Spiral Computed Tomography for the Diagnosis of Pulmonary Embolism in Critically Ill Surgical Patients

A Comparison With Pulmonary Angiography

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Hypothesis: Spiral computed tomographic pulmonary angiography (CTPA) is sensitive and specific in diagnosing pulmonary embolism (PE) in critically ill surgical patients.

Design: Prospective study comparing CTPA with the criterion standard, pulmonary angiography (PA).

Setting: Surgical intensive care unit of an academic hospital.

Patients: Twenty-two critically ill surgical patients with clinical suspicion of PE. The CTPAs and PAs were independently read by 4 radiologists (2 for each test) blinded to each other's interpretation. Clinical suspicion was classified as high, intermediate, or low according to predetermined criteria. All but 2 patients had marked pulmonary parenchymal disease at the time of the event that triggered evaluation for PE.

Interventions: Computed tomographic pulmonary angiography and PA in 22 patients, venous duplex scan in 19.

Results: Eleven patients (50%) had evidence of PE on PA, 5 in central and 6 in peripheral pulmonary arteries. The sensitivity and specificity of CTPA was, respectively, 45% and 82% for all PEs, 60% and 100% for central PEs, and 33% and 82% for peripheral PEs. Duplex scanning was 40% sensitive and 100% specific in diagnosing PE. The independent reviewers disagreed only in 14% of CTPA and 14% of PA interpretations. There were no differences in risk factors or clinical characteristics between patients with and without PE. The level of clinical suspicion was identical in the 2 groups.

Conclusions: Pulmonary angiography remains the gold standard for the diagnosis of PE in critically ill surgical patients. Computed tomographic pulmonary angiography needs further evaluation in this population.

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Pulmonary Embolism (PE) is a frequent and often undiagnosed cause of mortality in postoperative critically ill patients. In a prospective observational study done during a period of 18 months in our surgical intensive care unit (SICU), only 4 PEs were detected among 200 highly selected, severely injured patients with multiple risk factors for venous thromboembolism. Given that autopsy studies estimate the PE-related mortality rate of such patients to be 15% to 30%, it is likely that many PEs are not detected in a timely fashion.

Pulmonary angiography (PA) is currently the standard of reference for PE diagnosis. However, it is an invasive procedure, associated with morbidity and mortality, and requiring considerable technical and human resources. Ventilation-perfusion scan is safer and less invasive and, therefore, frequently used as the principal diagnostic test. The problem with this method is that, in almost half of the cases, the diagnosis is uncertain (intermediate probability), and there is approximately a 10% rate of false-negative and false-positive results with low-probability and high-probability tests, respectively. The reliability of the test becomes even more questionable in the presence of associated lung disease, as is typically found in SICU patients.

Recently, spiral computed tomographic pulmonary arteriography (CTPA) has emerged as a useful tool to diagnose PE. Multiple studies have examined its role...
PATIENTS AND METHODS

During a period of 11 months (August 1, 1999, to June 30, 2000), surgical patients who were admitted to the SICU and had clinical suspicion of PE were included in the study and underwent CTPA and PA. Clinical suspicion was raised when any of the following occurred: (1) acute arterial oxygen desaturation to less than 94% in the absence of new sepsis or other pulmonary pathologic findings, (2) sudden reduction of the ratio of arterial partial oxygen tension to fractional inspired oxygen to less than 200 in the presence of unchanged lung compliance, and (3) any sudden decrease in oxygenation associated with acute hemodynamic compromise, as shown by a systolic blood pressure lower than 100 mm Hg and/or a heart rate higher than 120 beats per minute, in the absence of obvious blood loss or new sepsis. Exclusion criteria from the study were (1) frank physiological instability, rendering transport to the radiology department dangerous; (2) renal function impairment (serum creatinine level >106 µmol/L [>1.2 mg/dL]) before or between the 2 tests; (3) severe pulmonary hypertension (systolic pulmonary pressure >60 mm Hg); (4) pregnancy; (5) a do-not-resuscitate order; (6) failure to undergo the first test within 24 hours of inclusion into the study or the second test within 24 hours of the first test; and (7) age younger than 18 years. The study was approved by the institutional review board of the Los Angeles County and University of Southern California Medical Center, Los Angeles.

In our SICU we treat approximately 800 surgical patients per year, of whom 60% are trauma patients. Eligible patients had both tests done as soon as possible from the time of clinical diagnosis and as close as possible to each other. Although the order of the tests was not predetermined, CTPA was usually done before PA because of easier accessibility. Serum creatinine levels were measured before inclusion, between the 2 tests, and daily after the completion of the tests. To evaluate the pulmonary sensitivity and specificity are comparable with PA’s. If the hypothesis holds true, this less invasive and more convenient test can be used by clinicians at a lower threshold to diagnose PE among SICU patients, leading to detection and earlier treatment of thromboembolic events that might otherwise remain undiagnosed.

RESULTS

There were 22 patients enrolled in the study, 17 trauma and 5 nontrauma patients with an average age of 38 years (range, 20–75 years). All patients had episodes of acute desaturation and were taken to the first study (usually CTPA) within an average of 10 hours of the first episode (range, 2–24 hours). The second study followed within an average of 8 hours of the first study (range, 7–21 hours). Five patients were receiving no or inadequate (single intermittent compression device) thromboprophylaxis. All 5 were trauma patients, had contraindications to heparin administration, and had multiple extremity fractures preventing the use of intermittent compression devices. All but 2 patients had marked lung
Patients with and without PE. A high level was established in 2. The level of clinical suspicion was identical among multiple emboli were found in 4 patients and bilateral emboli mental or subsegmental branches were obstructed. Multilateral pulmonary arteries. In the remaining 6, only segmental or subsegmental branches were obstructed. Multiple emboli were found in 4 patients and bilateral emboli in 2. The level of clinical suspicion was identical among patients with and without PE. A high level was established in 6 patients of each group, an intermediate level in 3, and a low level in 2. Table 2 compares patients with and without PE. No statistically significant differences were found between the 2 groups. All patients diagnosed as having PE were treated by heparinization (5 patients), vena caval filter (3 patients), or both (3 patients). One patient bled while receiving full anticoagulation with blood, and therapy was discontinued.

In 8 patients (36%) there was a discrepancy between the CTPA and PA findings. In 6 of them, CTPA failed to diagnose an existing PE (false negative) and in 2 more it diagnosed a PE that was not confirmed by PA (false positive). Both false-positive tests related to peripheral clots. However, of the 6 false-negative tests, 2 missed central pulmonary emboli. In all 8 tests there were substantial coexisting lung pathologic findings on CTPA. The sensitivity and specificity of CTPA to diagnose all PEs were 45% and 82%; central PEs, 60% and 100%; and peripheral PEs, 33% and 82%, respectively (Table 3). The 2 independent radiologists who interpreted the CTPAs agreed in 86% of the cases, ie, they disagreed on 3 cases. Similarly, the 2 different independent radiologists who interpreted the PAs also agreed in 86% of the cases. There was only 1 case in which there was disagreement between the radiologists in the interpretation of both CTPA and PA. Interpretation discrepancies occurred more frequently in patients with PE (6/11 [55%]) than in patients without PE (2/11 [18%]), but the P value of this comparison did not achieve statistical significance (P = .07).

<table>
<thead>
<tr>
<th>Criteria</th>
<th>PE Present (n = 11)</th>
<th>PE Absent (n = 11)</th>
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<tr>
<td>Age, y</td>
<td>39 ± 17</td>
<td>37 ± 10</td>
<td>.72</td>
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<tr>
<td>Male sex, No. (%)</td>
<td>8 (73%)</td>
<td>8 (73%)</td>
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<td>Blunt trauma, No. (%)</td>
<td>7 (64%)</td>
<td>6 (55%)</td>
<td>.68</td>
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<tr>
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<td>5 (45%)</td>
<td>5 (45%)</td>
<td>&gt;.99</td>
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<tr>
<td>Pulmonary infiltrates, No. (%)</td>
<td>10 (91%)</td>
<td>10 (91%)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Major fractures, No. (%)</td>
<td>7 (64%)</td>
<td>5 (45%)</td>
<td>.39</td>
</tr>
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<td>Head injury, No. (%)</td>
<td>2 (18%)</td>
<td>2 (18%)</td>
<td>&gt;.99</td>
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<td>6 (55%)</td>
<td>5 (45%)</td>
<td>.67</td>
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<tr>
<td>Days from admission to PE</td>
<td>7 ± 6</td>
<td>9 ± 13</td>
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</tr>
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<td>9 ± 6</td>
<td>.57</td>
</tr>
<tr>
<td>Hours from first to second test</td>
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<td>6 ± 4</td>
<td>.06</td>
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<td>ICU stay, d</td>
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<tr>
<td>Hospital stay, d</td>
<td>37 ± 23</td>
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<tr>
<td>Mortality, No. (%)</td>
<td>2 (18%)</td>
<td>2 (18%)</td>
<td>&gt;.99</td>
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*Values are mean ± SD unless otherwise specified. ICU indicates intensive care unit.

Nine patients had venous duplex ultrasonography of the upper and lower extremities within 24 hours of the initiating event. Three patients, 2 with peripheral emboli and 1 without PE, did not have a duplex scan. Duplex ultrasonography identified clots in peripheral veins of 4 patients with PE (2 subclavian, 1 internal jugular, and 1 superficial femoral vein) but did not find clots in another 5 patients with PE. Its sensitivity and specificity were 44% and 100%, respectively.

Four patients died, 2 with PE on the 25th and 83rd days after admission (22 and 38 days after the PE, respectively) and 2 without PE on the 35th and 96th days. None of these patients had a detailed autopsy. Their death was thought to be a result of multiple organ failure. Survivors stayed 20 ± 17 days in the SICU and 34 ± 22 days in the hospital.

Computed tomographic pulmonary angiography is increasingly frequently used for the diagnosis of PE because it is thought to be safer, more convenient, and equally sensitive compared with PA. A number of studies have compared CTPA with PA and found it to be more than 90% sensitive.8,10,12 However, other investigators have found sensitivity rates as low as 53%17 and cautioned against its widespread acceptance as the diagnostic test of choice.22-24 Re-
sults on the cost-effectiveness of CTPA are similarly conflicting, with one study concluding that CTPA is more cost-effective and another study, that it is less cost-effective than ventilation-perfusion scintigraphy.

The main reason for CTPA’s low sensitivity rates reported in some studies seems to be its inability to assess peripheral pulmonary vessels reliably. Obliquely oriented vessels, such as the segmental branches of the right middle lobe and lingual vessels, may be poorly visualized on CTPA. Technical problems related to the timing of contrast administration, the dose and concentration of the iodinated contrast material, and a hyperdynamic condition of the patient may affect the quality of the image. Poorly opacified pulmonary veins may be confused with thrombotic pulmonary arteries. Lymph nodes may be misinterpreted as intraluminal thrombi. Substantial pulmonary parenchymal disease may confound the picture. Goodman et al. showed that the sensitivity of CTPA dropped from 86% for central pulmonary arteries to 63% when peripheral branches were included. Other studies have claimed better results in analyzing peripheral pulmonary vessels in humans or animals, but the sensitivity is still low. Remy-Jardin et al. found that, by increasing the collimation from 3 mm to 2 mm, more subsegmental vessels could be analyzed.

The clinical significance of peripheral emboli is not clear. Most authors would agree that small clots do not cause important physiological abnormalities unless they are multiple or occur in the presence of preexisting respiratory compromise. This is exactly the case for critically ill patients. Patients in the SICU usually have marked abnormalities of their pulmonary function. At the same time, these are patients who may receive inadequate thromboprophylaxis and are at high risk for thromboembolic events. Such patients with marginal oxygenation do not have adequate respiratory reserve. One could hypothesize that even a relatively small insult, such as that from peripheral PE, may upset the delicate balance by which their pulmonary function is maintained. An additional risk associated with peripheral PE may be that it indicates the propensity of the patient to experience clotting and the probability of more severe PE in the future. For all of these reasons, although high sensitivity of a test to detect peripheral PE is not required if the test is designed for use in otherwise healthy individuals, high sensitivity becomes important when the test is used in critically ill surgical patients.

Our study is the first, to our knowledge, to address specifically SICU patients. We found that CTPA has a sensitivity of only 45% to detect PE when compared with the current diagnostic gold standard, PA. Most false-negative CTPAs failed to diagnose peripheral emboli, as shown by a sensitivity of 33% for peripheral PE. However, its ability to diagnose central emboli was also suboptimal, with a sensitivity of only 60%. Its specificity for all PE and central PE was 82% and 100%. These numbers show that CTPA is an inadequate test to rule out PE but a better test to rule in central PE. Almost all of our patients had substantial pulmonary parenchymal disease that in some cases made the interpretation of CTPA particularly difficult.

The interobserver variability was not different between the radiologists who interpreted the CTPA and the PA. In both tests, the independent radiologists disagreed in 14% of the cases. This variability is within the accepted range even for PA, when the test examines small emboli in peripheral pulmonary vessels. All 4 radiologists whom we used (2 for CTPA and 2 for PA) were experts with special training in their field and considerable experience with critically ill surgical patients. It is unknown what the variability would be under conditions in which radiology trainees interpreted the tests, as frequently occurs outside of working hours in many institutions. Nevertheless, the fact that CTPA findings can be consistently interpreted without major interobserver variability should be viewed as a strength of the test.

Venous duplex ultrasonography, although not a specific tool for the diagnosis of PE, has been used as a screening method to assist in the diagnosis. Not surprisingly, its sensitivity was very low (44%) and consistent with previous results from other studies. The absence of clots in extremity veins does not exclude the possibility that a patient may have had a PE. Extremity venous clots may be missed by duplex scanning because they are in areas inaccessible by this technique (pelvis, below the knee), because they have dislodged already and traveled to the lung, or simply because of technical limitations and operator dependency associated with ultrasonography. It is noteworthy that 3 of 4 patients with abnormal duplex scans had clots found in the venous system of the upper body, calling into question the common belief that such clots are not clinically significant.

D-Dimer assay, a test that measures the products of clot degradation, has been reported to have a very high negative predictive value, essentially excluding the probability of PE, if D-dimer levels are normal. Multiple techniques have been used, but the best results have been achieved with SimpliRED (American Diagnostica Inc, Greenwich, Conn), a whole-blood agglutination assay that can be performed by the bedside. The test is subject to substantial interobserver variability. We performed D-dimer assays in 13 patients and found a sensitivity of 37% and specificity of 40%. However, because we did not use the SimpliRED technique, which is currently considered the most reliable, we cannot comment further on these results.

An additional and very important finding of this study is the high incidence of PE that we realized during the study period. By decreasing the threshold of studying patients for PE, we diagnosed the disease even in patients with low clinical suspicion. The incidence of PE in this study was roughly 5 times higher than the incidence found in a previous study by Velmahos et al. of venous thromboembolism in SICU patients without liberal evaluation of symptoms associated with PE and higher than the incidence that is usually reported in the literature. As shown by the comparison of patients with and without PE, the known risk factors and clinical characteristics were similarly prevalent in the 2 groups. The level of clinical suspicion was identical in the 2 groups and did not help to identify the patients with higher probability of PE. Although reportedly useful in other populations, clinical symptoms are confounded by multiple coexisting factors in intubated critically ill surgical patients and cannot be used reliably. Only a high index of suspicion and a liberal policy of evaluating PE will uncover a potentially lethal disease in these patients. A lib-
eral policy would definitely be enhanced by a test that is safe, rapid, convenient, highly sensitive, and cost-effective. Computed tomographic pulmonary angiography seemed to offer promise to this direction. Unfortunately, the low sensitivity found in this study casts serious doubt as to its widespread use.

A main limitation of our study is the small sample size. We plan to continue the study to recruit more patients. A second limitation relates to the clinical significance of small emboli not diagnosed by CTPA. Although all of these patients were treated, we do not know the natural course of these emboli if they had been left without therapy. One could make the case that these events were not important because no significant differences were found in mortality, SICU stay, and hospital stay between patients with and without PE. Our population included very sick patients who required hospitalization in excess of 1 month on average. It is difficult to find outcome differences in such patients with the current sample size. Because therapy after PE targets the prevention of future PE rather than treatment of the current PE, there must be enough deaths from recurrent PE to realize a difference in mortality, owing to therapy started after the initial PE. With an overall death rate of 18%, as in this study, hundreds of patients must be included to identify a statistically significant decrease in mortality related to recurrent PE, if one exists. A third limitation may be associated with our population mix, which was skewed toward trauma (77% of all patients). In essence, our results may mostly represent critically injured patients rather than critically ill nontrauma patients. Whether this occurred because of a sampling bias or just because PE is more prevalent in trauma patients remains to be clarified by the enrollment of more patients. A fourth limitation could relate to the argument of using PA as the diagnostic standard of reference. If PA has a high false-positive rate, then new tests, like CTPA, that are compared with PA may erroneously show false-negative results. Although the real positive predictive value of PA can only be demonstrated in animals or by autopsy findings, previous literature suggests that the incidence of false-positive findings is very low. Because we used only solid criteria, such as intraluminal filling defect or abrupt interruption of blood flow, to diagnose PE, we believe that PA reflected accurately the presence or absence of PE and, therefore, was justifiably used as the diagnostic gold standard.

In summary, the findings of this pilot study raise considerable concern about the use of CTPA for the diagnosis of PE in critically ill surgical patients. If the primary quality of a test used to detect this potentially fatal disease is high sensitivity, CTPA has not stood up to the challenge. Pulmonary angiography remains the gold standard for PE diagnosis in critically ill surgical patients. Additional research, focused on these patients who present with diagnostic and therapeutic dilemmas, should be encouraged before CTPA is accepted as a reasonable alternative to PA.

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REFERENCES

Anthony P. Borzotta, MD, Portland, Ore: The authors have attempted to define the role of spiral computed tomography of the chest in the diagnosis of pulmonary embolism in critically ill surgical patients, 77% of whom were victims of trauma. The patients underwent close surveillance for PE, yielding a higher incidence than expected, confirmed by using both spiral CT and pulmonary angiography in all cases. Notably, 3 of 11 patients with PE had a normal D-dimer assay. Of these, 2 had a positive D-dimer assay; an effective noninvasive test for rule out pulmonary embolism. J Trauma. 2000;48:795-799.


In addition to pulmonary dysfunction, one can presume that some patients had hyperdynamic circulation. Kirchner, of Bochum, Germany, described the use of ultrafast detector technology to identify when a bolus of contrast exceeded a defined threshold within a scanned lung segment, automatically triggering initiation of the full CT scan. In the critically ill patient, how important is the timing of contrast injection and its route of delivery in making best use of CT imaging?

The second question regards clinical import. Although you found no useful association with the level of clinical suspicion for pulmonary embolism and its ultimate diagnosis, did you analyze the different elements in your clinical algorithm to see which were most effective? Last, in 2 studies of patients with clinical suspicion of pulmonary embolism but whose studies, including spiral CT scans, were negative, and who therefore did not receive any anticoagulation, subsequent PE rates of 1% to 3.1% were found, without mortality. Clearly, there were acute deteriorations in oxygenation in your patients, but only half had emboli, and no patient with an embolus died as a result. Would you expand on the possible consequences of overdiagnosis by pulmonary angiography of what may be clinically unimportant embolic events?

Jorge L. Rodriguez, MD, Minneapolis, Minn: I'd like to extend Dr Borzotta's last question of overdiagnosis by pulmonary angiogram. Many of your patients supposedly had a PaO2/FIO2 ratio less than 200, which is associated with ARDS. Do you think that the diagnosis of peripheral embolus is actually ARDS thrombosis secondary to hypoxia and platelet aggregation instead of thrombi from the lower extremities?

Theodore X. O'Connell, MD, Los Angeles, Calif: Do you think the poor sensitivity on CTPA is due to inherent problems with the technique or operator dependence, ie, how the procedure is done, the timing of the dye injection, collimation, and obviously the reading of the CTPA?

Dr Velmahos: Indeed, it's been shown in a recent study that changing the level of collimation from 3 to 2 mm increases the sensitivity. Because this is a recent paper, we didn't know about these data when we designed our study. We should consider changing the level of collimation and check whether it significantly improves the detection of pulmonary embolism in peripheral vessels. With regard to apnea, we do not institute a breath hold in all these critically ill patients because these patients are suffering, and we are studying whether the CTPA produces similar results without apnea. Hyperpneic dilution is a problem; therefore, we try to delay somehow the clearance of the contrast by injecting it always through a peripheral and not a central vein. We have observed anecdotally that when the cardiac output is very high, the sensitivity of CTPA is lower. We have not analyzed the significance of each one of the clinical signs in predicting pulmonary embolism. My arbitrary bias is that none of them is a good predictor in these critically ill patients. Are we overdiagnosing clinically unimportant events? This pertains to Drs Borzotta's and Rodriguez's question, and quite honestly I do not know the answer. I don't know the clinical significance of peripheral PE, but I suspect that in patients who have marginal respiratory function, peripheral PE may create major problems. We have to examine the clinical significance in a larger sample of patients.

Finally, Dr O'Connell's question, are the low sensitivity rates an inherent technical problem? An inherent technical problem is, because I think that the test, as it shows in these 22 patients, is not good enough. Maybe the test will become more sensitive as technology advances. In terms of diagnosis by the cardiologists, I would feel safe about these 2 people who were assigned to independently evaluate the CTPAs because they have both received special training on CTPA and therefore are considered experts in their field. So were the 2 angiographers. I would feel very comfortable with these persons' diagnostic skills.