

## Acute pulmonary embolism and chronic thromboembolic pulmonary hypertension: is there a relationship?

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Acute pulmonary embolism constitutes the third most frequent cardiopulmonary disease, after ischaemic heart disease and hypertension.

### Natural course of acute pulmonary embolism

The natural course of acute pulmonary embolism depends primarily on whether the embolism has been detected and treated [1-4]. The haemodynamic severity of acute pulmonary embolism largely depends on the previous state of the cardiopulmonary system in patients without any previous cardiopulmonary disease [1, 5], the degree of haemodynamic severity (*e.g.* that of pulmonary hypertension) depends exclusively on the extent of embolic obstruction [1, 4, 6]. Other factors effecting the natural course of acute pulmonary embolism include age of the embolus and spontaneous thrombolytic activity of the patient's pulmonary vasculature endothelium [3]. Fresh thrombi tend to dissipate into pieces on passage through the right ventricle thereby causing minor embolisms. Older organized thrombi pass unaltered into the pulmonary circulation and frequently get stuck on the pulmonary main branch causing obstruction of major pulmonary arteries [3, 5].

Treatment exerts a major effect on thrombosis. Mean mortality (one month) rates of treated and untreated pulmonary embolism are 8 and 30% respectively [1]. The mortality depends on the degree of pulmonary embolism (mean pulmonary pressure  $\geq 5.3$  kPa/40 mmHg<sup>-1</sup>) is 31%. It is as low as 5.6% in treated patients with moderate or mild pulmonary hypertension (mean pulmonary pressure  $< 5.3$  kPa/40 mmHg<sup>-1</sup>) [5, 6].

Thrombi can be removed from the pulmonary vasculature either by fibrinolysis or by fragmentation. Fibrinolytic dissolution of a thromboembolus is accomplished by the fibrinolytic activity of blood and intima of pulmonary arteries. However, there are interindividual variations in the degree of fibrinolytic activity of pulmonary vessels. The treatment of choice of massive pulmonary embolism - especially if it is accompanied by cardiogenic shock or hypotension or signs of right heart failure - is thrombolytic therapy-streptokinase [7, 8], urokinase [9, 10], or tissue plasminogen activator [11-14]. At present, the method of choice is *i.v.* administration of streptokinase. While intravenous administration of tissue plasminogen activator results in rapid remission of right ventricular dilatation on the echocardiogram [15], no significant difference in long-

term prognosis has yet been demonstrated between patients treated by streptokinase and those receiving costly rt-PA. In the experience reported by SHARMA *et al* [16], whereas thrombolytic therapy leads to pulmonary pressure normalization within 4 h, no significant decline in pulmonary pressure can be seen after heparin as late as 24 h after its initiation.

Regression of thromboembolic pulmonary vascular obstruction thus depends on the type of treatment, with thrombolytic therapy resulting in far more rapid removal of the vascular obstruction than heparin administration [7-11]. Moreover, regression of the vascular obstruction is dependent on the extent of initial obstruction and the interval to institution of therapy. Our experience shows that the sooner the therapy is initiated, the faster is the regression of pulmonary hypertension in acute pulmonary embolism [4, 5].

In 1975, DALEN and ALPERT [1] estimated the total annual prevalence of acute pulmonary embolism in the US at 630,000. 11% of patients with acute pulmonary embolism die suddenly (in less than 1 h). In the early 1980s the percentage of well diagnosed (and hence treated) cases of pulmonary embolism (surviving more than 1 h) in the United States was 29%. This attests to an improving diagnostic capability compared with the fifties and sixties when the proportion of correct diagnoses of pulmonary embolism was as low as 10-11% [17]. According to data released by DALEN and ALPERT [1], pulmonary embolism is not recognized and, as a result, remains untreated, in 71% of patients. The mortality of these patients averages 30%. The implication is that 280,000 persons survive undetected and untreated acute pulmonary embolism in the US each year. The fate of these patients is not clear. DALEN and ALPERT [1] believe that recurrent thromboembolic attacks and gradual development of pulmonary hypertension can be expected in half of these patients.

Patients with detected and properly treated acute pulmonary embolism are highly unlikely to develop chronic thromboembolic pulmonary hypertension [1, 3, 18-20].

### Recurrent pulmonary embolism

Pulmonary embolism tends to recur in some treated patients. The Urokinase study [8, 9] revealed that 15% of patients with acute massive pulmonary embolism had had two or more previous minor attacks before a



massive attack, and 20% of treated patients were found to have signs of recurrent pulmonary embolism within the first two weeks.

While the long-term prognosis of treated acute pulmonary embolism is good, an adverse effect is exerted by a concomitant disease. Our understanding of the course of subacute pulmonary embolism is more limited [19]. Subacute pulmonary embolism is characterized by dyspnoea persisting longer than in the acute form and, more importantly, progressing over 1–4 weeks without an acute attack or syncope. However, on follow-up at 4–6 yrs [19, 21], a small proportion of these patients is found to be hypertensive on the first appointment, and the condition tends to progress slowly. This may be due to the fact therapy was started late.

Recurrent embolism can thus be seen in treated patients with acute pulmonary embolism before therapy initiation and during the acute stage. However, acute as well as massive treated pulmonary embolism does not result in chronic thromboembolic pulmonary hypertension [5, 20, 22].

Which patients with acute pulmonary embolism are then hypothetically most likely to develop chronic thromboembolic pulmonary hypertension? First, they are those with undiagnosed, and hence, untreated acute pulmonary embolism and, also patients with recurrent minor embolism most often from the area of pelvic veins (so called "silent" recurrent pulmonary embolism) and perhaps even those with unsuccessful lysis of acute embolism (*e.g.* due to late start of therapy). Development of chronic thromboembolic hypertension may also be due to endothelial dysfunction.

### Chronic thromboembolic pulmonary hypertension

Quite surprisingly, chronic thromboembolic pulmonary hypertension is a rare condition and its prevalence in autopsy studies has not changed over the past 50 yrs. OWEN *et al* [23] found a 0.15% prevalence (12 deaths in a total of 8000 autopsies) of chronic thromboembolic hypertension over the years 1933–1953. URBANOVÁ and STANĚK [24] reported only three deaths with the same diagnosis in a series of 720 post mortem examinations at the Department of Cardiology of the Institute for Clinical and Experimental Medicine in a decade (1979–1989). The prevalence of 0.38% found in the group of URBANOVÁ and STANĚK [24] is thus virtually consistent with data furnished by OWEN *et al* [23].

The symptoms of thromboembolic pulmonary hypertension depend on embolus localization. If the major pulmonary artery branches are involved, the patient's medical history will contain data on recurrent dyspnoea attacks, pleural pain, and/or haemoptysis [5, 25, 26]. The patient may experience events of repeat pulmonary infarctions with signs of hypertension progressing up to right heart failure. While detection of this form should pose no greater problem, some patients are misdiagnosed to have recurrent bronchopneumonia [5]. The presence of segmental or lobal perfusion defects, with good ventilation on the ventilation scan supports the diagno-

sis [27]. In the silent form, microembolism leads to extensive obstruction of the pulmonary vasculature resulting in severe pulmonary hypertension. Repeat microembolism remains free of clinical manifestations for a long time, and the first symptoms making the patient to seek medical help is gradually increasing dyspnoea [5, 19]. Exertional dyspnoea with ECG signs of right ventricular hypertrophy of unclear origin should always alert the physician to the possibility of thromboembolic pulmonary hypertension. Development of repeat thrombophlebitis will enhance our suspicion. Still, differentiation of this form of pulmonary hypertension from primary pulmonary hypertension is extremely difficult in a number of patients [5, 26–29].

The presence of venous thrombosis or pulmonary embolism in the history, focal defects on the perfusion lung scan and positive pulmonary angiography indicate embolic origin of the pulmonary hypertension (table 1). In chronic thromboembolic pulmonary hypertension the size of bronchial collateral circulation markedly increases, which may be demonstrated by bronchial arteriography, in primary pulmonary hypertension no change of the collateral circulation occurs [30]. Acute response to a vasodilator drug may be positive in primary pulmonary hypertension, while it is negative in chronic thromboembolic pulmonary hypertension. Lung biopsy may markedly improve the differential diagnosis between those two conditions (table 2) [31].

Table 1. – Differential diagnostic aspects between primary pulmonary hypertension (PPH) and chronic thromboembolic pulmonary hypertension (TEPH)

	PPH	TEPH
venous thrombosis or pulmonary embolism in the history	0	+
perfusion lung scan focal defects	0	+
pulmonary angiography	0	+
bronchial collaterals	0	increased
vasodilators	+	0

Table 2. – Histopathologic findings in primary pulmonary hypertension (PPH) and chronic thromboembolic pulmonary hypertension (TEPH)

	PPH	TEPH
medical hypertrophy	+	-
fibrinoid necrosis	+	-
plexiform lesions	+	-
arterial thrombi of various ages	-	++
arteritis	+	rare



The difficulty of correct diagnosis is indicated e.g. by the report from Mayo Clinic, where 58% of cases with primary pulmonary hypertension had at autopsy recurrent pulmonary emboli [28]. Therefore chronic anticoagulant therapy is recommended in all patients with primary pulmonary hypertension [23].

Prognosis of chronic thromboembolic pulmonary hypertension relates to the degree of pulmonary hypertension (table 3). Prognosis is serious in all patients with mean pulmonary artery pressure  $\geq 4.0$  kPa (30 mmHg) [19]. The worst prognosis was observed in patients with elevated right arterial pressure ( $\geq 0.8$  kPa/6 mmHg<sup>-1</sup>). While 82% patients were surviving from those with mean right atrial pressure  $\leq 0.8$  kPa ( $p < 0.02$ ) after 4.8 yrs (1–15 yrs) only 18% were alive from those with elevated right atrial pressure [19, 23].

Table 3. – The prognosis of recurrent pulmonary embolism related to the degree of pulmonary hypertension

mean pulmonary artery pressure at 1st investigation	5-yr survival
2.7 kPa ( $\leq 20$ mmHg)	97%
2.8–4.0 kPa (21–30 mmHg)	94%
4.1–5.3 kPa (31–40 mmHg)	45%
5.4–6.7 kPa (41–50 mmHg)	32%
6.8–9.3 kPa (51–70 mmHg)	7.5%

#### Relation of acute pulmonary embolism and chronic thromboembolic pulmonary hypertension

We did not find any relationship between chronic thromboembolic pulmonary hypertension and the signs, number, and extent of pulmonary embolism in clinical examination, embolus localization, age or the extent of residual defect after acute pulmonary embolism on the pulmonary perfusion scan [18, 19, 34]. Thus, only a small proportion of patients with acute pulmonary embolism develop pulmonary hypertension; no explanation for this finding is yet available. Presumably the functional properties of the pulmonary vascular endothelium (e.g. the degree of individual fibrinolytic activity) may play a key role. However, no method has to date been developed allowing us to identify these patients at risk.

It can be reasonably concluded that a single attack of massive pulmonary embolism does not lead to chronic pulmonary hypertension. The long-term fate of patients with undetected and untreated pulmonary embolism (if they survive it, that is, since the mortality is 30%) depends rather on coexistent disease, but these patients still do not tend to develop chronic thromboembolic pulmonary hypertension. Chronic thromboembolic pulmonary hypertension has been, and remains to be, a rare condition.

#### References

1. Dalen JE, Alpert JS. – Natural history of pulmonary embolism. *Progr Cardiovasc Dis*, 1975, 17, 259–270.
2. Widimský J. – The prognosis of pulmonary embolism. *Cor Vasa*, 1979, 21, 221–227.
3. Messer JV. – Thromboembolic pulmonary hypertension. In: Weir EK, Reeves JT eds, *Pulmonary hypertension*, Mount Kisco, New York: Futura Publ. Co., 1984, 169–250.
4. Staněk V, Riedel M, Widimský J. – Haemodynamic monitoring in acute pulmonary embolism. *Bull Eur Physiopathol Respir*, 1978, 14, 561–572.
5. Widimský J. – Advances in clinical diagnosis of pulmonary embolism. *Acta Univ Carol med Monogr (Praha)*, 1983, 29, 401–484.
6. Widimský J, Staněk V. – Clinical diagnosis of haemodynamically significant pulmonary embolism in a coronary care unit. *Cor Vasa*, 1985, 27, 337–345.
7. Tibbitt DA, Davies JA, Anderson JA, et al. – Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. *Br Med J*, 1974, 1, 343–347.
8. Urokinase - streptokinase pulmonary embolism trial: phase II. results. *J Am Med Assoc*, 1974, 229, 1606–1613.
9. Urokinase pulmonary embolism trial: a national cooperative study. *Circulation*, 1973, 47, suppl. II, 1–108.
10. Francois G, Charbonnier B, Raynaud P, et al. – Traitement de l'embolie pulmonaire aiguë par urokinase comparee a l'association plasminogene-urokinase. *Arch Mal Coeur*, 1986, 79, 435–442.
11. Goldhaber SZ, Kessler CM, Heit J, et al. – A randomized controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. *Lancet*, 1988, 2, 293–298.
12. Goldhaber SZ. – Tissue plasminogen activator in acute pulmonary embolism. *Chest*, 1989, 95, 282 S–289 S.
13. Goldhaber SZ. – Thrombolysis in venous thromboembolism. An international perspective *Chest*, 1990, 97, suppl. 167S–181S.
14. Neuhaus KL, Tebbe U, Gottwick M, et al. – Intravenous recombinant tissue plasminogen activator (rt-PA) and urokinase in acute myocardial infarction: results of the German Activator Urokinase Study (GAUS). *J Am Coll Cardiol*, 1988, 12, 581–587.
15. Come PC, Kim D, Parker JA, et al. – Early reversal of right ventricular dysfunction in patients with acute pulmonary embolism after treatment with intravenous tissue plasminogen activator. *J Am Coll Cardiol*, 1987, 10, 971–978.
16. Sharma GVRK. – Immediate haemodynamic benefits in thrombolytic therapy in patients with acute massive pulmonary embolism. 15th World Congress I.U.A. Rome 1989, Abstr. p. 452.
17. Goldhaber SZ, Hennekens CH. – Time trends in hospital mortality and diagnosis of pulmonary embolism. *Amer Heart J*, 1982, 104, 305–306.
18. Widimský J. – Mechanisms of embolic pulmonary hypertension. Monogr. Pulmonary circulation - advances and controversies. Eds CA Wagenvoort, H Denolin Elsevier 1989, Amsterdam, New York, 1989, 75–86.
19. Riedel M, Staněk V, Widimský J, Préroutský I. – Long-term follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of haemodynamic and respiratory data. *Chest*, 1982, 81, 151–158.
20. Hall RJC, Sutton GC, Kerr IH. – Long-term prognosis of treated acute massive pulmonary embolism. *Brit Heart J*, 1977, 69, 1128–1134.



21. Sutton GC, Hall RJC, Kerr IH. – Clinical course and late prognosis of treated subacute massive, acute minor, and chronic pulmonary embolism. *Br Heart J*, 1977, 69, 1135–1142.
22. Paraskos JA, Adelstein SJ, Smith RE, *et al.* – Late prognosis of acute pulmonary embolism. *N Engl J Med*, 1973, 289, 55–58.
23. Owen WR, Thomas WA, Castleman B, *et al.* – Unrecognized emboli to the lungs with subsequent cor pulmonale. *N Engl J Med*, 1953, 249, 919–926.
24. Urbanová D, Staněk V. – Thromboembolic attacks in a cardiological department. *Čas Lék čes*, 1990, 129, 747–750.
25. Goodwin JF, Harrison CV, Wilcken DE. – Obliterative pulmonary hypertension and thromboembolism. *Br Med J*, 1963, 1, 777–783.
26. Sutton GC, Hall RJC, Kerr IH. – Clinical course and late prognosis of treated subacute massive, acute minor, and chronic pulmonary thromboembolism. *Br Heart J*, 1977, 39, 1135–1142.
27. Weir EK, Archer SL, Edwards JE. – Chronic primary and secondary thromboembolic hypertension. *Chest*, 1988, 93, 149S–154S.
28. Fuster V, Steele PM, Edwards WD, *et al.* – Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation*, 1984, 70, 580–587.
29. Wagenvoort CA, Wagenvoort N. – Primary pulmonary hypertension: a pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation*, 1970, 42, 1163–1184.
30. Endrys J, Král B, Hlava A, *et al.* – Collateral pulmonary circulation in chronic pulmonary embolism. In: Abstr Intern Symposium Pulmonary Circulation III., Praha, July 2–4, 1979: 43.
31. Wagenvoort CA. – Lung biopsies in the differential diagnosis of thromboembolic versus primary pulmonary hypertension. *Progr Resp Res*, 1980, 13, 16–21.
32. Frank H, Mlczech J, Lang I, Kneussl M, *et al.* – Influence of warfarin therapy in primary pulmonary hypertension. *Progr Respir Res*, 1990, 26, 119–124.
33. Widimský J. – Chronic thromboembolic disease. A prognostic study. 21st Annual meeting SEPCR and 5th annual meeting SEP, Paris 1986, Abstr II.

## The European Respiratory Review

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As soon as the European Respiratory Journal was born, a number of requests for publication of Supplements were received, in prolongation of a well established tradition by its predecessors, the Bulletin Européen de Physiopathologie Respiratoire and the European Journal of Respiratory Diseases. The requests were coming from organisers of conferences who frequently were members of SEP or SEPCR, from Working Groups of both Societies as well as from Drug Companies.

In April 89 our Managing Editor, Peter Howard, became afraid that the regular issues of the Journal be swamped with these supplements. Some came to the idea to publish a sister journal to be called the European Respiratory Review, the first issues coming now out of press. The Review will be distributed free to all members of the European Respiratory Society. It will be prepared in Sheffield with the same care as the Journal.

Any theme or topic within the scope of interest of the members of the Society and of the usual readers of the Journal might be tackled. Preference will however be given to issues covering all important aspects of one subject. Drug-related issues can be accepted provided that the scientific message is properly presented avoiding an overt commercial promotion.

In general the papers should be presented as review articles and contain material not yet critically evaluated in a refereed journal. Their scientific content will be checked by an Editor coming from the board of the Journal, selected among the Congress organisers, or specially appointed for the task. When necessary the manuscripts will be sent to outside reviewers. They might eventually be refused if they do not meet the standards of the Journal.

Requests for publishing an issue must be sent to the office of the Chief Editor of the European Respiratory Review, preferably well in advance (at least six months) of a meeting. They must include the complete scientific programme with the names of the contributors. To avoid late publishing of meeting proceedings, it is of paramount importance that the manuscript, prepared according to the ERJ rules be available at the time of the meeting, and certainly not later than two months after. Potential contributors should be clearly informed well in advance of the above requirements as well as of the expected length of their manuscript. This will determine the cost of the publication which must be financed by the Meeting organisers or sponsors.