Thrombophilia and Pulmonary Endarterectomy

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Abbreviations: ACT – activated clotting time; AFS – antifospholipid syndrom; CAD – coronary artery disease; CI – cardiac index; CPB – cardiopulmonary bypass; CTEPH – chronic thromboembolic pulmonary hypertension; CVVH – continual veno/venous hemofiltration; DHCA – deep hypothermic circulatory arrest; HIT – heparin induced trombocytopenia; mPAP – main pulmonary artery pressure; MTHFR – Methylenetetrahydrofolate Reductase; NYHA – New York Heart Association classification; PEA – pulmonary endarterectomy; PVR – pulmonary vascular resistance; TED – thromboembolic disease; 6MWT – six minute walking test

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Abstract: In the present study, we compared groups of patients with and without thrombophilia, who underwent pulmonary endarterectomy (PEA), definitive treatment for chronic pulmonary hypertension resulting from thromboembolic disease.

Methods and Patients: Between September 2004 and June 2007, we operated 54 patients with CTEPH. We divided our patients into three groups. Group I patients, had one or more signs of serious thrombophilia (15 patients), Group II patients, had no signs of thrombophilia (23 patients without thrombophilia and without Methylenetetrahydrofolate Reductase (MTHFR)), and Group III patients with MTHFR (16 patients with MTHFR only, without any serious thrombophilia).

Results: After the surgery, there was a statistically considerable improvement of hemodynamic parameters (mPA, CI, PVR) in all groups, without a statistical difference between the groups. Comparison of all these groups showed more complications in-group I (thrombophilia), in particular reperfusion oedema, pericardial effusion, and renal insufficiency.

Within one month, there was a considerable improvement or normalisation of haemodynamic parameters, an increase in walking distance at the six-minute walking test, and NYHA classification with no significant difference between the three groups.

Conclusions: Early hemodynamic results of patients with thrombophilia after PEA, were comparable to the results of patients without thrombophilia, when we looked at both clinical and hemodynamic improvements. We did not find any differences when we looked at the results between Group II and Group III (MTHF), when we considered the number and type of complications.

Patients with thrombophilia in Group I had statistically higher morbidity, especially when it came to a higher number of reperfusion oedema, pericardial effusion, and renal insufficiency.

Introduction

The aim of the present study was to compare groups of patients with and without thrombophilia who underwent pulmonary endarterectomy (PEA).

Pulmonary endarterectomy is now recognized as the definitive treatment for chronic thromboembolic pulmonary hypertension and can be performed with an acceptable risk of death. [1, 2]. Although the procedure is curative and in experienced hands carries low mortality and morbidity, it is performed only rarely. The problem is the fact that CTEPH is significantly under-recognized, and commonly misdiagnosed, and treated for a variety of other conditions.

For precise diagnosis and the correct treatment, it is very important to examine all risk factors of thromboembolism. One of the most important risk factors is hypercoagulability, as was recognized by Virchow in 1846. In our Center of pulmonary hypertension, we examined all patients with pulmonary hypertension, and genetically screened them for coagulations.

So far, there have been only a few reports of surgically treated patients with chronic thromboembolic pulmonary hypertension (CTEPH) and thrombophilia. [3, 4]

Chronic pulmonary thromboembolia develops without apparent cause in many patients, but in some of them, it is caused by blood coagulation abnormalities. The most common blood coagulation abnormalities in patients with CTEPH are antiphospholipid syndrome, protein C and S deficiency, mutation of factor V Leiden, prothrombin G20210A mutation, antithrombin deficiency and hyperhomocysteinemia [5]. Methylenetetrahydrofolate Reductase (MTHFR) gene mutation is diagnosed most often, but it is now not considered related to venous thrombosis, although this view is controversial [6, 7].

In a US PEA study, thrombophilia was found in 10% of patients [8], while in a Japanese studies, thrombophilia was found in Masuda study in 32% [9] and in Ogino study in13.6% [10] and finally, in our study, it was found in 27.8% of patients.

Methods and Patients

Between September 2004 and June 2007, we operated on 54 patients with CTEPH (34 males and 20 females; the average age was 55 years).

Incidence of thrombophilia in PEA patients and in normal Kazakhs population we can see in Table 1. We divided our patients into three groups. Group I patients with one or more serious thrombophilic risk factors (15 patients), Group II patients without thrombophilia (23 patients without thrombophilia without MTHFR) and Group III patients MTHFR (16 patients with MTHF only, without any serious thrombophilia).

Epidemiologic and demographical data in all groups of patients are summarized in Table 2. The mean pressure in the pulmonary artery (mPA) was 57 mmHg, and pulmonary vascular resistance (PVR) was 970 dynes.s-1.cm-5 and Cardiac Index (CI) was 2.0±0.45, without statistical differences in haemodynamic parameters in all three groups.

Table 1 – Incidence of thrombophilia in PEA patients

	Patients N=54	Patients %	Population Incidence %
AFS	4	7.4	2.0
F V Leiden	5	9.26	4.8
F II (Prothrombin)G 20210A	4	7.4	2.7
Deficit C protein	2	3.7	0.2–0.4
Deficit S protein	1	1.85	0.7
Hyperhomocysteinemia	2	3.7	3–10
/MTHFR/	22	40.7	15

Group I – thrombophilia – 15 patients, group II without thrombophilia, without MTHFR 23 patients, group III – MTHFR – 16 patients

We performed PEA by median sternotomy for bilateral exposure of exploration under deep hypothermia circulatory arrest, for safe exposure for distal branches of pulmonary artery. This technique was developed by Daily and Jamieson at the University of California in San Diego, and technical advances were described by Jamieson [11, 12].

For statistical evaluation, we used the software package ANCOVA© for Windows, SPSS Inc., USA. Statistical analysis was performed by analysis of variance (ANOVA), repeated measures ANOVA and Pearson χ^2-test, when comparing groups of patients. Data are given as the mean ±SD. Any value $p<0.05$ was considered statistically significant.

Results

Four patients had antiphospolipid syndrome, 5 mutation of factor V Leiden, 4 prothrombin G20210A mutation, 2 deficit of protein C, 2 suffered with hyperhomocysteinemia, 1 deficit of protein S and 22 patients had Methylenetetrahydrofolate Reductase (MTHFR) gene mutation as shown in Table 1.

We compared our three groups of patients and we did not strike any difference between them in weight, height, gender, duration of difficulties (DM, CAD, Renal insufficiency, NYHA). However, we did note a difference in age, where the youngest patients were in group I (with thrombophilia), and a difference in walking

Table 2 – Demographic and epidemiological data

Variables	Group I	Group II	Group III	P value
Age (years)	49.3 ± 17.58	56.35 ± 10.74	59.8 ± 10.96	p<0.05
Gender (% fem)	40	39	31.25	N.S.
mPA (mmHg)	56.4 ± 9.24	57.4 ± 10.11	57.5 ± 10.34	N.S.
PVR	914.2 ± 362.81	1030 ± 314.71	936.6 ± 256.09	N.S.
CI	2.09 ± 0.64	1.85 ± 0.34	2.11 ± 0.36	N.S.
DM	20%	8.6%	18.7%	N.S.
CAD	26%	17.4%	43.75	N.S.
Renal insuf.	46%	34%	18%	N.S.
Duration of difficulties (years)	7.45	6.9	7.25	N.S.
6MWT (m)	309.7 ± 97.61	299.5 ± 82.38	340.3 ± 104.28	N.S.
NYHA (average)	3.2 ± 0.56	3.17 ± 0.49	3.06 ± 0.44	N.S.

Table 3 – Operative data

Variables	Group I	Group II	Group III	P value
Time MO (min)	336.7 ± 38.93	326.7 ± 44.67	327.4 ± 33.35	N.S.
Circ. arest time (min)	39.7 ± 8.54	41.39 ± 12.41	36.06 ± 13.75	N.S.
Type III lesions (%)	27%	26.08%	25%	N.S.
Tricuspid isufic. (before surgery)	2.67	3.22	2.94	N.S.
Ventilation time (hour)	65 ± 55.98	53.39 ± 50.56	41.8 ± 41.55	N.S.

distance in 6MWT. The patients in group III (patient with MTHFR gene mutation) had longer walking distances, but these were not statistically significant. Other results are shown in Table 2.

Operative data are summarized in Table 3, and data comparison shows no statistical differences in arrest time, time of extracorporeal circulation or

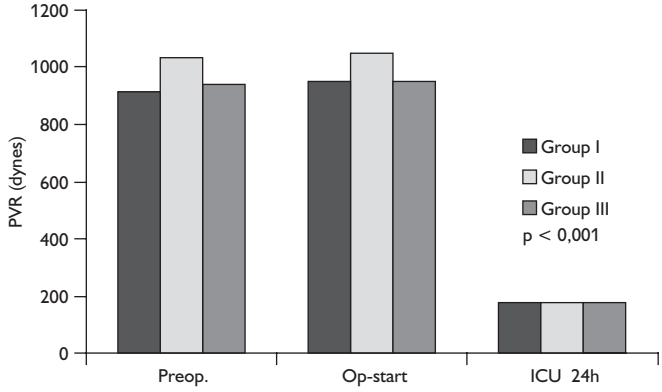

Figure 1 – Pulmonary vascular resistance.

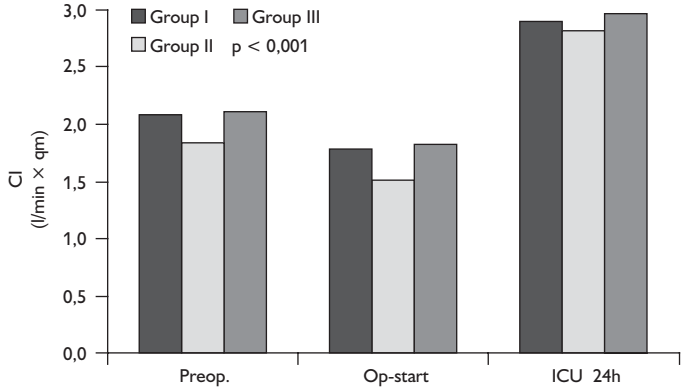

Figure 2 – Cardiac index.

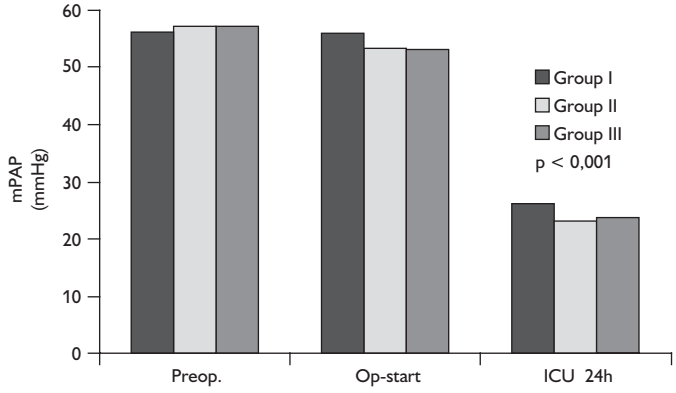

Figure 3 – Mean pressures in main pulmonary artery.

proportion number of type III lesions (peripheral from Jamieson intraoperative classification scheme), but instead, longer ventilation time after operation in Group I.

After the operation, there was a statistically considerable improvement of hemodynamic parameters (mPA, CI, PVR) in all groups, without statistical differences between the groups (Figures 1, 2, 3).

Postoperative care of patients undergoing PEA can be demanding, because of many complications. Most serious complication were persistent pulmonary hypertension and reperfusion oedema, which according to the literature, can be seen in approximately 10% of patients (in our group of patients was seen in 13%). Other complications include, bleeding from the lungs, pericardial effusions, pneumonia and renal insufficiency. These are summarized in Table 4. Rare complications were, gastro-oesophageal (GE) bleeding, peripheral paresis fibularis nerve, after compression during positioning patient with reperfusion oedema. Comparison of all groups shows more complications in-group I (thrombophilia),

Table 4 – Complications

Variables	Group I	Group II	Group III	total
NO complications	13.3	34.78	37.5	16 (29.6%)
Mortality	13.3	4.3	6.25	4 (7.4%)
Pericardial effusion	33.3[a]	13	6.25	10 (18.5%)
Reperf. oedema	26.6[a]	8.7	6.25	7 (12.9%)
Pulmonary Haemorrhage	6.7	4.3	6.25	4 (7.4%)
Renal insuff.	33.3	17.4	12.5	11 (20.4%)
CVVH	26.6	8.7	6.25	6 (11.1%)
Pneumonia	13.3	13.04	6.25	6 (11.1%)
Arrhythmia	6.7	13.04	–	4 (7.4%)
Delirium	6.7	13.04	–	4 (7.4%)
HIT	13.3	4.3	–	4 (7.4%)

[a]Statistically significant $p<0.001$

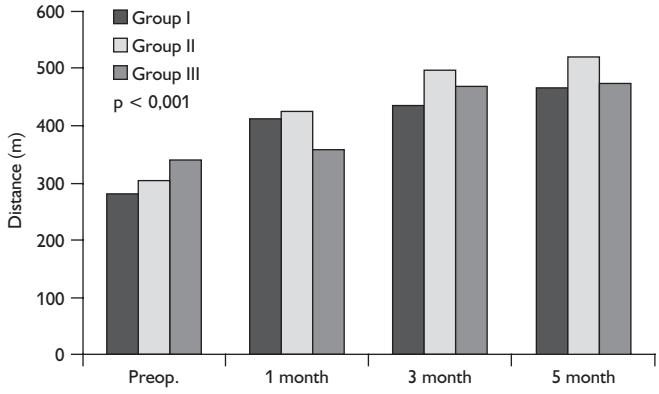

Figure 4 – Results of six minute walking test (6MWT).

in particular reperfusion oedema, pericardial effusion and renal insufficiency, but in this group, more patients had renal insufficiency before the operation.

Within one month, there was a considerable improvement or normalisation of hemodynamic parameters and an increase in walking distance on the six-minute walking test (Figure 4), with no significant differences between our three groups.

Discussion

Patients with thrombophilia (in group I) were statistically eminently younger, while the other monitored parameters were not ascertained as being that significantly different.

In group I we had more women, more patients with renal dysfunction. In group III (with MTHFR) we had more coronary artery disease (CAD), at least women, and were the most concerning observations for us, however, these differences were not statistically significant.

Higher occurrence CAD in patients with MTHFR brings an explicably higher hazard for arterial thrombosis .For venous thrombosis or for CTEPH this risk factor was not evidenced, even in our studies. Hence, nothing disagreed with it.

Occurrence MTHFR in our studies is twice higher, then that which they described in their literature.

We can assume that our groups can be distinguish and by the presence of peripheral infliction of pulmonary arteries (type III. accordance with Jamieson classification), which our work did not prove [13].

As we already stated in the introduction to the thrombofillic construction sequence cases, the risk factors of venous thrombosis and thromboembolic disease (TED) are high. Uncertain is however the relation between thrombofillic condition and CTEPH [14, 15]. As shows our small study occurrence of thrombofillic conditions at our patient with CTEPH and PEA do not differ from normal Kazakhs population (Table 1).

The aim of our study was the analysis of risk factors CTEPH, and the relation between thrombofilic conditions and PEA, because literature brings only case reports [9, 10].

Analysis our results shows, that the thrombofillic state is prognostically relevant, increases risk of surgical complication and requires longer time of treatment. It requires specific access to peroperative monitoring of anticoagulation and subsequently most important postoperative time.

Patients with antiphospolipid syndrome and positive record activated clotting time (ACT) demand special monitoring of anticoagulation [16].

Conclusions

PEA is a curative method for patients with CTEPH with a surgically accessible obstruction of the pulmonary artery. Early hemodynamic results of patients

with thrombophilia after PEA are comparable to results of patients without thrombophilia in clinical and hemodynamic improvements.

Patients in Group I with thrombophilia were operated younger and had higher postoperative morbidity and mortality, but clinical improvement and hemodynamic effect were the same as in patients without thrombophilia, as well as in patients with MTHFR.

We did not find any differences in the results between Group II and Group III (MTHF), when we compared the number and types of complications.

Patients with thrombophilia in Group I had significantly higher morbidity, especially higher numbers of reperfusion oedema, pericardial effusion and renal insufficiency. However, in this group, more patients had renal insufficiency before the operation, but this difference was not statistically significant.

Short-term results in our groups of patients showed comparable results in 6MWT. Adequate multidisciplinary approach in postoperative care is essential in all patients after PEA, but in patients with thrombophilia, it is a sine qua non condition.

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