Eur Respir Rev 2012; 21: 123, 27–31
DOI: 10.1183/09059180.00009111

REVIEW

Risk factors for chronic thromboembolic pulmonary hypertension

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ABSTRACT: Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension caused by obstruction and vascular remodelling of pulmonary arteries following pulmonary embolism. Risk factors that predispose patients to CTEPH include the size of the initial thrombus and numerous associated host or medical conditions. Haemostatic risk factors include elevated levels of factor VIII and phospholipid antibodies or intrinsic abnormalities in fibrinogen. Medical conditions that are associated with an increased risk of CTEPH include a history of splenectomy, cancer, ventriculoatrial shunt, chronic inflammatory disease, antiphospholipid antibodies and hypothyroidism. Although CTEPH is potentially curable by pulmonary endarterectomy (PEA), up to 40% of patients evaluated for PEA may be denied surgery depending on the level of surgical experience and disease accessibility after pre-operative assessment. Furthermore, an estimated 10–15% of patients are at risk for residual pulmonary hypertension following PEA surgery, due to significant concomitant small-vessel disease. However, pre-operative identification of small-vessel involvement remains a challenge. The current medications effective in the treatment of pulmonary arterial hypertension have not demonstrated efficacy in CTEPH. Accordingly, identification of CTEPH, followed by early referral for evaluation and treatment by an experienced PEA centre, is recommended.

KEYWORDS: Chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, pulmonary hypertension, risk factors, small-vessel disease

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subset of pulmonary hypertension (PH) characterised by the obstruction of pulmonary arteries with fibrotic material and vascular remodelling that leads to increased pulmonary arterial pressure (P_{pa}) and right ventricular failure [1]. CTEPH is thought to develop following a pulmonary embolism (PE) that fails to resolve in between 0.57% and 9.1% of patients [2–6]. The largest of these studies, conducted in the Netherlands by KLOK *et al*. [6], followed 866 patients with PE. They observed a total cumulative incidence of CTEPH of 0.57%. However, there are a significant number of patients with CTEPH who have no obvious history of acute PE, thought to range from 25% to 63% of patients with CTEPH [7–11]. Therefore, the true incidence of CTEPH is likely to be underestimated by studies that only follow patients after a PE [9], and highlights the fact that all patients with PH should be assessed for CTEPH even in the absence of prior PE.

Patients with CTEPH have a poor prognosis if left untreated but CTEPH can be cured in the majority of patients by a surgical procedure called pulmonary endarterectomy (PEA) [12]. However, CTEPH is often misdiagnosed and/or treated as pulmonary arterial hypertension (PAH) and this generally leads to delays in referral of patients for PEA [13]. In a European study of 679 patients between 2007 and 2009, diagnosis of CTEPH was made after a median of 14.1 months from onset of symptoms and 63% of patients were considered to have operable disease [11]. Better understanding of risk factors and underlying mechanisms of CTEPH could improve diagnosis and allow appropriate interventions to reach patients faster, thereby limiting disease progression and improving survival.

RISK FACTORS FOR CTEPH

Acute pulmonary embolism

The risk of developing CTEPH following an acute PE is increased by a number of factors. When 78 patients were followed for 5 yrs after an acute PE,

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Received:
Dec 16 2011
Accepted:
Jan 04 2012

PROVENANCE
Publication of this peer-reviewed article was supported by Bayer Pharma AG, Germany (article sponsor, *European Respiratory Review* issue 123).

European Respiratory Review
Print ISSN 0905-9180
Online ISSN 1600-0617

those who had persistent PH 1 yr after the PE were found to have had a higher P_{pa} at the time of diagnosis than those who did not have persistent PH ($p<0.0001$) [2]. Among 305 patients presenting with acute PE, 18 went on to develop CTEPH. Independent risk factors for CTEPH in that group were a previous PE, a large perfusion defect and idiopathic presentation [4]. Idiopathic PE was also associated with an increased incidence of CTEPH in 866 patients with acute PE. In that study, 1.5% of patients with idiopathic PE went on to develop CTEPH compared with 0.57% in the total population [6]. Both PENGO *et al.* [4] and KLOK *et al.* [6] found that all cases of CTEPH became apparent within 2 yrs of the PE.

Haemostatic risk factors

A number of procoagulant proteins and other haemostatic factors have been associated with an increased risk of CTEPH. Once a PE has occurred, these local factors may favour the formation of *in situ* thrombosis [14]. An elevated level of factor VIII was identified as a risk factor for CTEPH in a study of 122 patients compared with 82 healthy controls and 88 patients with PAH ($p<0.0001$ for both) [15]. This was confirmed in a recent comparison of factor VIII levels in 45 patients with CTEPH *versus* 200 patients with non-thromboembolic PH ($p=0.01$) [16]. Von Willebrand factor was also elevated in these patients compared with patients in the control group ($p=0.009$) [16]. Elevated expression of type 1 plasminogen activator inhibitor (PAI-1) has been found in neovessels within CTEPH thrombi [17, 18], which may affect clearance of the thrombus [14]. However, when PAI-1 was measured in plasma from patients with CTEPH, no difference was seen in the relative levels of plasminogen activator and PAI-1 compared with healthy controls [19], which may suggest that any changes in PAI-1 expression remain localised to the CTEPH thrombus.

Abnormalities in fibrinogen structure and function have also been observed in patients with CTEPH. *In vitro* studies have shown that fibrinogen from patients with CTEPH is more resistant to fibrinolysis than that from healthy controls [20]. Five fibrinogen variants have been identified in 33 patients with CTEPH [21]. A significant association has also been seen between heterozygous fibrinogen Thr312Ala and CTEPH in 214 patients with CTEPH *versus* 200 healthy controls ($p=0.02$) [22]. Interestingly, the exposure of endothelial cells to fibrin and fibrinogen was shown to increase the activation of the cells by thrombin suggesting that this process may have a role in vascular remodelling [23].

CTEPH may also be more common in people with non-O blood groups. In one study, 77% of patients with CTEPH were found to have non-O blood groups compared with 58% of patients with PAH ($p=0.003$) [15]. This was later confirmed by the same group (OR 2.09, 95% CI 1.12–3.94; $p=0.019$) [8]. Elevated plasma levels of lipoprotein(a) may also contribute to a hypercoagulable state and were found to be significantly raised in patients with CTEPH compared with patients with PAH ($p<0.002$) and healthy controls ($p<0.0002$) [24].

Associated medical conditions

Patients who have undergone a splenectomy have a significantly higher risk of developing CTEPH. In one study, 5.5% of patients with CTEPH had undergone a previous splenectomy compared with none in the non-thromboembolic PH group ($p<0.05$) [8]. This supported an earlier finding that 8.6% of patients with CTEPH had a history of splenectomy compared with 2.5% of patients with idiopathic PAH and 0.6% of healthy controls ($p<0.01$ for both) [25]. Association between splenectomy and CTEPH was further supported in a study where 9% of patients with CTEPH had undergone a previous splenectomy compared with 0.5% of patients who had an acute PE but did not go on to develop PH (OR 13, 95% CI 2.7–127) [7].

The association between splenectomy and CTEPH may be due to the presence of abnormal erythrocytes that would normally be filtered out of the blood by the spleen. The abnormal expression of phosphatidylserine on the surface of erythrocytes may trigger the coagulation process, resulting in the formation of thromboembolic material [26]. Reactive thrombocytosis may also be responsible for the increased risk of CTEPH following a splenectomy. Thrombocytosis occurs in ~75% of patients following splenectomy and can lead to a hypercoagulable state and thrombosis [7, 27]. However, thrombocytosis was not found to be significantly associated with an increased risk of CTEPH ($p=0.53$), although it should be noted that only one patient in the control group of that study had a history of splenectomy [7].

The presence of a ventriculoatrial (VA) shunt or infected pacemaker has also been linked with an increased risk of developing CTEPH. In one study, 2.8% of patients with CTEPH had a VA shunt compared with none of the patients with non-thromboembolic PH ($p<0.05$). In addition, 0.9% of patients with CTEPH had an infected pacemaker compared with none of the control group; however, this did not reach statistical significance [8]. Similar results were observed in another study where 6% of patients with CTEPH had a VA shunt compared with 0.5% of patients with acute PE who did not subsequently develop PH (OR 13, 95% CI 2.5–129) [7].

Infection may have a role in the association between VA shunts and CTEPH. A small study examined VA shunts from seven patients with CTEPH and found staphylococcal infection in six cases [28]. The same study also investigated staphylococcal infection in a mouse model of venous thrombosis and found that infection delayed thrombus resolution and upregulated transforming growth factor-β and connective tissue growth factor [28]. The authors hypothesised that staphylococcal infection enhances vascular remodelling, leading to failure of thrombus resolution and the subsequent development of CTEPH [28].

Patients with chronic inflammatory diseases such as osteomyelitis and inflammatory bowel disease may also be at greater risk of developing CTEPH. One study found that 10% of patients with CTEPH had a chronic inflammatory condition compared with none of the patients who had not developed CTEPH following a PE (OR 67, 95% CI 7.9–8,832) [7]. A later study by the same group failed to show a statistically significant link between inflammatory conditions and an increased risk of CTEPH, although there were numerically more cases of inflammatory bowel disease amongst patients with CTEPH than amongst those with non-thromboembolic PH (12 *versus* three, respectively) [8].

Inflammatory markers appear to be increased in patients with CTEPH compared with healthy controls. C-reactive protein

was significantly higher in patients with CTEPH compared with healthy subjects ($p<0.01$) [29]. Levels of the cytokines interleukin (IL)-1b, IL-2, IL-4, IL-8 and IL-10 have also been found to be increased in patients with CTEPH compared with healthy controls [30]. In addition, inflammatory cell infiltration has been observed in proximal pulmonary arteries from patients with CTEPH [31], further suggesting a role for inflammation in the progression of this disease.

Antiphospholipid syndrome is an autoimmune condition caused by antibodies against phospholipids and lupus anticoagulant that precipitate thrombosis [32]. Among 116 patients with CTEPH, antiphospholipid antibodies (APAs) were significantly increased compared with 83 patients with PAH ($p<0.005$) [33]. In a second study, APA and lupus anticoagulant were both increased in patients with CTEPH compared with patients with non-thromboembolic PH ($p=0.004$) [8]. Conversely, a recent study found no significant difference in APA levels between patients with CTEPH and those with non-thromboembolic PH [16].

An association has also been observed between CTEPH and hypothyroidism [8]. Approximately 20% of the patients with CTEPH in this study were receiving thyroid replacement therapy; significantly more than the 3.5% of patients with non-thromboembolic PH receiving treatment for thyroid disease ($p<0.05$) [8]. Patients with hypothyroidism are known to be at increased risk of thrombosis [34] and treatment with levothyroxine has been shown to increase levels of von Willebrand factor [35]. Therefore, it is uncertain whether the increased incidence of CTEPH in patients with hypothyroidism may be due to the treatment for the disease or due to the disease itself.

Patients who had previously suffered from cancer were also found to have an increased risk of developing CTEPH compared with those with non-thromboembolic PH (12.2% *versus* 4.3%; $p<0.05$) [8]. Previous studies have identified an increased risk of thrombosis in patients with cancer [36] but treatment-related factors may also be responsible [8].

RISK FACTORS FOR SMALL-VESSEL DISEASE IN CTEPH

Defining operability

Improving the knowledge and awareness of CTEPH risk factors may lead to earlier diagnosis and potentially curative surgical intervention. However, depending on a centre's operability definition (or threshold), nearly 40% of patients were deemed non-operable in a recent European CTEPH registry [11] while a further 10–15% of patients with CTEPH continue to suffer from PH following PEA [37]. Critical determinants of operability include the surgeon's skill and the experience of the PEA team. An inexperienced PEA team may be less aggressive with surgical recruitment and potentially turn away patients who, despite perceived risks, may do well with PEA performed at a more experienced centre. Furthermore, there is concern that an inexperienced surgeon may perform an incomplete endarterectomy, thereby resulting in only partial improvement rather than potentially curative treatment. Therefore, PEA should only be conducted by experienced surgeons at specialised centres [37].

THISTLETHWAITE *et al*. [38] classified CTEPH cases into four surgical categories based on endarterectomised specimens: type 1 and 2 lesions occur in the main lobar arteries and proximal segmental arteries, respectively, while type 3 lesions occur in more distal segmental arteries. An experienced surgeon can remove type 1–3 lesions with a high likelihood of haemodynamic improvement. However, type 4 lesions mostly result from distal vasculopathy with associated proximal intimal thickening, rather than intraluminal occlusion treatable with PEA [38], and represent conditions with a likely overlap with PAH. Therefore, patients in this group often have persistent post-operative PH caused by small-vessel disease [39].

Select associated medical conditions have been associated with an increased likelihood of being turned down for PEA. A history of splenectomy was present in 3.6% of patients with operable disease compared with 13.7% of patients with non-operable CTEPH ($p<0.001$) [10]. This observation is supported in the recent European CTEPH registry, in which there was a significant difference in a history of splenectomy between patients with operable and non-operable CTEPH (1.9% *versus* 5.7%, respectively; $p<0.0118$) [11]. This registry also found that patients deemed non-operable were more likely to have had previous major surgery ($p=0.0197$), a history of cancer ($p=0.0156$) and congestive heart failure ($p=0.0065$) than patients who were felt to be operable [11].

Small-vessel disease

Persistent PH from small-vessel disease following PEA remains the major cause of post-operative morbidity and mortality in CTEPH. There appear to be three categories of small-vessel disease that contribute to CTEPH: 1) obstruction of small sub-segmental and more distal arteries that are out of reach of the PEA surgeon; 2) pulmonary arteriopathy of small muscular arteries and arterioles distal to unobstructed elastic arteries; and 3) pulmonary arteriopathy of small muscular arteries and arterioles distal to obstructed elastic arteries [40]. Histopathology of lung tissue taken from patients with CTEPH has found plexiform lesions and intimal thickening of the small pulmonary arteries and arterioles [41, 42]. But the presence of small-vessel disease alone is not predictive of PEA success or failure [41], as the majority of patients with CTEPH have some degree of small-vessel abnormalities and yet have successful surgery [37].

Haemodynamic and radiographic data are currently utilised to gauge patients with CTEPH who are at risk for significant concomitant small-vessel disease and are, therefore, pivotal for the assessment of operability [40]. Patients with a high pre-operative pulmonary vascular resistance (PVR) but no concordant proximal obstruction, that is, where there is a discrepancy between haemodynamic and radiographic results, are considered to be at higher risk following surgery due to significant distal vasculopathy. In a study of 500 patients who had undergone PEA between 1998 and 2002, a high pre-operative PVR ($>1,000$ dyn·s·cm^{-5}) was associated with greater mortality following PEA than a lower PVR (10.1% *versus* 1.3%; $p<0.0001$). A higher post-operative PVR (>500 dyn·s·cm^{-5}) was also associated with increased mortality (30.6% *versus* 0.9%; $p<0.0001$) [39]. Recently, poor subpleural perfusion on selective pulmonary angiogram has been reported to be associated with increased post-operative mortality when compared with patients with intact peripheral perfusion (62.5% *versus* 2.7%; $p<0.0001$). Following multivariate analyses, only

the degree of subpleural perfusion was associated with postoperative mortality (p=0.0019), unlike 6-min walking distance, PVR or P_{pa}, indicating that assessing peripheral perfusion on selective pulmonary angiogram might be useful for determining the operability of CTEPH [43].

CONCLUSIONS

A number of risk factors predispose patients to develop CTEPH, including acute PE, splenectomy, infection and abnormal expression of procoagulant proteins. It is thought that plasmatic factors (hypercoagulation, blood group and platelet count) and a poorly defined, misguided vascular remodelling process (associated with inflammatory states) contribute to major vessel obstruction and small-vessel disease. Concomitant small-vessel disease presents a particular problem, as it may render CTEPH non-operable for even experienced PEA centres, or it may result in persistent PH following PEA. The degree of small-vessel disease may, in part, be related to the length of time a patient has PH with CTEPH. Accordingly, early diagnosis and prompt referral to an experienced PEA centre are recommended.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We received editorial assistance from Adelphi Communications (Bollington, UK), funded by Bayer Pharma AG (Berlin, Germany).

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