Pulmonary Embolism and Deep Venous Thrombosis in Trauma

Are They Related?

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Hypothesis: Pulmonary embolism (PE) and deep venous thrombosis (DVT) in trauma are related.

Design: Retrospective review of medical records.

Setting: Academic level I trauma center.

Patients: Trauma patients who underwent computed tomographic pulmonary angiography (CTPA) with computed tomographic venography (CTV) of the pelvic and proximal lower extremity veins over a 3-year period (January 1, 2004, to December 31, 2006) were reviewed. Data on demographics, injury type and severity, imaging findings, hospital length of stay, and mortality were collected.

Main Outcome Measures: Pulmonary embolism and DVT.

Results: Among 247 trauma patients undergoing CTPA/CTV, PE was diagnosed in 46 (19%) and DVT in 18 (7%). Eighteen PEs were central (main or lobar pulmonary arteries), and 28 PEs were peripheral (segmental or subsegmental branches). Pulmonary embolism occurred within the first week of injury in two-thirds of patients. Seven patients with PE (4 femoral, 2 popliteal, and 1 iliac) had DVT. Pulmonary embolism was central in 5 patients and peripheral in 2 patients. No significant differences were noted in any of the examined variables between patients with PE having DVT and those not having DVT.

Conclusions: Few patients with PE have DVT of the pelvic or proximal lower extremity veins. Pulmonary embolism may not originate from these veins, as commonly believed, but instead may occur de novo in the lungs. These findings have implications for thromboprophylaxis and, particularly, the value of vena cava filters.

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FOR DECADES, IT HAS BEEN taught that pulmonary embolism (PE) is a sequel of deep venous thrombosis (DVT).1,2 Forming in the lower extremity or pelvic veins, clots break off and travel to the pulmonary circulation. Therefore, DVT and PE should coexist in most patients, because part of the clot embolizes in the lung, and part remains attached to the vein. However, this has not been confirmed in practice. In a study3 of 149 patients with PE, less than one-third had positive DVT symptoms when evaluated by compression ultrasonography. Serial and detailed imaging of leg veins identified DVT in only 43% of 169 patients with PE.4 Among 131 trauma patients, 18 developed DVT or PE, but only 6 of 18 showed evidence of both.5 None of 4 trauma patients with PE among 12 with thromboembolic events showed evidence of DVT.6 Of 52 high-risk trauma patients, 12 developed DVT, and 2 developed PE (neither had DVT).7 Similarly, among 200 prospectively screened high-risk trauma patients, 26 developed DVT, and 4 developed PE. There was no progression to PE among the patients with DVT, and none of the patients with PE had DVT.8 Ultrasonography was used for DVT diagnosis in all of these studies. Limitations of this technique resulted in the failure to identify expected DVT. Ultrasonographic findings are operator dependent and may be inaccurate below the knee and (most important) in the pelvis.

Pulmonary embolism is usually diagnosed by computed tomographic pulmonary angiography (CTPA). Frequently, CTPA protocols include computed tomographic venography (CTV) of the pelvic and...
proximal lower extremity veins. Computed tomographic venography is highly accurate in diagnosing clots of the inferior vena cava and the iliac, femoral, and popliteal veins. It is feasible to simultaneously image the pulmonary and lower venous circulations to identify clots. Our study aims to correlate PE with DVT among critically injured patients who underwent CTPA/CTV for suggestion of PE.

METHODS

We reviewed the medical records of all trauma patients who underwent CTPA over a 3-year period (January 1, 2004, to December 31, 2006) at our academic level I trauma center. During that period, conventional pulmonary angiography and ventilation-perfusion imaging were essentially eliminated. We relied on CTPA for the diagnosis of PE. Lower extremity duplex venous ultrasonographic screening was performed weekly in patients at high risk for DVT (obesity, age >55 years, spinal cord injuries, major thoracolumbar spinal fractures, major pelvic and lower extremity fractures, multiple trauma with an Injury Severity Score >16, or intensive care unit admission with immobilization for ≥4 days).

Our CTPA imaging protocol included chest computed tomography (CT) to evaluate for PE and pelvic and lower extremity CT to evaluate for DVT. Images were obtained using a 16- or 64-section scanner (GE Lightspeed; GE Medical Systems, Milwaukee, Wisconsin). Each patient received 90 to 110 mL of contrast medium (Isovue-300 or Isovue-370; Bracco Diagnostics, Princeton, New Jersey) and a 40-mL isotonic sodium chloride solution flush through an 18-gauge needle with a flow rate of 4 mL/s using a power injector (Medrad Power Injector; Medrad, Indianola, Pennsylvania, or E-Z-EM EmpowerCT; E-Z-EM, Lake Success, New York). For thoracic images, imaging delay was fixed at 22 seconds for the 16-section CT scanner and 26 seconds for the 64-section CT scanner or was performed using a bolus tracking system (Smart Prep, GE Medical Systems) with the region of interest in the main pulmonary arteries. For lower extremities, imaging delay was fixed at 180 seconds. Thoracic imaging was performed from a caudal to cranial direction starting at the adrenal glands and ending at the apices of the lungs. Pelvic and lower extremity imaging was performed from the tibial plateaus to the iliac crests. Images were obtained in the helical mode in standard algorithm with a large field of view. For the 64-section CT scanner, we used a noise index of 30, 120 kV, and automatic mA (100 minimum and 800 maximum), 0.5-second rotation, 1.25-mm section thickness, 1.375 pitch, speed of 13.75, and interval of 1.25.

We collected data on the following: mortality, injury type, demographics, CTPA/CTV results, length of hospital stay, Injury Severity Score, thromboembolism prophylaxis, duplex ultrasonographic findings, and Abbreviated Injury Score for 6 body regions. The outcomes measured were PE and DVT. Patients with PE who had DVT were compared with patients with PE who did not have DVT. The t test was used for comparison of continuous variables and chi square or Fisher exact test for categorical variables. P < .05 was considered statistically significant. The study was approved by our institutional review board.

RESULTS

Two hundred forty-seven trauma patients underwent CTPA/CTV during the study period. Pulmonary embolism was diagnosed in 46 patients (19%) and DVT in 18 patients (7%); all patients were at high risk for venous thromboembolism. Eleven patients died; 3 of them had PE, and 8 did not have PE (P = .38).

ANALYSIS OF PE

Among 46 patients with PE, 18 (39%) had central PE involving the main or lobar pulmonary arteries, and the remaining 28 (61%) had peripheral PE involving the segmental or subsegmental branches. Multiple filling defects were found in 37 patients and were bilateral in 18. Pulmonary embolism was diagnosed at a median of 5.5 days (range, 0-40 days) after admission. In 30 patients (65%), the diagnosis was established within the first week of hospital stay and in 40 patients (87%) within the first 2 weeks; 10 patients developed PE within 48 hours of trauma (FIGURE). Only 2 of 46 patients (4%) were not receiving prophylactic anticoagulation therapy at the time of PE diagnosis. Pulmonary embolism contributed to the death of 2 patients, both recipients of prophylactic anticoagulation therapy. Different methods were used to treat PE, including unfractionated heparin sulfate therapy in 16 patients, therapeutic doses of low-molecular-weight heparin in 24 patients, vena cava filters in 10 patients (6 in combination with heparinization), and no treatment in 2 patients (who had peripheral clots only, manifested contraindications to heparin therapy, and were deemed noncandidates for a vena cava filter).

ANALYSIS OF DVT

Among 18 patients with DVT, the most proximal extension of the clot was in the iliac vein in 2, femoral vein in 9, and popliteal vein in 7. In 16 of 18 patients, DVT was discovered during evaluation for PE by CTPA/CTV. In the remaining 2 patients, DVT was found during routine duplex ultrasonography, which was performed 6 and 24 days after CTPA/CTV. Of 9 patients with femoral DVT, 7 underwent duplex ultrasonography within 4 days of CTV, and all had a positive test result. Four of 18 patients (22%) were not receiving prophylactic anticoagulation therapy at the time of DVT diagnosis.
CORRELATION OF PE AND DVT

Among 46 patients with PE, 7 (15%) also had DVT. There was no difference between patients with PE who had DVT and those who did not in age, sex, mortality, injury type, length of hospital stay, Injury Severity Score, chest Abbreviated Injury Score, and use of anticoagulation therapy and vena cava filters (Table). However, 5 of 7 patients (71%) with DVT had central PE compared with 13 of 39 patients (33%) without DVT (P = .09).

Table. Comparison of Patients Having Pulmonary Embolism (PE) With vs Without Deep Venous Thrombosis (DVT)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PE With DVT (n = 7)</th>
<th>PE Without DVT (n = 39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56 (18)</td>
<td>56 (15)</td>
<td>.99</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>4 (57)</td>
<td>25 (64)</td>
<td>.72</td>
</tr>
<tr>
<td>Blunt mechanism trauma, No. (%)</td>
<td>7 (100)</td>
<td>36 (92)</td>
<td>.45</td>
</tr>
<tr>
<td>Injury score, mean (SD)</td>
<td>17 (7)</td>
<td>17 (9)</td>
<td>.99</td>
</tr>
<tr>
<td>Chest Abbreviated Injury Score</td>
<td>1.1 (1.5)</td>
<td>1.1 (1.4)</td>
<td>.99</td>
</tr>
<tr>
<td>PE, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>5 (71)</td>
<td>13 (33)</td>
<td>.09</td>
</tr>
<tr>
<td>Peripheral</td>
<td>2 (29)</td>
<td>26 (67)</td>
<td>.09</td>
</tr>
<tr>
<td>DVT, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliac</td>
<td>1 (14)</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Femoral</td>
<td>4 (57)</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Popliteal</td>
<td>2 (29)</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Treatment at the time of PE, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic anticoagulation</td>
<td>5 (71)</td>
<td>34 (87)</td>
<td>.28</td>
</tr>
<tr>
<td>Inferior vena cava filter</td>
<td>1 (14)</td>
<td>3 (8)</td>
<td>.49</td>
</tr>
<tr>
<td>Hospital stay, mean (SD), d</td>
<td>24 (12)</td>
<td>21 (17)</td>
<td></td>
</tr>
<tr>
<td>Mortality, No. (%)</td>
<td>2 (29)</td>
<td>1 (3)</td>
<td>.06</td>
</tr>
<tr>
<td>PE contributed to mortality, No. (%)</td>
<td>1 (14)</td>
<td>1 (3)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviation: ellipsis, not applicable.

A fundamental theory is that PE originates from peripheral veins. If the course of a clot from these veins to the pulmonary circulation is effectively interrupted, then PE should be prevented. The development of inferior vena cava filters was based on this logic. However, PE and DVT do not coexist, a fact that has received inadequate notice. In a study of 9721 trauma patients, 998 had DVT, 522 had PE, and 82 had both, indicating that only 16% of patients with PE had coexisting DVT. The exact methods of monitoring for DVT could not be discerned from this registry analysis.

Based on these data, there is little evidence that PE originates from DVT of peripheral veins. This lack of association between PE and DVT has 4 possible explanations: (1) the diagnostic tools for DVT are insufficiently sensitive to detect it, even if it exists; (2) many clots originate in the upper extremities, and upper clots are missed because we focus on examining the lower extremities; (3) clots formed in the lower extremity veins do not break off but rather dislodge completely and embolize to the pulmonary circulation without leaving residual clot in the periphery; or (4) clots in the pulmonary circulation appear de novo and are unassociated with peripheral DVT.

The first argument refers primarily to duplex ultrasonography, which is reported to have low sensitivity in asymptomatic, pelvic, or below-the-knee DVT. Contrast venography, the traditional standard of reference, is reported to be unreliable in 11% to 15% of cases. Many centers use CTV to examine the veins of the pelvis and lower extremities at the time of CTPA. These protocols have been very successful. Results of CTV agreed with venous compression sonographic findings in 95.5% of cases in the multicenter study of the Prospective Investigation of Pulmonary Embolism Diagnosis II. Combined CTPA/CTV has been considered a “1-stop shopping” method for diagnosis of venous thromboembolism, with the addition of CTV improving detection of venous clots by 10% to 25%. It can no longer be argued that almost two-thirds of DVT episodes are missed in patients with proven PE solely because the diagnostic tools are inaccurate.

The second argument relies on undetected upper extremity DVT, which could be the origin of PE. Although other centers have reported a high rate of upper extremity DVT, this was refuted in a recent study from our center. Our center had a single case of brachial vein thrombosis among 911 trauma patients who were prospectively followed up, 86 of whom underwent routine screening by upper extremity duplex ultrasonography. At least in our center, the lack of association between DVT and PE cannot be attributed to undetected upper extremity DVT.

The third argument is that the entire clot is dislodged from the peripheral veins and embolizes centrally. Cadaveric studies have shown that this is false in patients with coexisting DVT and PE. Generally, only part of the clot (usually the free-floating tail) breaks off and embolizes. Significant clot burden remains adhered to the venous endothelium.

The fourth argument may be correct (ie, many clots are formed de novo in the pulmonary circulation). Au-
tonomic dysfunction may produce venous thrombosis. Adrenergia and inflammation may promote coagulation. Autonomic dysfunction is proven to exist after trauma. A poorly compensated adrenergic response causes pulmonary vascular endothelial phenomena that lead to local overcoagulation, vasospasm, and rapid occlusion. Endothelial inflammation induces production of circulating adhesion molecules and creates regional thrombosis. Although some episodes of PE are undoubtedly linked to peripheral DVT, many others could relate to clot formation anew in the pulmonary circulation. This theory may explain the ineffectiveness of vena cava filters in decreasing the incidence of PE. Large emboli of the main pulmonary arteries may be the products of clot fragmentation from pelvic or lower extremity DVT, but emboli of segmental or subsegmental pulmonary arteries may result from local acute thrombosis due to an inflamed vascular endothelium. This may explain the higher incidence (71% [5 of 7]) herein of central PE among patients with DVT compared with those without DVT. In our study, we did not collect information on all patients with DVT but rather only on those who had DVT related to an evaluation for PE; therefore, the true incidence of PE among patients with proximal DVT is unknown.

The lack of a diagnostic standard of reference for DVT is a limitation of this study. Despite encouraging reports on CTV from many centers, this technology is still under investigation. Although a comparative study vs contrast venography would be desirable, it is unlikely that it will be performed, as there is decreased use of contrast medium–enhanced venography and CTV is rapidly becoming the standard of care. Numerous CTVs but only 2 conventional venographies were performed in our hospital over the past 2 years. Studies involving new CTV technology are often limited because by the time of publication the method used is already surpassed by newer devices and protocols.

To our knowledge, this study is the first to doubt the traditional belief that PE originates from pelvic and proximal lower extremity veins. We propose that many PEs form primarily in the lungs and that the risk-benefit ratio of vena cava filters should be reconsidered. As CTV becomes more popular and accurate, this issue will be further explored, and it may be revealed that (not surprisingly) we have been preaching and practicing the wrong dogma for years.

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Searching for the Source of Venous Clots: An Unsolved Old Problem

Velmahos and colleagues question whether DVT and PE are temporally related following injury. After retrospectively studying 247 patients who underwent CTPA/CTV of the pelvic and proximal lower extremity veins, they concluded that few patients with PE have DVT. They postulate that PE may be formed de novo in the lungs.

The rationale for the study is the fact that, as documented by several other investigators, many patients with PE have no DVT. Or do they—but the diagnostic modalities are just not good enough to diagnose DVT?

The issue of diagnosing DVT in trauma patients is an important one. Perhaps more important is the way one screens for DVT. It seems that “the more you look, the more you find,” as noted in investigations comparing no screening with once-weekly or twice-weekly screens. The authors used duplex venous ultrasonography weekly for screening and performed CTV as the standard diagnostic modality for DVT with 16- and 64-section scanners. The conclusions are centered on the results of CTV. The lack of a control comparison for CTV is a significant limitation of the study. Most PEs were diagnosed within the first week, and 10 patients had PE within 48 hours after hospital admission. The authors did not report when those patients were screened for DVT (hopefully before they developed PE). Eighteen patients were found to have DVT, and only 2 were diagnosed using duplex ultrasonography, 6 and 24 days after CTPA/CTV! Perhaps a more consistent screening protocol implemented early after admission would have resulted in more diagnoses of DVTs. Among 46 patients with PE, only 7 had concurrent DVT.

The results of the study support my bias that DVT and PE may be temporally related. However, because there is a chance that the whole clot breaks off of extremity veins (upper and lower) and lodges in the lungs, attempts to make both diagnoses concurrently may lead to erroneous conclusions.

Velmahos et al. offered no mechanistic explanation for their hypothesis that clots may form de novo in the lungs. Is the endothelial response to shock and injury in the lung different from that in the endothelium of the deep venous system in the extremities? Would this happen because of inflammation or hypercoagulation?

Although intriguing, their hypothesis cannot be confirmed by these data. As a well-written and provocative article should be, it raises more questions than it answers. It is unlikely that the temporal relationship between DVT and PE will be answered by a well-designed clinical study. Perhaps the answer is in the basic science laboratory if one can demonstrate differences in clot formation and endothelial response in extremity veins and in the lung circulation.

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