Chapter 2

Acute pulmonary embolism: epidemiology and diagnosis

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Nature Reviews Cardiology, accepted for publication
ABSTRACT

Pulmonary embolism (PE) is a frequently occurring acute and potentially fatal condition. Numerous risk factors, both inherited and acquired, have been identified. Although mortality due to PE is high, treatment with anticoagulant medication can effectively reduce the risk of death and recurrence. Adequate diagnosis is mandatory to prevent pulmonary embolism (PE) related mortality and morbidity on one hand, and unnecessary treatment on the other. Since only approximately 1 in 5 will have the disease confirmed, the diagnostic workup for PE preferably includes safe, efficient and non-invasive methods to exclude the diagnosis. The first step in the approach to patients with suspected PE is to determine the clinical probability of PE and to perform a D-dimer test. In patients with a “non-high” or “unlikely” clinical probability and a normal D-dimer test PE can be excluded. Otherwise, additional imaging is required. Computed tomography (CT) or ventilation-perfusion scintigraphy, followed by additional testing in case of non-diagnostic test results, is the next step. Although various diagnostic strategies have been introduced and validated, selected patients may require a tailored approach. This review will present background information on the risk factors and clinical presentation of PE and discusses the latest advances in diagnostic management.
INTRODUCTION

Pulmonary embolism (PE) is an acute and potentially fatal condition, in which an embolism, usually a thrombus originating from one of the deep veins of the legs or pelvis, blocks one or more pulmonary arteries, causing impaired blood flow and increased pressure to the right cardiac ventricle (Figure 1). PE and deep vein thrombosis (DVT) are considered two entities of the same condition: venous thromboembolism (VTE). This is a frequently occurring disease, with an incidence of 1-3 per 1000 inhabitants per year in Western society (1-3), which makes it the third most common cardiovascular disorder in industrialized countries. Although mortality due to PE is high, treatment with anticoagulant medication can effectively reduce the risk of death and recurrence. However, treatment with anticoagulants has its own risks, most notably bleeding. Also, because the presentation of patients with symptoms of PE varies strongly, from asymptomatic to cardiogenic shock, and symptoms may be non-specific, the diagnosis can be difficult. This first review will present background information and will discuss the latest advances in the field of pulmonary embolism; i.e. the risk factors, clinical presentation and advances in the diagnostic management. The second review will present background information on the treatment and prevention of PE, including both established and novel anticoagulants.

BACKGROUND

The incidence of VTE correlates strongly with age. It is extremely uncommon in childhood (0.05 per 1000), but increases exponentially to nearly 8 per 1000 in old age (1-4) (Figure 2). Overall, men and women are affected equally. Women of reproductive age have slightly higher rates, due to an association between VTE and pregnancy and the use of oral contraceptives (1,5), while in older age men are more often affected than women. Mortality rate due to PE is as high as 25% if left untreated (6). However, with adequate anticoagulant therapy this decreases to about 2-8% in the three months after diagnosis (7-10). The actual figures, however, may possibly be higher than generally accepted, because the patients that die immediately or shortly before diagnosis are usually not included in clinical studies. In the acute phase, the mortality rate depends mainly on hemodynamic instability (systolic arterial hypotension), underlying co-morbidities and immobility (8,9,11). On the long-term, i.e. one year, co-morbid conditions such as malignancy, left-sided congestive heart failure and chronic lung disease are strong predictors of mortality (8,9,12). The 1-year mortality after PE is as high as 24-27%: malignancy is the most frequent cause of death (35-45%), while recurrent PE accounts for 2.5-7% of mortality (9,12).
Figure 1. Pathophysiology of pulmonary embolism. Pulmonary embolism usually originates from a thrombus formed in one of the deep veins in the leg or pelvis at sites of decreased blood flow, i.e. in the valve pockets (inset, bottom). Venous blood flow carries the clot via the right atrium and the right ventricle to the pulmonary arteries. Here the thrombus blocks one or more arteries, causing impaired blood flow and increased pressure to the right cardiac ventricle.
RISK FACTORS

Already in the nineteenth century, the German pathologist Virchow described a triad of three major elements which play a fundamental role in developing thrombosis, namely venous stasis, vessel wall injury and a hypercoagulable state (13). The first two components of the triad mostly represent acquired conditions, while hypercoagulability of the blood can be due to both inherited and acquired factors. An inherited (thrombophilic) condition can be found in approximately 50-60% of patients presenting with VTE (14-16). On the other hand, acquired risk factors such as immobility, surgery, malignancy or others are present in more than 50% of the patients with a first VTE (17). Most often, more than one cause is present, illustrating the fact that VTE is a multi-causal disease: the risk of VTE is the result of an interaction between various risk factors. These may simply add up or have a synergic effect (18). Only in approximately 20% of patients no risk factor can be identified (14,17). Risk factors for VTE are listed in Table 1. For some risk factors it is currently unknown whether they are congenital or acquired.

Inherited risk factors

Prothrombotic inherited risk factors are associated with either a reduced level of anticoagulant proteins or an increased level or an increased function of coagulation proteins. In the general population, thrombophilic abnormalities vary in prevalence and also in the risk of VTE they convey. The risk of a first venous thrombosis in carriers of a thrombophilic factor is summarized in Table 2. As can be appreciated from this Table, regardless of the increased
Table 1. Risk factors for pulmonary embolism

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Inherited</th>
<th>Mixed/unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobilization</td>
<td>Antithrombin deficiency</td>
<td>High levels of factor VIII</td>
</tr>
<tr>
<td>Plaster cast</td>
<td>Protein C deficiency</td>
<td>High levels of factor IX</td>
</tr>
<tr>
<td>Trauma</td>
<td>Protein S deficiency</td>
<td>High levels of factor XI</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Factor V Leiden (FVL)</td>
<td>High levels of fibrinogen</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Prothrombin 20210A</td>
<td>High levels of TAFI</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Dysfibrinogenemia</td>
<td>Low levels of TFPI</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Factor XIII 34val</td>
<td>APC-resistance in the absence of FVL</td>
</tr>
<tr>
<td>Hormonal replacement therapy</td>
<td>Fibrinogen (G) 10034T</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Non-O blood group</td>
<td>High levels of PCI (PAI-3)</td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous catheters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy/puerperum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor; PCI, protein C inhibitor; PAI-3, plasminogen-activator inhibitor-3. (Adapted from Rosendaal and Reitsma (26).)

relative risk due to the presence of a thrombophilic factor, the overall absolute risk remains low (19). Table 2 also states the absolute risk for asymptomatic patients with thrombophilia in high-risk situations, such as surgery, trauma, immobilization, pregnancy or use of oral contraceptives.

Deficiencies of the naturally occurring anticoagulants antithrombin, protein C and protein S substantially increase the risk of VTE, but are rare in the general population (less than 1%) (20-22). Among patients with thrombosis, the deficiencies are present in 5 to 10% of patients (14). Factor V Leiden, which causes activated protein C resistance, is a relatively common mutation, with a prevalence of approximately 5% in the Western population (23) and up to 20% in patients with VTE (24,25). It is a moderately strong risk factor, together with the prothrombin mutation 20210A and non-O blood group (26). Prothrombin G20210A is the second most prevalent form of thrombophilia, found in about 1% of the population and in 4 to 8% of patients with thrombosis (27). The mutation leads to increased prothrombin (factor II) concentrations, which leads to an increased risk of venous thrombosis (28). Non-O blood
Table 2. Risk of venous thrombembolism in asymptomatic carriers of thrombophilia.

<table>
<thead>
<tr>
<th>Type of thrombophilia</th>
<th>Relative risk compared to healthy controls</th>
<th>Overall absolute risk (%/year)</th>
<th>Surgery, trauma or immobilization (%/episode)</th>
<th>Pregnancy (%/pregnancy)</th>
<th>Oral contraceptive use (%/year of use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural anticoagulant deficiencies</td>
<td>7-10</td>
<td>0.4-1.0</td>
<td>8.1</td>
<td>4.1</td>
<td>4.3</td>
</tr>
<tr>
<td>FVL</td>
<td>3-7</td>
<td>0.1-0.7</td>
<td>1.8-2.4</td>
<td>1.9-2.1</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>3</td>
<td>0.1-0.4</td>
<td>2.0</td>
<td>2.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Elevated FVIII:c</td>
<td>2-11</td>
<td>0.3</td>
<td>1.2</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>5-16</td>
<td>2-3</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mild hyper-homocysteinemia</td>
<td>1.3-1.6</td>
<td>0.2</td>
<td>0.9</td>
<td>0.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

FVL, factor V Leiden; FVIII:c, factor VIII coagulant activity; F, factor. Adapted from Cohn et al. (19).

groups are associated with elevated levels of von Willebrand factor and factor VIII, which is related to a 2- to 4-fold increased risk of VTE (29-31). There is a high prevalence of non-O blood groups in the general population, which amplifies the risk of blood group as an important genetic risk factor.

Recently, association studies have been carried out to test common genetic variations in almost all coagulation proteins. In these studies, large sets of single nucleotide polymorphisms, which were first selected on the basis of haplotyping, are studied and compared between patients with VTE and unrelated individuals (32). Although common variants impart only a small, sometimes minimal risk, they are present in a large proportion of patients (32,33), and may therefore be responsible for a similar proportion of venous thrombotic events as the stronger but rarer risk factors (33). Currently, several ‘genome-wide association studies’ (GWAS) are underway, in which up to a million SNPs are tested in association studies (26). It is likely that these will add to the list of common and weak genetic risk factors. At present, it is unclear what the finding of these weak genetic risk factors will bring for the management of individual patients. In-depth insight into how genetic risk factors are involved in VTE may enable personalized risk profiling in selected patients (32). However, in order to be applicable in a clinical setting, the assays must be able to detect (a combination of) clinically relevant genetic factors in a rapid and affordable assay.

Acquired risk factors

Several acquired risk factors have been identified during the last decades (see Table 1). Among the risk factors conveying the highest risk for VTE are surgery (in particular orthopedic surgery,
surgery for cancer and neurosurgery), immobility for more than 48 hours, hospitalization, infection (all in the past three months), and cancer (17,34-36). Compared with non-cancer patients, the risk of developing symptomatic VTE is six to seven times higher in cancer patients (34,37), and about 8-14% of the VTEs are secondary to a known cancer (38-40).

Other medical disorders associated with increased risk for VTE include previous VTE, heart failure, ischemic stroke, acute respiratory failure/recent intubation, sepsis, acute rheumatic disease, inflammatory bowel disease and hormonal therapy (17,36). The antiphospholipid syndrome is an acquired form of thrombophilia. Autoimmune antibodies against phospholipids and cardiolipin are associated venous and arterial thrombosis and recurrent pregnancy loss (41).

**Association venous and arterial thrombosis**

Although venous thromboembolism (VTE) and arterial thrombosis have been seen as two different entities, more and more evidence is emerging about the link between the two. This association has been extensively studied in case-control and cohort studies of both retrospective and prospective design. In individuals with VTE, a higher risk of subsequent (fatal and nonfatal) arterial thrombotic events has been observed compared to subjects without VTE (42-44). Although the exact underlying mechanism of the association between VTE and arterial thrombosis remains undefined, it is hypothesized that this association is due to shared risk factors and/or aetiologic pathways (45,46). Obesity and diabetes mellitus were found to be associated with a higher incidence of both venous thrombosis and arterial thrombosis (43). Obesity has been shown to be an independent risk factor for VTE. A body mass index (BMI) of 25-30 kg/m2 was associated with a 1.7-fold increase in the risk of VTE in a recent large case-control study, while a BMI >30 kg/m2 increased the risk 2.4-fold (47). Similar results were found in earlier studies (46,48,49). There is a gradient of increasing risk with increasing BMI (47). Also, waist circumference (≥ 100 cm) and body weight are identified as individual predictors of VTE risk (47,50). Diabetes mellitus was shown to be a risk factor for VTE in several studies (43), but this was recently challenged (51). Apart from diabetes mellitus, hyperglycemia was associated with an increased risk of VTE (52), but this has not yet been confirmed in other studies. Similarly to these factors, high triglyceride levels as well as low HDL cholesterol levels have been found to be associated with both venous and arterial thrombosis (43,53). Following this observation, statins, which already proved useful in arterial thrombosis, also seemed to have a beneficial effect on VTE. In a large randomised controlled trial (54), 20 mg rosvastatin significantly reduced the occurrence of symptomatic VTE compared to placebo: there was a 43% decreased risk of VTE (hazard ratio, 0.57; 95%CI 0.37-0.86), without a difference between unprovoked or provoked VTE. The VTE rates were 0.18 and 0.32 event per 100 person-years of follow-up in the rosvastatin and placebo groups, respectively, with a somewhat larger benefit for the outcome of DVT than for PE. Hence, this trial supports the idea of a link between arterial and venous thrombosis.
DIAGNOSIS

While twenty years ago, the diagnosis of PE was confirmed in 30-35% of patients suspected of having the disease (55), the prevalence of PE in more recent management studies has decreased to 15-25% (38,39). At the same time, there is no evidence that the absolute number of detected cases of PE has increased. Therefore, it is most likely that the lower prevalence of confirmed PE in recent years reflects an increase in patients in whom PE is suspected (56). This could be due to an increased awareness of possible PE. Also, new and non-invasive diagnostic tests have simplified diagnostic protocols over the years, which could point towards a decreased threshold for testing in clinical practice (57,58).

Clinical presentation and the need for diagnostic strategies

The clinical presentation of PE can vary greatly, depending on the extent of obstruction of the vascular bed. Also, the overall physical condition of the patient (i.e. whether or not the patient has an underlying lung or heart disease) is of importance (59). The classical presentation of a patient with PE is of one with acute shortness of breath, pleuritic pain, coughing and hemoptysis. The patient’s leg may be swollen and red, pointing towards deep vein thrombosis. In case of massive PE, there could be circulatory collapse (hypotensive shock). On the other extreme, a person with small peripheral emboli may have few or even no complaints at all. The physical examination is often of little additive value. Tachypnea and tachycardia are common signs and crepitations or crackles may be heard on auscultation. A pleural rub could indicate pleural infarction. A loud P2, a right sided gallop and increased central venous pressure (neck vein distension) can be signs of pulmonary hypertension due to PE, but are non-specific. Presence of a swollen, red leg increases the likelihood of PE (59,60).

Because individual signs and symptoms have low specificity and sensitivity, there is no individual symptom, clinical sign, or even a combination of these that can be used to safely exclude or confirm the diagnosis (60). Additional tests, such as arterial blood gas analysis, electrocardiogram, or chest X-ray may show signs suggestive of PE, but are also not sensitive or specific enough to rule the diagnosis of PE in or out (60). The well-known diagnostic tests of earlier days, such as ventilation-perfusion (V/Q) scintigraphy and pulmonary angiography have the limitation that they are invasive and costly, and less accurate when used as a stand-alone test in the case of a ventilation-perfusion scintigraphy. These limitations may contribute to over- or undertreatment of PE, an occurrence that is not uncommon (61-63). Nowadays, diagnostic tests have been integrated in diagnostic algorithms consisting of sequential diagnostic tests in order to enforce an accurate diagnosis, while reducing costs and invasiveness at the same time (58) (Figure 3).
Clinical probability and D-dimer testing

The first step in the work up of patients with suspected PE is to determine the pre-test clinical probability of PE. For this purpose, several well-validated clinical decision rules (CDR) are available (64-68). Recent guidelines recommend the assessment of clinical probability in each patient with suspected PE before any further objective testing is ordered (69-72). The best known clinical decision rules are the Geneva score (66), the Revised Geneva Score (RGS) (68) and the Wells rule (67,73) (Tables 3 and 4). Currently, the most extensively validated and widely applied CDR is the Wells rule. In contrast to the Geneva score, which requires the results of a chest X-ray and blood gas analysis on room air, the Wells rule is composed of seven solely clinical variables obtained from medical history and physical examination. Also, this score includes the physician’s judgment on the likelihood of PE versus an alternative diagnosis. Both the trichotomous version (to stratify patients into three levels of clinical probability: low, intermediate and high) and dichotomous version (to stratify patients into two levels of clinical
### Table 3. Clinical decision scores

<table>
<thead>
<tr>
<th>Wells score</th>
<th>Geneva score</th>
<th>Revised Geneva score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Item</strong></td>
<td><strong>Score</strong></td>
<td><strong>Simpl.</strong></td>
</tr>
<tr>
<td>Previous PE or DVT</td>
<td>+1.5</td>
<td>+1</td>
</tr>
<tr>
<td>Heart rate &gt;100/min</td>
<td>+1.5</td>
<td>+1</td>
</tr>
<tr>
<td>Recent surgery or immobilization</td>
<td>+1.5</td>
<td>+1</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>+3</td>
<td>+1</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>+3</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical probability

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>2-6</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

Dichotomized 6

<table>
<thead>
<tr>
<th>Unlikely</th>
<th>Likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4</td>
<td>&gt; 4</td>
</tr>
</tbody>
</table>

Simpl, simplified; PE, pulmonary embolism; DVT, deep vein thrombosis

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probability: unlikely and likely) have been extensively validated (74). The more recently introduced RGS is composed of eight, solely objective clinical variables (68). The clinical decision scores all assign different weights to the variables. To facilitate the computation of the scores and to prevent miscalculations, the Wells rule and the RGS have recently been simplified. With the simplified Wells rule and the simplified RGS, all items are assigned one point (except for “heart rate” in the simplified RGS, in which a differentiation is applied depending on the
Table 4. Proportion of patients and prevalence of PE in the different probability categories of various clinical decision rules*

<table>
<thead>
<tr>
<th>Clinical decision rule</th>
<th>Level of validation</th>
<th>Probability category</th>
<th>Proportion of patients (%)</th>
<th>Prevalence of PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells rule, trichotomous</td>
<td>1</td>
<td>Low</td>
<td>30 - 74</td>
<td>1.3 – 28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate</td>
<td>22 - 63</td>
<td>9.6 - 54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>1.3 - 15</td>
<td>33 - 100</td>
</tr>
<tr>
<td>Wells rule, dichotomous</td>
<td>1</td>
<td>Unlikely</td>
<td>51 - 84</td>
<td>3.4 - 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely</td>
<td>16 - 48</td>
<td>23 - 49</td>
</tr>
<tr>
<td>Simplified Wells rule</td>
<td>3</td>
<td>Unlikely</td>
<td>70</td>
<td>11 - 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely</td>
<td>30</td>
<td>36 - 47</td>
</tr>
<tr>
<td>Geneva rule</td>
<td>1</td>
<td>Low</td>
<td>12 - 54</td>
<td>7 – 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate</td>
<td>38 - 60</td>
<td>30 - 41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>6 - 28</td>
<td>44 - 96</td>
</tr>
<tr>
<td>Revised Geneva rule</td>
<td>1</td>
<td>Low</td>
<td>31 - 52</td>
<td>7.9 - 9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate</td>
<td>45 -62</td>
<td>23 - 29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>2.3 - 7.6</td>
<td>71 - 84</td>
</tr>
<tr>
<td>Simplified revised Geneva, trichotomous</td>
<td>3</td>
<td>Low</td>
<td>36</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>Simplified revised Geneva, dichotomous</td>
<td>3</td>
<td>Unlikely</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely</td>
<td>35</td>
<td>42</td>
</tr>
</tbody>
</table>

* Adapted from Ceriani et al. (74). 1 Levels of validation according to McGinn et al. (117)
Level 1 - Impact analysis: At least 1 prospective validation in a different population and 1 impact analysis, demonstrating change in clinician behavior with beneficial consequences.
Level 2 - Broad validation: Demonstrated accuracy in multiple clinical settings with varying prevalence and outcome of disease.
Level 3 - Narrow validation: Validated in a similar clinical setting and population as in step 1.
Level 4 - Derivation: Derived but not validated or validated only in split samples, large retrospective databases, or by statistical techniques.

Rate) (Table 3) (75,76). Of note, the simplified Wells rule and the simplified RGS have not yet been validated prospectively in a clinical outcome study (see Table 3). A recent meta-analysis showed that the available CDRs for the clinical probability assessment of PE show similar accuracy (74). Because the scores are not necessarily equivalent, there may be a preference for
a score or cut-off depending on the familiarity with the score, the prevalence of PE in the local institution and the type of D-dimer assay that is used. Depending on the pre-test clinical probability, the next step in the work-up of suspected PE is to perform the D-dimer blood test. Several management studies have demonstrated that PE can safely be ruled out without the need for imaging techniques in patients with a low, low/intermediate or unlikely clinical probability together with a normal D-dimer test result (58,74,77,78). The clinical usefulness of this simple strategy is substantial, since PE can safely and non-invasively be excluded in approximately one third of patients, based on clinical probability assessment and D-dimer testing alone (38-40,77,78). The sensitivity between different D-dimer assays may vary (79). Although it depends on the method of clinical probability assessment which D-dimer assay should be used (74), the highly sensitive quantitative D-dimer assays, i.e. enzyme-linked fluorescent -, enzyme-linked immunosorbent - or latex quantitative assays are preferred (79). Even though the negative predictive value of some D-dimer assays is very high, the test should not be used as a stand alone (72). In patients with a ‘likely’ clinical probability for PE, the false negative rate of the D-dimer can be as high as 10% (80). Therefore, in all patients who have a high or likely clinical probability, further diagnostic testing is recommended irrespective of the outcome of the D-dimer test (69,80).

**Computed tomography for PE**

In patients with a “high” or “likely” pre-test clinical probability or in patients with an abnormal D-dimer test, further testing is always necessary. Computed tomographic pulmonary angiography (CTPA) is currently the first line imaging test and has been extensively studied in accuracy and outcome studies (39,40,81). An example of a CTPA-study showing pulmonary embolism is shown in Figure 4. A recent randomized diagnostic management trial showed that CTPA was equally capable of ruling out PE as V/Q scintigraphy: VTE was missed with the imaging test in 2 of 561 patients (0.4%) randomized to CTPA versus 6 of 611 patients (1.0%) undergoing V/Q scanning (difference, -0.6%; 95% confidence interval -1.6% to 0.3%) (81). Early types (single slice) CT-scans have a lower sensitivity for detecting PE, especially in the more peripheral pulmonary arteries, compared to newer multi-detector row CT (MDCT) scans. Whereas a negative result with the more sensitive multi-detector row CT (MDCT) is generally accepted to exclude PE without the need for additional imaging testing (38,39), compression ultrasonography of the lower extremities (CUS) is recommended to definitely rule out the diagnosis with a negative single-slice CT-scan (58). For MDCT, a recently executed large randomized outcome trial showed that a MDCT alone was non-inferior to MDCT combined with CUS of the legs (40). Therefore, CUS preceding MDCT is unnecessary.

CT venography (CTV) is an alternative to venous ultrasonography, in which the pelvis and leg veins are scanned 3-3½ minutes after intravenous injection of contrast material for CT pulmonary angiography to detect lower extremity venous thrombi (82). Although isolated DVT
was found in up to 2.6% of patients classified as ‘high risk’ for VTE who underwent a combination of CTPA and CTV in a recent prospective study (83), it must be taken into account that performing CTV also involves additional scanning time, additional costs, and importantly, additional radiation exposure compared to CTPA alone. Considering the limited role for CUS of the legs in the diagnostic workup when MDCT is performed, similarly, the role of CTV is limited. It is suggested that newer generation CT scans (16-/64-slice MDCT, up to even 256-slice MDCT or higher, more recently) may lead to a higher prevalence and a different distribution of PE, with unknown clinical consequences (84). In a recent study, the prevalence of isolated subsegmental emboli did indeed seem higher with 64-slice CTPA compared to 4-slice MDCT, although this difference did not reach statistical significance (84). Careful evaluation of the scans by multiple readers, however, showed a large proportion of patients (10%) to have inconclusive CT-scan results compared to what is usually reported in management studies. This indicates that the diagnosis of PE with multi detector-row CT could be less straightforward than assumed and caution remains necessary when interpreting the CT result (84,85).

Ventilation-perfusion scintigraphy

V/Q scintigraphy has long been the first line imaging test. However, there are two major drawbacks of the test, which limit its application in a clinical setting around the clock. One is the significant number of investigated patients (40-60%) with a non-diagnostic test result after V/Q. These patients all require additional testing. Second, V/Q scintigraphy requires expensive
ventilation materials, and these may not always be available. If, however, after clinical probability assessment and D-dimer testing, V/Q scintigraphy is the test of choice, a normal Q scan safely excludes PE and a high probability V/Q-scan confirms the diagnosis of PE (86,87). In case of a non-diagnostic outcome, additional testing is necessary to confidently exclude the diagnosis (86,87). In case of a “low/intermediate” or “unlikely” pre-test probability a subsequent bilateral CUS can exclude the diagnosis (73,81,88-91). Otherwise, patients should undergo serial CUS examination or CT scanning (73).

**Echocardiography**

Echocardiography may reveal signs which point in the direction of the presence of PE, such as an enlarged right ventricle and increased pulmonary artery pressure. Despite this, however, a recent meta-analysis showed that the overall positive likelihood ratio of echocardiography for PE was low, while the negative likelihood ratio was high – and comparable to CUS in the exclusion of PE (92). Only in patients with a “high” clinical probability, echocardiography was associated with a post-test probability of over 85%, allowing a more accurate diagnosis of PE. Therefore, there is only a limited role for echocardiography in patients with suspected PE: echocardiography is not recommended in stable patients and is only recommended in patients with suspected massive (unstable) PE if CTPA is not immediately available (93).

**Diagnostic strategies in selected patients**

**Renal insufficiency and iodine allergy**

Because CTPA requires the administration of iodine-based contrast material, CTPA is contraindicated in patients with a moderate or severe iodine allergy or renal impairment. However, clinical assessment and D-dimer testing can still be performed (94). If, after CDR and DD assessment, further diagnostic tests are necessary, some patients may be pretreated (in case of iodine allergy: with hydrocortisone and diphenhydramine; in case of renal insufficiency: prehydration with saline intravenously) and then imaged with CT. Alternatively, V/Q scanning can be done. In the future, gadolinium-enhanced magnetic resonance angiography (MRA) could be another and welcome alternative for this patient group (95,96). However, larger-scale studies on the accuracy are still awaited.

**Non-pregnant women of reproductive age**

Young women of reproductive age (younger than 50 years) are also a group of patients in whom CT-scanning should be performed with caution. Concerns have been raised recently, regarding the risk of cancer following radiation exposure with (repeated) CT scanning, and the increased risk of breast cancer, especially in young women (97,98). To give an indication: breast irradiation is approximately 50-100 times higher with CT angiography compared to ventilation-perfusion scanning (99,100) (101). Furthermore, from a recent study it was observed that there is a variation by age, gender and scanning protocol, rather than a constant
risk of cancer following CT-scanning (98). For a 20-year old woman this means that a single CTPA conveys an estimated life-time attributable risk cancer of one in 400 (102) to one in 114 (98). Yet these women are young and often otherwise healthy. Therefore, the expected diagnostic yield of a perfusion scan is high and might suffice in many cases to rule out the diagnosis, possibly in combination with a chest X-ray (103). A strategy including CDR, D-dimer and a combination of chest X-ray and perfusion scanning was recently evaluated retrospectively (104), and could reduce both costs and radiation exposure compared to a strategy with CTPA.

**Pregnant women**

During pregnancy the risk of developing pulmonary embolism is increased, and thrombotic complications are a major cause of maternal and fetal morbidity and mortality (105,106). However, although an early and accurate diagnosis is crucial, the diagnosis of PE is complicated: swelling of the legs, discomfort and shortness of breath are common during pregnancy, and the D-dimer increases throughout gestational age (107). Furthermore, there are concerns regarding radiation exposure to the mother and fetus (99). Finally, many of the common diagnostic tests for the workup of suspected PE have not been appropriately validated in pregnancy.

As a first step in the diagnostic workup of pregnant women with suspected PE a (bilateral) CUS should be considered. If thrombosis is found, the patient can be treated accordingly. A negative CUS result does not rule out PE (108), and therefore further imaging is necessary. CTPA is not necessarily contraindicated during pregnancy and would be the next step (109). Alternatively, a perfusion scan can be performed. The radiation dose to the fetus with CTPA is approximately 0.013 mSv (109), compared to 0.2 mSv with perfusion scintigraphy (110).

**Older patients**

Because the clinical utility of the D-dimer test decreases with increasing age (111,112), the proportion of older patients in whom PE can be excluded by clinical assessment and D-dimer testing is lower compared to the general population (10% vs. 32%, respectively) (113). Recently, a new D-dimer cut-off was suggested for patients above 50 years or age, which is dependent on the patient’s age, and is calculated as age x 10 μg/L (114). Combined with clinical probability assessment, this new cut-off greatly increases the utility of the D-dimer test for the exclusion of PE among elderly patients: i.e. it decreased the number needed to test in patients older than 70 years from 6.3 to 3.2, without reducing safety (114). The strategy seems promising, but awaits prospective validation. Regarding CT scanning, data on this specific subgroup of patients are limited. The largest analysis of older patients to date (>75 years) showed that it was safe to withhold anticoagulant therapy in patients with a normal CTPA (failure rate 0.3%; 95% CI 0.01-1.9%) (113).
Patients with suspected recurrent PE

Data on the diagnostic management of suspected recurrent PE is very limited. This is despite the fact that 10-20% of patients with PE will have a recurrence during the first two years after the initial event. The largest analysis of this subgroup of patients (259 patients) showed that excluding the diagnosis based on an unlikely CDR and normal D-dimer test result was safe (failure rate 0%), albeit that the upper 95% confidence interval limit was 6.9% (115). Also, the clinical utility was lower compared to the general population (i.e. PE was excluded based on the CDR/D-dimer in 16% vs. 32%, respectively). For CTPA, the failure rate after a negative CT-scan in patients with suspected recurrent PE was 0.8% (95% CI, 0.02-4.3%). Similarly to excluding the diagnosis with CDR and D-dimer, this failure rate is acceptable, but validation in larger populations is warranted.

CONCLUSION

Pulmonary embolism is a frequently occurring disease, affecting 1-3 in 1000 individuals annually. Many risk factors, both inherited and acquired have been identified. Adequate diagnosis is mandatory in order to prevent PE related morbidity and mortality, but also to prevent unnecessary treatment with anticoagulants. The current approach to exclude the diagnosis in a patient with suspected PE preferably includes safe, efficient and non-invasive diagnostic tests integrated in a diagnostic strategy. At the same time, adhering to these diagnostic algorithms improves patient care (39,62). The first step in the diagnostic workup of patients with suspected PE is assessment of the clinical probability, using a standardized clinical decision rule. In combination with D-dimer testing, the diagnosis can be safely excluded in a substantial proportion of patients, who will not have to undergo further testing. The next recommended step in patients who do require additional testing is MDCT or V/Q scanning. If the latter results in a non-diagnostic test result, additional testing is necessary.

Advances in the diagnosis of PE have improved the management of patients with suspected PE, making the diagnostic workup safer and more accessible. The introduction of clinical decision rules for the clinical assessment of the pre-test probability combined with D-dimer testing have considerably facilitated a safe and non-invasive exclusion of the diagnosis. Further research should help us improve the strategy for specific patient populations.

REFERENCE LIST


