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REVIEW

Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension: diagnosis and management

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Abstract

Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are two distinct clinical syndromes associated with adverse patient outcomes following a venous thromboembolism. Clinical manifestations of post-thrombotic syndrome include persistent pain, swelling and ultimately venous ulceration following a deep venous thrombosis. Patients experiencing chronic thromboembolic pulmonary hypertension may have symptoms ranging from exertional dyspnoea to overt right heart failure. From a physician's perspective, the most effective preventative strategy is good quality anticoagulation for prophylaxis of primary and secondary venous thromboembolism. The treatment of post-thrombotic syndrome mainly involves lifestyle modifications alongside the use of elastic compression stockings while patients with chronic thromboembolic pulmonary hypertension should be offered targeted surgical and medical treatment options available at expert centres. Further research is warranted for both conditions to determine the role of direct oral anticoagulants when used with a preventive or therapeutic intent.

Key words: Anticoagulation; Chronic thromboembolic pulmonary hypertension; Post-thrombotic syndrome; Venous thromboembolism

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Introduction

Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are complications following venous thromboembolism that have significant effects on patients' daily living, as well as causing burdens in terms of social and healthcare costs (Ramacciotti et al, 2006). Post-thrombotic syndrome is common, arising in 20–50% of cases following a deep vein thrombosis, while chronic thromboembolic pulmonary hypertension occurs less frequently, complicating 2.2% of cases of venous thromboembolism within 10 years, as recorded from follow up of a UK cohort, with excess mortality of 19% at 2 years (Martinez et al, 2018). Given the overall high incidence of venous thromboembolism (1–2 per 1000 of the UK population; All-Party Parliamentary Thrombosis Group, 2020) and the potentially devastating impact on survival and quality of life, hospital physicians should be able to identify and initiate the management of both presentations.

Post-thrombotic syndrome

Pathophysiology and risk factors

Post-thrombotic syndrome develops as a result of venous hypertension and chronic inflammation caused by incomplete recanalisation of the thrombosed veins and neovascularisation. This may lead to obstruction from residual thrombus, valve destruction and reflux, and further reinforce the venous insufficiency (Rabinovich and Kahn, 2018) (Figure 1). Higher levels of interleukin-6 and C-reactive protein during the inflammatory response of an acute deep vein thrombosis are associated with increased venous outflow resistance. This may indirectly lead to worse outcomes with progression to clinical post-thrombotic syndrome (Roumen-Klappe et al, 2009).

As expected, patients with existing risk factors for venous insufficiency are more prone to developing post-thrombotic syndrome, as summarised in Table 1.

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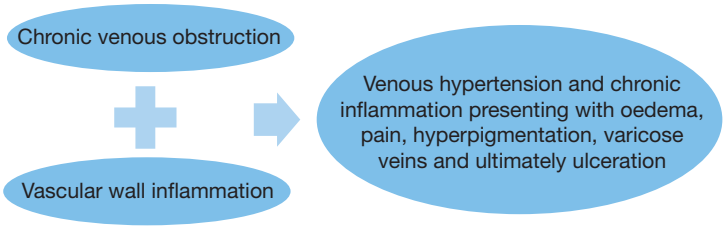

Figure 1. The pathophysiology of post-thrombotic syndrome.

Table 1. Risk factors for post-thrombotic syndrome

Risk factors	Examples
Patient-related	Older age
	Body mass index >30 kg/m^2
	Primary venous insufficiency
	Varicose veins at baseline
Deep vein thrombosis-related	Proximal (iliofemoral) location
	Ipsilateral recurrent deep vein thrombosis
	Residual thrombus at 3–6 months follow up
Other	Inadequate or poor-quality anticoagulation

From Galanaud et al (2016)

Patients with symptomatic deep vein thrombosis without any transient factors, such as surgery or trauma, have a higher risk of recurrence of venous thromboembolism if they are not taking anticoagulants, and this risk increases with time (30% at 8 years) (Rodger et al, 2016). The greatest risk factor for developing post-thrombotic syndrome is ipsilateral recurrence of a deep vein thrombosis (Prandoni et al, 1996). This highlights the role of good quality, long-term anticoagulation as the single most important step in preventing recurrence of venous thromboembolism and post-thrombotic syndrome, at least in patients without significant transient risk factors. However, extending fixed-term anticoagulation from 3 to 6 months did not alter the 10-year likelihood of developing post-thrombotic syndrome with regimens involving vitamin K antagonists (Shulman et al, 2006).

Diagnosis

Post-thrombotic syndrome does not have a static presentation – symptoms and signs can manifest from months to years after a deep vein thrombosis, can wax and wane over time and some can be indistinguishable from those of acute venous thromboembolism (Kahn, 2016). There are several diagnostic tools available for post-thrombotic syndrome, but the Villalta scale in combination with a validated quality of life questionnaire is the most evidence-based approach for holistic assessment of these patients (Soosainathan et al, 2013). When using the Villalta scale (Villalta et al, 1994; Table 2), a score of 5 or more at least 3 months following an initial deep vein thrombosis or the presence of a venous ulcer is sufficient for the diagnosis of post-thrombotic syndrome and the overall score is used to grade severity.

The symptomatology varies between patients, with the common feature of worsening towards the end of the day or after prolonged periods of walking or standing. Elevation of the affected limb offers some relief. Venous claudication may be present and is described as 'leg bursting' pain during exercise, resembling the pain of arterial claudication. This is caused by venous obstruction of major venous vessels (iliofemoral or popliteal veins). Some individuals may present with classic symptoms of post-thrombotic syndrome but have no documented history of venous thromboembolism, in which case compression ultrasound and/or further imaging should be pursued in order to detect an occult deep vein thrombosis, which would require treatment (Kahn, 2016).

Table 2. The Villalta scale	
Patient-reported*	Pain
	Cramps
	Heaviness
	Pruritus
	Paraesthesia
Physician-reported*	Oedema
	Skin induration
	Hyperpigmentation
	Venous ectasia
	Redness
	Pain on calf compression
Total points: severity	0–4: no post-thrombotic syndrome
	5–9: mild post-thrombotic syndrome
	10–14: moderate post-thrombotic syndrome
	>15 or presence of an ulcer: severe post-thrombotic syndrome

**Rating of severity for each outcome as 0=absent, 1=mild, 2=moderate and 3=severe. From Villalta et al (1994)*

The differential diagnosis in people with unilateral chronic lower limb oedema should include primary venous insufficiency, lymphoedema, venous outflow obstruction from a mass or arterial aneurysm, infections or static foot disorders, which lead to an ineffective 'calf venous pump' (Gasparis et al, 2020) and can be discerned by a thorough history and physical exam. One downfall of the Villalta score is that many of the scale's outcomes can present in clinical syndromes other than post-thrombotic syndrome and clinical judgement is advised when the score is applied and interpreted.

The physical exam should include an assessment of peripheral pulses as the presence of significant peripheral vascular disease precludes the use of elastic compression stockings, a useful adjunct in prevention and management of both deep vein thrombosis and post-thrombotic syndrome.

Prevention and treatment

Primary prevention is the cornerstone of management of post-thrombotic syndrome; this includes pharmacological and mechanical thromboprophylaxis at times of increased thrombotic risk to prevent venous thromboembolism. When this fails, secondary prevention with good quality anticoagulation following an existing deep vein thrombosis aims to reduce the risk of recurrence, specifically ipsilateral recurrence, which is a major risk factor for post-thrombotic syndrome. Analysis of a prospective cohort study confirmed that poor quality anticoagulation (international normalised ratio <2 for over 20% of the time during treatment for unprovoked deep vein thrombosis) increased the risk of developing post-thrombotic syndrome (Chitsike et al, 2012). A prospective study showed that patients that spent over half of their treatment time in the subtherapeutic range (international normalised ratio <2) were 1.5–5 times more likely to develop post-thrombotic syndrome (Van Dongen et al, 2005). Compared to vitamin K antagonists, direct oral anticoagulants can be more effective at reducing the risk of post-thrombotic syndrome, perhaps by allowing faster recanalisation of the thrombosed veins (Prandoni et al, 2017; 2020) and by having a more favourable pharmacokinetic profile compared to warfarin. This was supported by a systematic review and meta-analysis data comparing the use of rivaroxaban vs warfarin in preventing the development of post-thrombotic syndrome (Li et al, 2020) but larger, well-designed randomised trials are needed to confirm or refute these findings.

Elastic compression stockings have been widely used in both prevention and management of post-thrombotic syndrome with conflicting evidence. While small, randomised studies found that daily use of elastic compression stockings can reduce the risk of post-thrombotic syndrome by up to 50% (Brandjes et al, 1997; Aschwanden et al, 2008), the only placebo-controlled trial did not confirm any significant advantage over placebo (Kahn et al, 2014). A more recent sub-analysis of a large, cohort study found a significant benefit of use of elastic compression stockings in reducing post-thrombotic syndrome for patients who had residual vein thrombus on ultrasound imaging 3 months after the acute deep vein thrombosis episode (Prandoni, 2022). Therefore, the decision about when and how to prescribe elastic compression stockings following a deep vein thrombosis remains specific to the physician and patient, pending good quality evidence on their use.

Another matter of debate in risk reduction strategies for post-thrombotic syndrome is the use of catheter-directed thrombolysis. In theory, early resolution of the obstructed vein should reduce the risk of post-thrombotic syndrome, so pharmacological thrombolysis, mechanical thrombectomy or their combination makes theoretical sense. However, the evidence is inconclusive for systemic, catheter-directed thrombolysis or a combination of pharmaco-mechanical therapies in preventing post-thrombotic syndrome. In cases of proximal (ileo-femoral) deep vein thrombosis, catheter-directed pharmacomechanical thrombolysis did not result in overall reduction of the incidence of post-thrombotic syndrome or improvement in quality of life at 2 years (Vedantham et al, 2016). Nevertheless, it was associated with lower post-thrombotic syndrome severity scores at the expense of higher bleeding complications post procedure. In view of contradictory evidence, catheter-directed thrombolysis and catheter-directed pharmacomechanical thrombolysis may be considered in experienced centres for selected patients with acute (≤14 days), symptomatic, extensive, proximal deep vein thrombosis who have good functional capacity, life expectancy of over 1 year and low bleeding risk (Kahn et al, 2014).

All symptomatic patients with established post-thrombotic syndrome should be advised about the benefits of leg elevation, skin care with moisturisers and targeted interventions to encourage a healthy lifestyle. Randomised controlled trial data suggest that a 6-month structured exercise programme led to significantly improved venous insufficiency-related quality of life and post-thrombotic syndrome severity scores (Kahn et al, 2011), likely by strengthening the venous calf pump and promoting overall fitness. Unless there are specific contraindications, elastic compression stockings tailored to the patient are offered in all cases and intermittent pneumatic compression devices are recommended for moderate to severe cases, with duration of treatment guided by improvements in symptoms and patient tolerance (Cohen et al, 2012; Makedonov et al, 2020). In selected patients with severe and/or refractory symptoms, vascular specialist input is warranted to discuss endovascular interventions that may be of benefit (Vedantham et al, 2016). Patients who develop venous ulcers should have regular ulcer care with compression dressings as per guidance on management of venous insufficiency ulcers (Scottish Intercollegiate Guidelines Network, 2011). Post-thrombotic syndrome alone is not an indication for lifelong anticoagulation or extension of the duration of anticoagulation, which should be decided on the grounds of risk of recurrence of venous thromboembolism (Rabinovich and Kahn, 2018).

Chronic thromboembolic pulmonary hypertension

Pathophysiology and risk factors

The pathobiology of chronic thromboembolic pulmonary hypertension is more complex than that of post-thrombotic syndrome. Several mechanistic models have implicated the incomplete resolution of pulmonary vein thrombus in the development of chronic vessel occlusions, and vascular remodelling including wall thickening, ultimately leading to pulmonary hypertension and right heart failure (Lang et al, 2021). Right ventricular function is the major determinant of clinical outcomes including survival among patients with pulmonary hypertension (Hasoun, 2021). In response to an increase in pulmonary vascular resistance by a factor of 5–10, the right ventricle undergoes hypertrophy, chamber dilatation, fat deposition, fibrosis and metabolic shifts as pulmonary hypertension progresses.

The incidence of chronic thromboembolic pulmonary hypertension peaks 3–6 months after the index venous thromboembolism but can present even after years of anticoagulation for an underlying event without acute recurrence (Martinez et al, 2018). The median age at diagnosis is 63 years and both sexes are affected equally (Pepke-Zaba et al, 2011). Two observational studies (Pepke-Zaba et al, 2011; Martinez et al, 2018) tried to establish patient and venous thromboembolism-related risk factors that could be associated with the development of chronic thromboembolic pulmonary hypertension. Table 3 lists risk factors that are common in both of these studies. High-risk presentations with haemodynamic instability and intermediate-risk pulmonary embolism (according to the European Society for Cardiology classification; Konstantinides et al, 2020) were more likely to be complicated by chronic thromboembolic pulmonary hypertension than low-risk cases in a real-world cohort of patients that had experienced a symptomatic pulmonary embolism (Yu et al, 2018).

Diagnosis

Chronic thromboembolic pulmonary hypertension can be asymptomatic at first, before manifesting clinically with symptoms and signs of pulmonary hypertension, such as breathlessness, fatigue, oedema, haemoptysis or syncope. The symptoms are initially only present on exertion but progressively worsen to the point of experiencing symptoms at rest or developing overt right heart failure in advanced cases (Galiè et al, 2016). Of note, the culprit venous thromboembolism may have been undiagnosed and chronic thromboembolic pulmonary hypertension can be present in the context of an acute or subacute pulmonary embolism. On the other hand, most patients experience dyspnoea following a pulmonary embolism, as a result of deconditioning and other physiological changes, without having any pulmonary hypertension (Klok et al, 2020). These diagnostic challenges were confirmed in a multi-centre registry study that revealed a long median time to diagnosis of chronic thromboembolic pulmonary hypertension of 14 months since the initial presentation with symptoms to a healthcare provider (Pepke-Zaba et al, 2011).

Therefore, it would be sensible to suspect chronic thromboembolic pulmonary hypertension during the evaluation of patients with unexplained dyspnoea or physical findings of right heart failure in the appropriate clinical context, such as a history of current or prior venous thromboembolism, or in the presence of risk factors for thrombosis. Chronic thromboembolic pulmonary hypertension is diagnosed by the following criteria that must be met following at least 3 months of effective anticoagulation for a pulmonary embolism:

1. Presence of mean pulmonary artery pressure >20 mmHg with a normal pulmonary artery capillary wedge pressure
2. Mismatched perfusion/diffusion defects on ventilation/perfusion scan
3. Diagnostic signs of chronic thromboembolic pulmonary hypertension on computed tomography, magnetic resonance imaging or conventional pulmonary angiography (Klok et al, 2020).

Table 4 list the haemodynamic and imaging findings that indicate the correct diagnosis.

Initial investigation of suspected cases should begin with a transthoracic echocardiogram to assess the likelihood of pulmonary hypertension based on the peak tricuspid regurgitation velocity. Further investigation for underlying causes of heart and lung disease involves a detailed physical examination, basic blood laboratory tests and additional measurement of N-terminal pro-B type natriuretic peptide, electrocardiogram, pulmonary function testing, chest X-ray, arterial blood gases, sleep oximetry and further imaging studies (Galié et al, 2016).

In patients with suspected chronic thromboembolic pulmonary hypertension, that have echocardiography supporting the presence of pulmonary hypertension (Table 5), the

Table 3. Risk factors for chronic thromboembolic pulmonary hypertension

Venous thromboembolism-related	Recurrent venous thromboembolism
Patient comorbidities	Chronic obstructive pulmonary disease
	Splenectomy

From Bonderman et al (2008); Martinez et al (2018)

Table 4. Characteristic findings of chronic thromboembolic pulmonary hypertension

Ventilation/perfusion scan	Ventilation/perfusion mismatch
Right heart catheterisation	Mean pulmonary artery pressure >20 mmHg
	Pulmonary artery wedge pressure ≤15 mmHg
	Pulmonary vascular resistance ≥3 Wood units
Computed tomography pulmonary angiography	Ring-like stenoses
	Webs
	Chronic total occlusions

From Simonneau et al (2019)

ventilation/perfusion scan is more sensitive (96–97%) and specific (90–95%) than computed tomography pulmonary angiography for the detection of pulmonary hypertension. A normal or low probability ventilation/perfusion scan effectively rules out this diagnosis with the caveat of many non-diagnostic results (Tunariu et al, 2007). However, more recent work suggests both ventilation/perfusion and computed tomography pulmonary angiography are accurate methods for detecting chronic thromboembolic pulmonary hypertension, with computed tomography pulmonary angiography also identifying complications of pulmonary hypertension such as pulmonary artery dilatation. Patients with results suggestive of chronic thromboembolic pulmonary hypertension warrant referral to a tertiary pulmonary hypertension centre to consider further investigation (Konstantinides et al, 2020). The gold standard is right heart catheterisation, and selective pulmonary angiography in the anterior-posterior and lateral projections to illustrate typical findings of chronic thromboembolic pulmonary hypertension and help assess the suitability of the patient for a pulmonary endarterectomy is essential (Simonneau et al, 2019).

Prevention and treatment

As remodelled, chronically obstructed vessels are considered the mechanistic basis of pulmonary hypertension, anticoagulation to prevent extension and/or recurrence of venous thromboembolism is the main prevention strategy. In a subanalysis of a cohort study evaluating the role of residual pulmonary obstruction following pulmonary embolism, there were fewer chronic thromboembolic pulmonary hypertension events in the group remaining on anticoagulation at 3 years compared to those who discontinued this earlier (Pesavento et al, 2017). However, this study was neither designed nor powered to assess the effect of longer duration of anticoagulation. As direct oral anticoagulants are a safer, equally effective alternative to vitamin K antagonists in secondary prevention of venous thromboembolism (van Es et al, 2014), it would be interesting to assess their efficacy in reducing the incidence of chronic thromboembolic pulmonary hypertension in prospective studies. On the other hand, there is no definitive evidence that thrombolysis improves the long-term mortality, rates of dyspnoea or chronic thromboembolic pulmonary hypertension compared to

Table 5. Echocardiographic evaluation of suspected pulmonary hypertension

Echocardiography findings	Probability of pulmonary hypertension	Further steps
Peak tricuspid regurgitation velocity ≤2.8 m/s without any additional findings*	Low	Consider investigating other causes and follow up
Peak tricuspid regurgitation velocity ≤2.8 m/s with additional findings or peak tricuspid regurgitation velocity >2.8 m/s	Intermediate	Investigate for presence of left heart or lung disease and signs of severe pulmonary hypertension. If chronic thromboembolic pulmonary hypertension suspected, proceed straight to ventilation/perfusion scan

**Additional findings from the ventricles, right atrium, inferior vena cava and pulmonary artery indicating the presence of pulmonary hypertension (Galié et al, 2016)*

placebo in patients treated otherwise, as per consensus guidelines (Konstantinides et al, 2017; Humbert et al, 2022).

Once chronic thromboembolic pulmonary hypertension is diagnosed, patients usually remain under the care of a tertiary centre team with experience in managing this condition and remain on lifelong anticoagulation unless specifically contraindicated. All patients should be considered for pulmonary endarterectomy – this can significantly improve haemodynamic parameters, survival and exercise tolerance (Mayer et al, 2011). Pulmonary endarterectomy involves removing the obstructive thromboembolic material from the pulmonary arteries to relieve pulmonary hypertension and alleviate right ventricular dysfunction. Pulmonary vascular resistance pre- and immediately postoperatively is a good prognostic marker of long-term outcomes (Skoro-Sajer et al, 2014). Surgery requires cardiopulmonary bypass and periods of deep hypothermic circulatory arrest. Complications include reperfusion lung injury and persistent pulmonary hypertension. In Europe, the mortality can be as low as 4.7% if done in a specialised centre (Mayer et al, 2011).

An individualised preoperative assessment using a multidisciplinary approach is crucial following the diagnosis of chronic thromboembolic pulmonary hypertension to select patients who will benefit the most from this intervention. Patient-related factors assessed include preoperative World Health Organization grade and surgical accessibility of the thrombi, while age, degree of pulmonary vascular resistance and severity of right ventricular dysfunction are not considered to preclude pulmonary endarterectomy (Hoole and Jenkins, 2020). Patients who do not undergo pulmonary endarterectomy or experience recurrent pulmonary hypertension after pulmonary endarterectomy have a poor prognosis. Post pulmonary endarterectomy, all patients should be followed up in a specialised centre with at least one haemodynamic assessment 6–12 months post surgery, and should remain on lifelong anticoagulation (Humbert et al, 2022).

Patients deemed unsuitable for pulmonary endarterectomy should be evaluated for their eligibility for balloon pulmonary angioplasty, which is less invasive and has potentially comparable outcomes to pulmonary endarterectomy (Ogawa et al, 2017). Regardless of the surgical options available, all patients should be on lifelong anticoagulation, and diuretics and oxygen therapy if they become hypoxaemic or develop right heart failure (Galié et al, 2016). Warfarin was the anticoagulant of choice, but observational data suggest that direct oral anticoagulants can be a non-inferior alternative (Sena et al, 2020). A small randomised controlled trial showed that rivaroxaban was comparable to warfarin for anticoagulation post pulmonary endarterectomy with no excess thrombosis or mortality risk (Barati et al, 2023).

Simultaneously, targeted medical therapies such as riociguat (a first in class guanylate cyclase stimulator), bosentan and macitentan (both endothelin receptor antagonists) improve symptomatology and haemodynamic parameters in patients with chronic thromboembolic pulmonary hypertension post pulmonary endarterectomy or who are deemed non operable (Pepke-Zaba et al, 2011).

Conclusions

Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are debilitating complications following a venous thromboembolism and pose diagnostic and management challenges to hospital physicians. The investigation and treatment of suspected cases should begin as soon as possible after presentation to a general physician and be continued by specialist teams. The question of whether anticoagulation with direct oral anticoagulants is more effective than warfarin in preventing post-thrombotic syndrome remains unanswered. Finally, the non-inferiority of direct oral anticoagulant therapy vs warfarin in established chronic thromboembolic pulmonary hypertension is being examined, with an ongoing study expected to be completed in July 2023 (NCT04730037).

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Key points

- Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension should be suspected in all patients with persistent symptoms following venous thromboembolism.
- Post-thrombotic syndrome clinically presents with persisting pain, oedema, hyperpigmentation or venous ulcer.
- Symptoms of chronic thromboembolic pulmonary hypertension include dyspnoea on exertion, fatigue, syncope or clinical right heart failure.
- Good quality anticoagulation remains the cornerstone in the prevention of both post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.
- The management of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension requires multidisciplinary specialist input from centres with relevant expertise.

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