	***
49 ± 4 (8)	50 ± 5 (7)	NS	NS	NS	NS	NS	NS	*	NS	*	*
27 ± 3 (8)	27 ± 4 (6)	NS	NS	NS	NS	***	*	***	*	*	***
56 ± 5 (8)	61 ± 7 (6)	NS	NS	NS	NS	NS	**	***	NS	**	**
48.7 ± 7.9 (8)	54.2 ± 8.2 (8)	NS	NS	NS	NS	NS	NS	NS	NS	NS	*
93.5 ± 16.8 (7)	83.4 ± 31.3 (7)	NS	NS	NS	NS	NS	NS	***	NS	NS	NS
48.0 ± 8.9 (7)	42.7 ± 22.2 (7)	NS	NS	NS	NS	NS	NS	**	NS	NS	NS

arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; RVSWI = right ventricular stroke work index; RVEF = right ventricular ejection fraction; RVEDVI = right ventricular end-diastolic volume index; RVESVI = right ventricular end-systolic volume index; T_0 = before oxygen therapy; T_1 after three months of oxygen therapy

recorder (Electronics for Medicine). The mid-chest level was used as the zero pressure reference point. PAP and AP were recorded over 3 respiratory cycles. Mean pulmonary arterial pressure (mPAP) and mean arterial pressure (mAP) were electronically averaged. CO was determined by the thermodilution method using an Edwards Model 9520A cardiac output computer. Each cardiac output result was the mean of at least 3 determinations. For blood gas analysis, an automatic pH/blood gas system (Corning 175)

was used.

Hemodynamic measurement

Each hemodynamic parameter was measured under the following four conditions: (1) breathing room air at rest (hereafter called "Air"); (2) after 30 min oxygen inhalation through nasal prongs at a flow rate previously determined to raise the PaO_2 to 60 to 80 mmHg ("O₂"); (3) during oxygen inhalation with the legs placed on a bicycle ergometer ("O₂L"); (4) during

Fig.1. Effects of long-term oxygen therapy on mean pulmonary arterial pressure (mPAP), cardiac index (CI), stroke volume index (SVI), pulmonary vascular resistance (PVR), right ventricular stroke work index (RVSWI), and right ventricular ejection fraction (RVEF). Conditions of measurement: at rest breathing room air (Air), at rest breathing oxygen for 30 min (O₂), breathing oxygen in the legs-raised position (O₂L), and during exercise breathing oxygen (O₂Ex).

White circles show the values before oxygen therapy and black circles show the values after 3 months of oxygen therapy.

***p < 0.01; **p < 0.02; *p < 0.05

oxygen inhalation while undertaking single-stage 12.5 watt ergometer exercise ("O₂Ex").

RVEF measurement

Within 72 hours before or after right heart catheterization, the right ventricular ejection fraction (RVEF) was measured for each of the above-mentioned situations by the ⁸¹mKr first-pass method, which was reported in our previous study⁸.

Calculation

From the hemodynamic data, the following variables were derived; cardiac index (CI, l/min/m²), stroke volume index (SVI, ml/m²), pulmonary vascular resistance (PVR, dyne·sec·cm⁻⁵), systemic vascular resistance (SVR, dyne·sec·cm⁻⁵), and right ventricular stroke work index (RVSWI, g·m/beat/m²). The determination of right ventricular volume is anatomically very difficult compared to left ventricular volume. For this reason, we calculated the right ventricular end-diastolic volume index (RVEDVI, ml/m²) and the right ventricular end-systolic

volume index (RVESVI, ml/m²) from the values of RVEF (determined using ⁸¹mKr) and SVI (measured by the thermodilution method) using the following equation:

$$\begin{aligned} \text{RVEDVI} &= \text{SVI} / \text{RVEF}; \\ \text{RVESVI} &= \text{RVEDVI} - \text{SVI} \end{aligned}$$

Statistical analysis

The statistical significance of differences was tested using Student's paired t test, with p < 0.05 being regarded as statistically significant. Results were expressed as mean ± SD.

RESULTS

Table I shows the pulmonary function data at T₀ and T₁ for each patient. The subjects were 2 patients with restrictive ventilatory disturbance (Nos. 1 and 2), 5 patients with obstructive ventilatory disturbance (Nos. 3–7), and one patient with a combined ventilatory disturbance (Nos. 8). No differences were noted in vital capacity, forced expiratory volume in one second, PaO₂ or PaCO₂ between T₀ and T₁.

Fig. 2. Right ventricular ejection fractions (RVEF), right ventricular end-diastolic (RVEDVI) and right ventricular end-systolic (RVESVI) volume indexes, at rest and during exercise while breathing oxygen, in 8 patients before and after 3 months of oxygen therapy.

Means are noted at the sides of each panel.

O₂ = at rest breathing oxygen; O₂Ex = during exercise breathing oxygen

T₀ = before oxygen therapy; T₁ = after 3 months of oxygen therapy

Table II and Fig. 1 show the changes in hemodynamics evaluated under the conditions of "Air", "O₂", "O₂L" and "O₂Ex" at T₀ and T₁. Figure 2 shows the changes in RVEF, RVEDVI and RVESVI evaluated for conditions of "O₂" and "O₂Ex".

(1) Before oxygen therapy (T₀)

Under "Air", mPAP (31 ± 6 mmHg) and PVR (370 ± 150 dyne·sec·cm⁻⁵) were abnormally elevated. PCWP and RAP were in the upper range for normal persons. SVI and CI were slightly lower than normal and RVSWI was high. RVEF was normal for the group as a whole ($50.5 \pm 7.4\%$), although it was below the normal limit (45%) in 3 cases. All of the patients had arterial hypoxemia.

Under "O₂", PaO₂ and PvO₂ increased significantly while mPAP, PCWP, RAP, SVI, PVR, SVR, RVSWI and RVEF showed no change. CI decreased from 2.87 ± 0.35 to 2.69 ± 0.28 l/min/m² ($p < 0.02$), and HR significantly decreased from 75 ± 13 to 70 ± 12 per minute ($p < 0.01$).

Under "O₂L", an increase was noted in mPAP, RAP, CI, mAP ($p < 0.01$) and RVSWI ($p < 0.05$), but no change was seen in PCWP, SVI, RVEF and PVR. A significant decrease was found in PaO₂ and PvO₂ ($p < 0.05$).

Under "O₂Ex", mPAP, RAP, CI, SVI, HR and RVSWI were found to be significantly higher than under condition "O₂" ($p < 0.01$), whereas PCWP remained unchanged and PaO₂ and PvO₂ were significantly decreased ($p < 0.01$). PVR tended to increase, but not significantly, from 378 ± 123 dyne·sec·cm⁻⁵ ("O₂") to 418 ± 127 dyne·sec·cm⁻⁵ ("O₂Ex"). RVEF tended to decrease from $51.6 \pm 4.9\%$ ("O₂") to $48.7 \pm 7.9\%$ ("O₂Ex"), and RVEDVI and RVESVI increased significantly ($p < 0.02$).

(2) Following 3 months of oxygen therapy (T₁)

Under "Air", mPAP (29 ± 7 mmHg) and PVR (381 ± 209 dyne·sec·cm⁻⁵) were abnormally elevated, while PCWP and RAP were within the normal range. SVI and CI were low, and RVSWI was high, while all patients had arterial hypoxemia when breathing room air.

Under "O₂", PaO₂ and PvO₂ increased significantly while mPAP, PCWP, RAP, SVI, PVR, RVSWI and RVEF showed no change. CI tended to decrease, (but the change was not statistically significant), and HR decreased significantly ($p < 0.02$).

Under "O₂L", SVI was significantly higher than under "O₂" ($p < 0.05$). No change was seen in PCWP, mPAP, RAP, CI, PVR and RVEF. A significant decrease was found in PaO₂ and

PvO₂ ($p < 0.05$).

Under "O₂ Ex", PCWP, mPAP, RAP, HR, CI, mAP, PVR, and RVSWI were significantly higher than under "O₂". There was no alteration to SVI, but RVEF recorded under "O₂ Ex" ($54.2 \pm 8.2\%$) was significantly ($p < 0.05$) higher than that recorded under "O₂" ($48.8 \pm 6.8\%$). The RVEDVI tended to increase during exercise, while RVESVI remained unchanged throughout the exercise period.

(3) Effects of 3 months of oxygen therapy

(a) At rest breathing room air

For "Air", comparison between T₀ and T₁ reveals that RAP significantly decreased from 8 ± 3 mmHg (T₀) to 4 ± 2 mmHg (T₁) ($p < 0.02$). In the case of mPAP, the decrease from 31 ± 6 mmHg (T₀) to 29 ± 7 mmHg (T₁) was not statistically significant. The CI, SVI, PVR, RVEF and the degree of arterial hypoxemia showed no changes.

(b) Oxygen inhalation while at rest

Comparing the values obtained under "O₂" between T₀ and T₁, it can be seen that PCWP and RAP significantly decreased ($p < 0.01$), while mPAP, CI, SVI, PVR, RVEF showed no changes.

(c) Legs up during oxygen inhalation

Comparing the values for "O₂ L" at T₀ and T₁, it is seen that mPAP significantly decreased from 36 ± 5 mmHg (T₀) to 31 ± 6 mmHg (T₁) ($p < 0.02$). The PCWP, RAP also decreased, while CI, SVI, PVR and RVEF showed no changes.

(d) Oxygen inhalation during exercise

For "O₂ Ex", comparison between T₀ and T₁ shows that SVI decreased from 45 ± 13 ml/m² (T₀) to 41 ± 13 ml/m² (T₁) ($p < 0.05$), while mPAP, PCWP, RAP, and RVR showed no changes. The RVEF tended to increase, although not significantly, from $48.7 \pm 7.9\%$ (T₀) to $54.2 \pm 8.2\%$ (T₁).

DISCUSSION

In patients with chronic respiratory failure, right ventricular dysfunction is induced by an increase in right ventricular afterload, resulting from pulmonary hypertension and abnormally elevated pulmonary vascular resistance.^{1-3,5-9} During exercise this effect becomes more marked. Therefore, the daily activities of patients with chronic respiratory failure become severely restricted.^{1,6,7} The symptoms of these patients

can be improved by long-term oxygen therapy. A general improvement in the sense of well-being, an improved appetite, and increased alertness are frequently found in those patients treated with domiciliary oxygen.⁷ The prognosis of these patients may also be improved.^{2,6,7} This study monitored changes in right ventricular performance at rest, in the legs-raised position, and during exercise, in patients with chronic respiratory failure following long-term oxygen therapy.

(1) Effects on hemodynamics at rest

The results for mPAP, PVR and CI of patients breathing room air at rest were unchanged by the 3-month oxygen therapy. Several reports have been published regarding the effects of long-term oxygen therapy on the pulmonary circulation at rest. Abraham et al reported that 4 to 8 weeks of oxygen therapy, given for 24 hr a day, resulted in a marked decrease of mPAP from 42.5 mmHg to 32.5 mmHg.⁵ Stark et al reported a decrease of mPAP from 34 mmHg to 26 mmHg following 3 to 6 weeks of oxygen therapy given for 15 hr a day.⁹ However, in some recent reports, only a slight decrease was noted in mPAP following long-term oxygen therapy, e.g., from 29 mmHg to 26 mmHg after 6 months of oxygen therapy given for 24 hr a day,² and a decrease from 28 mmHg to 24 mmHg after 3 years of oxygen therapy given for 15 to 18 hr a day.¹⁰ Furthermore, according to the report of the Medical Research Council Working Party, 3 years long-term oxygen therapy, given for 15 hr a day, did not change mPAP.⁷ In all of the literature reporting that long-term therapy could decrease mPAP, CI was reported as remaining unchanged. Hence, the decrease in mPAP in these cases was attributed to a decrease in PVR.^{2,5,9,10} In our 3-month study, the mPAP decreased slightly, (but not statistically significantly), from 31 ± 6 mmHg to 29 ± 7 mmHg. The failure to confirm that long-term oxygen therapy could reduce established pulmonary hypertension was unexpected. However, this treatment did at least appear to prevent a further rise in mPAP. Oxygen treatment was withdrawn 4 hours or more before hemodynamic measurements were started after long-term oxygen therapy in all subjects. A report has been published which states that mPAP, while decreasing following continuous long-term oxygen therapy, shows a marked increase again after only 3 hours off oxygen treatment.¹¹ Thus it is possible that

the protocol for testing prevented detection of any improvement.

When measured while breathing oxygen for 30 min at T_0 , CI slightly decreased from 2.87 ± 0.35 l/min/m² to 2.69 ± 0.27 l/min/m², while no change was noted in SVI or RVEF (Table II, Fig. 1). This suggested that the decrease in CI was due to a decrease in HR. During oxygen administration, the sympathetic response to hypoxemia was presumably blunted and cardiac output decreased.¹² It is agreed among investigators that oxygen administration for 30 to 60 min exerts almost no effect on hemodynamics.^{2,12} In our study with 30 min oxygen administration, similar results were observed both before and after 3-months' oxygen therapy.

(2) Effects on hemodynamics when in the legs-raised position

No report has been published concerning changes in hemodynamics in patients breathing oxygen in this position, except for that of Timms et al on pressure changes.² According to Timms et al, mPAP, RAP and PCWP all increased in this position. They attributed this change to an increase in CI induced by an increase in venous return. It has been reported that the increased venous return induced by the legs-raised position leads to an increase of SVI in healthy individuals. However, in patients with cor pulmonale, SVI does not show such an increase. This is because the increase in preload due to an increase in venous return is associated with an increase in afterload. The net result is little or no augmentation of right ventricular stroke volume.¹³ A similar tendency was observed at T_0 in our cases, resulting in no increase in SVI and RVEF and significant elevation of mPAP. At T_1 , however, SVI actually demonstrated a small, but statistically significant increase, and both mPAP and PVR did not change significantly.

(3) Effects on hemodynamics during exercise

When measured during exercise no significant difference between T_0 and T_1 was recorded for the values of mPAP (54 ± 9 mmHg at T_0 and 53 ± 9 mmHg at T_1) and PVR (418 ± 127 dyne·sec·cm⁻⁵ at T_0 and 422 ± 199 dyne·sec·cm⁻⁵ at T_1). As mentioned above, the only report available concerning the hemodynamics during exercise of patients receiving long-term oxygen therapy is by Timms et al.² According to their report, 6 months of oxygen inhalation for 12 hours a day, resulted in no significant changes

in mPAP and PVR during exercise. In contrast, 6-month oxygen therapy involving 24 hours' a day inhalation, resulted in a significant decrease in mPAP (6 mmHg decrease) and PVR (108 dyne·sec·cm⁻⁵ decrease) during exercise, compared to the values recorded before the therapy. Possible explanations for the differing results obtained by the present study include the difference in duration (3 months instead of 6 months), and differences in inhalation times (15–18 hours in our study, and 12 or 24 hours in the study by Timms et al).

(4) Mechanism of improvement in right ventricular systolic performance

Under "Air" and "O₂", RVEF values at T_0 were within the normal range, i.e., $50.5 \pm 7.4\%$ and $51.6 \pm 4.9\%$, respectively. However, under "O₂Ex", RVEF at T_0 decreased slightly to $48.7 \pm 7.9\%$. Although not statistically significant this finding is consistent with the published RVEF data for patients with chronic obstructive pulmonary disease.^{1,14–16} The decrease seems to be attributable to right ventricular dysfunction caused by a marked increase in afterload occurring during exercise. It is known that in normal individuals under exercise conditions, the increase in RVEF is accompanied by an increase in stroke volume, which is thought to be due to increased ventricular contractility rather than to an augmentation of preload.^{16,17} However, in patients with chronic respiratory failure, the increase in stroke volume during exercise is severely limited so that the increase in cardiac output is determined by the increase in HR.¹⁷ In the present study, CI showed a marked increase under "O₂Ex" at both T_0 and T_1 , whereas SVI showed only a small increase (Fig. 1). At T_0 , RVEDVI during exercise increased significantly, but because of a simultaneous increase in RVESVI, RVEF tended to decline (Fig. 2). According to Ross et al, an increase in ventricular afterload will result in an increase in preload, and accordingly the ventricular performance is maintained.¹⁹ However, if the preload is not allowed to compensate for an increased afterload, there occurs a so-called "afterload mismatch", resulting in deterioration of the ventricular function.¹⁹ This is the probable schema of events that occurred in our patients before they received oxygen therapy. Increased right ventricular afterload during exercise may have caused an afterload mismatch, resulting in a reduction in RVEF and an increase in RVESVI.

On the other hand, following long-term oxygen therapy the RVEF during exercise ($54.2 \pm 8.2\%$) was significantly higher than the resting RVEF ($48.8 \pm 6.8\%$) in these patients ($p < 0.05$). RVEDVI tended to be higher during exercise than at rest, but no difference was noted between RVESVI during exercise and at rest (Fig. 2). In other words, following long-term oxygen therapy, the right ventricle was able to adequately cope with the exercise-induced increase in afterload.

In summary, after 3 months of oxygen therapy, the increased venous return induced by the legs-up position leads to an increase in SVI without a concomitant increase in afterload, and RVEF shows a significant increase against the exercise-induced increase in right ventricular afterload in patients with chronic respiratory failure. These findings suggest that right ventricular systolic performance is improved by 3 months of oxygen therapy.

(5) Limitations

This study has the following limitations. Firstly, it was impossible to repeat the exercise test within a short time interval, in patients with severe respiratory failure, under two conditions (air breathing and oxygen inhalation) to evaluate the effects of oxygen therapy. Secondly, we did not confirm that stable aerobic metabolism was prevailing in the patients. In a strict sense this confirmation is necessary to rule out the influence of lactic acidosis (caused by anaerobic metabolism during exercise) on the myocardial contraction and pulmonary vascular resistance. However, because the patients performed a single-stage submaximal exercise, which was discontinued immediately after the onset of symptoms, it is unlikely that the metabolism became anaerobic in the present study. Thirdly, right heart catheterization and determination of right ventricular ejection fraction with ^{81}mKr were not carried out simultaneously. However, since the patients' symptoms were stable, and the time lag between the two tests was shorter than 72 hours, this would be unlikely to affect the reproducibility of the obtained data.

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