The Role of Helical CT in the Diagnosis of Pulmonary Embolism

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Key Words

Pulmonary embolism · Diagnosis · Helical CT

Abstract

Diagnosing pulmonary embolism is problematic since clinical signs and symptoms of PE are aspecific. Diagnostic algorithms have been developed to rationalize the use of imaging tests in patients with a clinical suspicion of PE. An algorithm based on helical CT has gained widespread interest due to the availability of helical CT. However, these algorithms have often been implemented without appropriate assessment in clinical practice. If one is to implement helical CT as a first line diagnostic test for patients with clinically suspected pulmonary embolism it is important to note that a) CT is sensitive to larger emboli b) single slice technology may miss smaller subsegmental pulmonary emboli and c) outcome studies using a combination of normal single slice helical CT and normal compression ultrasonography rules out safely pulmonary embolism. In view of recent developments in multi row detector CT technology, large, well-designed studies are needed to determine the exact role of multi row helical CT in diagnosing PE.

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Introduction

Diagnosing pulmonary embolism (PE) is complicated since clinical signs and symptoms of PE are aspecific. Objective diagnostic testing is therefore mandatory but imaging of the pulmonary arteries is preferably not carried out in every patient because of costs and potential harm. Diagnostic algorithms have been developed to rationalize the use of non-invasive imaging tests. The clinical prediction rule developed by Wells et al consisting of seven items, rapidly stratifies patients into low and high probability of PE [1]. A combination of a low probability of PE according to this score and a negative D-dimer test in patients presenting at the emergency department with a clinical suspicion of PE, has a negative predictive value of 99.5% (CI, 99.1% to 100%) [2]. This diagnostic work-up safely withholds noninvasive imaging tests in around 30% of patients [2]. However, D-dimer testing has some limitations. There are a variety of D-dimer assays available with different test characteristics and variation in test results between hospitals for the same test. Also, d-dimer testing is less sensitive in certain patient groups (i.e. patients with infections, cancer, sepsis, pregnant patients and postoperative patients). When D-dimer results are abnormal or there is a high probability of PE, additional objective diagnostic testing is needed.

The utility of compression ultrasonography (CUS) of the leg veins as a first test is controversial due to the insensitiv-

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ity of CUS for diagnosing DVT in patients without leg complaints [3,4].

The gold standard for diagnosing PE is pulmonary angiography, but due to its invasiveness, costs and declining experience of radiologists with this technique it is infrequently performed. Perfusion/ventilation scintigraphy is one of the methods of choice since a normal perfusion scan virtually rules out pulmonary embolism and a high-probability V/Q scan has a high predictive value for PE. Disadvantage of this method is the 55-65 % percentage of indeterminate studies [5]. Helical CT is increasingly being used as the first line test for a clinical suspicion of PE. Helical CT has clear advantages, i.e. direct visualisation of thrombus, the possibility of making an alternative diagnosis, cost effectiveness and excellent interobserver agreement [6,7]. A diagnostic algorithm based on helical CT has gained widespread interest due to the availability of helical CT. These algorithms have however often been implemented without appropriate assessment in clinical practice. The fast introduction of multi-detector row helical CT with simultaneous acquisition of four, eight or sixteen sections per scanner rotation instead of a single section without proper evaluation of sensitivity and specificity for PE reinforces the need of obtaining firm evidence that helical CT is an appropriate diagnostic tool in diagnosing PE. It is the aim of this review to reconsider whether helical CT has all the requirements that are needed to recommend its clinical use.

Validation of a Diagnostic Test or Strategy

The evaluation of a new diagnostic test for venous thromboembolism is performed in three phases [8]. First, the test needs to be shown objective and reproducible (Figure 1). Second, the accuracy of the test needs to be assessed by comparing blindly the outcomes of the new test with outcomes of the gold standard (i.e. pulmonary angiography for PE or compression ultrasonography/venography for deep vein thrombosis) in consecutive patients. A wide spectrum of patients should be included in order to avoid a falsely high estimate of accuracy. In the third phase, the safety and effectiveness of the test or strategy is tested in a

Fig. 1. Validation of a diagnostic test or strategy

sufficient large sample of consecutive patients to determine whether management decisions can be based on the outcome of the test. All patients need to be carefully followed up to define the safety of the strategy in terms of false-negative test results, morbidity and mortality. A new diagnostic test can be recommended when the test has complied with the requirements of each of the three phases.

Accuracy Studies

Early studies of accuracy of helical CT for clinically suspected PE demonstrated a sensitivity ranging from 64 to 95% with a specificity ranging from 78 to 100% (table 1). These studies however did not all meet the rigorous methodological criteria for defining the accuracy of a diagnostic test [8].

Two large studies have been carried out evaluating single slice helical CT versus a reference method [16,17]. In the first study, in 299 consecutive patients older than 16 years who presented at the emergency department with a clinical suspicion of PE and an elevated D-dimer level, pulmonary embolism was established by using a validated algorithm that included clinical assessment, lower-limb

Table 1. Early studies evaluating helical CT for a suspicion of PE.

	Year	Pts(n)	PE(%)	Sensitivity(%)	Specificity(%)
Remy-Jardin [9]	1992	42	45	95	96
Teigen [10]	1995	60	39	65	97
Goodman [11]	1995	20	55	64	89
Remy-Jardin [12]	1996	75	57	91	78
van Rossum [13]	1996	249	17	95	97
Mayo [14]	1997	139	33	89	98
Garg [15]	1998	24	25	67	100
Weighted average		609	31	86 (81-91)	96 (93-97)

compression ultrasonography, lung scanning and pulmonary angiography in comparison with single slice helical CT scans that were withheld from clinicians and read three months after acquisition by blinded radiologists (figure 2). Twelve CT scans (4%) were inconclusive. Among patients with conclusive results, sensitivity of helical CT was 70% (95%CI: 62-78%) and specificity 91% (95%CI: 86-95%). In the second study, a different algorithm was studied with all patients starting with perfusion scintigraphy (figure 3) [17]. All normal scans were considered as negative for PE, all high-probability lung scans were considered positive for PE and all abnormal scans were followed by pulmonary angiography. Single slice helical CT was performed in all patients with perfusion defects. Among 517 study patients, helical CT correctly identified 88 of 128 patients with PE and 92 of 109 patients without PE, for a sensitivity and specificity of 69% (95 CI: 63-75%) and 84% (95% CI: 80-

89%) respectively. Further, if PE was present the localisation of the largest involved branch was scored and sensitivity of helical CT was calculated to be 86% (95%CI: 80-92%) for detecting segmental or larger PE and only 21% (95%CI: 14-29%) for subsegmental PE.

Both studies conclude that single slice helical CT should not be used as the sole diagnostic test in patients with clinically suspected PE.

Outcome Studies in Validating Helical CT

To demonstrate the validity of withholding anticoagulant treatment in patients with normal helical CT, three large studies with comparable algorithms, have appeared recently in the literature (18-20).

In the first study, 1041 consecutive in- and outpatients with suspected PE were included and underwent helical CT and ultrasonography of the legs [18]. PE was diagnosed in 360 (34.6%) patients; 55 of these patients had a positive ultrasonography despite a negative helical CT (5.3%). Of 601 patients with negative helical CT and ultrasonography (figure 4), 76 were clinically assessed as having a high probability of PE and lung scanning or pulmonary angiography followed which showed PE in four (5.3%, 95%CI: 1.5-13.1). Of the remaining 525 patients, 18 patients were treated with anticoagulants for other reasons than venous thromboembolism and of the 507 patients that were not treated, nine experienced venous thromboembolism during the 3-months follow up period (1.8%, 95%CI: 0.8-3.3). Of note in this study are the less convincing results in inpatients (VTE rate 4.8%, 95%CI: 1.8-10.1 compared to 0.8% in outpatients), the 9.1% rate of inconclusive results of helical CT and/or ultrasonography, the high false-negative rate of the strategy in patients with a high clinical probability of PE and negative findings on helical CT and ultrasonography (5.3%, 95%CI: 1.5-13.1). The rate of VTE events in inpatients may have been overestimated due to the fact that only two of the six events that occurred during follow up were confirmed by objective tests and the other four were deaths judged to be possibly due to VTE. It was concluded that anticoagulants could be safely withheld in patients with a low or intermediate probability of PE and negative findings on helical CT and compression ultrasonography.

Van Strijen et al. evaluated single detector helical CT as the primary diagnostic test in suspected pulmonary embolism [19]. In this multicenter, prospective clinical outcome study, 510 consecutive in- and outpatients with a clinical suspicion of PE underwent helical CT (figure 5). If CT scan results were normal or inconclusive, compression ultrasonography was performed on the same day and if normal, repeated at day 4 and 7. Anticoagulation was only start-

Fig. 2. Flow chart of the accuracy study by Perrier et al.

Fig. 3. Flow chart of the accuracy study by van Strijen et al.; NA - not available.

ed when helical CT was positive for the presence of PE or when compression ultrasonography was positive for the presence of deep vein thrombosis (DVT). All patients were followed during three months with instructions to report any symptoms or signs of PE or DVT. Helical CT identified PE in 125 of 510 (24.3%) patients, an alternative diagnosis in 130 patients (25.3%) and CT scans were normal in

248 patients (48.6%). Compression ultrasonography revealed DVT in 2 patients, both on the initial examination. In the group with normal CT scans, one patient developed nonfatal PE. In the group with an alternative diagnosis, one patient developed DVT during follow up, while in another patient fatal PE could not be ruled out as a contributing cause of death on day 22. Thus, a total of 3/376 patients

Fig. 4. Flow chart of outcome study by Musset et al.

(0.8 %, 95 % CI 0.2-2.3 %) had recurrent VTE after a CT indicating no PE at study entry. This study shows that single-detector helical CT can be used safely as the primary diagnostic test for a clinical suspicion of PE. The value of performing compression ultrasonography after a negative helical CT in patients with a clinical suspicion of PE but no suspicion of DVT was limited.

Finally, Perrier et al. evaluated a diagnostic strategy for pulmonary embolism starting with a prediction rule combined with implicit judgement, followed by D-dimer testing, venous ultrasound and helical CT (figure 6) [20]. A normal D-dimer ruled out PE in 280 patients (29%) and the finding of a DVT by compression ultrasonography established the diagnosis in 92 patients (9.5%). Helical CT was required in the remaining 61% of patients and showed PE in 124 patients (12.8%). PE was considered ruled out in the 450 patients with a negative ultrasound and CT scan and a low to intermediate clinical probability. The 8 patients with a negative ultrasound and negative CT scan despite a high clinical probability, proceeded to pulmonary angiography and two more pulmonary embolisms were diagnosed. In the

685 patients classified as not having PE who were not anticoagulated, the 3-month thrombo-embolic risk of VTE was 1.0% (95%CI: 0.5-2.1%). All thromboembolic events occurred in the 406 patients with a low-to-intermediate clinical probability of PE, a negative ultrasound and a negative helical CT scan, yielding a 3-month thromboembolic risk of 1.7% (95%CI: 0.8-3.5%) compared with 0 % (95%CI: 0-1.4%) in the 268 patients with normal D-dimer levels. It can be concluded that in patients with elevated D-dimer levels, a strategy based on a clinical prediction rule and ultrasound combined with helical CT appeared safe and effective.

As is summarised in table 2, the recurrence rate of VTE in negative helical CT varies considerably. This is largely due to differences in design of the studies, patient selection and follow up. Taking into account the three largest and well-designed studies, it can be concluded that recurrence of VTE is 0.8-1.8% in an algorithm using helical CT combined with ultrasonography.

An issue often debated is the limitation of helical CT to accurately detect small peripheral emboli. Results of early studies in which single-detector row CT was compared with

Fig. 5. Flow chart of the ANTELOPE II-study

Table 2. Outcome studies in validating helical CT

Author	Year	N	Recurrence
Ferretti [21]	1997	164	5.4%
Garg [22]	1999	126	1.3%
Lomis [23]	1999	143	0%
Goodman [24]	2000	198	1.0%
Ost [25]	2001	103	4.2%
Gottsater [26]	2001	305	1.4%
Musset [27]	2002	525	1.8% (0.8-3.3)
van Strijen [19]	2003	512	0.8% (0.8-3.5)
Perrier [20]	2004	450	1.7% (0.8-3.5)

selective pulmonary angiography demonstrated the high accuracy of CT for detection of PE to the segmental arterial level but suggested that subsegmental pulmonary emboli may be overlooked on CT scans. Sensitivity of single-detector row CT for detecting subsegmental PE in a large accuracy study was only 21% (95%CI: 14-29%) compared to 86% (95%CI: 80-92%) for segmental or larger PE [17]. CT technology is rapidly developing and has brought recent years the advent of multi-detector row CT allowing coverage of

the entire chest with 1-mm or submillimeter resolution within a short single breath-hold. Use of multi-detector row CT significantly improves pulmonary arterial visualization in the middle and peripheral lung zones and increases the detection rate of subsegmental emboli [27,28]. However, no clinical outcome studies have evaluated multi-detector row helical CT in diagnosing PE.

Another problem relating to the detection rate of small peripheral emboli, is the unknown relevance of these small clots that might have gone unnoticed in the past. The percentage of these small peripheral emboli in subsegmental arteries has been reported to range from 6% to 30% [5,29]. It is yet unknown whether treatment of these small emboli results in a better clinical outcome of the patient. From the three outcome-studies discussed above, in which patients with a normal single detector helical CT and normal repeated ultrasonography did not receive anticoagulation, it may indirectly be concluded that small emboli that cannot be detected by CT do not need anticoagulant treatment in patients in stable cardiopulmonary condition at presentation in view of the low thromboembolic rate at three months follow-up (0.8- 1.8 %, 95 % CI 0.2-2.3 %).

Fig. 6. Flow chart with results of the outcome study by Perrier et al.

Conclusions

If one is to implement helical CT as a first line diagnostic test for patients with clinically suspected pulmonary embolism it is important to note that a) CT is sensitive to larger emboli b) single slice technology may miss smaller subsegmental pulmonary emboli and c) outcome studies using a combination of normal single slice helical CT and normal compression ultrasonography rules out safely pulmonary embolism. In view of recent developments in multi row detector CT technology, large, well-designed studies are needed to determine the exact role of multi row helical CT in diagnosing PE. Currently, in the Christopher study, in a large clinical outcome study coordinated from Leiden, more than 3000 patients with clinically suspected PE are being diagnosed in 12 participating hospitals in the Netherlands, according to an algorithm involving clinical decision rule and D-dimer to exclude PE and multi row helical CT to assess the presence of PE in patients with a high clinical probability or an abnormal D-dimer test. The primary endpoint is the occurrence of VTE during three months follow up after normal initial tests. Results of this study are expected in 2005. Finally, there is great need to perform phase IV studies evaluating cost-effectiveness of different helical CT based strategies when implemented in clinical practice [30].

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