

459. Acute and chronic pulmonary thromboembolic disease

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Prognostic factors of pulmonary embolism: results of a prospective multicenter study

Olivier Sanchez¹, Vincent Caille², Francis Couturaud³, Gérard Pacouret⁴, Nicolas Meneveau⁵, Franck Verschuren⁶, Pierre-Marie Roy⁷, Florence Parent⁸, Arnaud Perrier⁹, Christine Lorut¹⁰, Bernard Tardy¹¹, Ludovic Trinquart¹², Marie-Odile Benoit¹³, Guy Meyer¹. ¹Service de Pneumologie et Soins Intensifs, Université Paris Descartes, Hôpital Européen Georges Pompidou, Paris, France; ²Service de Réanimation Médicale, Hôpital Ambroise Paré, Boulogne, France; ³Service de Médecine Interne, Hôpital La Cavale Blanche, Brest, France; ⁴USCI, Service de Cardiologie A, Hôpital Trousseau, CHRU de Tours, Tours, France; ⁵Service de Cardiologie, CHU Jean Minjoz, Besançon, France; ⁶Service des Urgences, Cliniques universitaires Saint Luc, Bruxelles, Belgium; ⁷Service d'Accueil des Urgences, CHU d'Angers, Angers, France; ⁸Service de Pneumologie, Hôpital Antoine Béclère, Clamart, France; ⁹Division of General Internal Medicine, Geneva University Hospital, Genève, Switzerland; ¹⁰Service de Pneumologie, Hôtel Dieu de Paris, Paris, France; ¹¹Service des Urgences et Réanimation Médicale, CHU St-Etienne Bellevue, St-Etienne, France; ¹²Unité de Recherche Clinique, Hôpital Européen Georges Pompidou, Paris, France; ¹³Biochimie, Hôpital Européen Georges Pompidou, Paris, France

Introduction: The short-term prognosis of pulmonary embolism (PE) depends on hemodynamic status and underlying disease. The prognostic value of other clinical variables, right ventricular dysfunction (RVD) assessed by echocardiography, and increased levels of cardiac biomarkers is less well established.

Aim: To evaluate the prognostic factors of PE

Design: Multicenter prospective study

Methods: Echocardiography and blood samples were obtained on admission in unselected consecutive patients with acute PE for independent assessment of brain natriuretic peptide (BNP), N-terminal(NT)-proBNP, cardiac troponin I (cTnI) levels and RVD. The main outcome was all cause 30-days mortality.

Results: 592 consecutive patients with acute PE were included in 11 centers. 41 (7%) patients had massive PE defined by persistent shock. 56 (9.4%) patients received fibrinolysis. 30-days mortality was 4.4% (95%CI, 2.9 – 6.4) and was significantly higher in patients with massive PE as compared to normotensive PE patients (26.8% (95%CI, 14.2 – 42.9) vs 2.7% (95%CI, 1.5 – 4.5)). On multivariate analysis, shock at admission (OR 7.7; 95%CI, 2.9 – 20.4; p<0.0001), chronic renal failure (OR 5.0; 95%CI, 1.5 – 17.0, p=0.009), and BNP (OR 1.7; 95%CI, 1.2 – 2.4, p=0.003) were associated with 30-days mortality. In normotensive patients, chronic renal failure (OR 5.1; 95%CI, 1.3 – 20.4, p=0.02), cancer (OR 4.3; 95%CI, 1.3 – 14.3, p=0.01) chronic respiratory failure (OR 4.1; 95%CI, 1.03 – 16.6, p=0.04) and NT-proBNP (OR 1.5; 95%CI, 1.1 – 2.2, p=0.02) were associated with 30-days mortality.

Conclusion: Clinical variables are associated with a much higher 30-days mortality risk than RVD assessed by cardiac biomarkers or echocardiography.

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Diagnosing pulmonary embolism by multi-detector computed tomography alone or combined with lower limb venous ultrasonography: a randomized non-inferiority trial

Marc Righini, Grégoire Le Gal, Drahomir Aujesky, Pierre-Marie Roy, Olivier Sanchez, Franck Verschuren, Olivier Rutschmann, Michel Nonent, Jacques Cornuz, Frederic Thys, Cedric Petit Le Manach, Marie-Pierre Revel, Pierre-Alexandre Poletti, Guy Meyer, Dominique Mottier, Thomas Perneger, Henri Bounameaux, Arnaud Perrier. *Division of Angiology and Hemostasis, Division of General Internal Medicine, Department of Internal Medicine, Department of Radiology, Clinical Epidemiology, Geneva University Hospital, Geneva/Switzerland, Switzerland; Department of Internal Medicine and Chest Disease, Brest University Hospital, Brest, France; Department of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland; Emergency Department, Saint-Luc University Hospital, Bruxelles, Belgium; Emergency Department, Angers University Hospital, Angers, France; Service of Pneumology and Service of Radiology, Hopital Europeen Georges-Pompidou, Paris, France*

Background: Recent data suggest that multi-slice computed tomography (MSCT) combined with D-dimer measurement may safely rule out pulmonary embolism (PE). We compared this combination with a strategy in which both a negative lower limb vein ultrasonography (US) and a negative MSCT were required to rule out PE.

Methods: We included 1819 consecutive outpatients with clinically suspected PE in a multicentre non-inferiority randomized controlled trial comparing two strategies: clinical probability assessment and either 1) D-Dimer measurement and computed tomography (DD-CT strategy) or 2) D-Dimer measurement, lower limb vein US and computed tomography (DD-US-CT strategy). The main outcome was the 3-month thromboembolic risk in patients left untreated based on the exclusion of PE by the diagnostic strategy.

Findings: The prevalence of PE was 21% in both study arms. In the per-protocol analysis, the 3-month thromboembolic risk was 0.3% (95% CI: 0.1-1.1) in the DD-US-CT arm and 0.3% (95% CI: 0.1-1.2) in the DD-CT arm, a non-significant difference (0.0; 95% CI: -0.9 to 0.8). Results were similar in the intention-to-diagnose analysis. In the DD-US-CT arm, US showed a deep venous thrombosis, hence allowing foregoing MSCT, in 9% of patients. The mean cost per patient was 20 to 30% higher in the DD-US-CT strategy.

Interpretation: The strategy combining D-Dimer and MSCT is as safe as the strategy combining D-dimer, MSCT and lower limb vein compression US for excluding PE. Although the diagnostic yield of US is low when performed before MSCT, it may remain of interest in patients with a contraindication to CT.

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Predictive value of fibrinogen/D-dimer ratio in patients with pulmonary embolism: a retrospective study

Elena Parazzini¹, Michele Ciccarelli¹, Lucia Testoni¹, Giuseppe Boari², Antonio Voza¹, Massimo Giorgino¹, Alfonso Maiorino¹, Salvatore Badalamenti¹, Stefano Centanni³. ¹Emergency Department, Istituto Clinico Humanitas, Rozzano/Milan, Italy; ²Department of Statistical Sciences, Cattolic University of Milan, Milan, Italy; ³Respiratory Medicine Unit, University of Milan, Ospedale San Paolo, Milan, Italy

Fibrinogen and D-dimer are elevated in many diseases presenting signs and symptoms similar to those seen in patients with pulmonary embolism (PE). High D-dimer level is predictive of PE with low specificity (21%) and very high sensibility (>90%). So far has been poorly investigated the diagnostic value of fibrinogen/D-dimer ratio (F/D ratio) in patients with PE. The purpose of this study is to evaluate if F/D ratio could be predictive for PE more than D-dimer measurement alone. We analysed data from 360 patients who attended our emergency department during year 2006 with clinically suspected PE and with no more than one week symptoms onset. We selected one hundred and two patients who underwent fibrinogen and D-dimer tests and pulmonary angio CT at their arrival in emergency. On the basis of CT analysis, 54 of 102 patients were PE positive and 48 PE negative. Fibrinogen, D-dimer and F/D ratio were different in PE-positive compared with PE-negative patients [medians (and ranges): fibrinogen 430 (84 – 679) vs 528 (203 – 1314) mg/dl, P< 0.02; D-dimer 3128 (581 – 40639) vs 1332 (359 – 6826) ng/ml, P< 0.0001; F/D ratio 0.1314 (0.0021 – 0.5886) vs 0.7469 (0.0426 – 2.2513), P< 0.0001]. Analysing our data by receiver operating characteristics (ROC), F/D ratio ≤ 0.347 resulted to be predictive for PE with high specificity (96%) and high sensibility (98%), while D-dimer alone was predictive with low specificity (31%) and high sensibility (100%). In conclusion our findings suggest that F/D ratio could become a valid tool for PE diagnosis. Our results seem to be encouraging even if they need to be confirmed by further and prospective studies on a greater number of patients.

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Chronic thromboembolic pulmonary hypertension and associated medical conditions

Diana Bonderman¹, Heinrike Wilkens², Samo Wakounig³, Pavel Jansa⁴, Iveta Simkova⁵, Amadea Martitschnig¹, Julia Dudczak¹, Roela Sadushi¹, Nika Skoro-Sajer¹, Walter Klepetko⁶, Irene Lang¹. ¹Division of Cardiology, Medical University of Vienna, Vienna, Austria; ²Pneumology, Allergology and Environmental Medicine, University Hospital of Saarland, Homburg/Saar, Germany; ³Core Unit of Medical Statistics and Informatics, Medical University of Vienna, Vienna, Austria; ⁴Department of Cardiology and Angiology, General Teaching Hospital, Prague, Czech Republic; ⁵Department of Cardiology, Medical University of Slovakia, Bratislava, Slovakia; ⁶Department of Cardiothoracic Surgery, Medical University Vienna, Vienna, Austria

Rationale: CTEPH is characterized by nonresolving pulmonary thromboemboli. Specific CTEPH-predisposing medical conditions, such as splenectomy, ventriculoatrial (VA-) shunt and certain inflammatory disorders have been identified.

Objective: We sought to confirm known and to identify novel CTEPH risk factors in a large cohort of prevalent CTEPH cases collected in 3 European centers offering pulmonary endarterectomy.

Methods: Data from CTEPH patients were compared with pulmonary arterial hypertension cohorts utilizing logistic regression analysis.

Main Results: The study population comprised 585 patients assessed at the time of diagnosis between 1996 and 2007. Among 401 patients with CTEPH were 53% females, mean age was 56±14 years and the median (lower quartile, upper quartile) pulmonary vascular resistance was 822 (571, 1095) dynes.s.cm-5. The data confirmed that patients with VA-shunts and patients with infected pacemakers (odds ratio (OR) and 95% confidence interval 76.40 [7.67-10351], p=0.001), splenectomy (OR 17.87 [1.56-2438], p=0.017), previous venous thromboembolism (VTE) (OR 4.52 [2.35-9.12], p<0.001), recurrent VTE (OR 14.49 [5.40-43.08], p<0.001), blood groups non-0 (OR 2.09 [1.12-3.94], p=0.019), and lupus anticoagulant/anti-phospholipid antibodies (OR 4.20 [1.56-12.21], p=0.004) have an increased risk for CTEPH. Thyroid replacement therapy (OR 6.10 [2.73-15.05], p0.001) and a history of malignancy (OR 3.76 [1.47-10.43], p=0.005) emerged as novel CTEPH risk factors.

Conclusions: This European database confirmed previous knowledge on CTEPH risk factors, and identified thyroid replacement therapy and a history of malignancy as new medical conditions associated with CTEPH.

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Prevalence of pulmonary hypertension in patients after splenectomy

Diana Bonderman, Bernhard Dareb, Amadea Martitschnig, Nika Skoro-Sajer, Irene Lang. *Cardiology, Medical University of Vienna, Vienna, Austria*

Background: Patients after splenectomy are at increased risk of developing chronic thromboembolic pulmonary hypertension (CTEPH). However, the prevalence of CTEPH among splenectomized individuals is unknown.

Methods: In the context of the pulmonary hypertension (PH) screening program at the Medical University of Vienna, 1100 general practitioners and internal medicine specialists in Vienna and Lower Austria were invited to refer patients (pts) at least one year after splenectomy. Screening was performed by transthoracic echocardiography with Doppler. In cases of elevated systolic pulmonary arterial pressure (sPAP>40mmHg) and absence of left ventricular or valvular dysfunction, right heart catheterization was performed.

Results: Between November 2006 and October 2007, 91 pts were referred (50males/41 females). Mean age was 52.6±14.2 years. Median time since splenectomy was 143 months. Reasons for splenectomy were trauma (n=39), hematological disorders (n=18), surgical complications (n=18) and others (n=16). CTEPH was newly diagnosed in 4 pts who had suffered from exertional dyspnea.

Conclusion: CTEPH was diagnosed in 4.4% of pts after splenectomy. Echocardiographic screening for CTEPH is useful after splenectomy, especially in pts with unexplained dyspnea.

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Prognostic factors in surgically-treated chronic thromboembolic pulmonary hypertension

Robin Condliffe^{1,2}, David G. Kiely², J. Simon R. Gibbs³, Paul A. Corris⁴, Andrew J. Peacock⁵, David P. Jenkins¹, Kim Goldsmith¹, J. Gerry Coghlan⁶, Joanna Pepke-Zaba¹. ¹Pulmonary Vascular Disease Unit, Papworth Hospital, Cambridge, United Kingdom; ²Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, United Kingdom; ³Department of Cardiology, Hammersmith Hospital, London, United Kingdom; ⁴Northern Vascular Unit, Freeman Hospital, Newcastle-upon-Tyne, United Kingdom; ⁵Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow, United Kingdom; ⁶Department of Cardiology, Royal Free Hospital, London, United Kingdom

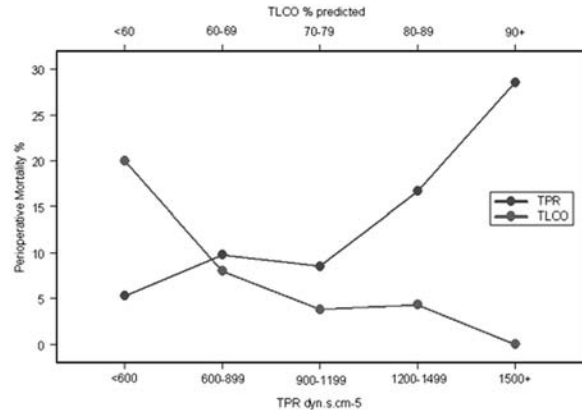
Background: A limited number of prognostic factors have been assessed in chronic thromboembolic pulmonary hypertension (CTEPH) patients undergoing pulmonary endarterectomy (PEA).

Aims: To identify prognostic variables for surgically-treated patients in the UK national CTEPH cohort.

Methods: Multiple variable logistic regression analysis was performed using data for all surgically-treated CTEPH patients diagnosed in the UK pulmonary hyper-

tension service between January 2001 and June 2006. Pulmonary hypertension was defined as a mean pulmonary artery pressure ≥ 25 mmHg.

Results: 236 patients diagnosed during this period underwent PEA. In univariate analysis non-white ethnicity, higher baseline total pulmonary resistance (TPR), and lower baseline cardiac index, exercise capacity and gas transfer (TLCO) predicted perioperative death. In multivariable analysis lower TLCO (Odds Ratio 0.30; 0.11,0.87) and exercise capacity (Odds Ratio 0.31; 0.13,0.74) were independent predictors of mortality. Perioperative mortality, based on both TLCO and the currently used parameter of pulmonary resistance, in patients diagnosed after 2002 is shown below.



Conclusion: Gas transfer and exercise capacity independently predict perioperative mortality in surgically-treated CTEPH patients. These newly identified variables could be incorporated into decision-making regarding suitability for PEA.

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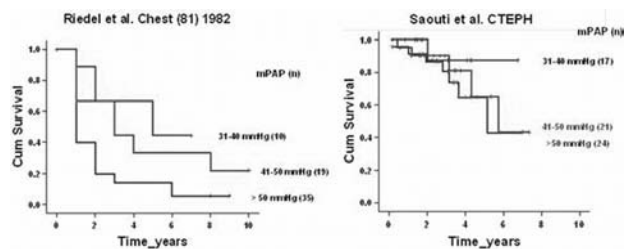
Longterm survival of inoperable chronic thromboembolic pulmonary hypertension (CTEPH)

Nabil Saouti, Frances de Man, Anco Boonstra, Anton Vonk-Noordegraaf. *Pulmonary Diseases, Institute for Cardiovascular Research ICaR-VU, VU University Medical Center, Amsterdam, Netherlands*

Introduction: Until now little is known about the longterm survival of inoperable CTEPH. A historical cohort of Riedel et al. (Chest 1982; 81:151-8) have shown survival rates of patients with pulmonary thromboembolism not medical treated for CTEPH. The aim of our study is to describe our longterm survival of CTEPH treated by means of PAH specific medication and compare these data with the Riedel cohort.

Methods: This retrospective study presents 93 patients followed-up over the period 1999 and 2007 diagnosed as having CTEPH, not eligible for surgery. The diagnosis CTEPH was made by ventilation/perfusion scintigraphy and catheter-directed pulmonary angiography. Treatment algorithms used in this group of patients was similar as used in the treatment of PAH including bosentan, sildenafil and flolan.

Results: Our data compared with that of Riedel et al. show that for patients with a mean pulmonary artery pressure (mPAP) between 31-40 mmHg the 5-years survival is 88% (SE 0,12) vs. 45% (SE 0,17), for a mPAP between 41-50 mmHg the 5-years survival is 65% (SE 0,17) vs. 33% (SE 0,11) and for a mPAP >50 mmHg the 5-years survival is 65% (SE 0,13) vs 14% (SE 0,06).



Conclusion: These data show that longterm survival of CTEPH in a medical treated group is much better than the historical medical untreated cohort.

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Regression of high flow-induced pulmonary vasculopathy after flow correction is improved by TBC3711

Olaf Mercier, Saadia Eddahibi, Elisabeth Marcos, Elie Fadel. *LCE UPRES EA 2705, Hôpital Marie Lannelongue, Le Plessis Robinson, France*

Introduction: Postembolic pulmonary hypertension is due to partial obstruction of pulmonary arteries and may resolve after pulmonary endarterectomy (PTE). Persistent pulmonary hypertension may reflect vessel alterations induced by high flow

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in unobstructed territories. We evaluated the effect of TBC3711, an ETA antagonist on the regression of the pulmonary vasculopathy (PV) after flow correction

Methods: An aorto-pulmonary shunt was performed for 5 wks in piglets to induce pulmonary overflow. Studies were performed in shunted animals, 1 wk after shunt closure, 5 wks after shunt closure and 1 wk after shunt closure associated to TBC3711 treatment given during the last 15 days. Those groups were compared to a sham group. Morphometry, smooth muscle cell (SMC) proliferation by PCNA and apoptosis by TUNEL, and quantification of ET and Angiopoetin (Ang) pathways by RT-PCR were studied

Results: Media thickness was increased in shunted animals (35% vs 56%, $P<0.0001$), started to decrease 1 wk after the shunt closure (50%, $P=0.062$) and remained higher than sham values 5 wks later (41%, $P<0.001$). A complete regression of media thickness was observed 1 wk after shunt closure in animals treated with TBC3711. Medial hypertrophy was related to SMC proliferation and its regression to SMC apoptosis. mRNA steady states of ET-1, ETA, Ang-1 and Tie 2 were increased in shunted animals and returned to normal values 1 wk after shunt closure

Conclusion: Anti-ETA therapy may increase the regression of high flow-induced pulmonary vasculopathy after flow-correction and could be given before PTE to patients with severe associated PV.