Clinical Outcomes after Investigation for Pulmonary Embolism using CT Angiography and Venography

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Abstract

Background: The diagnosis of pulmonary embolism (PE) still requires long work-up periods and multiple tests.

Objective: We aim to assess clinical outcomes after a negative investigation using a combined protocol of CT pulmonary angiography and CT venography (CTA/CTV) as a sole diagnostic test in unselected patients with suspected PE.

Methods: This retrospective cohort study enrolled consecutive patients with suspected PE who were investigated with a combined CTA/CTV protocol. Patients who had an initially negative investigation and were not anticoagulated were followed for 6 months for the occurrence of recurrent venous thromboembolic events.

Results: Out of 425 patients with suspected PE, 62 (14.6%) had venous thromboembolism diagnosed on the initial CTA/CTV. The mean age was 56 ± 19 years and 61% of the population fell into the low clinical probability category. Isolated deep vein thrombosis represented 21% of all venous thromboembolic events, and when considering the whole population, CTV was associated with an increment in diagnostic yield of 3.1%. Our cohort was composed of 320 patients with initially negative CTA/CTVs and who were not anticoagulated. After 6 months of follow up, only three patients presented with recurrent thromboembolic events (0.9%; 95% CI -0.1% - 2.0%) and none were fatal. There were no PE-related deaths.

Conclusion: Our study suggests that a diagnostic strategy that utilizes CTA/CTV as a sole diagnostic test can safely rule out PE in a low to moderate risk population and is associated with favorable outcomes with a negative predictive value of 99.1%. (Arq Bras Cardiol 2012;99(2):740-746)

Keywords: Pulmonary embolism; computed tomography; thorax; phlebography.

Introduction

The majority of patients with clinically suspected pulmonary embolism (PE) has an alternative diagnosis for their symptoms, and the prevalence of confirmed PE among these suspected cases ranges from 16% to 26% in contemporary series[1-3] .Thus, one of the greatest challenges in the work up of PE is to rapidly and safely rule out the disease, avoiding unnecessary anticoagulation and expediting the diagnostic strategy.

Computed tomography (CT) has rapidly become the preferred method for excluding or confirming the diagnosis of PE[4-6].However, uncertainty remains about the sensitivity of pulmonary CT angiography (CTA) as a single diagnostic method, and additional testing for deep vein thrombosis (DVT) has become an integral part of most diagnostic algorithms[7]. CT venography (CTV) has comparable accuracy as compression ultrasonography (CUS) for the diagnosis of DVT[8] with the added advantage of being performed in conjunction with CTA (CTA/CTV). The combination of CTA and CT venography is a very attractive strategy because it is able, at the same time and with no additional contrast material, to detect emboli in the pulmonary circulation and residual thrombi in the deep veins of the legs[2,8], although it exposes the patients to additional radiation.

The goals of this study were to determine the diagnostic value of adding CTV to CTA and assess clinical outcomes after a normal CTA/CTV as a sole diagnostic test in unselected patients with clinically suspected PE.

Patients And Methods

Study Population and Data Collection

A CT based algorithm that uses the combination of CTA and CTV has been the method of choice for the work up of PE since 1999 at our institution, a tertiary care non-academic hospital. Using the radiology department's database, we retrospectively enrolled all patients with clinically suspected PE who were investigated with a CTA/CTV between January 2004 and December 2007. This represents an unselected population since ventilation-perfusion (V/Q) scintigraphies were performed only when there were contra-indications for the use of contrast material, and D-Dimer measurement had not been incorporated into our diagnostic algorithm at

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the time of patient recruitment for the study. Based on the report of the interpreting radiologist the studies were classified as following: positive for PE, PE and DVT or isolated DVT, negative and inconclusive. Patients were excluded if they had inconclusive studies due to technical limitations. Patients with negative studies were contacted by telephone in order to verify the occurrence of recurrent venous thromboembolic events or death during the 6-month period that followed the CTA/CTV. The patients that used oral anticoagulants at any time and for any duration within this 6-month period were also excluded. All clinical and demographic data were obtained from the medical chart, radiological records or directly from the patients. A clinical probability of PE was estimated based on the following risk factors: malignancy (excluding skin cancer); previous venous thromboembolism; surgery within a month the CTA/CTV (Intra-abdominal, thoracic and orthopedic surgery) and bed-ridden state. The presence of at least one of the above risk factors identified the high-risk group. The low-risk group was comprised of patients with none of the risk factors[9].

During the telephone interview, the investigators utilized a standardized questionnaire to determine life status and circumstances of death, occurrence of venous thromboembolic events and use of anticoagulation. The cause of death was determined based on the information present in the death certificate, the patients' charts, and on information collected from the family members. Death was attributed to PE if it was preceded by symptoms suggestive of recurrent venous thromboembolism (VTE), if it was sudden with no other plausible cause or if it was confirmed on autopsy. A recurrent venous thromboembolic event was defined as PE or DTV confirmed by objective tests, or death attributed to PE occurring within the 6-month period following the CT study.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, was approved by the research ethics committee and verbal consent was obtained from all patients (IRB: MCO/UFBA – n° 70/2004).

CTA/CTV protocol

All studies were performed on a GE High-Speed single-detector helical CT scanner (General Electric Medical Systems, Milwaukee, Wis.). The lungs were scanned from the lowest portion of the diaphragm to approximately 2 cm above the aortic arch during a 25 to 30-second single breath hold and sequential 5 mm-thick images of the lower extremities were acquired at 2 cm intervals from approximately 10 cm bellow the popliteal fossa up to just above the iliac crest, 3 minutes after completion of the CTA. For all studies, 150 ml of contrast was administered intravenously at a rate of 3 ml per second.

Results

Baseline clinical characteristics

A total of 425 patients with suspected PE were investigated with a CTA/CTV. The general characteristics of this population are detailed in table 1. The mean age was 56 ± 19 years, there was a predominance of females (63.1%) and the majority of the population was composed of outpatients presenting to the emergency room (70.1%). Over half of the population (57%) had at least one traditional risk factor for venous thrombosis. The most frequent symptom and sign was dyspnea and tachypnea present in 55% and 67% of the patients, respectively. The high-risk group was comprised by 164 patients (38.6%) and the remaining 261 patients formed the low risk group (61.4%).

Table 1 - General characteristics

Clinical Characteristics	All patients (n=425)
Age (mean ± SD) y	56 ± 19
Females	268 (63,1%)
White	238 (56%)
Emergency room patients	298 (70,1%)
Coexisting conditions	
Heart Failure	34 (8,0%)
Cancer	56 (13,2%)
COPD	71 (16,7%)
Atrial Fibrillation	22 (5,2%)
Surgery within the past month	95 (22,4%)
Previous VTE	41 (9,6%)
Estrogen use/pregnancy	17 (4,0%)
Obesity	34 (8,0%)
Central venous catheter	9 (2,1%)
Symptoms and signs	
Dyspnea	235 (55,3%)
Chest pain	226 (53,2%)
Calf pain	47 (11,0%)
Hemoptysis	32 (7,5%)
Syncope	13 (3,1%)
Leg edema	53 (12,5%)
Tachycardia (> 100 beats/min)	102 (24,0%)
Tachypnea (> 20 breaths/min)	283 (66,6%)

Results of CTA/CTV and other imaging modalities

Of the 425 CTA/CTV studies only 9 (2.1%) were considered inconclusive. Sixty-two patients (14.6%) had positive scans, and of those, 14 (22.6%) had isolated PE, 35 (56.4%) had PE and DVT, and 13 (21%) had isolated DVT (Figure 1). The rate of venous thromboembolism according to the clinical probability was 9.2% and 23.2% in low and high-risk groups, respectively. Isolated DVT comprised 21% of the diagnosed VTE events (13/62 patients). It was found in 13 of the 425 patients, resulting in an incremental diagnostic value of CTV for the whole population of 3.1% (95% CI 1.4% - 4.7%). The diagnostic contribution of CTV for the high risk group (9/164 – 5.5%; 95% CI 2.0% - 8.9%) was much greater than for the low risk patients (4/261 – 1.5%; 95% CI 0.04% - 3.0%) (Table 2). Ventilation-perfusion scintigraphies were performed in only three of these patients (0.9%), one was interpreted as low probability and the other two as normal or near normal. Compression ultrasonography (CUS) was also performed in 25 additional patients (7.8%). In only one, a deep vein thrombosis was demonstrated and this was considered a recurrent event.

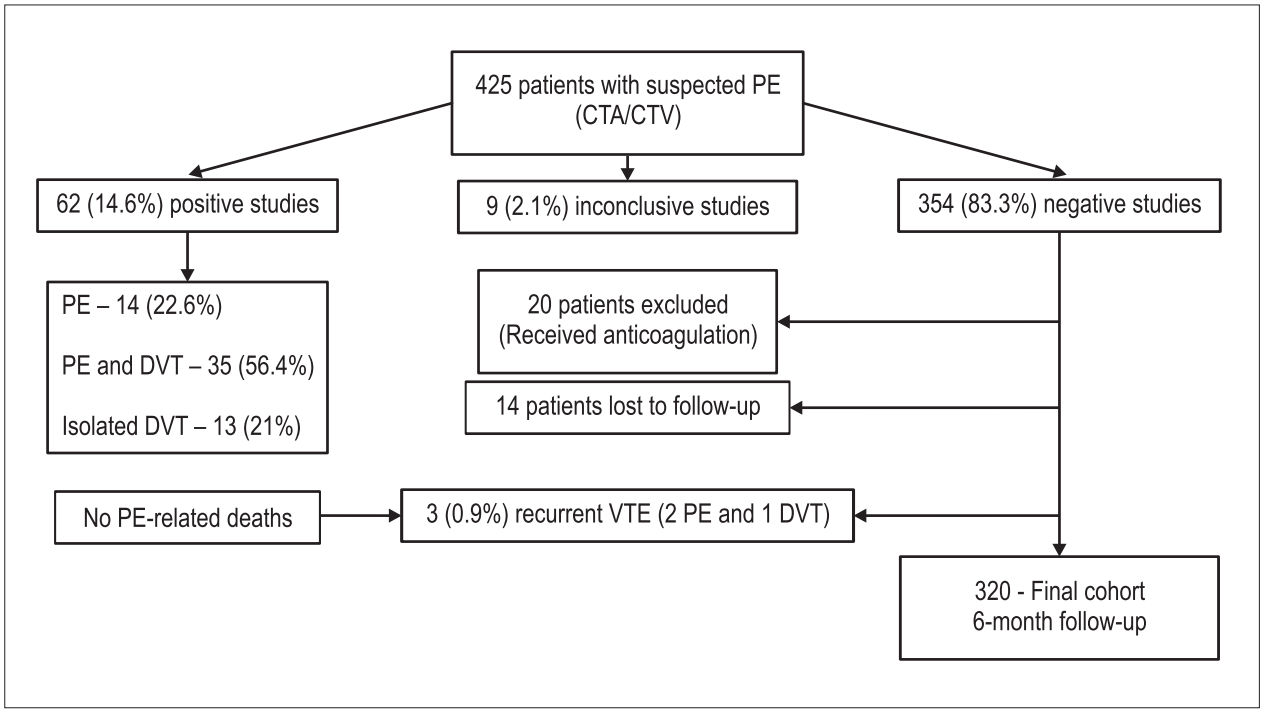

Figure 1 - *Patient selection and clinical outcomes*

Table 2 - Clinical outcomes according to clinical probability

Pre-test probability	N (%)	VTE rate	Isolated DVT	Recurrence rate*	NPV
Low	261 (61,4%)	24 (9,2%)	4/261 (1,5%)	2/193 (1,0%)	99,0%
High	164 (38,6%)	38 (23,2%)	9/164 (5,5%)	1/127 (0,8%)	99,2%
Total	425	62 (14,6%)	13/425 (3,1%)	3/320 (0,9%)	99,1%

**Denominator represents patients with negative CTA/CTV not taking anticoagulants and with complete follow-up.*

Clinical outcomes

A total of 354 patients (83.3%) had negative CTA/CTV studies. During follow up, 20 patients received oral anticoagulation and were excluded: Previous VTE (6); atrial fibrillation (6); heart failure (3); valve prosthesis (2); systemic lupus + anti-phospholipid antibodies (2); peripheral arterial thrombosis (1). Additionally, 14 patients could not be contacted and were also excluded. The remaining 320 patients comprised our retrospective cohort.

During the 6-month follow up period, recurrent venous thromboembolic events were diagnosed in three of the 320 patients with an initially negative investigation (0.9%; 95% CI -0.1% - 2.0%). Of these, two patients presented with PE (0.6%) and one other patient with DVT (0.3%). The first patient developed chest pain 7 days into a hospitalization for investigation of abdominal pain. A CTA/CTV was negative for VTE but a duplex scan done on the same day revealed a partial thrombosis involving the left tibial and popliteal veins. The second patient with a long-standing diagnosis of congestive heart failure presented with progressive dyspnea. The CTA/CTV showed only a large right pleural effusion. She was submitted to a therapeutic thoracentesis and three days later, since her symptoms did not abate, a new CTA/CTV was ordered. This time an embolus in the right interlobar pulmonary artery was visualized. A third patient presented to the emergency room with dyspnea and a CTA/CTV did not show VTE. She was discharged home and returned ten days later with worsening symptoms. A new CTA/CTV revealed bilateral subsegmental emboli.

The calculated negative predictive value of CTA/CTV for recurrent VTE was 99.1%. The recurrence rate was 1.0% (95% CI -0.4% - 2.5%) and 0.8% (95% CI -0.8% - 2.3%) in low and high-risk patients, respectively (Table 2). None of the three patients with recurrent VTE died during the 6-month follow up period. Of the 320 patients with negative CTA/CTV who were not anticoagulated and completed the 6-month follow up period, 36 died (11.3%), but none of the deaths was attributed to PE. The one occurrence of sudden death was considered cardiac in origin since the patient had a history of ischemic cardiomyopathy in advanced stage. The causes of death in this population are detailed on table 3.

Table 3 - Causes of death among the 320 patients with negative CTA/CTV

Causes of death	N (%)
Cancer	16 (44.4%)
Infection/sepsis	10 (27.8%)
COPD	2 (5.5%)
Congestive heart failure	2 (5.5%)
Stroke	2 (5.5%)
Acute myocardial infarction	1 (2.8%)
Sudden cardiac death*	1 (2.8%)
Interstitial lung fibrosis	1 (2.8%)
Upper gastrointestinal bleeding	1 (2.8%)
TOTAL	36(11.3%)

** Patient with advanced ischemic cardiomyopathy.*

Discussion

The development of a simple, practical and safe diagnostic strategy that is widely available and applicable to the majority of patients with suspected PE is a highly desirable goal. Over the past 20 years, the diagnostic strategies for PE have been marked by an excessive number of sequential tests, long workup periods and the frequent need for invasive procedures[10]. The introduction of pulmonary CTA[11] and subsequently lower extremities CTV[12] has presented the possibility of overcoming most of the above limitations of older diagnostic strategies. The current study confirms the significant incremental diagnostic value of CTV, which can be used in place of CUS, and the clinical utility of CTA/CTV for safely ruling out the diagnosis of PE as a sole diagnostic test.

Diagnostic contribution of CTV

The accuracy of CTV was demonstrated in a recent meta-analysis of 13 studies comparing it with CUS (except one study that used venography), with pooled estimates of sensitivity and specificity of 96% and 95%, respectively[8]. Although most guidelines and experts recommend lower-extremity imaging before safely ruling out PE, particularly in moderate to high risk patients[7,13], some authors have charged the debate as to the absolute need for systematically searching for DVT in all patients with an initially negative CTA[14,15]. Our data showed that 21% of the VTE events were isolated DVT detected on CTV (13/61 patients), which means that these patients with negative CTAs would have been wrongly classified as not having VTE and left untreated. We found an incremental diagnostic value of CTV for the whole population of 3.1% (95% CI 1.4% - 4.7%). These data are in accordance to the current literature which shows incremental values that varies from 2.0% to 5.0%[9,16-18] considering the entire study population rather than only the cases of VTE. More recently, the PIOPED II study reiterated the importance of systematic DVT testing by showing a sensitivity of 90% with the combined CTA/CTV protocol as opposed to 83% with CTA alone[2]. We were also able to identify a subgroup of patients with a higher probability of PE, in whom the incremental value of CTV was approximately 4-fold greater when compared to low risk patients (5.5% versus 1.5%). Therefore, our data show that CTV may replace CUS in those patients who require DVT testing and also help define a more select group of patients with a higher risk of PE, which may derive a greater diagnostic value from a strategy that combines CTA and CTV, reducing cost and radiation exposure.

Clinical outcomes after a negative CTA/CTV

Another important contribution of the current study is the demonstration that a diagnostic strategy based solely on CTA/CTV is associated with favorable outcomes. Our data showed that in patients who had an initially negative CTA/CTV, anticoagulation could be safely withheld irrespective of the pre-test clinical probability. We found a VTE recurrent rate of 0.9% during the 6 months that followed the negative test, a finding similar to that reported by other authors and other diagnostic strategies. A systematic review of all prospective studies using conventional pulmonary angiography found that patients with negative results had an overall rate of recurrent VTE of 1.7%[19]. Moores et al[20] reported similar findings in a more recent meta-analysis of outcome studies of patients managed with CTA with a 3-month rate of subsequent VTE after a negative test of 1.4% (95% CI 1.1% - 1.8%). To the best of our knowledge, the only other outcome study that used CTA/CTV as the sole diagnostic test involved only 181 intensive care unit patients followed for one month and found a negative predictive value of 97.1%[21]. The PIOPED II[2], one of the most important investigations on the accuracy of CTA/CTV for the diagnosis of PE, did not formally report outcome data. The authors used a composite reference standard comprising a number of non-invasive tests in order to rule out or confirm the diagnosis of PE and concluded that CTA/CTV was diagnostic only when clinical assessment and test results were concordant. Additional testing was recommended in cases of inconsistencies between the clinical probability assessment and imaging results. Our study, on the other hand, showed very similar negative predictive values regardless of the pre-test clinical probability (table 2). In the high clinical probability group for instance, a category in which the negative predictive value of CTA has been questioned, the negative predictive value was 99.2%. The discrepancy between the PIOPED conclusions and our results stem from the fact that two different reference standards were used in order to assess the accuracy of CTA/CTV.

The PIOPED investigators used a composite reference standard to diagnose and rule out PE that included V/Q scans, lower extremities CUS and in 225 patients (27%) conventional pulmonary angiography (CPA). In our study, on the other hand, we used clinical outcomes after CTA/CTV as a measure of safety of the diagnostic strategy. The accuracy of a diagnostic test is usually measured by comparing its performance with a reference gold standard, and in the case of PE, CPA has been considered the reference test. However, besides its invasive nature, CPA also has its own limitations concerning accuracy and interobserver agreement[22,23]. Such limitations of the reference standard partially compromise the assessment of the diagnostic characteristics of new tests. Outcome studies,

on the other hand, assess new diagnostic tests based on the occurrence of clinical events after the tests are applied, and do not rely on the diagnostic characteristics of a reference test, thus, overcoming these limitations.

Single-detector versus Multi-detector CT

Our study used only single-detector CT (SDCT) scanners and whether our results are applicable to newer technology is debatable. Multi-detector CT (MDCT) is the state-of-the-art technology for PE diagnosis although a considerable number of medical centers around the world still use SDCT. Sensitivity for the diagnosis of PE has improved from 66%-93%[24] with SDCT to 83%-100% with MDCT[2,25]. In spite of this improvement in sensitivity, in some studies the use of MDCT has not been shown to reduce the importance of CTV when added to CTA[2,17]. Therefore, the use of both tests were recommended by most PIOPED II investigators[26]. Additionally, in outcome studies, despite being able to diagnose more pulmonary emboli, MDCT has shown very similar recurrent rates when compared to SDCT[3,15,27]. Since most additional emboli diagnosed with MDCT are subsegmental and the increment in diagnostic accuracy did not translate into better outcomes, some authors have cast doubts upon the clinical significance of small peripheral PE and raised the concern of overdiagnosis[28]. Isolated subsegmental emboli answer for less than 10% of all PE[29] and when left untreated has been associated with very good outcomes[30,31]. In a recent publication, the authors reported the 3-month clinical outcomes of 93 patients found to have isolated subsegmental emboli. At the end of the follow up period, none of the patients that did not receive anticoagulation had recurrent events[30], a finding confirmed in another series[31]. An interesting report showed that the location and size of the subsegmental emboli detected on CPA were inconsistent with clinical, radiographic and scintigraphic findings, suggesting that isolated microemboli are serendipitous findings of no clinical significance[32]. In fact, incidentally found PE on contrast-enhanced CT done for different reasons is seen in approximately 2% of inpatients[33].

Nonetheless, recent large prospective studies using multi-detector CTA have favored its use as a stand-alone test[34,35]. Perrier et al[34] have assessed whether a strategy of D-dimer measurement and MDCT, without the use of CUS or CTV, might safely rule out PE. All patients with negative findings on CTA underwent CUS but only a very small proportion of them had DVT (0.9%; 95% CI 0.3% - 2.7%)[34]. The same group of investigators tested the very same hypothesis in a randomized trial and showed that regardless whether the diagnostic strategy included CUS, the 3-month thromboembolic risk was exactly the same[35]. It is important to emphasize that both studies recruited only a small number of high risk patients, and, as demonstrated by the current study with SDCT and by others with MDCT[17], the systematic use of CTV is associated with a significant incremental diagnostic value and should probably be recommended for these high risk patients independent of the technology utilized.

Limitations

First, as a retrospective cohort, our study may suffer from biases inherent to the process of retrospectively collecting data, relying upon revision of medical records and patients' recollections. Second, fourteen patients with an initially negative CTA/CTV could not be contacted and were, therefore, excluded. Reviewing these patients' clinical characteristics revealed a group of young and low risk individuals. The mean age was 52 ± 16 years, 50% were females and none of them presented a high-risk feature as defined in this study. If one considers the recurrent rate encountered in our low risk patients (1.0%), one would expect, at most, only a single additional VTE recurrence. In this case, the total number of recurrent VTE events would be 4 out of 320 (1.2%; 95% CI 0.0% - 2.5%) and, therefore, it would not compromise the overall results and conclusions.

Conclusion

To the best of our knowledge, this is the first outcome study to utilize a combination of single detector CTA and CTV as the sole diagnostic test in unselected patients with suspected PE. Unlike the majority of previously published outcome studies, this one was carried out entirely in a tertiary community hospital, and thus, closer to the environment where most internists practice. Our study suggests that the addition of CTV to CTA results in a significant increase in the number of patients diagnosed with VTE particularly in the high-risk group. Additionally, a strategy that uses CTA/CTV as the sole diagnostic test for ruling out PE is associated with very favorable outcomes and appears to be safe in the majority of patients with suspected PE. This strategy ought to be tested in larger prospective studies and utilizing state-of-the-art technology.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any post-graduation program.

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