Clinical course of unoperated mild chronic thromboembolic pulmonary hypertension

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Abstract

Background: Pulmonary endarterectomy is the treatment of choice for a majority of patients with chronic thromboembolic pulmonary hypertension (CTEPH), however, haemodynamic criteria for the surgery have not been established. It is still unknown whether patients with mild CTEPH should be operated on and what is the clinical course of unoperated, anticoagulated mild CTEPH.

Aim: To determine the clinical course in chronically anticoagulated, unoperated patients with mild CTEPH.

Methods: A single-centre, non-randomised, follow-up study involved 10 anticoagulated, unoperated patients (3 males and 7 females aged 46 to 77 years) with mild CTEPH (mean pulmonary artery pressure [MPAP] \leq 30 mm Hg and pulmonary vascular resistance \leq 300 dynes \times s \times cm⁻⁵, \geq 2 METs achieved during symptom limited treadmill exercise test) selected from 73 consecutive patients with CTEPH. The 3-year follow up included yearly echocardiographic evaluation of pulmonary artery systolic pressure (PASP), right ventricular end-diastolic diameter (RVEDD) and acceleration time (AcT) as well as NYHA functional class and symptom-limited treadmill exercise test.

Results: All the patients survived the 3-year follow-up. The PASP, RVEDD and AcT (mean \pm SD) at baseline and at the end of follow-up were 43.9 \pm 6.1 mm Hg and 25.6 \pm 8.0 mm Hg, p = 0.0017, 25.4 \pm 4.9 mm and 17.8 \pm 3.82 mm, p = 0.00006, 68.3 \pm 10.0 ms and 104.4 \pm 16.48 ms, p = 0.0004, respectively. The NYHA functional class improved from 2.1 \pm 0.32 to 1.3 \pm 0.48, p = 0.002 and was accompanied by the trend to improve results of exercise test.

Conclusions: The results of the study suggest that patients with mild CTEPH can be treated successfully by anticoagulation alone with excellent 3-year survival rate, improved functional status and with gradual decrease of pulmonary pressure and right ventricular overload.

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

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INTRODUCTION

Prognosis of patients with chronic thromboembolic pulmonary hypertension (CTEPH) is poor and pulmonary endarterectomy represents the treatment of choice in patients with proximal embolism [1, 2]. Haemodynamic criteria of patient selection for the procedure are not uniform, and the outcome of unoperated, anticoagulated patients with CTEPH and mean pulmonary arterial pressure (MPAP) < 30 mm Hg is fairly good, according to several earlier studies [3–5]. So far, the management of patients with mild CTEPH has not been unequivocally established. Some authors suggest, that patients with this type of CTEPH should not initially be operated on, but rather anticoagulated with regular clinical follow-up [5–7]. Little is known of the course of mild, unoperated, anticoagulated CTEPH.

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METHODS

A prospective, single-centre, nonrandomised observation of 10 patients (3 men, 7 women aged 46–77 years) with recently diagnosed mild CTEPH was carried out. The patients were selected from a group of consecutive CTEPH patients hospitalised between January 2004 and March 2007. The diagnosis of CTEPH was based on history, pulmonary angiography and haemodynamic study. The disease was defined as MPAP \geq 25 mm Hg and pulmonary capillary wedge pressure < 15 mm Hg in patients with exertional dyspnea for at least 3 months. Mild CTEPH criteria included MPAP \leq 30 mm Hg and pulmonary vascular resistance (PVR) \leq 300 dynes \times s \times cm⁻⁵. None of these patients had a history of overt and treated episode of venous thromboembolism.

In none of the patients significant comorbidities were found, that could have influenced the severity of pulmonary hypertension, based on history, clinical examination, chest X-ray, spirometry, blood gases, blood chemistry, echocardiography and cardiac catheterisation. In every patient trans-tricuspid pressure gradient was obtained on Doppler echocardiography. Patients expressed their informed consent in writing, and the local bioethical committee approved the study.

After initial examination, a 3-year follow-up was planned in each patient, with yearly clinical reassessment, treadmill exercise tolerance test, functional NYHA class and echocardiographic evaluation of pulmonary artery systolic pressure (PASP), right ventricular end-diastolic dimension (RVEDD) and pulmonary flow acceleration time (AcT). Recurrent venous thromboembolic episodes, bleeding, cardiac and pulmonary disease and neoplasmatic disease were also analysed. Patients were receiving life-long treatment with oral anticoagulants with recommendation of dose sufficient to keep international normalised ratio (INR) between 2.0 and 3.0. The dosage was then modified by a family physician on a monthly basis and once a year in-hospital at the follow-up visit. No patient was receiving vasodilators aiming at the pulmonary vasculature or had venous filter implanted. The probability of pulmonary embolism recurrence was defined as clinical probability of the event which could not be excluded based on d-dimer testing.

Procedures

Pulmonary angiography was preceded by right heart and pulmonary artery catheterisation. Proximal pulmonary embolism was detected if chronic thromboembolic changes were found in main, lobar and segmental branches. Peripheral pulmonary embolism was diagnosed if thromboembolic changes were found in peripheral vessels, distal to the segmental branches. Exercise tolerance was assessed during the maximal, symptom-limited treadmill test according to the Bruce protocol. Maximal exercise capacity was calculated in an automated manner by the device (Marquett Electronic Inc.), producing results as the number of METs achieved during exercise. Transthoracic echocardiography was performed with use of the Vivid 7 or Vivid 3 system equipped with multifrequency transducer. The RVEDD was measured from the M-mode recording and AcT was obtained from pulsed wave Doppler measurement of flow in the right ventricular outflow tract. Maximal velocity of the tricuspid regurgitation was measured by continuous wave Doppler and PASP was calculated by the modified Bernoulli rule, assuming constant right atrial pressure at the level of 5 mm Hg.

Statistical analysis

The analysis was carried out with Statistica[®] 6.0 package (Stat Soft, Inc., Tulsa, USA). Data were expressed as means \pm SD. The Shapiro-Wilk test was used to check for the normality of data distribution. Homogeneity of variance was verified with Brown and Forsythe test. Depending on the result, Student t test for homogenous variance or its counterpart for nonhomogenous variance were used. Whenever parametric tests were not applicable, the non-parametric Mann Whitney U test was applied. Analysis of variance (ANOVA) was used for measurement testing on three or more data groups. In cases where the null hypothesis on group equality was rejected, the Bonferroni test was used as the *post-hoc* test.

RESULTS

Pulmonary angiography showed chronic bilateral proximal thromboembolic changes in 4 patients and distal changes in 6 patients. The MPAP values in the haemodynamic study were between 25 and 30 mm Hg. The estimated CTEPH duration was 3 months to 2 years. Baseline characteristics and haemo-dynamic data are presented in Tables 1 and 2. All the patients survived the 3-year follow-up period. The PASP and RVEDD values assessed by echocardiography were gradually decreasing and AcT increased in all patients during follow-up. All patients experienced NYHA class improvement of at least 1 class. The results of the echocardiographic assessment, treadmill test, and NYHA functional class at baseline and at

Table 1	 Characteristics of 	f the 10 p	patients with	mild CTEPH
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Parameter	Mean ± SD	Range
Age [years]	63.7 ± 11.8	46–77
MPAP [mm Hg]	27.7 ± 1.6	25–30
PASP [mm Hg]	43.9 ± 6.08	35–58
RVEDD [mm]	25.4 ± 4.9	16–30
AcT [ms]	68.3 ± 10	50–85
METs [number]	4.2 ± 1.48	2–6
NYHA class	2.1 ± 0.32	2–3

AcT — pulmonary artery flow acceleration time; CTEPH — chronic thromboembolic pulmonary hypertension; METs — multiplicity of the resting oxygen consumption; MPAP — mean pulmonary artery pressure on echocardiography; PASP — pulmonary artery systolic pressure on echocardiography; RVEDD — right ventricular end-diastolic dimension

ID	Sex	Age	MPAP	PVR	PCWP	Cardiac index
		[years]	[mm Hg]	[dynes × s × cm ⁻⁵]	[mm Hg]	[L/min/m²]
1	Male	76	25	160	13	2.7
2	Female	49	25	170	8	3.2
3	Female	46	27	200	10	2.5
4	Female	72	28	212	13	2.5
5	Female	56	28	220	8	2.8
6	Female	68	28	230	12	2.7
7	Female	56	28	280	12	2.3
8	Male	71	29	250	11	2.9
9	Male	77	29	210	10	3
10	Female	66	30	300	14	2.2

Table 2. The results of baseline pulmonary haemodynamic study in 10 patients with mild CTEPH

PCWP — pulmonary capillary wedge pressure; PVR — pulmonary vascular resistance; rest abbreviations as in Table 1

Table 3. The PASP, METs, RVEDD, AcT and NYHA functional class results at baseline and during the 3-year follow-up in 10 patients with mild CTEPH

Parameter	Baseline	At 1 year	At 2 years	At 3 years	Р
PASP [mm Hg]	43.9 ± 6.1	30.6 ± 9.6	$\textbf{32.0} \pm \textbf{8.8}$	25.6 ± 8.0	0.0017
METs [number]	4.2 ± 1.48	5.2 ± 2.35	4.6 ± 1.65	4.5 ± 1.43	0.2
RVEDD [mm]	25.4 ± 4.9	20.3 ± 4.92	18.5 ± 4.35	17.8 ± 3.82	0.00006
AcT [ms]	68.3 ± 10.0	93.4 ± 13.73	95.6 ± 17.4	104.4 ± 16.5	0.0004
NYHA class	2.1 ± 0.32	1.7 ± 0.48	1.7 ± 0.48	1.3 ± 0.48	0.002

Abbreviations as in Table 1

the yearly visits 1, 2 and 3 are presented in Table 3 and Figures 1 and 2.

The INR values during follow up were between 1.09 and 3.07. Mean INR value was within the therapeutic range (2.0–3.0) in all patients. Only probable pulmonary thromboembolic episodes were observed in 3 patients, none of them fatal. A single case of small bleeding was recorded during follow-up.

DISCUSSION

The CTEPH is a rare condition, although it is more common than it was earlier believed. Its etiopathogenesis was not completely elucidated but it seems that thromboembolic process plays a central role [8]. Apart from cases that are a consequence of an acute thromboembolic episode [9], many others, just as in our study group, result from asymptomatic or symptomatic but unrecognised and non-anticoagulated thromboembolic events [10, 11].

For the majority of CTEPH patients pulmonary endarterectomy is the treatment of choice. Peri-operative mortality has been reduced to 4.4% [1] and 75% of the patients survive 6 years post-intervention, whereas the same proportion of



Figure 1. Pulmonary artery systolic pressure (PASP) on echocardiography during the 3-year follow-up in 10 patients with mild chronic thromboembolic pulmonary hypertension

medically treated patients survive only 3 years [6, 7]. Results of the last two studies, however, showed that the prognosis



Figure 2. The NYHA functional class during the 3-year follow-up of 10 patients with mild chronic thromboembolic pulmonary hypertension

of unoperated patients with MPAP < 30 mm Hg and preserved exercise capacity is fairly good. Haemodynamic criteria of patient selection for the operation are not uniform and usually include PVR > 300 dynes \times s \times cm⁻⁵ or MPAP > 30 mm Hg[12, 13] and in some centres MPAP > 40 mm Hg [14]. Clinical practice shows that also patients below these thresholds, i.e. with low MPAP and low PVR are operated on, as a prevention of the pulmonary vasculature remodelling and disease progression, whereas others receive anticoagulation and avoid exposition to peri-operative risks.

To the best of our knowledge this is the first long-term and comprehensive observation of the natural history of unoperated, anticoagulated patients with mild CTEPH. We found that all patients with MPAP < 30 mm Hg and PVR < < 300 dynes × s × cm⁻⁵ who achieved \geq 2 METs at baseline, survived the 3-year follow-up and improved their NYHA status. These clinical benefits were reinforced by the gradual decrease of pulmonary arterial pressure observed in all the patients. Apart from one patient, PASP dropped to values below 36 mm Hg i.e. to the range which corresponds to "pulmonary hypertension unlikely" category as defined by the recent ESC and ERS guidelines [9]. The decrease of pulmonary pressure was accompanied by reduction of right ventricular pressure overload on echocardiography and a trend for increase of METs achieved on treadmill.

The results of our observation of patients with mild CTEPH not related to any identifiable thromboembolic episode treated with anti-thrombotic medication are concordant with earlier long-term studies of patients with mild and moderate CTEPH related to clinically overt and anticoagulated thromboembolic episode. Riedel et al. [3] found that in patients with MPAP < 30 mm Hg, severe pulmonary hypertension does not develop and that their 10-year survival is as high as 80%. Another study by our group showed favourable prognosis of patients with MPAP < 30 mm Hg who achieved > 2 METs during symptom-limited exercise test. Mortality analysis of the group demonstrated that none of the 3 deaths was related to CTEPH progression but was due to chronic obstructive pulmonary disease progression (2 cases) or fatal thromboembolism recurrence (1 case). In another 1-year observation of CTEPH patients by our group, favourable course of the disease of patients with mild pulmonary hypertension and good exercise tolerance was confirmed [5]. In the present study, all the patients achieved at least 2 METs at baseline, had no comorbidities and well controlled anticoagulation was the reason that only 2 probable recurrent thromboembolic episodes were recorded during follow-up [4].

The reason why mild CTEPH has such a favourable course is not clear but seem to be related to anticoagulation initiation at an early stage of the disease. All the patients, however, were past the "honeymoon" period, demonstrating progressive exertional dyspnea lasting for 3 months to 2 years. Our results point to a major role of thromboembolic process at least at early stages of CTEPH development. It is possible that continuous anticoagulation can diminish the number and clinical significance of asymptomatic thromboembolic episodes, that can deteriorate the course of CTEPH. Moreover, the role of anticoagulation in prevention of *in-situ* thrombosis should not be underestimated [15–17]. Early diagnosis is the most important prerequisite of successful treatment.

Limitations of the study

Conclusions of our study are limited by a small number of patients included. Moreover, pulmonary pressure was assessed by haemodynamic study only at baseline. For pulmonary artery pressure changes during 3-year follow-up echocardiography was used. Echocardiography is a very good method of noninvasive pulmonary artery pressure assessment in patients in whom trans-tricuspid gradients are measurable, yet it can underestimate the values obtained in the haemodynamic study [18]. Moreover, there are discrepancies concerning upper limits of normal PASP values [10].

CONCLUSIONS

In summary, our study demonstrated favourable long-term course of mild CTEPH, i.e. in anticoagulated, unoperated patients with MPAP \leq 30 mm Hg, with PVR \leq 300 dynes × × s × cm⁻⁵ and achieving at least 2 METs on treadmill. The results of our observation, being in concordance with the commonly accepted major criteria for patient selection for pulmonary endarterectomy in CTEPH, suggest that these patients do not need to be exposed to the operative risks. We believe

that as soon as the diagnosis is made, anti-thrombotic treatment should be implemented and that these patients should be regularly followed-up with echocardiography, NYHA functional class and exercise tolerance assessment. Our results should be confirmed in a longer prospective observation of a greater number of patients with mild CTEPH, randomised for conservative or surgical treatment.

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Conflict of interest: none declared

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Przebieg kliniczny nieoperowanego, łagodnego, przewlekłego zakrzepowo--zatorowego nadciśnienia płucnego

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Streszczenie

Wstęp: Endarterektomia płucna jest leczeniem z wyboru u większości chorych z zakrzepowo-zatorowym nadciśnieniem płucnym (CTEPH), jednak hemodynamiczne kryteria doboru do tego zabiegu nie są w pełni ustalone. W praktyce klinicznej operuje się pacjentów ze stosunkowo niskimi wartościami nadciśnienia płucnego i oporów płucnych w celu zapobieżenia remodelingowi naczyń płucnych i progresji schorzenia, podczas gdy inni chorzy są poddani wyłącznie antykoagulacji i nie są narażani na ryzyko operacji.

Cel: Celem pracy było ustalenie przebiegu klinicznego u nieoperowanych chorych z łagodnym CTEPH, poddanych przewlekłej antykoagulacji.

Metody: Trzyletnia jednoośrodkowa, nierandomizowana obserwacja 10 nieoperowanych, poddanych antykoagulacji chorych (3 mężczyzn i 7 kobiet w wieku 46–77 lat) z łagodnym CTEPH, tj. ze średnim ciśnieniem płucnym (MPAP) \leq 30 mm Hg i naczyniowym oporem płucnym (PVR) \leq 300 dyn × s × cm⁻⁵ oraz \geq 2 METs uzyskanych w czasie ograniczonego objawami testu wysiłkowego na bieżni Marquetta, wybranych z grupy 73 kolejnych pacjentów z CTEPH. Obserwacja obejmowała coroczną ocenę echokardiograficznie ocenionego skurczowego ciśnienia w tętnicy płucnej (PASP), końcoworozkurczowego wymiaru prawej komory (RVEDD), czasu przyspieszenia przepływu w tętnicy płucnej (ACT), klasy czynnościowej wg NYHA oraz tolerancji wysiłku za pomocą testu wysiłkowego na bieżni Marquetta. Ponadto u każdego chorego wykluczono inne niż CTEPH przyczyny nadciśnienia płucnego i regularnie kontrolowano leczenie przeciwzakrzepowe.

Wyniki: Wszyscy pacjenci przeżyli 3-letni okres obserwacji. Wartości PASP, RVEDD i AcT (średnia \pm SD) w badaniu wstępnym i na koniec obserwacji wynosiły odpowiednio 43,9 \pm 6,1 mm Hg i 25,6 \pm 8,0 mm Hg (p = 0,0017), 25,4 \pm 4,9 mm i 17,8 \pm 3,82 mm (p = 0,0006), 68,3 \pm 10 ms i 104,4 \pm 16,48 ms (p = 0,0004). Klasa wg NYHA poprawiła się z 2,1 \pm 0,32 do 1,3 \pm 0,48 (p = 0,002) i obserwowano trend do zwiększenia liczby METs osiągniętych podczas ograniczonego objawami testu wysiłkowego — z 4,2 \pm 1,48 do 4,5 \pm 1,43 (p = NS).

Wnioski: Wyniki obserwacji sugerują, że chorzy z łagodną postacią CTEPH, niespełniający zasadniczych kryteriów kwalifikacji do endarterektomii płucnej mogą być leczeni tylko antykoagulacyjnie, ze 100-procentowym 3-letnim przeżyciem, poprawą stanu czynnościowego oraz ze stopniowym zmniejszeniem nadciśnienia płucnego i przeciążenia prawej komory. Badanie echokardiograficzne, ocena klasy wg NYHA i tolerancji wysiłku mogą być pomocne w monitorowaniu tych chorych i podjęciu decyzji o sposobie leczenia.

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

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