Pulmonary embolism without deep venous thrombosis: De novo or missed deep venous thrombosis?

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BACKGROUND: Pulmonary embolus (PE) is thought to arise from a deep venous thrombosis (DVT). Recent data suggest that PE can present without DVT, inferring that PE can originate de novo (DNPE). We examined the relationship between DVT and PE in trauma patients screened for DVT with duplex sonography (DS). We sought to validate the incidence of PE without evidence of DVT and to examine the clinical significance of this entity.

METHODS: We reviewed the medical records of all trauma patients from July 2006 to December 2011 with PE who also had serial surveillance DS (groin to ankle). Demographics, severity of injury, interventions, signs and symptoms of PE, as well as chest computerized tomography findings were collected. Patients with no DS evidence of DVT either before or within 48 hours of PE diagnosis (DNPE) were compared with those with DVT (PE + DVT).

RESULTS: Of 11,330 patients evaluated by the trauma service, 2,881 patients received at least one DS. PE occurred in 31 of these patients (1.08%): 19 (61%) were DNPE, and 12 (39%) were PE + DVT. Compared with patients with PE + DVT, patients with DNPE were significantly younger and had more rib fractures, pulmonary contusions, infections, pulmonary symptoms, and peripherally located PEs on computerized tomography.

CONCLUSION: This is the first report of the clinical course of DNPE without embolic origin in a population with comprehensive duplex surveillance. In our series, DNPE seems to be more prevalent after trauma, to be clinically distinct from PE following DVT, and to likely represent a local response to injury or inflammation; however, further research is warranted to fully understand the pathophysiology of DNPE. (*J Trauma Acute Care Surg*. 2014;76: 1270–1274. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Care management study, level III.

KEY WORDS: Pulmonary embolism; de novo pulmonary embolism; deep venous thrombosis; venous thromboembolism; chest injury.

Pulmonary embolism (PE) is a potentially morbid complication in trauma patients, with an incidence ranging from less than 1% to 24%.[1,2] The embolus is thought to arise from the deep venous system. However, several investigators have proposed that PE can occur without an associated deep venous thrombosis (DVT), which has been termed *de novo PE* (DNPE).[1,3–5] Using the National Trauma Data Bank, which does not collect data on duplex surveillance for DVT, Knudson et al.[1] found a DNPE incidence of 80%. Velmahos et al.[3] reported an incidence of 85% using computerized tomography (CT) venography and weekly duplex sonography (DS), but the timing of DS screening in relation to PE diagnosis was unclear. In addition, two studies found an association between chest injury and PE, postulating that lung injury and subsequent inflammation leads to the development of DNPE[1,4] but provided no clinical correlation or description. Therefore, the pathophysiology of DNPE remains unclear.

Our goal was to identify the incidence of PE without evidence of DVT in a population undergoing comprehensive lower extremity DS surveillance. We examined the clinical course of each trauma patient who had a PE to determine if there was a difference in the clinical presentation and outcome of patients with DNPE compared with those with PE and associated DVT (PE + DVT).

PATIENTS AND METHODS

Demographic and clinical data were collected retrospectively on all trauma patients evaluated by the Scripps Mercy Hospital San Diego Level I Trauma Service between July 1, 2006, and December 31, 2011. Patients aged 18 years or older who received surveillance lower extremity DS were eligible for the study. Patients with documented PE within 6 weeks of initial trauma were identified for further evaluation. Those diagnosed with PE at time of admission from a nontraumatic cause and those not primarily managed by the trauma service were excluded from the analysis. This project was approved by the Scripps Health Institutional Review Board.

The diagnosis of PE was made by either CT pulmonary angiography or CT chest with intravenous contrast. PEs were classified by location as either central (right/left pulmonary artery or lobar) or peripheral (segmental or subsegmental). CTs were obtained either for clinical suspicion of PE or for the evaluation of chest trauma. Electronic medical records were reviewed for signs and symptoms of PE in the 24 hours before diagnosis, which included hemoptysis, dyspnea, chest pain, syncope, fever (>100.4°F), oxygen desaturation (>5% decline from baseline), hypoxia (PAO_2 < 80 torr) or hypocapnia (PAO_2 < 40 torr), hypotension (systolic blood pressure < 90 mm Hg), change to airway pressure release ventilation or PAO_2/FIO_2 ratio between 200 and 300, S1Q3T3 (prominent S wave in lead I, Q wave in lead III, and inverted T wave in lead III) on electrocardiogram, right bundle branch block on electrocardiogram, increased troponins, right ventricular dilation on echocardiogram or CT, tachypnea (respiratory rate > 20), and tachycardia (heart rate > 100).

The DVT surveillance protocol included lower extremity DS from the groin to ankle, performed twice weekly on intensive care unit patients and once weekly on ward patients throughout the study period. Patients were eligible for surveillance if nonambulatory for more than 72 hours or at moderate to very high risk as defined by the American College of Chest Physician guidelines.[6] Upper extremity (UE) surveillance was not performed but was obtained for symptoms (UE edema or pain). Echocardiograms and all CTs of the abdomen, pelvis, and extremities of patients with DNPE were reviewed to rule out incidental extremity, pelvic, or cardiac thrombi not documented by DS.

Clinical data indicative of inflammation, local injury, or hypercoagulability were recorded. This included presence of a documented infection, blood product transfusion (packed red blood cells, fresh frozen plasma, and platelets), pulmonary contusions, rib fractures, and placement of chest tubes. All patients were also evaluated for the use of chemical prophylaxis

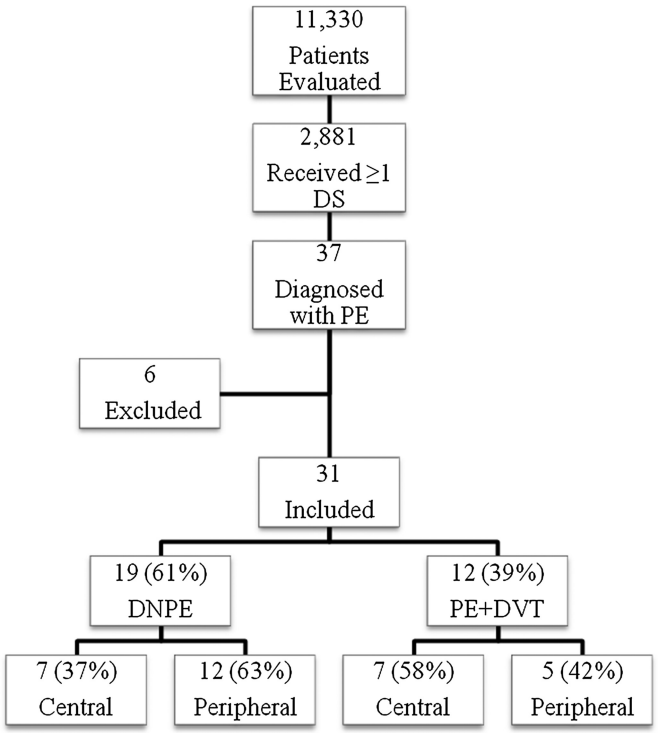

Figure 1. CONSORT flow diagram of PE + DVT and DNPE populations.

(enoxaparin 30 mg every 12 hours). A patient was considered to be on chemical prophylaxis if initiated at least 24 hours before PE diagnosis. Placement of inferior vena cava (IVC) filters before the diagnosis of PE was noted. Therapeutic anticoagulation was documented for the treatment of PE or DVT. The following were considered complications of anticoagulation: 2-g/dL drop in hemoglobin, packed red blood cell transfusion of two or more units, or a hemorrhagic complication requiring an intervention.

Patients diagnosed with DNPE were compared with patients with PE + DVT. χ^2 or Fisher's exact tests were used for comparing categorical variables and Student's *t* test was performed for continuous variables. Significance was attributed to a $p < 0.05$.

RESULTS

During the 5.5-year interval, 11,330 patients were evaluated by the trauma service and 2,881 patients underwent surveillance DS. Of those, 37 were diagnosed with PE. After excluding patients found to have PE on admission and those not primarily managed by the trauma service, 31 patients (1.08%) were included. Twelve patients (39%) had DVT either before or immediately following PE diagnosis (Fig. 1). DVT was located below the knee in nine patients, above the knee (popliteal or above) in two patients, and the internal jugular vein in one patient. In addition, 10 of the 12 patients had a follow-up DS, all of which showed presence of DVT after PE diagnosis.

Nineteen patients (61%) had no evidence of DVT (DNPE). Among these patients, 11 had DS before diagnosis of PE, 3 patients had DS the same day, and 5 patients had DS within 48 hours after diagnosis. Of the 19 DNPE patients, 5 (26%) had limited DS examinations because of bandages, cast, or external fixators. However, one of these five patients had a negative bilateral lower extremity CT venography on the day of PE diagnosis. All but one patient in the DNPE group had a CT of the abdomen, pelvis, or extremities, which revealed no incidental DVTs. Ten of these had pelvic CTs within 48 hours of PE diagnosis. Four patients in the DNPE group also received an echocardiogram, all of which were negative for right atrial or ventricular clot.

Pulmonary thrombi were more often located peripherally in the DNPE group, while the PE + DVT group more often had PEs affecting multiple lobes or were bilateral (Table 1). DNPE patients were younger, had more rib fractures, had more pulmonary contusions, received more blood products, and were more likely to have infection compared with the PE + DVT group. The most common infection in the DNPE group was pneumonia (4 of 5). In the DNPE group, four of five patients with a pulmonary contusion had thrombus located on the same side as their contusion as did five of six patients with rib fractures. The majority of PEs occurred in the first week following injury (Fig. 2).

The DNPE group had more signs and symptoms of PE compared with the PE + DVT group, although this was not statistically significant (Table 2). Peripheral location of thrombus also tended to have more signs and symptoms than those centrally located. Therapeutic anticoagulation was initiated in 26 of 31 patients. Of these, three patients developed complications,

TABLE 1. Descriptive Statistics of PE Patients With and Without Accompanying DVT

Exposure	PE + DVT, n = 12 (39)	DNPE, n = 19 (61)
Male sex, n (%)	10 (83.3)	16 (84.2)
Age, mean (SE)	54.2 (5.1)	30.1 (3.4)*
Chest AIS score, mean (SE)	1.2 (0.5)	1.8 (0.4)
Injury Severity Score (ISS), mean (SE)	17.3 (2.4)	19.1 (3.1)
Pelvic fracture, n (%)	2 (16.7)	1 (5.3)
LE fracture, n (%)	2 (16.7)	4 (21.1)
Chest tube, n (%)	3 (25.0)	5 (26.3)
Blood products, n (%)	6 (50.0)	10 (52.6)
Infection, n (%)	1 (8.3)	5 (26.3)
Pneumonia	0	4
Wound	1	1
Chemical prophylaxis, n (%)	4 (33.3)	6 (31.6)
Pulmonary contusion, n (%)	1 (8.3)	5 (26.3)
Rib fractures, n (%)	1 (8.3)	6 (31.6)
PE location		
Peripheral, n (%)	5 (41.7)	12 (63.2)
Central, n (%)	7 (58.3)	7 (36.8)
No. PEs		
Single, n (%)	4 (33.3)	15 (78.9)
Multiple, n (%)	8 (66.7)	4 (21.1)*

*$p \leq 0.05$.
LE, lower extremity.

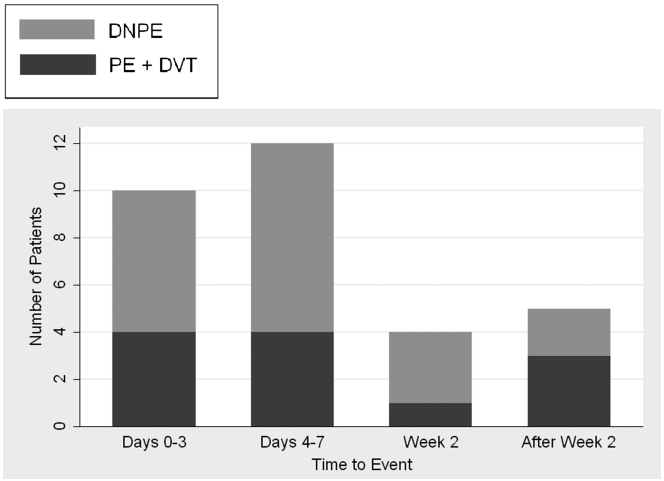

Figure 2. Days to PE histogram.

all of whom required transfusions. Two patients, one in each group, had IVC filters placed before the diagnosis of PE. There were no deaths in either group.

DISCUSSION

In this series of trauma patients, DNPE was more prevalent than PE + DVT, making up 61% of our PE population, which is in agreement with previous reports.[1,3] DNPE occurred early after injury, was associated with ipsilateral pulmonary injury, and seemed to be more symptomatic than the conventional PE + DVT group.

Virchow's triad of stasis, endothelial damage, and hypercoagulability is the sine qua non for DVT. In the extremities, stasis seems to cause venous hypoxia,[7,8] which in as little as 30 minutes results in venous endothelial secretion of Weibel-Palade bodies.[9] These granules are rich in von Willebrand factor and P-selectin, which bind platelets and monocytes.[7] Monocytes are known to secrete tissue factor, which promotes local thrombosis.[10] These same processes could also occur in the lung. The lung contains alveolar macrophages, which secrete tissue factor and cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor α.[10,11] IL-6 increases acute phase reactants, most importantly, fibrinogen.[12] Trauma patients are at a known risk of atelectasis from either chest or abdominal injuries. With a drop in alveolar PAO_2, hypoxic vasoconstriction ensues, which likely results in the same endothelial response as noted in the extremities, thus inducing local thrombosis in the pulmonary vessels.

Recent studies have suggested that inflammation may contribute to this process.[1,3] Inflammation, like hypoxia, activates the endothelium, causing externalization of von Willebrand factor and P-selectin via Weibel-Palade bodies.[7] This concept supports studies demonstrating an increased incidence of thromboembolism in patients with inflammatory bowel disease or recent infection.[13,14]

Knudson et al.[1] found that chest Abbreviated Injury Scale (AIS) score greater than 2 increased the probability of PE by 42% but had a minor effect on DVT. We found DNPE to be associated with ipsilateral rib fractures, pulmonary contusion, and infection. These factors could certainly evoke a local hypercoagulable milieu, especially in traumatized peripheral pulmonary vessels.

One explanation for challenging the existence of DNPE is that a DVT is simply missed. However, comprehensive radiographic evaluation, including CT pelvis and lower extremity venograms, undermines the argument that PE without DVT is a result of missing a pelvic vein or IVC thrombus. Isolated pelvic and IVC thrombus were found in less than 4% of CT venograms for workup of PE.[3,15,16] One prospective study evaluating the incidence of UE DVT in trauma patients with UE DS surveillance found an incidence of only 1%; therefore, the likelihood of missing a non–lower extremity DVT source is low.[17]

It has been suggested that PE without DVT is a result of embolization of the entire venous clot. We found that 10 of the 12 PE + DVT patients with complete DS examinations after PE had residual clot in the lower extremities. In addition, cadaveric studies of patients with PE revealed a DVT at the time of death in 59% of patients.[18] These findings would suggest that, in most cases, only a portion of the clot is dislodged to form the embolus.

This is the first study with comprehensive lower extremity duplex surveillance of patients with DNPE. Velmahos et al.[3] studied PE and its association with DVT but did not evaluate all patients who developed PE with DS, only "high-risk" patients. Moreover, the below-knee venous system was not evaluated by CT venography, which has recently been shown to have significant risk of PE, similar to above-knee clot.[19]

The possible existence of DNPE generates several questions. First, in our study population, DNPEs were more often peripherally located and none were fatal; therefore, do they warrant anticoagulation? Heparin is known to have antithrombotic effects, but it also decreases inflammatory markers such as IL-6 and C-reactive protein[20] and displays vasodilatory effects.[21] Vasodilation likely helps increase pulmonary blood flow to areas

TABLE 2. Signs and Symptoms

Signs and Symptoms	PE + DVT, n = 12, n (%)	DNPE, n = 19, n (%)
Fever	3 (33.3)	10 (58.8)
Hemoptysis	0 (0)	1 (5.3)
SOB	4 (33.3)	11 (57.9)
Chest pain	5 (41.7)	11 (57.9)
Syncope	1 (8.3)	0 (0)
Desaturation	9 (75.0)	16 (84.2)
Hypoxia/hypocarbia	4 (33.3)	10 (52.6)
Hypotension	2 (16.7)	3 (15.8)
APRV or P/F ratio 200–300	1 (8.3)	2 (10.5)
Increased troponins	1 (8.3)	0 (0)
Right ventricular dilation	1 (8.3)	0 (0)
Tachypnea	11 (91.7)	16 (84.2)
Tachycardia	9 (75.0)	16 (84.2)
No. signs/symptoms		
0–3	5 (41.7)	3 (15.8)
4–7	7 (58.3)	16 (84.2)

APRV, airway pressure release ventilation; P/F ratio, PAO_2/FIO_2 ratio; SOB, shortness of breath.

compromised by clot. Moreover, without follow-up imaging, it is not known if extension of thrombus occurs. Therefore, treating the thrombus, blunting the inflammatory response, and improving pulmonary blood flow with heparin may decrease morbidity in patients without contraindications to anticoagulation. Second, if clot does not arise from the extremities, is there any role for IVC filters in these patients? We would submit that IVC filters would offer little value for PE prophylaxis in patients without a DVT to embolize. Finally, since this process likely represents pulmonary clot without an embolic source, is de novo pulmonary *embolus* a misnomer? A more correct term would be de novo pulmonary *thrombosis* because this more accurately describes the pathogenesis.

Limitations of this study include those inherent to a retrospective study. PE is a rare occurrence, and finding statistically significant differences in a small population is challenging. Multivariable analysis would be necessary to validate and strengthen our findings; however, it would not be useful given our small sample size. In addition, this series demonstrated that DNPE patients were more symptomatic. This may be caused by more chest trauma or infection; however, chest AIS score was similar between groups, and we attempted to limit these confounders by obtaining only signs and symptoms in the 24 hours before PE diagnosis. There is a possibility that, despite our comprehensive screening program, DVTs were missed. Although embolization from a UE thrombus is rare, patients only underwent UE DS for symptoms, and screening was not performed. The CTs of the abdomen and pelvis were not venous phased studies, and consequently, the IVC and pelvic veins were not optimally examined for the presence of thrombus. Therefore, it is possible that an IVC or pelvic thrombus was missed; however, as previous studies have shown, isolated IVC or pelvic thrombus is a rare occurrence.[3,15,16] Finally, four patients in the DNPE group did not undergo complete radiographic visualization of the lower extremities secondary to bandages, in which DVTs could have been present.

In conclusion, this study describes the clinical course of 31 patients with PE and comprehensive surveillance DS. In this series, de novo pulmonary thrombosis was clinically distinct from PE and seemed to be more prevalent and symptomatic than pulmonary emboli originating from the deep venous system. They were usually single, were peripherally located, and more often occurred ipsilateral to pulmonary injury. A prospective multicenter study using upper and lower extremity DS surveillance and, possibly, CT venography of the abdomen and pelvis to rule out DVT in patients diagnosed with PE is needed to further elucidate the pathophysiology of de novo pulmonary thrombosis.

AUTHORSHIP

J.-M.V.G., A.L.Z., E.J.O., S.R.S., and M.J.S. designed this study. J.-M.V.G., A.L.Z., E.J.O., and S.R.S. searched the literature. J.-M.V.G., C.E.D., C.B.S., J.B., A.L.Z., E.J.O., S.R.S., and M.S.S. collected the data. J.-M.V.G., A.L.Z., E.J.O., S.R.S., C.E.D., and J.B. analyzed the data. J.-M.V.G., A.L.Z., E.J.O., S.R.S., M.J.S, C.E.D., C.B.S., and J.B. participated in the data interpretation and manuscript preparation.

DISCLOSURE

The authors declare no conflicts of interest.

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