Factors associated with diagnosis and operability of chronic thromboembolic pulmonary hypertension

A case-control study

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Summary

Chronic thromboembolic pulmonary hypertension (CTEPH) and idiopathic pulmonary hypertension (IPAH) share a similar clinical presentation, and a differential diagnosis requires a thorough workup. Once CTEPH is confirmed, patients who can be safely operated have to be identified. We investigated risk factors associated with CTEPH and IPAH, and the criteria for the selection of operable CTEPH patients. This case-control study included 436 consecutive patients with CTEPH and 158 with IPAH in eight European centres, between 2006 and 2010. Conditions identified as risk factors for CTEPH included history of acute venous thromboembolism ($p < 0.0001$), large size of previous pulmonary embolism ($p = 0.0040$ in univariate analysis), blood groups non-O ($p < 0.0001$ in univariate analysis), and older age ($p = 0.0198$), whereas diabetes mellitus ($p = 0.0006$), female gender ($p = 0.0197$) and higher mean pulmonary artery pressure ($p = 0.0103$) were associated with increased likelihood for an IPAH diagnosis. Operability of CTEPH patients was associated with younger age ($p = 0.0108$), proximal lesions ($p \leq 0.0001$), and pulmonary vascular resistance below 1200 dyn.s.cm^{-5} ($p = 0.0080$). Non-operable CTEPH patients tended to be less differentiable from IPAH patients by risk factor analysis than operable patients. This study confirmed the association of CTEPH with history of acute venous thromboembolism and blood groups non-O, and identified diabetes mellitus and higher mean pulmonary artery pressure as factors suggesting an IPAH diagnosis. Non-operable CTEPH is more similar to IPAH than operable CTEPH regarding risk factors.

Keywords

Chronic lung disease, endarterectomy, pulmonary arterial hypertension, risk factor

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Introduction

Idiopathic pulmonary arterial hypertension (IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are two important subgroups of pulmonary hypertension. IPAH is characterised by an increased pulmonary vascular resistance (PVR) subsequent to functional loss of precapillary pulmonary microvasculature. In CTEPH, increased PVR is a consequence of major vessel thrombotic obstruction. Small-vessel disease in CTEPH, which may be caused by overperfusion of non-occluded lung areas, presents histological similarities with the pulmonary arteriopathy of IPAH (1).

Both conditions are characterised by different risk factors. Several studies point toward an association of IPAH with specific features of the metabolic syndrome (2) and possibly with autoimmune thyroid disease (3). CTEPH may develop after a pulmonary thromboembolic event (4, 5) and has been associated with the presence of coagulation abnormalities and chronic inflammatory disorders (6-8). Independent predictors of CTEPH also include previous splenectomy, ventriculoatrial shunt, and infected pacemaker (9, 10). Malignancy, and thyroid replacement therapy have recently been reported as additional risk factors for CTEPH (10). The identification of clinical conditions that differentiate CTEPH from IPAH could support the elaboration of a difficult and often delayed diagnosis.

A differential diagnosis is crucial for outcome since CTEPH is potentially curable by pulmonary endarterectomy (PEA) (1). However, many patients with CTEPH are considered non-operable due to predominantly distal thromboembolic pathology, or concomitant small-vessel arteriopathy (11). Despite growing ex-

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perience in diagnosis and operative technique, no consensus has been reached on criteria for pre-operative patient selection.

We performed a case-control-study comparing 436 consecutive patients with CTEPH with 158 patients with IPAH. Objectives were to identify medical conditions conferring an increased likelihood for CTEPH vs IPAH and to define the characteristics of patients selected for PEA in current practice.

Patients and methods

Study design

A case-control design was used to compare newly (≤ 6 months) diagnosed CTEPH and IPAH patients. CTEPH patients had been included in an international prospective registry between February 2007 and January 2009 (12). Registry centres were requested to have concomitantly diagnosed patients with IPAH from September 2006 onward. This study was conducted in accordance with the amended Declaration of Helsinki. Formal ethics approval was obtained.

Inclusion criteria

Patients were 18 years or older and did not receive any pulmonary hypertension-targeted treatment before diagnosis/enrolment. Pulmonary hypertension was confirmed by right heart catheterisation indicating a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest and a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg.

IPAH patients had a normal perfusion scintigram with few exceptions presenting with patchy perfusion inequalities. CTEPH patients had pulmonary hypertension caused by abnormalities that were detected in ventilation/perfusion scan, computed tomography (CT) scan, and/or in pulmonary angiography (►Table 1 and ►Table 2). Prior to diagnosis, CTEPH patients were required to have had at least three months of effective anticoagulation.

Operability

Criteria for inoperability of CTEPH patients have been described previously (1, 13). The decision to operate was based on surgeon's best judgment and experience.

Data collection

Data were obtained from assessments that are routinely performed in clinical practice. Thrombophilic disorders included antiphospholipid antibodies/lupus anticoagulant (APA/LAC), protein S and C deficiency, activated protein C resistance, factor V Leiden mutation, prothrombin gene mutation, antithrombin deficiency, elevated factor VIII, hyperhomocysteinaemia or methylenetetrahydrofolate reductase mutation, and heparin-induced thrombocytopenia. In the presence of generalised defects in V/Q scintigraphy or pulmonary angiography, the most proximal level of the observed lesions was reported.

Statistical analysis

Results are expressed as medians with first and third quartiles (Q1;Q3) or percentages of patients.

The prognostic relevance of putative risk factors for CTEPH vs IPAH was investigated by univariate and multivariate analyses. Predefined variables considered for analysis are listed in ►Table 3.

Table 1: Demographic and clinical characteristics by diagnosis.

	IPAH (n = 158)	CTEPH (n = 436)	Operable CTEPH (n = 284)	Non-operable CTEPH (n = 152)
Age, years	59 [42;69]	65 [53;73]	63 [49;72]	68 [57;75]
Gender, % female	66.5	49.3	45.8	55.9
Ethnicity, % white	91.1	95.9	95.4	96.7
Weight, kg	72 [62;87]	74 [64;86]	75 [66;88]	72 [63;81]
NYHA class, % I+II/ III/ IV	20.3/71.5/8.2	22.7/65.6/11.7	23.2/64.8/12.0	21.7/67.1/11.2
6MWD, m	352 [257;425] (n = 146)	324 [250;425] (n = 379)	338 [250;432]	315 [241;400]
Time to diagnosis, months	14.6 [6.9;30.9] (n = 145)	14.2 [7.5;34.9] (n = 414)	15.0 [7.4;32.8]	13.2 [7.8;42.0]
DLCO/VA, % predicted	67 [40;80] (n = 122)	74 [60;85] (n = 228)	74 [60;85]	73 [61;85]
Haemoglobin, g/dl	14.8 [13.9;15.9] (n = 154)	14.6 [13.4;15.8] (n = 418)	14.6 [13.3;15.9]	14.7 [13.5;15.8]

Values are expressed as medians with first and third quartiles [Q1;Q3] or percentages. (n): patients with the assessment. 6MWD: 6-minute walking distance, DLCO/VA: carbon monoxide diffusing capacity in the lung per unit alveolar volume, NYHA: New York Heart Association.

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Table 2: Haemodynamic/imaging characteristics by diagnosis.

	IPAH (n = 158)	CTEPH (n = 436)	Operable CTEPH (n = 284)	Non-operable CTEPH (n = 152)
Right heart catheterisation				
mPAP, mmHg	52 [44;60] (n = 158)	48 [39;55] (n = 436)	48 [40;56]	47 [38;55]
RAP, mmHg	9 [5;14] (n = 154)	9 [6;13] (n = 425)	9 [6;13]	8 [5;13]
PAWP, mmHg	10 [7;12] (n =158)	10 [8;14] (n = 411)	10 [8;14]	10 [7;14]
PVR, dyn.s.cm^{-5}	821 [612;1131] (n = 156)	724 [492;968] (n = 414)	735 [513;940]	700 [416;1084]
Cardiac index, L.min^{-1}.m^{-2}	2.2 [1.8;2.6] (n = 154)	2.2 [1.8;2.7] (n = 427)	2.2 [1.8;2.7]	2.3 [1.8;2.7]
Echocardiography				
RV enlarged, %	92.0 (n = 150)	86.5 (n = 421)	89.7	80.7
Any pericardial effusion, %	26.1 (n = 142)	14.1 (n = 396)	16.4	10.0
Scintigraphy				
Abnormal perfusion scan, %	0[a] (n = 158)	98.3 (n = 351)	99.6	96.0
Abnormal ventilation scan, %	0 (n = 158)	18.4 (n = 331)	16.3	22.4

Values are expressed as medians with first and third quartiles [Q1;Q3] or percentages. (n): patients with the assessment. [a]39 IPAH patients had minor non-segmental patchy abnormalities. mPAP: mean pulmonary arterial pressure, PVR: pulmonary vascular resistance, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, R(L)V: right (left) ventricle.

Variables identified as risk factors for CTEPH with p-value < 0.2 in univariate analysis adjusted for gender and age were included in a multiple logistic regression model. Limiting this analysis to non-missing data meant modelling was done for 461 patients out of 594 (the parameters 'size of PE', 'blood group other than O' and 'carbon monoxide diffusing capacity in the lung per unit alveolar volume, DLCO/VA' reported for a small number of patients were not included in multivariate analysis, despite a p-value < 0.2). Results are presented as odds ratios (OR) and p-values calculated using the Wald Chi-square test.

The same methodology without age and gender adjustment was applied to the identification of risk factors associated with non-operability in CTEPH patients (►Table 4). Limiting this analysis to non-missing data meant modelling was done for 222 patients out of 436.

Data were analysed with the SAS® software package version 9.3.

Results

Study population

Eight European centres enrolled 436 CTEPH patients into the CTEPH registry, and concomitantly diagnosed 158 IPAH patients; 284 CTEPH patients were considered operable.

CTEPH patients were older than IPAH patients (65 vs 59 years, ►Table 1). The female/male ratio was 1.0 for CTEPH and 2.0 for IPAH. Clinical status reported as NYHA class distribution and exercise capacity tended to be more compromised in CTEPH patients, despite comparable delays in diagnosis. As reported previously (12), non-operable CTEPH patients tended to be older and to include more women than operable patients.

Dyspnoea was the most frequently reported symptom in patients with CTEPH and IPAH (98.9% and 99.4%, respectively), oedema, fatigue, and haemoptysis tended to be more frequent in CTEPH (40.4% vs 27.2%, 23.6% vs 15.8%, and 4.8% vs 0.6%, respectively), whereas chest pain, syncope, and dizziness were more common in IPAH (19.6% vs 13.8%, 19.0% vs 14.2%, and 17.1% vs 5.3%, respectively).

Pulmonary function parameters were indicative of a mild pulmonary restrictive disorder in both patient groups, especially in the IPAH group.

CTEPH and IPAH diagnoses

►Table 2 illustrates haemodynamic and imaging characteristics of CTEPH vs IPAH; mPAPs and PVRs were higher in IPAH, in concordance with larger right ventricles and a higher incidence of pericardial effusion, whereas PAWPs were similar in both groups.

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Table 3: Putative risk factors associated with CTEPH vs IPAH diagnoses – results of univariate analyses adjusted for age and gender.

Risk factors	IPAH (n = 158)	CTEPH (n = 436)	Odds ratio (p-value)
Clinical history of acute VTE	11 (7.0)	341 (80.2) (n = 425)	49.01 (< 0.0001)
• Recurrent PE[a]	1 (11.1) (n = 9)	97 (31.4) (n = 309)	2.72 (> 0.2)[a]
• Massive and sub-massive PE[a]	1 (16.7) (n = 6)	113 (78.5) (n = 144)	13.03 (0.0040)[a]
Ventriculoatrial shunt	0 (0)	6 (1.4)	9.64 (0.1583)
Rheumatoid arthritis	0 (0)	7 (1.6)	8.04 (0.1855)
Haemoptysis			6.32 (0.0365)
Prolonged immobility (non-hospital)	1 (0.6)	13 (3.0)	3.89 (0.1351)
Blood group other than O	46 (53.5) (n = 86)	208 (79.1) (n = 263)	3.12 (< 0.0001)
Antiphospholipid antibodies/ lupus anticoagulant	4 (3.1) (n = 127)	23 (5.8) (n = 395)	2.40 (0.1123)
Fatigue			1.75 (0.0257)
Oedema			1.63 (0.0191)
Splenectomy	3 (1.9)	14 (3.2) (n = 431)	1.37 (> 0.2)
Neurologic disease	6 (3.8)	17 (3.9)	1.26 (> 0.2)
Varicose veins and/or chronic venous insufficiency	23 (14.6)	84 (19.3)	1.24 (> 0.2)
Family history of DVT or PE	10 (6.6) (n = 152)	29 (6.7)	1.22 (> 0.2)
History of cancer	18 (11.4)	67 (15.5)	1.21 (> 0.2)
Prolonged hospitalisation	27 (17.2)	96 (22.2)	1.18 (> 0.2)
Thrombophilic disorder	41 (32.3) (n = 127)	140 (35.4) (n = 395)	1.07 (> 0.2)
Congestive heart failure	2 (1.3)	6 (1.4) (n = 432)	0.90 (> 0.2)
Syncope			0.85 (> 0.2)
Chest pain			0.81 (> 0.2)
Previous major surgery	39 (24.8)	98 (22.5)	0.78 (> 0.2)
Obesity	48 (30.4)	101 (23.3)	0.78 (> 0.2)
Inflammatory bowel disease	1 (0.6)	3 (0.7)	0.74 (> 0.2)
Fracture	13 (8.2)	29 (6.7)	0.72 (> 0.2)
Pacemaker	2 (1.3)	5 (1.2)	0.69 (> 0.2)
Major trauma	7 (4.4)	15 (3.5)	0.65 (> 0.2)
Thyroid disorder and replacement therapy	20 (12.7)	35 (8.1)	0.63 (0.1284)
Smoking	71 (45.8)	154 (35.5)	0.56 (0.0040)
Osteoarthritis	4 (2.5)	7 (1.6)	0.52 (> 0.2)
Protracted travel	3 (1.9)	5 (1.2)	0.52 (> 0.2)
Coronary disease and/or myocardial infarction	25 (15.8)	46 (10.6)	0.40 (0.0013)
Dizziness			0.35 (0.0008)
Diabetes mellitus	25 (15.8)	23 (5.3)	0.22 (< 0.0001)
Dialysis-dependent renal failure	3 (1.9)	1 (0.2)	0.21 (0.1637)
Klippel-Trenaunay syndrome	4 (2.5)	1 (0.2)	0.17 (0.0916)
DLCO/VA, % predicted, OR per 10% predicted	67 (n = 122)	74 (n = 228)	1.17 (0.0007)
Oxygen saturation, %, OR per 5%	94	93	0.95 (> 0.2)
Haemoglobin, g/dl, OR per 1 g/dl	14.8 (n = 154)	14.6 (n = 418)	0.93 (0.0065)
Cardiac index, $L.min^{-1}.m^{-2}$	2.2 (n = 154)	2.2 (n = 427)	1.09 (> 0.2)
PAWP, mmHg, OR per 1 mmHg	10	10 (n = 411)	1.05 (0.0473)
RAP, mmHg, OR per 1 mmHg	9 (n = 154)	9 (n = 425)	1.00 (> 0.2)
PVR, $dyn.s.cm^{-5}$, OR per 100 $dyn.s.cm^{-5}$	821	724 (n = 414)	0.94 (0.0084)
mPAP, mmHg, OR per 10 mmHg	52	48	0.72 (< 0.0001)

Values are expressed as numbers (percentages) or median. (n): patients with the assessment (only reported when three or more patients did not have the assessment). [a]For those patients with previous PE. Odd ratios for CTEPH are presented for patients with 1 vs >1 PE and for patients with massive or sub-massive PE vs segmental PE. Nephrotic syndrome, infection of ventriculoatrial shunt or pacemaker and Klinefelter syndrome were not observed. DLCO/VA: carbon monoxide diffusing capacity in the lung per unit alveolar volume, mPAP: mean pulmonary arterial pressure, DVT: deep-vein thrombosis, PE: pulmonary embolism, PVR: pulmonary vascular resistance, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, VTE: venous thromboembolism.

Conditions associated with CTEPH vs IPAH

The selection of medical conditions potentially associated with CTEPH vs IPAH was based on current disease understanding (8-10). The most distinctive feature between CTEPH and IPAH was the presence of a clinical history of acute venous thromboembolism (VTE), which was reported in 80.2% of CTEPH patients compared with 7.0% of IPAH patients (►Table 3). Conditions associated with CTEPH compared with IPAH in univariate analyses included clinical history of acute VTE, large size of previous pulmonary embolism (PE), blood groups other than O, and higher DLCO/VA, whereas diabetes mellitus, coronary disease and/or myocardial infarction, smoking, and higher haemoglobin were associated with an increased risk for IPAH. Symptoms such as haemoptysis, fatigue and

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Table 4: Conditions associated with operability in CTEPH patients – results of univariate analyses.

Risk factors	Operable CTEPH (n = 284)	Non-operable CTEPH (n = 152)	Odds ratio (p-value)
V/Q scintigraphy defect: (right and/or left lung)			
• Total lung defect • Segmental mismatch • Sub-segmental mismatch	19 (9.0) 183 (86.3) 10 (4.7) (n = 212)	4 (3.6) 87 (77.7) 21 (18.8) (n = 112)	8.87 (0.0009)[a] 4.30 (0.0003)[a]
Pulmonary angiography obstruction in: (right and/or left lung)			
• Main pulmonary artery • Lobar arteries • Segmental arteries	51 (26.6) 122 (63.5) 19 (9.9) (n = 192)	14 (14.7) 46 (48.4) 35 (36.8) (n = 95)	6.47 (< 0.0001)[b] 4.80 (< 0.0001)[b]
Blood group other than O	160 (82.5) (n = 194)	48 (69.6) (n = 69)	4.53 (> 0.2)
PVR < 1,200 dyn.s.cm^{-5}	239 (89.2) (n = 268)	119 (81.5) (n = 146)	1.87 (0.0311)
Antiphospholipid antibodies/ lupus anticoagulants	18 (6.8) (n = 265)	5 (3.8) (n = 130)	1.71 (> 0.2)
Dialysis-dependent renal failure	1 (0.4) (n = 283)	0 (0) (n = 150)	1.60 (> 0.2)
Clinical history of acute VTE	228 (82.9) (n = 275)	113 (75.3) (n = 150)	1.59 (0.0619)
Centre expertise[c]			
• High • Medium • Low	142 (50.0) 98 (34.5) 44 (15.5)	70 (46.1) 49 (32.2) 33 (21.7)	1.52 (0.1238)[c] 1.50 (0.1623)[c]
Left ventricular systolic dysfunction	3 (1.1) (n = 261)	1 (0.8) (n = 133)	1.20 (> 0.2)
Thrombophilic disorder	97 (36.6) (n = 265)	43 (33.1) (n = 130)	1.16 (> 0.2)
Pacemaker/Ventriculoatrial shunt	7 (2.5) (n = 283)	4 (2.6) (n = 151)	0.89 (> 0.2)
Coronary disease / myocardial infarction	28 (9.9) (n = 283)	18 (11.9) (n = 151)	0.81 (> 0.2)
COPD	32 (11.9) (n = 270)	20 (14.1) (n = 142)	0.81 (> 0.2)
Splenectomy	6 (2.1) (n = 280)	8 (5.3) (n = 151)	0.40 (0.0947)
Age, years, OR per 10 years	63	68	0.76 (0.0003)
NYHA class, % I+II / III / IV	23.2/64.8/12.0	21.7/67.1/11.2	
• III vs I/II • IV vs I/II			0.91 (> 0.2) 0.99 (> 0.2)
6MWD, m	338 (n = 249)	315 (n = 130)	0.99 (> 0.2)
DLCO/VA, % predicted, OR per 10% predicted	74 (n = 140)	73 (n = 88)	0.99 (> 0.2)
Oxygen saturation, %, OR per 5%	93 (n = 284)	93 (n = 152)	1.00 (> 0.2)
Haemoglobin, g/dl, OR per 1 g/dl	14.6 (n = 267)	14.7 (n = 151)	0.98 (> 0.2)
mPAP, mmHg, OR per 10 mmHg	48 (n = 284)	47 (n = 152)	1.08 (> 0.2)
RAP, mmHg, OR per 1 mmHg	9 (n = 276)	8 (n = 149)	1.02 (> 0.2)
PAWP, mmHg, OR per 1 mmHg	10 (n = 267)	10 (n = 144)	1.03 (0.1489)
PVR, dyn.s.cm^{-5}, OR per 100 dyn.s.cm^{-5}	735 (n = 268)	700 (n = 146)	0.97 (> 0.2)
Cardiac index, L.min^{-1}.m^{-2}, OR per 1 L.min^{-1}.m^{-2}	2.2 (n = 276)	2.3 (n = 151)	0.91 (> 0.2)

Values are expressed as numbers (percentages) or median. (n): patients with the assessment. [a]Odd ratios for operability are presented for patients with total lung defect or segmental mismatch compared with patients with sub-segmental mismatch. [b]Odd ratios for operability are presented for patients with obstruction in main or lobar arteries compared with patients with obstruction in segmental arteries. [c]Centre expertise was defined as high for centres performing more than 50 PEAs per year, medium for 11 to 50 PEAs per year, and low for 1 to 10 PEAs per year. Odd ratios for operability are presented for patients operated in centres with high or medium expertise compared with patients operated in centres with low expertise. COPD: chronic obstructive pulmonary disease, 6MWD: 6-minute walking distance, DLCO/VA: carbon monoxide diffusing capacity in the lung per unit alveolar volume, mPAP: mean pulmonary arterial pressure, NYHA: New York Heart Association, OR: odd ratio, PVR: pulmonary vascular resistance, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, VTE: venous thromboembolism, PEA: pulmonary endarterectomy.

oedema were more likely to be associated with CTEPH and dizziness with IPAH. Among haemodynamic parameters, higher PAWP tended to be associated with CTEPH and higher mPAP and PVR with IPAH. Parameters further identified in multivariate analysis as independent risk factors for CTEPH included clinical history of acute VTE (OR = 42.95, p < 0.0001) and older age (OR per 10 years = 1.26, p = 0.0198), whereas diabetes mellitus (OR = 0.16, p = 0.0006), female gender (OR = 0.49, p = 0.0197) and higher mPAP (OR per 10 mmHg = 0.72, p = 0.0103) were associated with an increased risk for IPAH (▶Figure 1A).

Risk factors for operable/non-operable CTEPH vs IPAH

Independent risk factors for operable CTEPH vs IPAH were the same as for CTEPH vs IPAH (except for older age) (Figure 1): clinical history of acute VTE (OR = 52.51, p < 0.0001) was associated with operable CTEPH, whereas diabetes mellitus (OR = 0.15,

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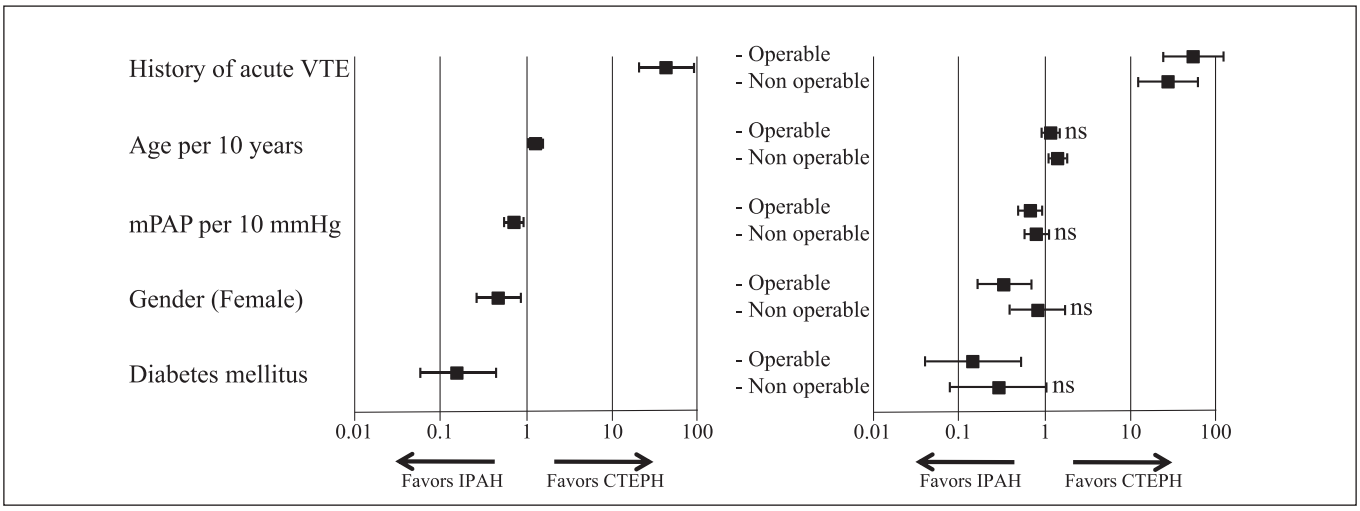

Figure 1: Odd ratios and 95% confidence limits for risk factors identified in multivariate analysis. Results are presented for CTEPH patients vs IPAH patients (A) and for operable/non-operable CTEPH patients versus IPAH patients (B) (n = 461 patients with complete data). mPAP: mean pulmonary arterial pressure, VTE: venous thromboembolism.

p = 0.0024), female gender (OR = 0.33, p = 0.0021), and higher mPAP (OR per 10 mmHg = 0.66, p = 0.0071) were IPAH characteristics. When comparing non-operable CTEPH with IPAH, only clinical history of acute VTE (OR = 27.69, p < 0.0001) and age (OR per 10 years = 1.38, p = 0.0185) were still identified as independent risk factors for CTEPH. With fewer risk factors identified, non-operable CTEPH patients tended to be less differentiable from IPAH patients in risk factor analysis than operable patients.

Conditions associated with operability in CTEPH

Conditions that were considered as potentially associated with operability in CTEPH patients are presented along with univariate analyses (►Table 4). In multivariate analysis, patients with a lower PVR (< 1,200 dyn.s.cm^{-5}) (OR = 3.27, p = 0.0080) and proximal lesions as detected by pulmonary angiography were more likely to be operable: obstruction of main pulmonary artery (OR = 10.77, p < 0.0001) and lobar arteries (OR = 5.61 p < 0.0001), compared with obstruction of segmental arteries, were conditions associated with operability. On the other hand, older age (OR per 10 years = 0.72, p = 0.0108) was an independent risk factor for non-operability.

Discussion

This case-control study involved eight European centres, which concomitantly diagnosed 436 patients with CTEPH (operable and non-operable cases) and 158 patients with IPAH, thus providing a large contemporary database for the comparison of both disease entities. The proportion between the numbers of patients in each group mirrors the CTEPH/IPAH relative incidence in Europe (about 3:1 [14]). A clinical history of acute VTE and older age were strongly associated with CTEPH, whereas diabetes mellitus, increased mPAP, and female gender were independent risk factors for IPAH. Operability of CTEPH patients was strongly associated with younger age, proximal lesions, and PVR below 1200 dyn.s.cm^{-5}.

The contemporary CTEPH and IPAH patient profiles

In line with previous reports (1, 10), CTEPH was equally common in men and women in their sixth decade. The demographic characteristics of IPAH patients confirmed a trend observed in recent years (15-18) suggesting that the average patient diagnosed with IPAH is now older (59 years in this registry) than in the 1980s, (36.4 years in the NIH registry (19). In the recent COMPERA registry (20) and in case report studies (21), IPAH diagnoses have been made in patients older than 70 years, suggesting that the disease also occurs in the elderly. Nevertheless, when compared with CTEPH, IPAH remains a disease of younger and predominantly female patients.

CTEPH: a thromboembolic disorder

The thromboembolic nature of CTEPH was confirmed by a strong association with a history of acute VTE, as observed in previous studies (10). A previous PE classified as 'massive' or 'sub-massive' was an additional risk factor for CTEPH in univariate analyses, but recurrent PE (occurring twice or more) was not. The rate of history of acute VTE was particularly elevated in this cohort with 80% patients reporting the event, compared with 58% and 69% in previous European studies (10, 22). Increased awareness for thromboembolism in participating centres may have contributed to higher detection. Blood group other than O was also a predictor for CTEPH diagnosis and has been reported as a specific feature of the CTEPH patient population (7). Coagulation abnormalities and autoimmune or haematologic disorders have been documented in

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patients with VTE and to a lesser extent in patients with CTEPH (6, 7, 10). In the present study, a thrombophilic disorder was present in one third of CTEPH patients but the proportion was similar in IPAH patients, precluding identification of a specific diagnosis factor.

Haemodynamics in IPAH and CTEPH

In the present study, mPAP was identified as a risk factor for PAH, which is in line with other reports indicating that mPAP is lower in CTEPH than in PAH (10, 23), possibly because of a limited right ventricular adaptation in CTEPH (23), or less severe vascular involvement.

IPAH and diabetes mellitus

A strong association has been reported between diabetes mellitus and pulmonary hypertension (24). In the general population aged 20-79 years living in the European countries involved in the present study, the prevalence of diabetes mellitus reported by the International Diabetes Federation (25) is 7.9%. Age matched occurrences in our study were above this value for patients with IPAH (14.5%) and below for patients with CTEPH (5.3%). The REVEAL study similarly identified 14.2% patients with diabetes mellitus among IPAH patients (2), implying that this condition is relatively common in IPAH. Glycosylated haemoglobin A1c (HbA1c) has been proposed as an independent predictor of long-term prognosis in PAH (26) suggesting a link between IPAH and diabetes involving a possible common autoimmune origin.

Operability of CTEPH patients in current practice

PEA is the treatment of choice for CTEPH but the success of the procedure is dependent on appropriate pre-operative patient selection. In the absence of established guidelines, the decision to operate is based on the surgeon's judgment. In this European cohort of CTEPH patients, an independent criterion for surgery was the presence of accessible chronic thromboembolic disease assessed by pulmonary angiography. The assessment of the degree of pulmonary hypertension in relation to lesion localisation is also essential for the decision to perform surgery. An excessive increase in PVR may arise from a distal, small vessel arteriopathy that will not be amenable to surgery. Most studies have associated high pre-operative PVR (above 900 to 1,100 dyn.s.cm^{-5}) with increased PEA mortality (1, 11, 22, 27). In the present investigation, a PVR over 1200 dyn.s.cm^{-5} was predictive of non-operability. However, a PVR over 1200 dyn.s.cm^{-5} should not be considered a contraindication to operate, as patients with an elevated PVR will definitively benefit from surgery performed by an experienced surgical team. Non-operable CTEPH patients are more likely to have a secondary vasculopathy of peripheral pulmonary vessels, with histological features resembling those seen in IPAH (28). The present analysis of risk factors associated with a CTEPH or IPAH diagnosis identified fewer risk factors for non-operable CTEPH patients suggesting that non-operable patients are harder to differentiate from IPAH patients than operable patients and require careful radiological imaging. Non-operable CTEPH patients are also more frequently treated with PAH-specific therapies (12).

Limitations

The limitations of the study are inherent to a registry design: some assessments were not systematically collected leading to missing values and under-reporting, which may explain why the aetiological importance of previously described medical risk factors, such as ventriculoatrial shunt, APA/LAC, previous splenectomy, and history of cancer (6, 10) could not be validated. Furthermore, centre expertise expressed by the number of PEAs per year was not statistically correlated with the adjudication of operability, and may not be an appropriate surrogate for expertise.

Conclusion

The findings of the present study confirms the thromboembolic nature of CTEPH by reporting a high rate of history of acute VTE and a strong association between a CTEPH diagnosis and a history of acute VTE or blood groups other than O. Diabetes mellitus emerged as an independent risk factor for IPAH.

A variable degree of small vessel arteriopathy can contribute to the development of CTEPH and histopathologic studies have indicated overlap in the microvascular pathology of IPAH and CTEPH. In particular, patients with non-operable CTEPH are more likely to have significant distal small vessel disease representing an extreme of the CTEPH disease spectrum that is more difficult to differentiate from IPAH. Currently there is no pre-operative classification system allowing for surgical risk stratification, and the expertise of the operating team is crucial in the decision to operate. Patients should be referred for evaluation by a multidisciplinary team experienced in PEA.

What is known about this topic?

- Chronic thromboembolic pulmonary hypertension (CTEPH) and idiopathic pulmonary hypertension (IPAH) share a similar clinical presentation but differ in associated medical conditions.
- IPAH may be associated with specific features of the metabolic syndrome and possibly with autoimmune thyroid disease.

What does this paper add?

In a case-control-study comparing 436 consecutive patients with CTEPH with 158 patients with IPAH, we found that

- a clinical history of acute VTE, large previous pulmonary embolism, blood groups other than O and older age are associated with CTEPH;
- diabetes mellitus, increased mPAP, and female gender are independent risk factors for IPAH;
- operability of CTEPH patients is strongly associated with younger age, proximal lesions, and PVR below 1200 dyn.s.cm^{-5}.

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Conflicts of interest

D. Ambroz has received reimbursement from the industry for attending symposia and fees for speaking. M. Delcroix has received fees for serving as investigator, speaker, consultant, or steering committee member from Actelion, Bayer, Eli Lilly, GSK, Novartis, Pfizer and United Therapeutics. He has received educational grants from Actelion, GSK, Pfizer and Therabel, and research grants from Actelion,Pfizer and GSK. M. Delcroix is holder of the Actelion Chair for Pulmonary Hypertension and the GSK Chair for research and education in pulmonary vascular pathology at the Catholic University of Leuven. I. M. Lang has received speaker fees and/or educational grants from Actelion, GSK, United Therapeutics, Bayer and AOPOrphan Pharma, and has acted in advisory boards for Actelion, GSK, Pfizer, Lilly, Servier and AstraZeneca. I. M. Lang has received a fellowship grant from the US Tobacco Research fund in 1991. E. Mayer has received speaker fees from Bayer, Pfizer and Actelion and consulting fees from Bayer and Actelion. J. Pepke-Zaba has received reimbursement of travel expenses, speaker fees and research funds from Actelion, GSK, Pfizer, Bayer, Lilly and United Therapeutics, and has participated in advisory boards of Actelion, Pfizer, Bayer, Lilly, United Therapeutics and Novartis. G. Simmoneau has served as a consultant, served on scientific advisory boards and has been investigator in trials involving Actelion, Bayer, Eli Lilly, GSK, Novartis and Pfizer. A. Torbicki has served as consultant for Actelion, Eli Lilly, GSK, and mondoBiotech, and has received honoraria from Bayer Schering, Eli Lilly and Sanofi-Aventis. A. Torbicki has conducted research supported by Actelion, Bayer Schering, BMS, Eli Lilly, GSK, mondoBiotech and Pfizer. None of the other authors declares any conflicts of interest.

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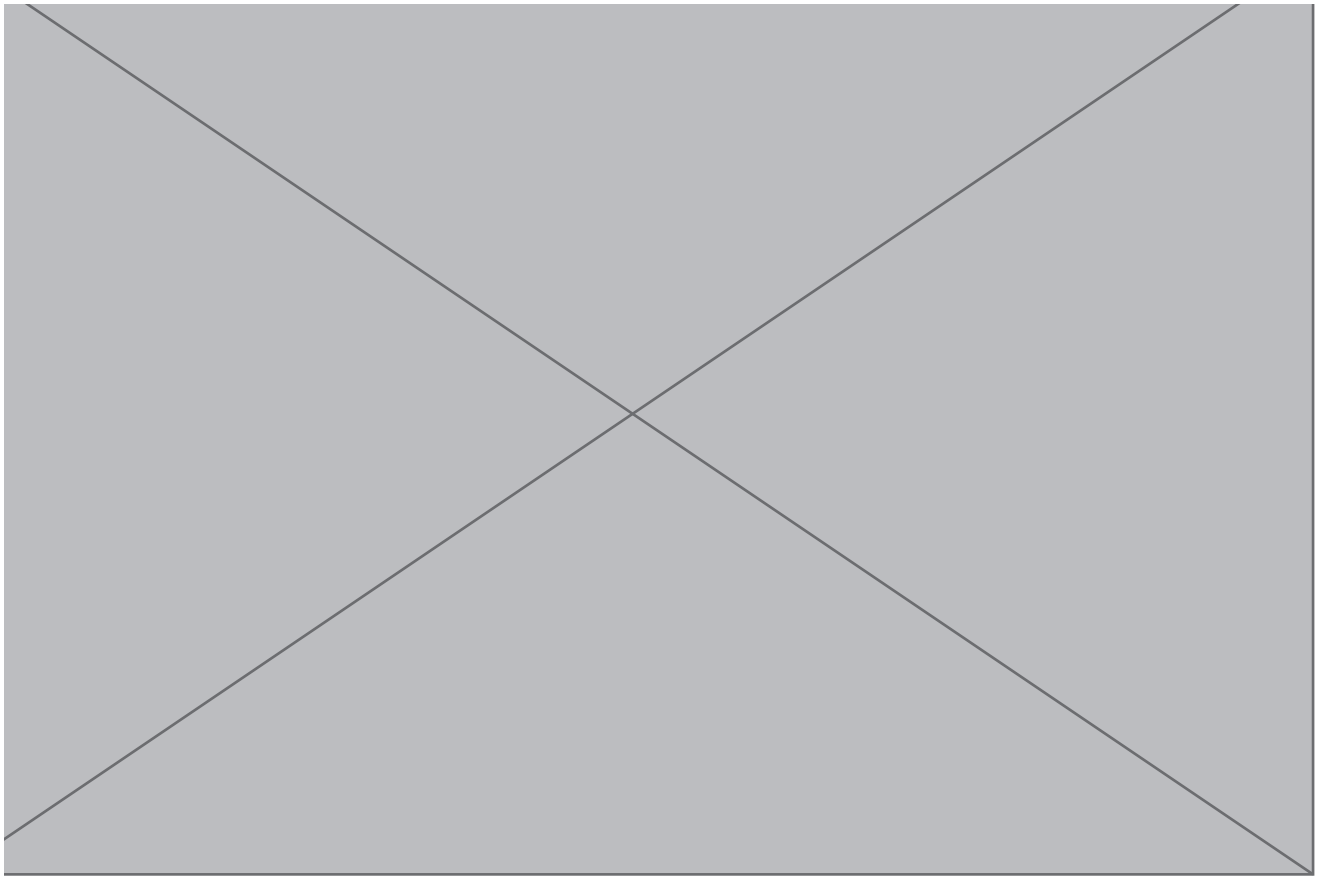

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