Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension

T Iwase, N Nagaya, M Ando, T Satoh, F Sakamaki, S Kyotani, H Takaki, Y Goto, Y Ohkita, M Uematsu, N Nakanishi, K Miyatake

Abstract

Objective—To assess acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Design—Cardiopulmonary exercise testing was performed in 20 patients with CTEPH before thromboendarterectomy (baseline), one month after (early phase), and four months after (late phase). Peak oxygen uptake (peak VO₂) and the ventilatory response to carbon dioxide production (VE-V̇CO₂ slope) were measured for assessment of exercise capacity and ventilatory efficiency. Right heart catheterisation was performed in all patients before and one month after surgery.

Results—Baseline peak VO₂ decreased and VE-V̇CO₂ slope increased along with the increase in pulmonary vascular resistance in patients with CTEPH. After thromboendarterectomy, the ve-V̇CO₂ slope decreased greatly from baseline to the early phase (mean (SD), 50 (9) to 37 (7), p < 0.05) and reached a steady level thereafter. In contrast, a continued increase in peak VO₂ was noted from the early to the late phase (16.9 (4.1) to 21.1 (5.0) ml/kg/min, p < 0.05). The decrease in the ve-V̇CO₂ slope from baseline to the early phase, but not the increase in peak VO₂, correlated strongly with the decrease in pulmonary vascular resistance after surgery (r = 0.75, p < 0.01).

Conclusions—Thromboendarterectomy may cause an immediate improvement in ventilatory efficiency, possibly through its beneficial haemodynamic effects. In contrast, exercise capacity may continue to improve towards the late phase, reflecting peripheral adaptation to exercise. (Heart 2001;86:188–192)

Keywords: thromboendarterectomy; exercise capacity; pulmonary thromboembolism; pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is the result of obstruction of the pulmonary arteries by thrombus.1 Most patients with CTEPH have severe exercise limitation because of the cardiopulmonary effects of the condition.2 For example, Janicki and colleagues have shown a decrease in peak exercise oxygen consumption (peak VO₂) and an increase in the regression slope relating minute ventilation to carbon dioxide output (VE-V̇CO₂ slope) in patients with CTEPH, using cardiopulmonary exercise testing.3 Unfortunately, pulmonary thromboendarterectomy has been shown to ameliorate pulmonary hypertension in patients with CTEPH.4 5 However, little information is available about the effects of thromboendarterectomy on exercise capacity and ventilatory efficiency. Peak VO₂ is determined not only by the maximum cardiac output during exercise but also by the potential for oxygen extraction in exercising muscle.6 On the other hand, the increase in the ve-V̇CO₂ slope is associated with increased physiological dead space resulting from an impaired increase in pulmonary perfusion during exercise.7 Thus we hypothesised that peak VO₂ and the ve-V̇CO₂ slope may represent differing aspects of cardiopulmonary and peripheral responses after thromboendarterectomy.

To assess the acute and chronic effects of thromboendarterectomy on exercise capacity and ventilatory efficiency, we examined serial changes in peak VO₂ and the ve-V̇CO₂ slope after thromboendarterectomy, and the relations between changes in peak VO₂ and ve-V̇CO₂ slope and those of haemodynamic variables after thromboendarterectomy.

Methods

STUDY SUBJECTS
Pulmonary thromboendarterectomy was performed in 21 patients with CTEPH between January 1996 and December 1999. One patient died from the surgical procedure. The remaining 20 consecutive patients with CTEPH (11 men and nine women, mean age 43 years, range 22–65 years) were enrolled in the study (table 1). All patients complained of dyspnoea on effort, and the mean duration of symptoms before surgery was 57 months (range six months to 11 years).

Anticoagulation was initiated in all the patients when we made the diagnosis of CTEPH and this was continued during the follow up period after surgery. Vasodilators such as calcium antagonists and beraprost sodium, an oral prostacyclin analogue, were used in 13 patients. Use of drugs was unchanged before and after surgery, except in
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CARDIOPULMONARY EXERCISE TESTING

tments in pulmonary hypertension. discontinued because of significant improve-
three patients in whom vasodilators were
chronic thromboembolic pulmonary hypertension
Table 1 Baseline characteristics in 20 patients with
Demographics
Age (years) (mean (SD)) 43 (14)
Sex (male/female) 11/9
Aetiology
Coagulopathies 8
Deep vein thrombosis 16
NYHA functional class
II 3
III 17
Medicinal drug use
Anticoagulant agents 20
Digoxin 6
Diuretics 10
Nitrates 2
Calcium antagonists 3
Oral prostanycin analogue 8
Home oxygen 20

Values are n, except when stated.
NYHA, New York Heart Association.

three patients in whom vasodilators were discontinued because of significant improvements in pulmonary hypertension.
The diagnosis of CTEPH was made as follows. In brief, patients with clinical symp-
toms suggesting CTEPH initially underwent electrocardiography, chest radiography, eco-
cardiography, and lung scanning. When pulmo-
ary hypertension and right ventricular
enlargement were identified by echocardiog-
raphy, and perfusion defects were found on
ventilation/perfusion lung scanning, we sus-
pected the presence of CTEPH rather than
primary pulmonary hypertension. The diagno-
sis was confirmed by pulmonary angiography.
The characteristic angiographic findings of
CTEPH—such as “pouching”, pulmonary
arterial webs or bands, intimal irregularity,
abrupt narrowing of major pulmonary vessels,
and obstruction of lobar vessels—were found
in all patients.
Cardiac catheterisation was performed to
confirm precapillary pulmonary hypertension
(mean pulmonary arterial pressure > 25 mm Hg with pulmonary capillary wedge pressure < 12 mm Hg) and to rule out other
causes of pulmonary hypertension, such as
genital heart disease, valvar heart disease,
ischaeic heart disease, and cardiomyopathy.
The criteria for pulmonary thromboendar-
terectomy used in our institute were as defined
by Moser and colleagues: calculated pulmo-

ary vascular resistance at rest greater than
300 dynes.s.cm⁻⁵ in a symptomatic patient;
thrombus location in the main, lobar, or
segmental arteries; absence of severe associated
disease; and the willingness of the patient to
accept the surgical risks. All subjects provided
written informed consent.
To compare baseline exercise capacity and
ventilatory efficiency in patients with CTEPH
with the normal value for each variable, we also
studied 24 healthy volunteers matched for age
and sex (12 men and 12 women; mean age 46
years, range 21–75 years; mean height 1.64 m,
range 1.47–1.80 m; mean weight 62 kg, range
41–87 kg). None was taking any drugs.
CARDIOPULMONARY EXERCISE TESTING
Cardiopulmonary exercise testing was per-
formed in 20 patients with CTEPH before
thromboendarterectomy (baseline), one month
after (early phase), and four months after (late
phase). The exercise test was performed on an
upright bicycle ergometer. After a one minute
warm up at 0 W, exercise work load was
increased in a ramp pattern at 15 W/min to
the symptom limited maximum. Heart rate was
monitored with standard ECG leads, and
blood pressure was measured at the brachial
artery with a sphygmomanometer. Breath by
breath gas analysis was performed using a
respiromonitor (AE280, Minato Medical Sci-
ence, Osaka, Japan) connected to a personal
computer running analysing software. Exercise
capacity was evaluated by peak VO₂, which was
defined as the value of averaged data dur-
ing the final 15 seconds of exercise. Ventilatory
efficiency on exercise was represented by the
VE-VCO₂ slope, which was determined as the
linear regression slope of VE and VCO₂ from
the start of exercise until the RC point (the time up
until which ventilation is stimulated by CO₂
output and end tidal CO₂ tension begins to
decrease).

HAEMODYNAMIC STUDIES
Right heart cathetertisation was performed in
all patients before and one month after surgery. Haemodynamic variables including mean pulmo-
nary arterial pressure, mean right atrial pres-
sure, and mean pulmonary wedge pressure
were measured. Cardiac output was deter-
mined by the Fick method. Pulmonary
vascular resistance was calculated according to
the standard formula.

PULMONARY THROMBOENDARTERECTOMY
Pulmonary thromboendarterectomy was per-
formed by a previously described method.
After a median sternotomy, cardiopulmonary
bypass was initiated. Pulmonary thromboen-
darterectomy was initially performed on the
right pulmonary artery under intermittent cir-
culatory arrest using deep hypothermia. Any
loose thrombi in the lobar artery were re-
moved, and pulmonary thromboendarterec-
tomy was then carried out from lobar artery to
the segmental arteries. After this the left
pulmonary artery was incised and pulmonary
thromboendarterectomy performed in a same
way. The pulmonary arteries were then sutured
and the patients weaned from cardiopulmon-
ary bypass after restoration of body tempera-
ture to normal levels.

STATISTICAL ANALYSIS
All data are expressed as mean (SD). Compari-
sions of variables between the two groups were
made by the unpaired Student t test. Correla-
tion coefficients between haemodynamic vari-
ables and cardiopulmonary exercise test results
were determined by linear regression analysis.
Changes in haemodynamics and exercise
capacity after thromboendarterectomy were
compared by the paired Student t test.
Comparisons of the time course of peak VO₂ or
the VE-VCO₂ slope were made by one way
analysis of variance (ANOVA) for repeated
measures, followed by Scheffé’s multiple com-
parison test. A probability value of p < 0.05
was considered significant.
Results

BASELINE EXERCISE CAPACITY

Baseline peak work load was significantly lower in patients with CTEPH than in the age matched healthy subjects (Fig 1). Baseline peak \( V_O_2 \) was also lower in patients with CTEPH than in the healthy subjects, whereas the \( V-E-V_O_2 \) slope was much higher than the normal value. There was a negative correlation between pulmonary vascular resistance and peak \( V_O_2 \) \( (r = -0.50, p < 0.05) \) and a positive correlation between pulmonary vascular resistance and the \( V-E-V_O_2 \) slope \( (r = 0.46, p < 0.05) \). A negative correlation was also found between mean pulmonary arterial pressure and peak \( V_O_2 \) \( (r = -0.61, p < 0.05) \), and a positive correlation between mean pulmonary arterial pressure and the \( V-E-V_O_2 \) slope \( (r = 0.45, p < 0.05) \). Peak \( V_O_2 \) and \( V-E-V_O_2 \) slope were correlated with cardiac output \( (r = 0.50 \text{ and } r = -0.45, \text{ both } p < 0.05) \); however, neither was significantly correlated with pulmonary capillary wedge pressure \( (r = -0.26; r = 0.35, \text{ both } NS) \).

TIME COURSE OF EXERCISE CAPACITY AND VENTILATORY EFFICIENCY

Pulmonary thromboendarterectomy caused an early improvement in haemodynamic responses: mean pulmonary artery pressure and pulmonary vascular resistance were notably decreased, while cardiac output was increased (Table 2). The \( V-E-V_O_2 \) slope decreased from baseline to the early phase \( (30 (9) \text{ to } 37 (7), p < 0.05, \text{ fig 2}) \) and reached a steady level thereafter, at around 33 (5). In contrast, a continued increase in peak \( V_O_2 \) was noted from baseline to the early phase, as well as from the early phase to the late phase \( (\text{baseline, 12.1 (3.6) ml/kg/min; early phase, 16.9 (4.1) ml/kg/min; late phase, 21.1 (5.0) ml/kg/min; fig 2}) \).

CHANGES IN EXERCISE CAPACITY AND VENTILATORY EFFICIENCY AND HAEMODYNAMIC IMPROVEMENTS

After thromboendarterectomy, there was no correlation between peak \( V_O_2 \) and pulmonary vascular resistance \( (r = -0.41, p = 0.07) \). In contrast, there was still a positive correlation between the \( V-E-V_O_2 \) slope and pulmonary vascular resistance \( (r = 0.54, p < 0.05) \). The increase in peak \( V_O_2 \) from baseline to the early phase did not correlate significantly with the decrease in pulmonary vascular resistance \( (r = 0.42, p = 0.06, \text{ fig 3}) \). However, the decrease in the \( V-E-V_O_2 \) slope from baseline to the early phase correlated strongly with the decrease in pulmonary vascular resistance \( (r = 0.75, p < 0.001) \). There were no correlations between changes in cardiac output and either peak \( V_O_2 \) or \( V-E-V_O_2 \) slope \( (r = 0.16; r = 0.35, \text{ both } NS) \).

Table 2  Haemodynamic variables before and after thromboendarterectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP (mm Hg)</td>
<td>44 (10)†</td>
<td>19 (6)*</td>
</tr>
<tr>
<td>sPAP (mm Hg)</td>
<td>81 (17)</td>
<td>32 (10)*</td>
</tr>
<tr>
<td>PVR (dynes.s.cm⁻¹)</td>
<td>916 (335)</td>
<td>212 (141)*</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.3 (0.7)</td>
<td>4.6 (1.4)*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>8 (3)</td>
<td>8 (6)</td>
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<td>RAP (mm Hg)</td>
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Values are mean (SD).

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Values are mean (SD).

† p < 0.05 v before surgery.

CO, cardiac output; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; sPAP, systolic pulmonary arterial pressure.
Exercise capacity after pulmonary thromboendarterectomy

Discussion

There is little information about the acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with CTEPH. In the present study we showed first, that baseline peak VO₂ decreased and the VE-VCO₂ slope increased in parallel with an increase in pulmonary vascular resistance in patients with CTEPH; second, that the VE-VCO₂ slope decreased significantly from baseline to the early phase after thromboendarterectomy and reached a steady level thereafter, whereas there was a continuous increase in peak VO₂ from baseline to the late phase; and third, that the decrease in the VE-VCO₂ slope from baseline to the early phase, but not the increase in peak VO₂, correlated strongly with the decrease in pulmonary vascular resistance after surgery. Thus exercise capacity and ventilatory efficiency may represent differing responses after thromboendarterectomy, as indicated by peak VO₂ and the VE-VCO₂ slope. We noted a continued increase in peak VO₂ from the early to the late phase after surgery, as well as from baseline to the early phase, suggesting that exercise capacity may continue to improve toward the late phase after thromboendarterectomy. These results support an earlier report that patients who underwent thromboendarterectomy showed continued improvement in quality of life over several months. Surprisingly, the increase in peak VO₂ after surgery did not correlate with the decrease in pulmonary vascular resistance. Peak VO₂ is influenced not only by cardiac output during exercise, but also by oxygen extraction in skeletal muscles and vasodilatation of the nutrient arterioles within working skeletal muscles. Thus peripheral adaptation to exercise in the late phase, as well as haemodynamic improvement in the early phase, may contribute to the increase in peak VO₂ and the improvement in exercise capacity after surgery. The baseline VE-VCO₂ slope was higher in patients with CTEPH than in healthy subjects, suggesting the presence of an exaggerated ventilatory response to exercise (impaired ventilatory efficiency) in patients with CTEPH. One of the possible reasons for the increased ventilatory response during exercise could be the presence of significant ventilation–perfusion mismatch. In the present study, the VE-VCO₂ slope decreased significantly from baseline to the early phase after thromboendarterectomy and reached a steady level thereafter. In addition, the decrease in the VE-VCO₂ slope correlated strongly with the decrease in pulmonary vascular resistance. Thus we first demonstrated that unlike exercise capacity, the ventilatory efficiency was rapidly improved after thromboendarterectomy in association with acute haemodynamic changes. These results are consistent with recent reports that some vasodilators improve ventilatory efficiency in association with the reduction in pulmonary vascular resistance. Considering that lung perfusion scans and pulmonary angiography show major improvements in pulmonary perfusion after thromboendarterectomy, it is possible that the decrease in the VE-VCO₂ slope may result from a decrease in physiological dead space caused by improvement in the ventilation to perfusion ratio. In contrast, the VE-VCO₂ slope did not change from the early to the late phase after surgery. In the present study, right heart catheterisation was not performed in the late phase. However, it is well known that both pulmonary vascular resistance and angiographic findings are unaltered during a follow up period ranging from 3–16 months after surgery, which may be responsible for the lack of change in the VE-VCO₂ slope in the late phase after surgery.

CLINICAL IMPLICATIONS

Cardiopulmonary exercise testing may allow non-invasive and relatively inexpensive assessments of exercise capacity and ventilatory response to exercise in patients with CTEPH. Baseline peak VO₂ decreased and the VE-VCO₂ slope increased in relation to the degree of pulmonary vascular resistance. In addition, the immediate postoperative improvement in pulmonary vascular resistance was reflected by the decrease in the VE-VCO₂ slope. Peripheral adaptation to exercise in the late phase is likely to parallel the increase in peak VO₂. Thus the
combined measurement of peak VO\textsubscript{2} (exercise capacity) and the VO\textsubscript{2}-V\textsubscript{CO\textsubscript{2}} slope (ventilatory efficiency) may serve as a non-invasive indicator of the severity of CTEPH and of the likely efficacy of surgical treatment.

CONCLUSIONS
Pulmonary thromboendarterectomy may result in an immediate improvement in ventilatory efficiency, probably through its beneficial haemodynamic effects. In contrast, exercise capacity may continue to improve toward the late phase, and this improvement may be related to peripheral adaptation to exercise.


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