

Results of one-year anticoagulation in patients with newly detected chronic thromboembolic pulmonary hypertension not treated with pulmonary endarterectomy

Renata Romaszkiwicz, Jerzy Lewczuk, Piotr Piszko, Jacek Jagas,
Lucyna Lenartowska, Bartosz Ludwik, Wiesława Sawa, Krzysztof Wrabec

Department of Cardiology, Regional Specialistic Hospital, Wrocław, Poland

Abstract

Introduction: Currently pulmonary endarterectomy is considered the method of choice in patients with chronic thromboembolic pulmonary hypertension (CTEPH). It is not known if this option should be recommended in all suitable patients as it is highly variable with respect to prognosis. There is also doubt about selection of adequate time to refer patients with CTEPH for surgery.

Aim: To establish whether some patients with CTEPH may clinically benefit from isolated anticoagulation with drugs and if the use of anticoagulation may have any impact on the time of patient referral for pulmonary endarterectomy.

Methods: The prospective analysis involved 29 patients (9 male, 20 female) aged 37 to 82 years, with pulmonary arterial systolic pressure ranging from 39 to 133 mmHg and newly diagnosed CTEPH who had not been treated with pulmonary endarterectomy and were not receiving anticoagulation. Survival, functional status according to NYHA classification, duration of thromboembolism, exercise tolerance and echocardiographic parameters of right ventricular overload before and at one year after initiation of therapy with anticoagulants were evaluated.

Results: During follow-up, 3 patients with PASP ranging from 120 to 133 mmHg died. In 26 patients with PASP 39–115 mmHg, who survived, improvement in echocardiographic parameters of right ventricular overload, better exercise tolerance as well as functional status according to NYHA classification was observed. In 12 survivors, pulmonary pressure returned to normal.

Conclusions: The results of this study suggest that favourable effects of isolated anticoagulation are likely in patients with newly detected CTEPH, mild and moderate baseline pulmonary hypertension and acceptable exercise tolerance. They also indicate the necessity of anticoagulation in these patients prior to possible referral for pulmonary endarterectomy.

Key words: chronic thromboembolic pulmonary hypertension, anticoagulation, pulmonary endarterectomy

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH), a relatively rare complication of acute pulmonary embolism (APE), significantly impairs quality of life of affected patients and has an unfavourable impact on their prognosis. The current treatment of choice is pulmonary endarterectomy,

which is associated with lower operative mortality and favourable long-term prognosis [1, 2]. Most experts share the opinion that the operation should be performed as soon as possible after the diagnosis is established and also in patients with mild pulmonary hypertension and low class according to NYHA [3]. However, in clinical practice there are some doubts

Address for correspondence:

Jerzy Lewczuk MD, Oddział Kardiologii, Wojewódzki Szpital Specjalistyczny, ul. Kamińskiego 73a, 51-124 Wrocław,
tel./fax: +48 71 325 39 44, e-mail: lewczuk@wssk.wroc.pl

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about these indications and adequate time of patient referral for surgery [4]. The results of previously published studies suggest favourable outcomes in such patients receiving only treated medical therapy [5, 6].

The purpose of this study was to assess survival, changes of the echocardiographic parameters of right ventricular overload as well as functional NYHA class and exercise tolerance in patients with newly diagnosed CTEPH who were treated with anticoagulation instead of surgical pulmonary endarterectomy.

Methods

Patients

The prospective, single centre, non-randomised study involved 29 consecutive patients with newly detected CTEPH (9 male, 20 female; aged 37-82 years) who neither received anticoagulation nor had undergone pulmonary endarterectomy. Patients were enrolled in this study while hospitalised at our ward, as well as regional cardiological, pulmonological and internal medicine departments. Diagnosis of CTEPH was established based on:

- a) history and clinical report analysis that indicated disorder duration of at least 6 weeks but without clinical features of recurrence [7],
- b) results of pulmonary angiography that revealed chronic embolisation of pulmonary vascular bed, and
- c) pulmonary hypertension evidence in the preliminary haemodynamic study of pulmonary circulation and/or in echocardiography.

In 24 patients pulmonary hypertension was defined as mean pulmonary arterial pressure (MPAP) >20 mmHg, while in 5 patients without invasive measurements it was defined as pulmonary arterial systolic pressure (PASP) >40 mmHg calculated in echocardiography [8]. Inclusion criteria comprised:

1. No comorbidities that could have any impact on mortality and examined parameters. Thus, each patient underwent history analysis and physical examination. In order to assess studied parameters chest X-ray, spirometric study, blood gas analysis and echocardiography as well as pulmonary angiography and haemodynamic study of pulmonary circulation were performed.
2. Availability of acquisition during measurements of pressure gradient across tricuspid valve in echocardiography.

Pulmonary endarterectomy was not performed because of concomitant peripheral embolism in 6 patients and proximal form of disease with mild pulmonary hypertension (MPAP <30 mmHg or PASP <50 mmHg) in 9 patients. Fourteen patients with proximal type of disease and severe pulmonary

hypertension (MPAP \geq 30 mmHg or PASP \geq 50 mmHg) refused the operation because of high surgical risk.

Informed written consent was obtained from all patients.

Management

An initial clinical examination involved functional status assessment according to NYHA classification, exercise tolerance evaluation by means of treadmill exercise test and measurements of right ventricular overload parameters using echocardiography. Then chronic oral anticoagulation with acenocumarol at dose adjusted to recommended INR between 2 and 3 was initiated. Efficacy of anticoagulation was monitored at the beginning and at the end of one-year follow-up. Moreover, we recommended that patients have INR checked at least once a month and to have medication dose adjusted according to general practitioner advice. Nobody had prescribed vasodilators or underwent venous filter implantation. Patients were obliged to inform their physicians about potential adverse events during therapy. In each patient, recurrence of APE or bleeding events was assessed.

Pulmonary angiography

Selective pulmonary angiography was carried out through ulnar or jugular vein puncture and was preceded by haemodynamic examination of the pulmonary circulation. Proximal pulmonary embolism was defined when obstruction involved the main pulmonary trunk, both pulmonary arteries and lobar as well as segmental vessels. Distal pulmonary embolism was detected if embolic changes were confined to the vessels located distally from segmentary pulmonary arteries. Changes were classified as "chronic" when they presented as blurred filling defects in the vessels that resulted in a decrease in or obstruction to flow and filling lesions in the form of irregular webs and bands.

Exercise test

Exercise tolerance was calculated during the maximum, symptom-limited treadmill test conducted according to the Bruce protocol. Maximum exercise capacity was measured using a Marquette Electronic Inc. device that automatically yielded results in METs (multiples of resting oxygen consumption) achieved during exercise.

Echocardiography

Transthoracic echocardiography was performed using Hewlett Packard 77020 equipped with a probe

of variable frequency. The following parameters were measured:

- 1) end-diastolic right ventricular dimension (RVED) in the substernal view,
- 2) end-diastolic left ventricular dimension (LVED) to receive RVED/LVED ratio,
- 3) maximum pressure gradient across tricuspid valve in order to calculate PASP according to modified Bernoulli equation, assuming the presence of constant pressure in the right atrium equal to 10 mmHg [9], and
- 4) acceleration time of flow in the pulmonary artery (AcT).

Statistical analysis

Examined parameters calculated at baseline and after one year of follow-up in the whole group and at baseline in particular subgroups were compared using Student's t-test. A value of $p < 0.05$ was considered statistically significant.

Results

Pulmonary angiography revealed bilateral chronic pulmonary embolism, located proximally in 23 and distally in 6 patients. The MPAP values, calculated automatically during haemodynamic examination of pulmonary circulation, performed in 24 patients, ranged from 20 to 54 mmHg. In 5 patients without haemodynamic examination, PASP evaluated in echocardiography was 43 to 93 mmHg. Duration of pulmonary thromboembolism ranged from approximately 6 months to 2 years. Previously undetected APE incident initiating development of CTEPH was noted in 6 patients. In the remainder in whom it was not possible to reveal a symptomatic APE event in the past, onset of CTEPH development was defined as the time of onset of exertional dyspnoe. Clinical characteristics of patients with CTEPH are presented in Table I.

Twenty-six patients survived one year. Three patients died due to progressive right ventricular failure. Autopsies were not performed. Non-survivors had in the baseline examination RASP as high as 120, 127 and 133 mmHg, respectively (Figure 1) and all of them were found in NYHA

Table I. Characteristics of studied patients

Parameters	
Age (years)	60±13 (37-82)
PASP (mmHg)	67.3±29.1 (39-133)
RVED/LVED	0.66±0.2 (0.32-1.4)
AcT (ms)	63.2±14.8 (40-90)
Exercise time (min: s)	6:37±3:45 (1:30-15:32)
METs	3.82±2.3 (2-10)
Thromboembolism duration time (months)	6.74±3.4 (6-24)

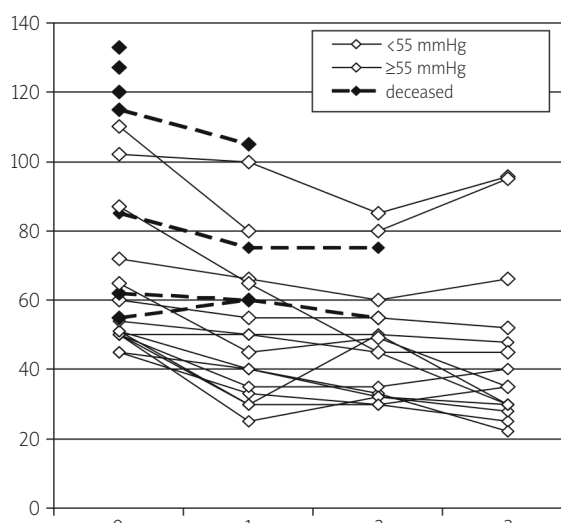


Figure 1. Individual values of PASP at baseline and after one-year follow-up

functional class III or IV, and reached 2 METs during treadmill exercise test. Changes of echocardiographic parameters, exercise tolerance before and after one year of follow-up in 26 survivors are outlined in Table II.

In 12 out of 26 survivors, pulmonary pressure regressed to normal values within one year. Table III presents comparative characteristics of 12 patients with

Table II. Examined parameters in 26 patients who survived one year, before and at the end of 12-month therapy with oral anticoagulant

Parameter	Before	After one-year follow-up	p
PASP (mmHg)	60.5±21.8	49.4±21.7	0.00001
RVED/LVED	0.6±0.2	0.5±0.2	0.01
AcT (ms)	65.2±14.5	87.2±20.2	0.00001
METs	4.0±2.3	4.7±2.6	0.03
Exercise time (min: s)	07:06±03:40	08:10±04:03	0.02

Table III. Comparison of clinical and echocardiographic parameters between patients with normalisation of pulmonary hypertension (n=12) and survivors with preserved pulmonary hypertension (n=14)

Parameter	PASP \leq 40 mmHg after one-year follow-up n=12	PASP $>$ 40 mmHg after one-year follow-up n=14	p
Age (years)	61.9 \pm 12.5	61.1 \pm 12.4	NS
PASP (mmHg)	39.0 \pm 8.4	68.6 \pm 21.4	0.03
RVED/LVED	0.45 \pm 0.1	0.68 \pm 0.2	0.03
AcT (ms)	87.7 \pm 20.1	67.1 \pm 16.2	0.005
METs	4,0 \pm 1,98	4,7 \pm 2,8	NS
Exercise time (min: s)	07:22 \pm 03:14	07:51 \pm 04:22	NS
Mean annual INR	2.22 \pm 0.35	2.26 \pm 0.58	NS
Duration of thromboembolism (months)	6.84 \pm 2.7	6.48 \pm 4.4	NS

normal pulmonary pressure at the end of one-year follow-up and 14 subjects without pulmonary arterial pressure normalisation. The INR values throughout one-year follow-up ranged from 1.0 to 3.84, and mean annual INR 2.28 \pm 0.51 was within the recommended therapeutic range (INR 2-3). Results of functional assessment according to NYHA classification at baseline and after one year of follow-up are shown in Table IV. During one-year follow-up, no patients presented symptoms suggesting recurrent APE or bleeding.

Discussion

Prevalence of CTEPH has not been established so far. Although incidence of this disease is usually reported from 0.1% to 0.5%, recently Pengo et al. reported the cumulative incidence of 3.8% in two-year follow-up in patients who experienced an APE incident [10]. Therefore, the true prevalence may be much higher because many APE events are asymptomatic and diagnostic accuracy of currently used methods remains unsatisfactory [11, 12]. These observations were confirmed in our group of 29 patients with CTEPH including 5 in whom acute symptomatic embolic events were not properly diagnosed in the past, and in the remainder they were asymptomatic.

Table IV. Functional NYHA class in 29 patients with newly detected CTEPH before and at one year (12th month of anticoagulation)

Functional NYHA class	Number of patients	
	Before treatment	After one year of anticoagulation
II	3	16
III	20	7
III/IV	6	3 (3 deaths)

Prognosis, especially in the advanced stage of CTEPH, is poor. In patients with MPAP $>$ 30 mmHg 2-year mortality is 30% and 5-year approximately 55%. The worst prognosis was documented in patients with MPAP $>$ 50 mmHg with 2-year mortality of up to 80% [6]. It is widely accepted that first-line treatment in these patients is surgical pulmonary endarterectomy. Operative mortality decreased significantly to as low as 4.4% in the leading centres and 6-year survival following successful operation reached 75% [1, 2]. This is in contrast with medically treated CTEPH patients with averaged two-fold limitation of long-term survival in comparison to surgically treated individuals [6]. Moreover, nowadays surgical pulmonary endarterectomy may be performed relatively safely on a wide spectrum of patients, including those with concomitant disorders and peripheral lesions. Currently only comorbidities that significantly limit survival are considered contraindications to such surgical procedure [1, 3].

In clinical practice, many patients with CTEPH are not operated on. In individuals with thrombotic peripheral lesions, risk of operation increases [3]. Clinical observations indicate that not even all patients with localisation of lesions suitable for surgery should be exposed to the operative risk. This includes patients who present good exercise capacity and particularly those with mild or moderate pulmonary hypertension. Reports devoted to the assessment of prognosis of CTEPH patients suggest that it may be favourable in subjects treated medically with MPAP $<$ 50 mmHg who reached more than 2 METs in the exercise test [5, 6]. It seems that diseases coexisting with pulmonary thromboembolism may be responsible for poor prognosis in CTEPH patients treated medically. In the study reported by Pengo et al. that involved 223 patients with

mean follow-up of 94 months 21% of patients died because of reasons not related to thromboembolisation, mainly of cardiovascular disease and cancers [10]. In the study evaluating survival of CTEPH patients, neoplastic disorders and COPD were noted in only 16.3% but were responsible for 31.1% of deaths [5].

There are doubts concerning the optimal timing of CTEPH patients' referral for pulmonary endarterectomy. Ribeiro et al. found that detection of pulmonary hypertension 6 weeks or later after the embolic event identified patients at risk of CTEPH in spite of routine anticoagulation [7]. Thus, in some centres such patients presenting persistent pulmonary hypertension following APE are qualified for pulmonary endarterectomy [3]. In our group we observed that prolongation of anticoagulation up to one year after the APE event caused further decrease in arterial pulmonary pressure and even its normalisation within this period, as well as after 6 weeks [13]. These results are consistent with findings of the clinical study of Riedel, who recommended 6-month anticoagulation prior to surgical pulmonary endarterectomy in CTEPH patients [4].

The results of our study confirmed that prognosis was unfavourable in patients with severe pulmonary hypertension and poor exercise tolerance. Prior to surgery, three patients who died during follow-up as a result of rapid progression of right ventricular failure had PASP 120, 127 and 133 mm Hg, respectively, were found in NYHA functional class III/IV and reached only 2 METs in the baseline exercise test. Although these patients fulfilled criteria for pulmonary endarterectomy, they did not accept the risk of operation.

Twenty-six patients with lower PASP 39 – 115 mmHg survived one year of follow-up and presented significant improvement of studied echocardiographic parameters: decrease in pulmonary arterial pressure and improvement in other parameters of right ventricular overload. There was also significant improvement in exercise capacity as well as in most patients in functional status according to NYHA classification. Pulmonary hypertension diagnosed at baseline with echocardiography in 12 patients regressed to normal, i.e. to PASP <40 mmHg. Comparing patients with normalised PASP at the end of one-year anticoagulation to those without, we noted that the first group had less pronounced right ventricular overload at baseline. No differences with respect to age, exercise tolerance or pulmonary embolization duration were found.

Efficiency of anticoagulant therapy and associated complications could have an impact on the results of our study. However, mean annual INR was in the therapeutic range and the group of patients who presented pulmonary arterial pressure normalisation did not differ

with respect to the average annual INR value from patients with sustained pulmonary hypertension at the end of one-year follow-up. It is likely that due to careful INR monitoring and adjustment of oral anticoagulant dosage no evidence of bleeding or recurrence of APE was noted during one-year follow-up.

The reasons for such favourable one-year course of newly detected CTEPH are not completely clear. However, association with anticoagulation seems justified. A crucial role of thromboembolic processes at least in the early stage of CTEPH is suggested. Continuous and properly managed anticoagulation in these patients could beneficially modulate the course of the disease, preventing recurrence of embolic and thrombotic events "in situ" [14, 15]. Atheropatic changes might have already been sustained in three patients with very high baseline pulmonary pressure who died during follow-up, in whom anticoagulation was not able to favourably influence clinical status [16].

The results of our study, including spectacular pulmonary arterial pressures normalisation after one-year long anticoagulation in 12 patients with CTEPH, have practical clinical aspects. They support the opinion against early referral of patients with newly detected CTEPH and good exercise capacity without pronounced pulmonary hypertension for pulmonary endarterectomy. They are consistent with the opinion of Riedel et al. suggesting the necessity of anticoagulation prior to referral for surgery [4]. Simultaneously, the results of our observation impose urgent referral of CTEPH patients with pronounced pulmonary arterial pressure and poor exercise capacity for pulmonary endarterectomy.

Follow-up of clinical course of newly detected CTEPH limited to one year did not allow favourable long-term prediction in patients who presented improvement or normalisation of pulmonary hypertension during this period. The possibility that not all patients suitable for pulmonary endarterectomy must undergo this operation should be confirmed in further studies with longer follow-up. Our results also challenge the value of CTEPH diagnosis criteria. It may be so that CTEPH in patients with normalisation following anticoagulant therapy should be called persistent thromboembolic pulmonary hypertension.

Conclusions

The results of our study suggest that favourable prognosis after isolated anticoagulation is likely in patients with newly detected CTEPH, mild and moderate baseline pulmonary hypertension and acceptable exercise tolerance. They also indicate the necessity of anticoagulation in such patients prior to possible referral for pulmonary endarterectomy.

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Wyniki rocznej antykoagulacji chorych ze świeżo rozpoznanym przewlekłym zakrzepowo-zatorowym nadciśnieniem płucnym niepoddanych endarterektomii płucnej

Renata Romaszkiwicz, Jerzy Lewczuk, Piotr Piszko, Jacek Jagas,
Lucyna Lenartowska, Bartosz Ludwik, Wiesława Sawa, Krzysztof Wrabec

Oddział Kardiologii, Wojewódzki Szpital Specjalistyczny, Wrocław

Streszczenie

Wstęp: Endarterektomia płucna jest obecnie uważana za postępowanie z wyboru u chorych z przewlekłym zakrzepowo-zatorowym nadciśnieniem płucnym (CTEPH). Nie wiadomo jednak, czy należy ją zalecać u wszystkich dogodnych, ale znacznie zróżnicowanych rokowniczo chorych. Wątpliwości budzi też wybór terminu kierowania chorych z CTEPH na zabieg.

Cel: Ustalenie, czy niektórzy chorzy z CTEPH mogą odnieść korzyści kliniczne wyłącznie z leczenia antykoagulacyjnego i czy zastosowanie antykoagulacji może mieć wpływ na termin kierowania na zabieg endarterektomii płucnej.

Metoda: Przeprowadzono prospektywną obserwację 29 chorych (9 mężczyzn, 20 kobiet) w wieku 37–82 lat, ze skurczowym ciśnieniem w tętnicy płucnej (PASP) wahającym się od 39 do 133 mmHg, ze świeżo rozpoznanym CTEPH, niepoddanych endarterektomii płucnej i wcześniej nieantykoagulowanych. Oceniono przeżycie, zmiany klasy czynnościowej NYHA, czas trwania zatorowości, tolerancję wysiłku i echokardiograficzne parametry przeciążenia prawej komory przed i rok po antykoagulacji.

Wyniki: W czasie obserwacji wystąpiły 3 zgony chorych z wyjściowym PASP wahającym się od 120 do 133 mmHg. U 26 chorych z PASP od 39 do 115 mmHg, którzy przeżyli, obserwowano zmniejszenie się echokardiograficznych cech przeciążenia prawej komory serca, poprawę tolerancji wysiłku i klasy czynnościowej NYHA. U 12 z nich ciśnienie płucne się znormalizowało.

Wnioski: Wyniki badania sugerują możliwość korzystnego rokowania wyłącznie u antykoagulowanych chorych ze świeżo rozpoznanym CTEPH, łagodnym i umiarkowanym nadciśnieniem płucnym i dobrą tolerancją wysiłku. Przemawiają też za potrzebą przeprowadzenia u tych chorych antykoagulacji przed ewentualnym skierowaniem na zabieg endarterektomii płucnej.

Słowa kluczowe: przewlekłe zakrzepowo-zatorowe nadciśnienie płucne, leczenie przeciwzakrzepowe, endarterektomia płucna

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Adres do korespondencji:

dr hab. med. Jerzy Lewczuk, Oddział Kardiologii, Wojewódzki Szpital Specjalistyczny, ul. Kamieńskiego 73a, 51-124 Wrocław,
tel./faks: +48 71 325 39 44, e-mail: lewczuk@wssk.wroc.pl

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