Cardiothoracic CT: one-stop-shop procedure? Impact on the management of acute pulmonary embolism

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Abstract In the treatment of pulmonary embolism (PE) two groups of patients are traditionally identified, namely the hemodynamically stable and unstable groups. However, in the large group of normotensive patients with PE, there seems to be a subgroup of patients with an increased risk of an adverse outcome, which might benefit from more aggressive therapy than the current standard therapy with anticoagulants. Risk stratification is a commonly used method to define subgroups of patients with either a high or low risk of an adverse outcome. In this review the clinical parameters and biomarkers of myocardial injury and right ventricular dysfunction (RVD) that have been suggested to play an important role in the risk stratification of PE are described first. Secondly, the use of more direct imaging techniques like echocardiography and CT in the assessment of RVD are discussed, followed by a brief outline of new imaging techniques. Finally, two risk stratification models are proposed, combining the markers of RVD with cardiac biomarkers of ischemia to define whether patients should be admitted to the intensive care unit (ICU) and/or be given thrombolysis, admitted to the medical ward, or be safely treated at home with anticoagulant therapy.

Keywords Pulmonary embolism · Risk stratification · CT · Cardiac biomarkers · Right ventricular dysfunction

Introduction

Pulmonary embolism (PE) is a common and potentially fatal cardiovascular disorder. The clinical presentation of acute PE reveals a wide spectrum, ranging from mild dyspnea to cardiac arrest. The short-term mortality of PE also varies widely, ranging from less than 1% in hemodynamically stable patients with non-massive PE and no signs of right heart overload to over 90% in patients who present with cardiorespiratory arrest [1].

In the treatment of PE two groups of patients are traditionally identified. Given the high mortality risk in hemodynamically unstable patients, aggressive therapies such as thrombolytics, inotropic vasoactive drugs, embolectomy, or thrombus fragmentation are indicated [2–4]. In the large group of normotensive patients, anticoagulant treatment is started as the risk of an adverse event due to more aggressive treatment is considered higher than the relatively low risk of PE-related death.

Recent studies have demonstrated that up to 55% of normotensive patients with PE have asymptomatic right ventricular dysfunction (RVD). These normotensive patients with RVD have a higher risk of an adverse outcome with an estimated 30-day mortality directly related to PE between 3 and 10% [5], and an absolute increase in early PE-related mortality of 4–5% [6], or a doubling of the risk of all-cause death during 3-month follow-up [7]. This is significantly higher than the early PE-related mortality in the overall group of normotensive patients (1–7%) [8, 9]. It has been debated that normotensive PE patients with RVD might benefit from thrombolytic therapy [10, 11]. In contrast, there may also be a subgroup of hemodynamically stable patients without RVD that have a very low risk of adverse outcomes and in whom early hospital discharge or even home treatment may be considered.
Risk stratification is a frequently used method to identify subgroups of patients that may benefit from different diagnostic or treatment methods based on a different risk profile. In this review, we discuss the parameters that are currently proposed for prognostic stratification of patients with acute PE. These parameters can, from a practical point of view, be classified into three groups: the first group consists of clinical parameters that can be immediately obtained at bedside, mainly to assess hemodynamic status and distinguish high-risk from non-high-risk PE patients. The second group contains biomarkers of myocardial injury, and finally, markers of RVD make up the third group. Both cardiac biomarkers and markers of RVD can be used to further stratify non-high-risk PE patients into intermediate- and low-risk subgroups [3]. Based on the literature currently available, a potential risk stratification strategy is proposed. The benefit of this and other risk stratification strategies, however, is currently under investigation and has to be demonstrated in prognostic studies before implementation in clinical practice can be recommended. Before we discuss the parameters that are currently considered for clinical risk stratification of patients with PE, we will first expound the pathophysiology of PE to understand the broad clinical spectrum of PE.

**Pathophysiology of PE**

PE can lead to RVD and eventually cardiac failure due to several mechanisms (Fig. 1). At first, PE leads to pulmonary artery (PA) obstruction, which increases the pulmonary vascular resistance. This, in turn, results in an increase in right ventricular (RV) afterload, causing RVD, together resulting in a decreased RV output. At the same time the clot induces the release of neurohumoral substances stimulating arterial vasoconstriction and hypoxemia, thereby increasing pulmonary vascular resistance and RV afterload. Eventually, when RVD is the result of the PE, an increase in RV volume and RV dilatation can be the next step. Because the heart is contained within the pericardium, an increase in RV volume also leads to a shift of the interventricular septum to the left, decreasing the left ventricular (LV) preload and output. In the end, this leads to a decreased cardiac output.

As a consequence of the increased RV afterload, the increased RV wall tension, and increased oxygen demand of the RV, the coronary perfusion of the RV will decrease, leading to ischemia. This in turn stimulates further RVD. Finally, pre-existent cardiopulmonary disease further contributes to the severity of the hemodynamic alterations.

The large differences in outcome in PE are assumed to be related both to the embolus burden and the cardiopulmonary status [12]. Wood et al. proposed a relationship between the severity of the embolic event, characterized by both the embolus size and the cardiopulmonary function, and the mortality in patients with PE. They state that the combination of the embolus size and the cardiopulmonary function leading to shock seems to be associated with a mortality of approximately 30%. Furthermore, a slightly further increase in severity would lead to cardiac arrest, having a mortality of at least 70%, and eventually lead to sudden death. However, it remains unclear which exact combinations of embolus load
and cardiopulmonary status may lead to hemodynamic instability and consequently an exponential increase in mortality rates in normotensive patients with PE. Therefore, it might be of interest to know if there are any predictors that account for this rapid increase in mortality. It is thought that in the group of normotensive patients RVD is an important indicator of an increase in mortality [12].

Clinical parameters

The most important clinical prognostic factors for PE are hypotension and shock [13]. As mentioned before, these patients with hypotension and shock are at high risk, having a short-term mortality of approximately 30% [12]. Because of hemodynamic instability, computed tomography (CT), pulmonary angiography or scintigraphy usually is not performed in the immediate diagnostic workup, and the diagnosis is usually made on the basis of high clinical suspicion and signs of RV failure on echocardiography [3].

However, clinical factors may not only be useful for the initial identification of potentially fatal PE patients, but some of them can also be used to identify patients at the other end of the clinical spectrum, namely those that are at low-risk of an adverse outcome. A commonly used prognostic model is the Pulmonary Embolism Severity Index (PESI) based on 11 patient factors that are all independently associated with short-term mortality and non-fatal adverse outcomes (Table 1) [7, 14]. The PESI was developed to identify low-risk patients who may be potential candidates for outpatient treatment or early hospital discharge.

Cardiac biomarkers

Cardiac biomarkers are currently used in the diagnostic workup of acute chest pain and dyspnea. However, there is increasing evidence that they may also be relevant in PE risk stratification [15]. Cardiac biomarkers can be subdivided into two major groups: markers of RVD, particularly brain natriuretic peptides, and markers of myocardial injury, of which troponins are the most important representatives.

Brain natriuretic peptides

Brain natriuretic peptides (BNP) or N-terminal proBNP (NT-proBNP) are cardiac biomarkers released with increased myocardial stretch. There is increasing evidence that the BNP and NT-proBNP levels are directly related to the severity of RVD [16, 17]. In a systematic review, Sanchez et al. found a relative risk for predicting 30-day mortality of 9.5 for BNP and 5.7 for pro-BNP in patients with proven PE [18]. Although the negative predictive value (NPV) of BNP/NT-proBNP is very high (94–100%), the positive predictive value (PPV) is rather low (12–26%) [3]. Consequently, these biomarkers seem especially useful to identify patients with PE who are at low risk of an adverse outcome.

Cardiac troponins

Elevated levels of troponins (either I or T) are found in patients with acute myocardial infarction due to injury of myocardial cells [19]. Troponin-T is released when RV ischemia is present. Elevated troponin T levels were found in 32% of patients with massive and moderate PE, but not in patients with mild PE [20]. Furthermore, Sanchez et al. revealed a strong relationship between elevated troponin T levels and 30-day mortality [18]. Although elevated troponin levels are associated with increased early mortality, the PPV is low (12–44%) [3]. In contrast, normal troponin T levels revealed a high NPV of 99–100% for both fatal and non-fatal adverse events [3]. Troponin levels may therefore be useful either as a marker of low risk of an adverse outcome when they are normal or as a marker of high risk when they are elevated.

Other biomarkers

The latest biomarkers studied include the fatty acid binding proteins (FABPs), which have been proposed as more
sensitive markers of myocardial injury than troponin T and NT-proBNP [21], and are associated with several adverse outcomes, including shock, intubation and cardiopulmonary resuscitation [22]. D-dimer is a biomarker of fibrinolysis and inflammation, and is elevated in the presence of an acute clot. In patients with PE, plasma D-dimer levels were found to be higher in patients who died of PE than in those who survived [23]. Growth differentiation factor 15 (GDF-15) is a cytokine released in the heart in response to ischemia or pressure overload. In patients with acute PE, GDF-15 was an independent predictor of a complicated 30-day course and of long-term mortality [24].

Although all these relatively new biomarkers can be considered of additional value in relation to the prognosis of PE, they have not yet been evaluated in prospective studies, and their potential role as an independent predictor of adverse outcome in PE patients still needs to be determined.

**Imaging assessment in RVD**

As mentioned before, RVD is an important prognostic indicator in patients with PE. Whereas cardiac biomarkers are an indirect parameter of RVD, it can be more directly assessed using imaging methods such as echocardiography and computed tomography angiography (CTA).

**Echocardiography**

Echocardiography is widely used for the assessment of RVD in patients with PE [25]. Although a generally accepted definition of RVD in echocardiography is lacking [3], echocardiographic findings that are helpful and frequently used in the diagnosis of RVD are: RV dilatation, RV free wall hypokinesis, paradoxal septal wall motion, PA dilatation, a systolic pressure gradient between RV and LV >30 mmHg, and PA flow acceleration time <80 ms [10, 18, 26, 27]. RV dilatation as a marker of RVD is mostly determined by the ratio of RV end-diastolic diameter/LV end-diastolic diameter, with a ratio ≥0.6–1.0 considered abnormal according to several authors [18]. In the International Cooperative Pulmonary Embolism Registry (ICOPER) RV hypokinesis was revealed to be an independent predictor of 30-day mortality in normotensive patients (hazard ratio 1.94, 95% CI 1.23–3.06) [28]. It was already found to double the risk of death within the ensuing 3 months in a study published by the same group [7]. In a retrospective analysis by Sukija et al. paradoxal septal wall motion increased the in-hospital mortality in patients with acute PE [29]. The other indirect signs of RVD, i.e., dilatation of the right PA, a systolic pressure gradient between the RV and right atrium (RA) >30 mmHg, and a PA flow acceleration time <80 ms, have also been used by several authors in defining RVD [15, 26, 30–32].

**Computed tomography**

While pulmonary angiography has long been considered the gold standard in the diagnosis of PE, nowadays computed tomography angiography (CTA) is the first imaging method of choice in the workup of patients with suspected PE [33]. Besides diagnosing PE by direct visualization of the thrombus, CTA can also be helpful in the risk stratification of patients with PE. As with echocardiography the RV/LV diameter ratio as a parameter of RVD can easily be assessed on CT [3]. On axial views a RV/LV ratio ≥0.9–1.5 has been shown to be directly correlated with RVD and adverse outcome [34]. The PPV is low (10%), but a RV/LV ratio <1 has a high NPV (100%) [35]. Two examples of patients with extensive PE and RVD are given in Figs. 2 and 3. One patient suffered cardiac arrest and died shortly after; the other patient was hemodynamically stable at presentation.

The additional value of a four-chamber view in the assessment of the RV/LV ratio has been mentioned, but these data are inconclusive [36–39]. These contradicting results, together with the necessity of additional software and extra time in order to obtain a RV/LV ratio on four-chamber view, make assessment on the axial views the preferred method these days.

When the results of studies on the prognostic role of RVD assessed on echocardiography are taken together with those assessed on CT, the relative risk of RVD for predicting death is 2.4 [18]. Furthermore, RVD may also predict poor pulmonary clot resolution at 6 months, and a higher incidence or venous thromboembolism (VTE) recurrence was demonstrated when RVD was present [40].

**Controversial markers of RVD**

Several other parameters in predicting RVD on CTA have been mentioned, such as dilatation of the superior vena cava (SVC) and azygos vein (AV), resulting from an acute increase in blood volume and pressure in the RA. A study of Ghaye et al. in patients with severe PE revealed significantly different diameters of the SVC and AV between survivors and non-survivors, but only the AV diameter was found to predict mortality [41]. Another study not only demonstrated the AV diameter as a predictor of mortality in acute PE, but the SVC diameter was also significantly correlated to mortality [42]. A more recent publication showed the AV diameter to be significantly increased in the severe PE group compared with the non-severe PE group, whereas no statistically significant difference in diameter of the SVC was present [43].
The dilatation of the AV has so far been revealing the strongest correlation with adverse outcome in PE patients, but whether there is an additional value as compared to other independent predictors of adverse outcome in PE has not been determined yet.

Because the increase in blood volume and pressure in the RA and eventually in the RV can also cause backflow in the inferior vena cava (IVC), enlargement of the diameter of the PA, and straightening, bowing or paradoxal movement of the interventricular septum, these parameters have been the subject of several studies as a potential marker of RVD. However, these studies show discrepancies regarding the potential of these markers as an independent predictor of both fatal and non-fatal adverse outcomes [42, 44–46]. Although, for instance, the diameter of the PA has long been used as a parameter of RVD in echocardiography, Van der Meer et al. did not find a significant relationship between PA to ascending aorta diameter ratio and PE-related mortality [35].

If and how these parameters can be used in a risk stratification model has to be the subject of future prospective research.

Thrombus load

As already stated, the clinical spectrum of PE and the large differences in outcome are considered to be related to both thrombus load and cardiopulmonary status. Because of its excellent clot imaging, CTA can also be used for the quantification of the thrombus load in the pulmonary vascular tree, for which four different scoring systems have been proposed. A detailed discussion of these individual scoring systems is beyond the scope of this article. The modified Walsh and the Miller scores, which are both angiographic scores adapted to the needs of spiral CT, quantify the severity of pulmonary obstruction [47]. Both scores, however, do not differentiate between partial and complete obstruction of a pulmonary vessel. The more recent scores proposed by the groups of Qanadli and Mastora, which were primarily developed for CTA, not only give information about thrombus load, but also about the degree of obstruction [48, 49].

Despite its excellent clot imaging, the literature shows mixed results in the usefulness of the PA obstruction index as a predictor of RVD and mortality. Qanadli et al. found that a CT obstruction score of 40% or greater correlates well with RV dilatation by identifying more than 90% of the patients with PE and RV dilatation [49]. These results were confirmed in the study of Van der Meer et al., reporting an 11.2-fold increased risk of dying of PE for patients with an obstruction index of 40% or higher [35]. In a more recent study of Bazeed et al. a significant difference in the PA obstruction index of more than 50% between survivors and non-survivors of PE was present [50]. On the contrary, no association between clot burden and mortality was revealed by others [42, 44, 46]. Therefore, based on the current literature, there is insufficient support for a vascular obstruction score to be used in a risk stratification system of patients with PE.

Other biomarkers

New CT techniques: ECG-gated CTA and dual-source CT

Recent developments in CT might be able to further help us in the risk stratification of PE. ECG-gated CTA gives the possibility for dynamic and functional cardiac assessment [51]. Information can be obtained about the ejection fraction, RV/LV volumes ratio, RV wall motion abnormality,
foramen ovale patency (right to left shunt), and intracardiac thrombus \[45, 52\], information that is currently provided by echocardiography. By using dedicated three-dimensional software for post-processing, obtaining these measurements does not have to be time-consuming, making it potentially useful in the acute clinical setting. Dual-source CT can be used in the diagnosis of PE in several ways. Using high-pitch dual spiral protocols, the so-called flash technique, it is possible to scan the complete chest in less than a second \[53\], which is particularly helpful to obtain diagnostic quality in dyspneic patients. It can also easily be used for functional assessment of the heart using ECG gating. In addition, by using the dual-energy technique, it not only gives direct information on thrombus load, but also functional information on lung perfusion can be obtained at the same time \[54, 55\]. This perfusion information can be

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**Fig. 3** CTPA performed in a 22-year-old male patient complaining of progressive dyspnea and chest pain, revealing extensive pulmonary emboli including the main pulmonary artery with dilatation of the main pulmonary artery (a, diameter 33 mm) and the right side of the heart (b). The wedge-shaped subpleural consolidation (c) is caused by pulmonary infarction (d, pulmonary window setting). Because of the extensive load and the right ventricular dysfunction at CT, the patient was admitted to the ICU for thrombolytic treatment. The patient became hypotensive shortly after arrival but recovered quickly after treatment. The follow-up CTPA after 1 week shows clearance of thrombus from the main pulmonary artery with normalization of its diameter (e, diameter 25 mm) and normalization of the right ventricle. There is still extensive thrombus present on both sides.
useful, as small subsegmental emboli, compared to large non-occlusive emboli, can more easily result in complete obstruction of the pulmonary vascular bed and therefore may have a significant effect on the hemodynamic status. More research in this area needs to be done to prove its additional value in the risk stratification of PE.

Computer-assisted detection (CAD) software has been developed for the assessment of CTA in PE. First, CAD can be used as a second reader for improvement of the detection of peripheral PE [56]. Second, CAD may also be utilized for automated quantification of thrombus load [33], which is likely to lead to a significant reduction of the assessment time and therefore making evaluation of the thrombus load better applicable in the clinical setting. The incorporation of a CAD system was found to significantly improve assessment of PE severity. This was accomplished by increasing the observer’s sensitivity and correctly raising the percentual embolic occlusion of the pulmonary arterial bed. Consequently, this better accuracy of the severity assessment resulted in improved agreement on the risk stratification of PE patients [57].

### Potential risk strategies

In patients with PE, risk stratification models can be used to identify both patients who are either at high risk or at low risk of an adverse outcome after PE. Based on evidence currently available, the European Society of Cardiology (ESC) has defined principle markers useful for risk stratification in acute PE (Table 2) [3]. Of these, markers of RVD and cardiac biomarkers are likely to be the most attributable to a potential risk stratification system.

Several potential risk stratification models have been proposed. In some of these recommended algorithms markers of RVD and cardiac biomarkers were taken into consideration [3, 5, 15, 58]. Some authors combined cardiac biomarkers and echocardiography, selecting patients initially based on levels of BNP or troponin and secondly on signs of RVD on echocardiography [15]. In other strategies, it is proposed that imaging techniques like CTA or echocardiography should be used as a first step to establish the presence of RVD in a selected group of patients, namely those with an intermediate to high PESI.

### Table 2  Principal markers considered useful for risk stratification in acute pulmonary embolism [3]

| Clinical markers | Shock Hypotension |
|------------------|------------------|
| Markers of RVD   | RV dilatation, hypokinesis, or pressure overload on echocardiography |
|                  | RV dilatation in CT |
|                  | BNP of NT-proBNP elevation |
|                  | Elevated right heart pressure at right heart catheterization |
| Markers of myocardial injury | Cardiac troponins |

RVD=right ventricular dysfunction RV=right ventricle CT=computed tomography BNP=brain natriuretic peptide

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**Fig. 4** The estimated prevalence and mortality of different risk factors in patients with pulmonary embolism (adapted from Becattini et al. 2008) [5]. RVD=right ventricular dysfunction, TnT=troponin T, BNP=brain natriuretic peptide
Hemodynamically stable

Establish diagnosis PE

RV function:
Echocardiography, MDCT, BNP levels

≥1 abnormal

Markers of injury:
Troponin, H-FABP’s

no risk factors

≥1 abnormal

ICU and/or thrombolysis

Medical ward

Outpatient treatment

other risk factors no bleeding risk

Cardiac biomarkers:
Troponin, BNP levels (H-FABP’s)

≥1 abnormal

RV function:
Echocardiography, MDCT

normal

no risk factors

normal

other risk factors no bleeding risk

Medical ward

Outpatient treatment
score and increased troponin levels [58]. Since CTA is the first imaging modality of choice in the diagnosis of PE in hemodynamically stable patients [33], additional information on RVD is obtained simultaneously and can therefore easily be incorporated in a risk stratification strategy. The clinical relevance and therapeutic consequence of any of these strategies, however, have so far not been evaluated in prospective studies, and their clinical value, therefore, remains uncertain.

Becattini et al. published a scheme in 2008 in which the prevalence of different features in patients with PE (asymptomatic, no RVD on ultrasound, RVD on ultrasound ± increased troponin levels, hypotension and shock) was related to their mortality [5]. By introducing CT and the cardiac biomarkers defined by the ESC [3] in this scheme, we might be able to identify subgroups of hemodynamically stable patients that are either at high or low risk of both fatal and non-fatal adverse outcome (Fig. 4).

In the clinical management of hemodynamically stable patients, there are several options. Depending on the risk stratification, the management may range from outpatient treatment to admission to intensive care unit (ICU) and/or thrombolysis (Figs. 5a and b) [3, 59, 60]. There are currently no data available on whether thrombolysis and/or observation in the ICU is the best treatment option for high-risk PE patients, i.e., with RVD, in the hemodynamically stable group. The results of an ongoing study on the benefit of thrombolysis in this high-risk PE group, including the patients that also have abnormal troponin levels (ClinicalTrials.gov NCT 00639743), will provide data that can be used in future risk stratification and treatment of this patient group. As mentioned before, whether outpatient treatment in low-risk patients is a good alternative to the initial conventional in-hospital i.v. heparin treatment for at least 5 days is currently under investigation (OTPE trial).

We propose two different risk stratification models in hemodynamically stable PE patients based on Becattini’s proposed clinical management strategy and the revised Becattini prevalence scheme (Fig. 4). In Becattini’s management proposal based on risk stratification, markers of dysfunction (ultrasound, MDCT, BNP levels) should be assessed first in hemodynamically stable patients with proven PE [5]. If normal, the patient can be admitted to a medical ward. If at least one marker of dysfunction is abnormal, markers of cardiac injury should be assessed (troponin, H-FABPs). Only patients in whom these markers are also abnormal should be admitted to the ICU.

The first proposed model (Fig. 5a) closely resembles Becattini’s strategy. The main difference is the inclusion of other risk factors such as bleeding risk, and treatment with thrombolysis and outpatient treatment in the algorithm. Outpatient treatment can be a good option if both RVD and signs of myocardial injury are absent. In the second model (Fig. 5b), the cardiac biomarkers troponin, BNP and/or FABP are taken into consideration before assessing the presence of RVD by either CT or echocardiography. In this model, outpatient treatment can only be considered if the cardiac biomarkers reveal no abnormalities. If these biomarkers are abnormal, two options are left: admission to the medical ward when signs of RVD are absent or admission to the ICU in combination with thrombolysis if RVD is present.

As CT is the first imaging method of choice in the diagnosis of acute PE and currently considered the gold standard for PE, assessment of RV function on CT is a practical first step and should be evaluated in every patient with PE at CT. Cardiac echocardiography in general has a lower availability and has no proven additional value once CT has been performed. Laboratory testing including cardiac biomarkers should be obtained in every patient with suspected PE or acute cardiac disease. We think that this combination of CT and blood tests is the easiest strategy, most time-efficient, and probably most cost-effective. However, like the risk strategies proposed by other authors, these strategies need further prospective validation before they can be implemented in clinical practice.

Summary

In the large group of normotensive patients with PE, there seems to be a subgroup of patients with an increased risk of an adverse, even lethal, outcome, which might benefit from more aggressive therapy than the current standard therapy with anticoagulants. Risk stratification is a commonly used method to define subgroups of patients with either a high or low risk of an adverse outcome. Clinical parameters, biomarkers, or imaging markers of myocardial injury and RVD have been suggested to play an important role in the risk stratification of PE. In this overview we propose two risk stratification models combining parameters that have
already been shown to be independent predictors of adverse outcomes, namely markers of RVD, either assessed with CT, echocardiography or BNP, and cardiac biomarkers of ischemia to stratify patients into those that should be admitted to the ICU and/or be given thrombolysis, admitted to the medical ward, or can be safely treated at home with anticoagulant therapy. Like the risk strategies previously proposed by other authors, these strategies need further prospective validation before they can be implemented in clinical practice. New developments in CT, such as ECG-gated CTA and dual-source CT, have the potential to further help us in the risk stratification of PE as these new techniques give us the possibility to obtain both functional and dynamic information at the same time in patients with suspected PE.

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