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# Venous thromboembolism in intensive care patients

Ana T. Rocha, MD*, Victor F. Tapson, MD

*Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Box 3221, Durham, NC 27710, USA*

Venous thromboembolism (VTE) represents a spectrum of disease that encompasses deep venous thrombosis (DVT), pulmonary embolism (PE), and, in critically ill patients, often includes central venous catheter (CVC)–associated thrombosis. PE is the most serious manifestation of VTE and remains one of the leading causes of unexpected deaths in hospitalized patients [1,2]. Although critically ill medical patients are thought to be at a higher risk for VTE, this population is heterogeneous and underinvestigated [3].

This article reviews particular aspects of the epidemiology, risk factors, prophylaxis, diagnosis, and treatment of VTE in critically ill patients.

## Epidemiology

Venous thromboembolic events are considerably more common in hospitalized and severely ill patients than in the outpatient setting [4]. The reported rate of DVT ranges from 22% to almost 80% depending on patients' underlying clinical characteristics. In general medical wards, DVT is reported in 9% to 27.5% of patients without prevention [5,6]. Likewise, without prophylaxis, postoperative DVT can be detected in 6% to 22% of general surgical patients and in as many as 50% of patients with multisystem or major trauma [7,8]. The estimated prevalence of DVT is 22% to 35% in neurosurgical patients and exceeds 50% to 80% in acute spinal cord injury patients [9].

Most patients in the intensive care unit (ICU) have multiple risk factors for VTE, but only a few studies have focused on this complex population (Table 1). When routine screening for DVT with either fibrinogen leg scanning or serial Doppler ultrasonography is performed in medical–surgical ICU patients, DVT is detected in 26% to 32% of patients receiving no prophylaxis [10–15]. Ten percent to 30% of medical–surgical ICU patients experience DVT within the first week of admission, and approximately 60% of trauma patients have DVT within the first 2 weeks, most of which are silent episodes [9]. Hirsch et al [14] assessed the risk for VTE in 100 consecutive medical ICU patients who received VTE prophylaxis (61%). Seventy percent of DVTs could be detected with a single screening ultrasound within the initial 5 days of hospitalization, resulting in therapeutic interventions in two thirds of events. The incidence of VTE in patients treated with intermittent pneumatic compression (IPC) devices or any heparin regimen did not differ from the incidence in patients receiving no prophylaxis (34% and 32%, respectively). Nevertheless, the lack of randomization and the small sample size in this study limit any conclusions about the efficacy of individual methods of prophylaxis.

Although the risk for VTE found in previous studies has been unexpectedly high, the incidence of DVT may still be underestimated. The screening techniques that have been used have limited sensitivity for isolated calf and pelvic thrombi, leading to a high percentage of false-negative results. Nevertheless, fewer DVT can be detected by clinical assessment alone. In an observational study of medical–surgical ICU patients in whom no imaging screening was performed, the incidence of clinically relevant DVT or PE was much lower than the incidence in the previous studies (5.4%) [16]. This finding could be anticipated, because the clinical signs and symptoms of DVT and PE are frequently underinvestigated.

* Corresponding author.
*E-mail address:* rocha002@mc.duke.edu (A.T. Rocha).

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Table 1
Studies of the incidence of deep venous thrombosis in intensive care patients

| Study (year) | Population | DVT screening test | Design | Number/total (%) with DVT | | |
|---|---|---|---|---|---|---|
| | | | | No prophylaxis | LDUH[a] or LMWH[b] | SCD |
| Moser et al (1981) | 34 respiratory ICU patients, 76% were intubated | Fib I daily for 3–6 days | Prospective cohort | 3/34 (9) | NA | NA |
| Cade (1982) | 119 coronary and medical ICU patients | Fib I daily for 8 days (range, 4–10) | Blind RCT | NR/NR (29) | NR/NR (13)[a] | NA |
| Ibarra-Perez et al (1988) | 192 high-risk pulmonary patients | Fib I, Doppler US, SGP daily until ambulatory | Prospective cohort | 12/46 (26) | 1/39 (2.6)[a] | 0/39 (0) |
| Hirsch et al (1995) | 100 medical ICU patients, 80% were intubated | Doppler US twice weekly | Prospective cohort | 10/31 (32) | 17/43 (40)[a] | 6/18(33) |
| Marik et al (1997) | 102 medical–surgical ICU patients, 68% were intubated | Single Doppler US at day 4–7 | Prospective cohort | 2/8 (25) | 5/68 (7)[a] | 5/26 (19) |
| Fraisse et al (2000) | 223 medical ICU patients with COPD, 100% were intubated | Doppler US weekly until completion of the study | Multicenter, double-blind RCT | 24/85 (28.2) | 13/84 (15.5)[b] | NA |

*Abbreviations:* COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; Fib I, fibrinogen I 125 scan of the legs; ICU, intensive care unit; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; NA, not applicable; NR, not reported; RCT, randomized controlled trial; SCD, sequential compression devices; IPG, impedance plethysmography; US, ultrasonography.

[a] LDUH, 5000 U subcutaneously, twice daily:

[b] LMWH, nadroparin, 3800 anti-Xa IU or 5700 anti-Xa IU according to body weight, subcutaneously, once daily.

*Mortality*

Postmortem studies show that most fatal emboli arise from the deep venous system in the lower limbs, but only a minority of these patients have symptoms of DVT, and even a smaller percentage undergo an investigation for these symptoms before death [2]. Approximately 48% to 60% of DVT found in ICU patients are located above the knee and carry greater risk for embolization [12,14]. Even though the rate of symptomatic PE in high-risk trauma patients is low (0.7% to 2%), PE can be found in a much larger percentage of patients at autopsy [8,9]. In one study, PE was identified in 17 of 66 ICU patients (27%) undergoing autopsy, and only half of these events were diagnosed before death [17].

Several experts suggest that not all PE are clinically relevant. Nonetheless, in the study by Hirsch and colleagues [14] in which 100 medical ICU patients had ultrasound screening until discharge from the ICU, the inhospital mortality rate among patients with DVT was 50% higher than the rate for patients without DVT. Confirmation of this trend toward an increased mortality among patients with symptomatic and silent VTE needs to be confirmed in larger cohorts of ICU patients.

*Morbidity*

In many clinical settings, undetected and clinically evident VTE can impact on the morbidity of severely ill patients [18,19]. Significant additional morbidity from DVT relates to local complications such as stasis ulcers or recurrent thrombosis, which are sequelae of the postphlebitic syndrome, CVC-related thrombosis with associated line malfunctioning, and potential CVC-related infection [20]. Furthermore, recovery from the original critical illness (eg, weaning from mechanical ventilation) can be affected adversely by these complications [3].

## Risk factors

Most critically ill patients have one or more recognizable risk factors for VTE. In one cohort of 225 patients admitted to a medical–surgical ICU, the average number of risk factors was four [21]. Surgical ICU patients, multiple trauma victims, and patients with severe head or injury are at extremely high risk for VTE [22]; however, less than 30% of patients hospitalized because of VTE are surgical.

Some nonsurgical situations, such as ischemic strokes and acute myocardial infarction, have been clearly identified as associated with an increased risk for VTE [23]. Acute and chronic illness, immobility, advanced age, respiratory failure, and procedural and pharmacologic interventions may also predispose ICU patients to VTE. The at-risk situations in nonsurgical patients are less well defined, and traditionally recognized DVT risk factors have failed to identify patients in whom VTE developed in some series. In a prospective ultrasound series of 100 medical ICU patients, there was no difference in age, gender, body mass index, diagnosis of cancer, recent surgery, duration of hospitalization before DVT, and use of DVT prophylaxis in patients with DVT and those without [14]. In another series of 119 medical–surgical ICU patients, DVT was found mainly in men and was associated with circulatory impairment, respiratory failure, and recent vascular and cancer surgery [11]. Cook and co-workers [16] demonstrated that, among 93 mixed medical–surgical ICU patients, acquired VTE risk factors were mechanical ventilation, immobility, a femoral venous catheter, sedatives, and paralytic drugs. In contrast, heparin prophylaxis, aspirin, and thromboembolic disease stockings conferred a lower risk, but only warfarin and intravenous heparin were associated with a statistically lower risk of VTE (odds ratio [OR], 0.07 and 0.04, respectively).

The assessment of VTE risk in surgical and medical patients requires a consideration of individual risk factors and their interactions to assist in developing adequate recommendations for prophylaxis and treatment [24]. Table 2 lists several of the general risk factors for the development of VTE in adult patients. Special factors that are unique to the ICU patient, including CVC-related thrombosis, infections complicating CVC-related thrombosis,

Table 2
Risk factors for venous thromboembolism

| | |
|---|---|
| Previous venous thromboembolism | Inherited hypercoagulable states |
| Increased age (> 40 years) | Protein C deficiency |
| Obesity | Protein S deficiency |
| Malignancy | Antithrombin III deficiency |
| Pregnancy | Dysfibrinogenemia |
| Congestive heart failure | Factor V Leiden mutation |
| Immobilization | Prothrombin gene mutation |
| Recent surgery | Hyperhomocysteinemia |
| Trauma | Acquired hypercoagulable states |
| Mechanical ventilation | Lupus anticoagulant |
| Central venous catheterization | Anticardiolipin antibody |

and upper extremity DVT, are discussed in the following sections.

### *Central venous catheter–related venous thromboembolism*

Central venous catheter–related DVT is an important complication of intensive care, because venous catheters are commonly placed in the ICU patient, and thrombosis follows 35% to 67% of long-term catheterizations [25,26]. CVC-related thrombosis may develop as soon as 1 day after canulation and is initially asymptomatic [27,28]. Despite inconsistency from study to study, some investigators have identified factors that increase the risk for thrombotic complications related to CVC use. These conditions can be described as technical factors and host factors (Table 3).

Animal studies have linked some older catheter materials, such as Teflon, polyethylene, and polyvinyl, with higher rates of thrombosis than seen with silicone and Silastic [29]. Most contemporary catheters are made of polyurethane coated with hydromer, which is highly biocompatible and generates the least amount of thrombin formation [30,31].

According to recent studies, the rate of CVC-related thrombosis seems to vary slightly with the site of insertion. Femoral catheters have been associated with a higher incidence of thrombosis, with rates as high as 25% and abnormal Doppler ultrasound findings in as many as 48% of screened patients [32]. Nevertheless, in a study of mixed medical–surgical ICU patients undergoing an intensive ultrasound screening protocol, the incidence of femoral CVC-related DVT was much lower (9.6%) [28]. In that study, the risk of thrombosis was unrelated to the number of insertion attempts, arterial puncture or hematoma, the duration of catheterization, coagulation status, or the type of infused medications. Martin and colleagues [33] reported that the incidence of CVC-related axillary vein thrombosis was 11.6%, and that the risk increased when catheterization exceeded 6 days. Thrombosis rates ranging from 4% to 28% have been reported after subclavian vein canulation [34–37] and rates from 4% to 33% after internal jugular vein catheterization [37,38].

Although catheterization of the femoral vein is convenient and has potential advantages, this practice seems to be associated with a greater risk of thrombotic events than catheterization of the upper body venous system. Nevertheless, questions regarding the frequency of clinically meaningful complications secondary to CVC-related femoral thrombosis, such as PE, remain unanswered.

### *Infections complicating central venous catheter–related thrombosis*

Nosocomial blood stream infections are noteworthy causes of morbidity and mortality among ICU patients and frequently complicate the use of CVCs. In a prospective study of ICU adult patients with a CVC, the total days of hospitalization and the total number of intermittent infusions through the CVC were the best predictors of nosocomial infections [39]. CVC thrombosis also has been associated with an increased incidence of blood stream infection in an autopsy series of cancer patients [40].

Debate continues concerning the increased risk of thrombotic and infectious complications with femoral vein catheterization versus its alternatives [41]. In a randomized controlled trial performed in eight ICUs in France, 289 patients were assigned to have femoral vein or subclavian vein catheters placed [42]. Femoral catheterization was associated with significantly higher overall thrombotic complications (21.5% versus 1.9%, respectively) and complete thrombosis of the vessel (6% versus 0%, respectively). The femoral route was also related with a higher incidence of overall infectious complications (19.8% versus 4.5%, respectively) but not major infectious complications, such as clinical sepsis with or without blood stream infection (4.4% versus 1.5%, respectively). A longer duration of catheterization, insertion in two sites, and

Table 3
Factors associated with an increased risk of central venous catheter–related thrombosis and mechanical complications

| Technical factors | Host factors |
|---|---|
| Material: polyvinyl and polyurethane > silicone, silastic, and coated polyurethane | No prophylactic or therapeutic heparin use |
| Non–heparin-bonded catheters | More than one central venous catheter simultaneously |
| Placement of catheter during the night | Extremes of age (preterm neonates and age >64 years) |
| Site: femoral and internal jugular > subclavian veins and axillary veins | Comorbidities (cancer, dehydration, and impaired tissue perfusion) |
| Duration of canulation (>6 days) | Thrombophilic states |

placement during the night all led to an increased risk of mechanical complications.

Heparin-bonded catheters have been correlated with significantly fewer thrombotic complications and possibly with a decreased incidence of positive CVC-related blood culture in critically ill pediatric patients [25]. In a double-blind controlled trial, 209 critically ill children (aged 0 to 16 years) were randomly assigned to receive heparin-bonded venous catheters (HB-CVC) or non–heparin-bonded venous catheters (NHB-CVC) [43]. The investigators evaluated the risk of infection and thrombosis using an intensive protocol consisting of blood cultures performed at baseline and every 3 days and screening ultrasonography until the catheters had been removed. Heparin bonding was associated with a significant reduction in infections, with a hazards ratio of 0.11. The incidence of infection was 4% and 33% in the HB-CVC and NHB-CVC groups, respectively, and the incidence of thrombosis 0% and 8% in these groups, respectively.

Complications in 265 internal jugular vein and subclavian vein catheterizations were prospectively evaluated in an observational study of adult patients [37]. CVC-related thrombosis was independently associated with the internal jugular vein route (relative risk [RR], 4.13) and age greater than 64 years (RR, 2.44) and negatively correlated with therapeutic heparin use (RR, 0.47). Moreover, the risk for CVC-related sepsis was approximately threefold higher when thrombosis occurred. Randolph and co-workers [44] conducted a meta-analysis to evaluate the effect of heparin on thrombus formation and infection associated with CVC. The prophylactic use of heparin significantly decreased CVC-related thrombosis (RR, 0.43) and bacterial colonization of the CVC (RR, 0.26), with a trend toward decrease of CVC-related bacteremia (RR, 0.26).

Taken together, these data suggest that the development of thrombosis might negatively affect the CVC-related infectious complications in critically ill children and adults. The use of an HB-CVC with or without heparin has consistently been associated with less thrombus formation around the CVC and a trend toward less CVC-related infections. Whether mechanical methods of VTE prophylaxis have effects comparable with those of heparin on blood stream infections is still unknown.

*Deep venous thrombosis of the upper extremity*

Upper-extremity DVT is common in patients with systemic illness and in those with venous catheters [45]. Although, traditionally, upper-extremity DVT has been thought to cause few complications and offer a small risk for PE, this concept has been challenged recently. Thrombosis of the deep venous system of the upper body is likely to be missed because imaging of these vessels is not usually part of the investigation for PE. In a review of 329 cases of axillary or subclavian vein thrombosis, PE was reported in 9.4% of patients [36]. Monreal and colleagues [46] showed that CVC-related, upper-extremity DVT resulted in PE in 15% of patients studied with a ventilation–perfusion scintigraphy scan. More recently, Prandoni and co-workers [20] studied 58 consecutive patients with clinically suspected upper-extremity DVT using three ultrasound techniques and venography. Symptomatic upper-extremity DVT was associated with a CVC, thrombophilic state, or previous leg vein thrombosis. In patients with positive results for DVT of the upper extremities, a ventilation–perfusion scan with or without pulmonary angiography was performed and PE documented or highly probable in 36% of patients.

Complications from upper-extremity DVT are less frequent than after lower-extremity DVT; however, they are not trivial and should not be overlooked in patients with underlying cardiopulmonary compromise.

## Prophylaxis for venous thromboembolism

Routine DVT prophylaxis (Table 4) is the most efficient and cost-effective way to prevent fatal and nonfatal VTE [47,48]; however, recent studies have shown that, even in high-risk critically ill patients, prophylactic measures are frequently underused [49,50]. Goldhaber [51] showed in a mixed medical–surgical ICU that DVT prophylaxis was applied to one-third of patients. Likewise, Keane et al [49] reported that, although 87% of their medical ICU patients had at least one risk factor for thrombosis, VTE prophylaxis was only prescribed to 32.9% of the patients with a mean delay of 2 days. Computerized order entry sets and intensive education have been shown to improve the rate of VTE prophylaxis [52]. Nevertheless, there is increasing concern about VTE occurring in the setting of (failed) prophylaxis [53,54].

The Sixth ACCP Consensus Conference on Antithrombotic Therapy [6] compiled an extensive review of available literature on VTE prophylaxis including 630 references. A large body of evidence in this review suggests the efficacy and safety of low-dose unfractionated heparin (LDUH) and low molecular weight heparin (LMWH) as DVT prophylaxis in surgical patients. Mechanical devices have proved useful as VTE prophylaxis in some surgical populations [50,55,56]. Less data are available in

Table 4
Recommended venous thromboembolism prophylaxis for intensive care unit patients

| Intensive care population | Recommended prophylaxis |
|---|---|
| Medical patients | |
| Medical intensive care (including cancer, bedrest, heart failure, severe lung disease) | LDUH q12h or q8h, or LMWH<br>ES or SCD if anticoagulation is contraindicated |
| Acute myocardial infarction | Prophylactic anticoagulation with SC LDUH, 5000 U q12h or q8h, or therapeutic SC UFH, or IV UFH |
| Acute ischemic stroke | LDUH, LMWH, or danaparoid; consider combination with mechanical prophylaxis with ES or SCD<br>ES or SCD if anticoagulation is contraindicated |
| Hemorrhagic stroke | SCD |
| Acute spinal cord injury | LMWH preferred; consider mechanical prophylaxis with ES or SCD in combination with LMWH or LDUH<br>ES or SCD if anticoagulation is contraindicated early after injury |
| Surgical patients | |
| Trauma | LMWH, ES, and/or SCD if LDWH is delayed or contraindicated early after trauma |
| Neurosurgery | SCD with or without ES; consider combination of mechanical method with LDUH or LMWH postoperatively |
| High-risk general surgery (non-major surgery and age >60 years or additional risk factors, or major surgery and age >40 years or additional risk factors) | LDUH, LMWH, or SCD; consider mechanical prophylaxis with ES or SCD in combination with LMWH or LDUH<br>ES or SCD if anticoagulation is contraindicated early after surgery |
| Major orthopedic surgery (hip replacement, knee replacement, hip fracture) | LMWH or adjusted-dose warfarin; consider mechanical prophylaxis with ES or SCD in combination with LMWH or warfarin; LDUH not recommended |

*Abbreviations:* ES, elastic stockings; IV, intravenous, LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; SC, subcutaneous; SCD, sequential compression devices; UFH, unfractionated heparin.

medical patients and even less in critically ill patients [57]. Based on the extrapolation of data from surgical and medical noncritically ill patients, the committee suggested the use of LDUH or LMWH for prophylaxis in the critically ill population. Elastic stockings or compression devices were suggested for patients with a high risk for bleeding.

*Balancing the risk of thrombosis and bleeding*

When compared with other ICU patients, critically ill medical patients frequently have chronic underlying illness and present with hematologic failure as a result of malignancy or sepsis [19]; consequently, they may be prone to bleeding complications, causing concerns about the safety of antithrombotic drugs in these patients. Overt bleeding and thrombocytopenia are usually considered contraindications for pharmacologic VTE prophylaxis and treatment with anticoagulants. When deciding about appropriate management of VTE in critically ill patients, intensivists must carefully balance the risks of thrombophilia and bleeding. Nevertheless, the objective assessment of risk factors is rarely performed, and the presumed propensity for bleeding may lead physicians to avoid heparins as VTE prophylaxis and to opt for no prophylaxis instead. In a retrospective study of the choice of VTE prophylaxis in a medical ICU, the presence of one or more risk factors for bleeding was associated with underuse of prophylaxis, including mechanical methods (Rocha AT, Tapson VF. 2002.).

One of the feared complications in the ICU is gastrointestinal bleeding. In one respiratory ICU, gastrointestinal bleeding occurred in 20% of patients. Risk factors were the diagnosis of adult respiratory distress syndrome, an increasing number of days on a ventilator, the number of days in the ICU, and the development of thrombocytopenia [58]. Nevertheless, the use of heparin therapy was not associated with an increased risk of gastrointestinal hemorrhage. Supporting this observation are abundant data from meta-analyses and placebo-controlled, randomized studies demonstrating either no increase or a small increase in the absolute rate of major bleeding with the prophylactic use of LDUH or LMWH [59–61]. The results of three meta-analyses of the therapeutic use of heparins also suggest that LMWH drugs are as safe as unfractionated heparin with respect to major

bleeding complications and seem to be slightly more effective in preventing thromboembolic recurrences [62–64].

Heparin-induced thrombocytopenia with or without thrombosis is another underrecognized problem that may occur in 1% to 2% of heparin recipients and in rare instances may result in limb amputation. The pathophysiology of this immune-mediated condition implicates the heparin–platelet factor 4 complex as the culprit antigen in most patients [65]. Heparin-induced thrombocytopenia may have a delayed onset (6–10 days); therefore, awareness and frequent platelet counts are required for early diagnosis and treatment [66]. Unfractionated heparin is approximately eight to ten times more likely to cause heparin-induced thrombocytopenia than is LMWH [67]. LMWH is not recommended as treatment for heparin-induced thrombocytopenia, because approximately 50% of patients may have persistence or worsening of the condition [68]. Because of the increased risk for thrombosis, an alternative intravenous anticoagulant (lepirudin or argatroban) should be used to treat heparin-induced thrombocytopenia until platelet count recovery [69].

A careful evaluation of the risk for thrombosis and bleeding is recommended in all critically ill patients. In a mail survey of 44 ICUs in Canada, the directors of the units answered that decisions about the type of VTE prophylaxis employed were made for the most part on a case-by-case basis (62.1%), rather than by preprinted orders (17.2%), institutional policies (20.7%), or formal practice guidelines (6.9%) [70]. The best way to accomplish adequate patient assessment and to improve the implementation of methods of VTE prophylaxis remains to be determined. Whether any particular approach leads to better use of resources and, more importantly, to improvement of patient outcome are unanswered questions.

### *Pharmacologic methods of venous thromboembolism prophylaxis*

Venous thromboembolism prophylaxis with either LDUH or LMWH given subcutaneously is the preferred option and should be offered to most critically ill patients. One large randomized controlled trial showed a significant reduction in the incidence of DVT in critically ill patients using LDUH when compared with placebo (11% and 31%, respectively) [71]. The MEDical patients with ENOXaparin (MEDENOX) trial [5] also established a reduction in the risk for VTE among 1102 acutely ill medical patients when a placebo was compared with a LMWH (enoxaparin) (14.9% and 5.5%, respectively). Nevertheless, these trials excluded mechanically ventilated patients and patients with severe sepsis. In one of the few randomized controlled trials among mechanically ventilated patients, Fraisse and co-workers [15] evaluated 223 patients with acute decompensated chronic obstructive pulmonary disease (COPD). They demonstrated a 45% decreased incidence of DVT with another LMWH (nadroparin) when compared with placebo. The rates of adverse events, particularly hemorrhage, were similar in both groups.

Recent data suggest that LMWH is more effective than LDUH for VTE prophylaxis in critically ill trauma patients [72], and that high-dose LMWH is more effective than placebo or low-dose LMWH in seriously ill medical patients [6]. LMWH also seems superior to LDUH for the prevention of venographically proven lower-extremity DVT in acute stroke patients [6]. Mismetti and co-workers [73] performed a meta-analysis based on data for several heparins used in internal medicine, excluding patients sustaining acute myocardial infarction or stroke. A significant decrease in DVT and clinical PE was observed with heparin in a comparison with controls (RR, 56% and 58%, respectively; $P < 0.001$) without a significant difference in the incidence of major bleeding or death. Nine trials comparing LMWH with LDUH (4669 patients) were also included and showed no significant difference in DVT, clinical PE, or mortality; however, the use of LMWH seemed to reduce the risk of major hemorrhage by 52% in a comparison with LDUH.

Attia et al [9] have systematically reviewed the literature on different methods of DVT prophylaxis in patients admitted to ICUs and patients sustaining trauma, neurosurgery, or spinal cord injury. The use of subcutaneous LDUH reduced the rate of VTE by 50% when compared with no prophylaxis. Overall, the use of LDUH decreased the incidence of DVT by 20%, whereas the use of LMWH decreased the incidence by a further 30%. These investigators urged caution regarding the interpretation of results of combined trials, because methods of prophylaxis proven in one group do not necessarily generalize to other critically ill patient groups.

### *Mechanical methods of venous thromboembolism prophylaxis*

Mechanical prophylaxis with sequential compression devices (SCD), also referred to as IPC, is an attractive form of VTE prophylaxis owing to the lack of bleeding risk and proven efficacy in postoperative circumstances [50,74]. These devices have been suggested to have a hemodynamic action (increase of

blood flow velocity) and to stimulate endogenous fibrinolytic activity via the production of tissue-type plasminogen activator by the vascular endothelium, which might contribute to their antithrombotic properties [75]. In most surgical studies, the investigators have used devices that compressed the legs and thighs intraoperatively and for 1 to 5 days after operation. Even when IPC devices are applied to the arms during and after surgery, they may reduce the incidence of leg DVT to half the incidence in control patients, and blood fibrinolytic activity is maintained at preoperative values [76].

In a nonrandomized study, the use of graded compression stockings, LDUH, and aspirin was associated with a statistically significant reduction in DVT when compared with no prophylaxis in high-risk pulmonary patients [12]. Marik and co-workers [13] studied 102 critically ill medical–surgical patients using screening Doppler ultrasonography during the first week of ICU stay. DVT was detected in 25% of the patients receiving no prophylaxis, in 7% receiving LDUH, and in 19% receiving SCD. The difference between the SCD and LDUH groups did not reach significance, but the study lacked power to detect statistical differences. In a meta-analysis of five controlled trials of moderate- and high-risk surgical patients, the incidence of DVT detected by fibrinogen uptake test was 9.9% with SCD and 20.3% in control patients [59]. Wells and colleagues [74] performed a meta-analysis showing that mechanical prophylaxis was efficacious for moderate-risk postoperative patients with a pooled OR of 0.28 in five randomized trials. More recently, a different group of investigators documented similar findings for critically ill surgical patients [9]. They found that mechanical devices led to a 68% risk reduction of VTE; however, they were unable to evaluate thromboprophylaxis with mechanical methods for medical–surgical patients owing to a lack of sufficient information.

Although encouraging, not all of the available data favor mechanical methods of prophylaxis. In a small prospective trial of multiple trauma patients with severe head injury, similar rates of DVT and angiographically proven PE were found in patients receiving SCD (29%) or no prophylaxis (22%) [22]. Recently, Jimenez and co-workers [77] demonstrated that IPC devices failed to decrease the incidence of DVT in critically ill patients with a contraindication for heparin.

Controversy continues regarding the proper indication and compliance with the use of mechanical devices [23,53,78]. The presence of leg ulcers or peripheral arterial occlusive disease may preclude the use of SCD. Nevertheless, the combination of prolonged immobility and the high nursing-to-patient ratio in the ICU seems to be an ideal setting for improved compliance with mechanical devices.

*Combination of prophylactic methods*

The concomitant use of bilateral SCD and other forms of prophylaxis has been studied in a few patient groups. In a randomized trial of 2551 consecutive cardiac surgical patients, SCD in combination with LDUH led to a 62% reduction in postsurgical PE in comparison with prophylaxis with LDUH alone (1.5% and 4%, respectively) [55]. Kamran et al [79] reported a 40-fold reduction in the risk for DVT in nonhemorrhagic stroke patients when SCD were combined with LDUH versus LDUH alone. In neurosurgical patients, the use of LMWH as an adjunct to mechanical prophylaxis has been favorable, with a pooled OR of 0.59 when compared with SCD alone [60]. It seems logical to consider the combination of SCD with pharmacologic prophylaxis in high-risk ICU patients, but data continue to be sparse.

Heparins are beneficial in the prevention of VTE in critically ill medical and surgical patients and should be considered the first-line prophylaxis for most ICU patients, unless there is a significant risk of bleeding. Although SCD are not associated with bleeding risks and are generally recommended as an alternative in patients in whom the risk of bleeding is high, little is known about their efficacy as the sole method of VTE prophylaxis for critically ill medical patients. SCD may be most beneficial when used in conjunction with pharmacologic methods in a subgroup of high-risk patients. More research is needed to define the overall efficacy, risk-to-benefit ratios, and cost-effectiveness of the different methods of VTE prevention in critically ill patients.

## Diagnosis of deep venous thrombosis and pulmonary embolism in the intensive care unit

Investigation for VTE happens infrequently in ICU patients owing to several factors. First, ICU patients frequently have underlying systemic illnesses that may mask common presenting signs and symptoms of VTE. Second, an increasing number of ICU patients now receive VTE prophylaxis as part of general ICU care and are assumed to be fully protected. Third, the presence of relative contraindications, such as renal impairment, mechanical ventilation, and hemodynamic compromise, makes definitive testing for PE more difficult. Furthermore, some of the current diag-

nostic tools perform less well in the critically ill, impairing efforts to diagnose VTE.

*Clinical features*

Diagnosing PE in ICU patients represents a significant challenge. In patients with respiratory failure, the usual clinical manifestations of PE are often already present owing to severe underlying pulmonary disease, and any superimposed manifestations of PE become less apparent [17]. Furthermore, signs and symptoms, such as dyspnea, tachypnea, hypoxia, chest pain, tachycardia, fever, hypotension, and hemoptysis, are common in the ICU but nonspecific for PE. Most patients with cardiopulmonary disease have an elevated alveolar–arterial difference of more than 20 mm Hg during acute PE. Nevertheless, as many as one third of patients with acute PE who are younger than 40 years and who do not have preexisting cardiopulmonary disease may have a $PaO_2$ greater than 80 mm Hg and a normal alveolar–arterial difference [80]. Lightheadedness and syncope can be caused by PE with a large clot burden but are seen less often in the ICU. Abnormalities in the chest radiograph occur in most patients with PE. Radiographic findings such as atelectasis, pleural effusions, and infiltrates are common but may be secondary to coexisting cardiopulmonary processes; therefore, a high index of suspicion is necessary in patients with risk factors, because fatalities following PE usually occur within hours of the initial event [10].

Massive PE is a devastating clinical entity often undiscovered until autopsy. An unexplained drop in systolic blood pressure of more than 40 mm Hg or a systolic blood pressure of less than 90 mm Hg for 15 minutes is associated with respiratory decompensation in most cases [81]. Acute right ventricular failure may progress to death within minutes to hours after the embolic event, and prompt diagnostic and therapeutic intervention are imperative. Although clinical suspicion is crucial, objective testing is required to confirm or exclude the presence of PE and should be carried out thoroughly once the suspicion is raised. Hemodynamic instability may hinder a standard diagnostic evaluation, giving bedside tests a paramount role in guiding therapeutic interventions.

*Diagnostic algorithms*

Standardized diagnostic approaches to VTE are designed to obviate the need for invasive procedures and their associated morbidity in an already severely ill group of patients. Clinical assessment protocols have been developed and tested in the emergency room and in inpatient settings [20,30,35,82–86]. Using a clinical model in 1239 patients with suspected PE, Wells and colleagues [83] showed that the pretest probability was low in 3.4%, moderate in 27.8%, and high in 78.4% of patients with PE. Only 0.5% of patients with a low- to-moderate pretest probability and a non–high-probability scan who were considered negative for PE actually had PE or DVT during 90-day follow-up. A combined strategy using negative D-dimer results and a simplified "Wells model" safely excluded PE in a large proportion of patients [87]. This strategy had a negative predictive value of 99.5% by including the following seven variables: clinical symptoms of DVT, no alternative diagnosis, heart rate greater than 100 beats/minute, immobilization or surgery in the previous 4 weeks, previous DVT or PE, hemoptysis, and malignancy. Perrier and colleagues [88] showed that, in 1034 emergency room patients with low clinical probability of PE by empiric assessment and nondiagnostic ventilation–perfusion scans plus a negative lower-limb venous compression ultrasonography, the 3-month risk for VTE was low (1.7%). This approach eliminated the need for pulmonary angiography in 21.5% of the patients.

Ideally, the coupling of reliable clinical assessment and noninvasive imaging techniques would be preferred when evaluating the ICU patient with suspected VTE. Unfortunately, none of the clinical models described previously have been validated in the ICU. Nevertheless, it appears logical to incorporate a preclinical probability of PE based on the knowledge of risk factors and presenting signs and symptoms into diagnostic algorithms in an attempt to guide further diagnostic and therapeutic decisions.

In Figs. 1 and 2, the authors propose diagnostic algorithms for suspected PE in hemodynamically stable and unstable critically ill patients, respectively.

*Electrocardiography*

Electrocardiography is of limited diagnostic utility in suspected PE [89]. Nonspecific electrocardiographic abnormalities may develop in acute PE, including T-wave changes, ST-segment abnormalities, and left or right axis deviation. Occasionally, electrocardiographic changes occur that are more suggestive of PE, including the S1Q3T3 pattern, right bundle branch block, P-wave pulmonale, and right axis deviation [90]. In patients with massive acute PE, an increase in the amplitude of the negative T wave in precordial leads after thrombolytic therapy has been shown to reflect improvement in cardiopulmonary hemodynamics [91].

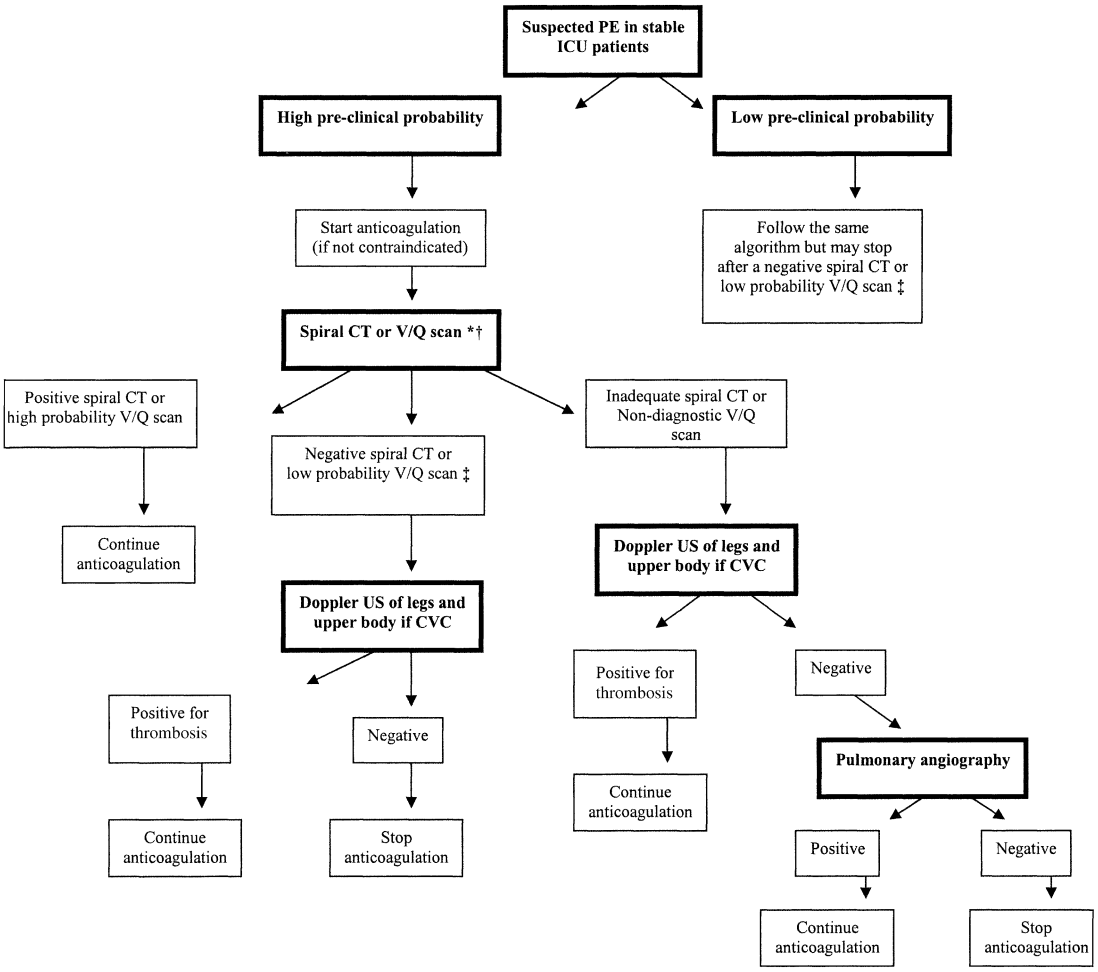


Fig. 1. Diagnostic algorithm for suspected pulmonary embolism in hemodynamically stable patient. CVC, central venous catheterization; ICU, intensive care unit; PE, pulmonary embolism; US, ultrasonography; V/Q scan, ventilation–perfusion lung scan. Notes: * Decision about spiral CT versus V/Q scan will depend on local availability, reader's experience, and presence of contraindications for intravenous contrast. † If a ventilation scan cannot be performed, an isolated perfusion scan can be useful if the scan reveals significant perfusion defects in the absence of radiographic explanation, or if it is near normal or normal. ‡ Consider stopping work-up at this point if there is low preclinical probability of pulmonary embolism.

*End-tidal $CO_2$*

An increase in dead space and a decrease in end-tidal $CO_2$ are known to occur in embolism that involves more than 25% of the pulmonary vasculature [42,43,92,93]. In one study, Johanning and colleagues [94] evaluated the value of negative D-dimer testing and changes in dead space from baseline to exclude PE in critically ill patients. A statistically significant increase in dead space from baseline was found in patients with PE and a decrease in patients without PE. Continuous monitoring of end-tidal $CO_2$ tension has been used to monitor the trends in mean pulmonary artery pressure and cardiac index during thrombolytic therapy in mechanically ventilated patients with massive PE [95]. In this small study, recurrent embolism was detected in two patients by sudden reduction of the end-tidal $CO_2$. Nevertheless, there is a great deal of overlap among absolute values of end-tidal $CO_2$ in patients with COPD, and several other cardiopulmonary conditions may alter the difference between the $PaCO_2$ and end-tidal $CO_2$, decreasing its specificity for PE. High respiratory rates lower mixed–expired $CO_2$ because of increased sampling of the anatomic dead space. Variation in $CO_2$ production affects mixed–expired $CO_2$, and, in many patients with large emboli,

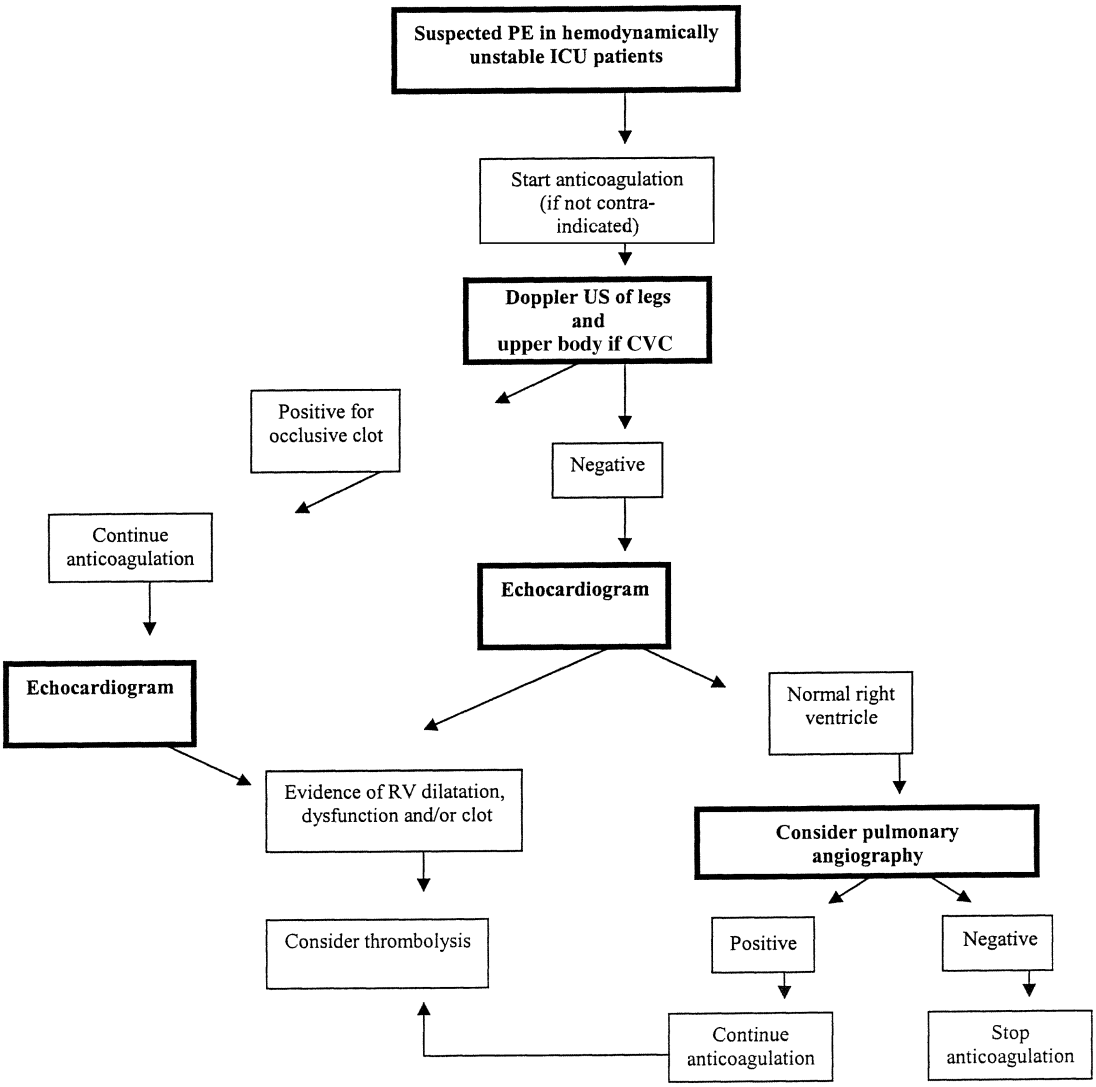


Fig. 2. Diagnostic algorithm for suspected pulmonary embolism in hemodynamically unstable patient. CVC, central venous catheterization; ICU, intensive care unit; PE, pulmonary embolism; RV, right ventricular; US, ultrasonography. * If spinal computed tomography scan or portable perfusion scan can be performed, then one of these should be the initial test.

it is extremely difficult to obtain a steady-state end-tidal $CO_2$ [93]. Moreover, the measurement of dead space can be normal in as many as one third of patients with PE. For these reasons, the utility of end-tidal $CO_2$ and the difference between the $PaCO_2$ and end-tidal $CO_2$ measurements as part of the diagnostic armamentarium in patients with suspected PE remains limited.

*D-dimer levels*

D-dimer levels are sensitive to the process of fibrin formation and dissolution occurring with ongoing thrombosis. Several D-dimer assays have been tested owing to their good negative predictive value for VTE. Currently available assays are based on latex agglutination, immunofixation techniques, or ELISA. The latter assay is the gold standard for measuring D-dimer levels; however, virtually all D-dimer assays have variable negative predictive value and lack specificity, because they are influenced by the presence of comorbid conditions, such as cancer, myocardial infarction, congestive heart failure, surgery, and infectious diseases, which are frequently found in critically ill patients. In a study of more

than 1000 patients, a normal D-dimer test result was useful in excluding PE in patients with a low pretest probability of PE or a nondiagnostic ventilation–perfusion lung scan [96]. On the other hand, in patients with cancer, a negative D-dimer test does not reliably exclude DVT, because it has a significantly lower negative predictive value in these patients when they are compared with patients without cancer [52]. Furthermore, the accuracy of a rapid quantitative D-dimer assay is dependent on embolus location [97]. The sensitivity is 93% for larger emboli versus 50% for smaller subsegmental emboli.

The choice of the cutoff value for D-dimer testing is dependent on the method and the patient population studied. In the outpatient setting, a plasma D-dimer concentration below 500 μg/L allows the exclusion of PE in 29% of suspected cases [98]. Withholding anticoagulation from such patients is associated with a conservative 1% risk of VTE during follow-up. It is not yet known whether it is safe to withhold anticoagulation for suspected VTE in hospitalized individuals, particularly ICU patients, on the basis of negative D-dimer levels [99]. More solid recommendations about the utility of D-dimer levels for the diagnosis and management of VTE cannot be made at this time. Prospective management studies validating the utility of D-dimer measurement for the diagnosis of VTE in the ICU setting are needed.

*Contrast venography*

Venography remains the gold standard for the diagnosis of DVT; however, less invasive methods such as venous ultrasound have become the standard of care [100]. Because of its invasive nature and the availability of adequate alternatives, venography can be reserved for patients with nondiagnostic Doppler ultrasonography or in whom clinical suspicion is high despite negative serial ultrasonography.

*Impedance plethysmography*

Impedance plethysmography allows portable and noninvasive evaluation of DVT. It measures changes in the electrical impedance of the venous system during sequential inflation and deflation of a blood pressure cuff [101]. The sensitivity ranges from 75% to 96% and is higher among high-prevalence groups and very low in asymptomatic patients [102]. The specificity ranges from 45% to 84%. Impedance plethysmography can be problematic, especially in pregnant and obese patients, and in patients with heart failure, chronic DVT, or severe peripheral vascular disease. The sensitivity and specificity depend largely on adhering to the validated protocol. Because of these limitations, impedance plethysmography has largely been supplanted by tests using ultrasonography.

*Ultrasonography*

Venous ultrasonography is the preferred noninvasive test for the diagnosis of a first symptomatic proximal DVT owing to its high accuracy [103]. Inability to compress the common femoral or popliteal vein is diagnostic of DVT in symptomatic patients with a positive predictive value of about 97%. Full compressibility of both of these sites excludes proximal DVT in symptomatic patients with a negative predictive value of about 98% [104]. Venous ultrasonography is much less reliable for the diagnosis of asymptomatic, isolated distal, and recurrent DVT than for the diagnosis of proximal DVT in symptomatic patients. Doppler ultrasonography may also miss pelvic venous clots when compared with venous phase spiral CT imaging [105]. For symptomatic DVT in the upper extremities, compression ultrasonography and color flow Doppler imaging are accurate methods of detection [20]. Doppler ultrasonography is required for the evaluation of subclavian vein thrombosis, because the clavicle precludes adequate compression of this vein. Routine diagnostic screening with ultrasonography is expensive and cannot be recommended for high-risk ICU patients [106].

*Echocardiography*

Right ventricular failure is the ultimate cause of death in patients who die of acute PE [107]. Transthoracic echocardiography has been suggested as a rapid, more readily available, and less invasive diagnostic technique for PE [108]. Hypokinesis and dilation of the right ventricle often accompany massive PE, and as many as 80% of patients with documented PE have imaging or Doppler evidence of right ventricular enlargement or dysfunction, which may suggest the diagnosis [109,110]. Echocardiography is useful in identifying substantial pulmonary hypertension with or without right ventricular dysfunction during acute cor pulmonale, but neither of these conditions is specific for the diagnosis of PE [111]. Transesophageal echocardiography may also identify intracardiac and main pulmonary artery clots, as shown in 12 of 24 patients with unexplained shock and distended neck veins in one study [108]. Because transesophageal echocardiography may miss clots in the left pulmonary artery, lobar, and segmental arteries, it has a relatively low sensitivity (58%) in identifying PE in patients with cor pulmonale [112].

Transesophageal echocardiography may clarify the diagnosis of PE within minutes without the need for further testing in ICU patients; however, a negative study does not exclude left proximal or lobar PE. Some echocardiographic findings, such as moderate-to-severe right ventricular hypokinesis, persistent pulmonary hypertension, a patent foramen ovale, and a free-floating right-sided heart thrombus, are markers of an increased risk of death or recurrent thromboembolism [113].

Echocardiography is not recommended as a routine imaging technique to diagnose suspected PE; however, it can be considered in patients presenting with suspected acute PE associated with hemodynamic instability, because it can be performed at the bedside to identify acute PE with right ventricular failure and to guide therapy with thrombolysis or embolectomy in addition to anticoagulation.

*Ventilation–perfusion scintigraphy*

Ventilation–perfusion scintigraphy scans are noninvasive and have an overall sensitivity of 96% for PE, making them an attractive screening technique. Nevertheless, only a minority of patients have diagnostic scans, and 33% of the patients with nondiagnostic scans ultimately have angiographically proven PE [114]. The test has important limitations in complex critically ill patients with other concomitant pulmonary derangements owing to frequent matched ventilation–perfusion defects. In one study, the ventilation–perfusion scans correlated poorly with pulmonary angiography results and with examinations at autopsy; the scan generally was inadequate to rule in or rule out PE [17]. Data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) [114] showed that intermediate-probability scans occurred in 43% of patients with prior cardiopulmonary disease and in 60% of patients with more complex underlying disease (ie, COPD). These findings were most likely the result of the distortion of ventilation and perfusion by the underlying pulmonary disease. A retrospective analysis of the PIOPED data demonstrated that the sensitivity of a high-probability, ventilation–perfusion scan in critically ill patients (only 33%) did not differ from that in noncritically ill medical patients [115]. Nevertheless, of the 850 subjects included in the study, only 46 were mechanically ventilated, and, as was true in the noncritically ill patients, most of the ventilation–perfusion scans had intermediate probability. If a ventilation scan cannot be performed, a perfusion scan with one or more segmental perfusion defects can be considered diagnostic of PE [116]. A positive perfusion scan has a positive predictive value of 95% and a negative scan a negative predictive value of 81%.

Dealing with the nondiagnostic scans is troublesome, particularly in the critical care arena. Combining the preclinical assessment with the results of the imaging test becomes crucial in determining the need for further testing and management. The combination of clinical assessment and lower-extremity studies using ultrasonography or impedance plethysmography can be useful when the lung scan is nondiagnostic. Perrier and colleagues [88] showed that, in the emergency room setting, anticoagulant treatment could be safely withheld in patients with a low clinical probability of PE and a nondiagnostic ventilation–perfusion scan provided that Doppler ultrasonography of the lower extremities was normal. Pulmonary angiography is recommended, particularly for hemodynamically unstable patients, as well as the consideration of serial noninvasive venous studies for stable patients. Because this strategy has not yet been tested in the ICU setting, additional evaluation for patients with nondiagnostic scans should be individualized.

*Spiral computed tomography*

The use of a spiral CT angiogram for the diagnosis of acute PE has received a great deal of attention over the past decade [80]. Spiral CT seems particularly attractive as the initial diagnostic test for patients with suspected PE and associated lung disease, because in approximately 50% of these patients, ventilation–perfusion scans are nondiagnostic. Another advantage of spiral CT is the ability to evaluate the thorax for other disease processes potentially causing the patient's symptoms [17,18]. According to a systematic review of 15 studies, the sensitivity of spiral CT ranges from 53% to 100% and the specificity from 81% to 100% [117]. Nevertheless, most high-quality studies with adequate gold standards have excluded critically ill and ventilated patients. In one of the few studies in ICU patients, Velmahos and colleagues [118] evaluated 22 critically ill surgical patients with marked pulmonary parenchymal disease using spiral CT and pulmonary angiography. They reported a sensitivity of 45% for all PEs and a sensitivity of 60% for central PEs in a comparison with angiography. The wide variation in sensitivity among studies probably reflects variable readers and institutional experience, technical factors, and the populations studied. Currently, the literature indicates that spiral CT may not be sufficiently sensitive in identifying subsegmental clots to permit its use as a screening test. Whether clots found in the peripheral pulmonary arteries significantly affect the outcomes of critically ill patients

remains to be established. The ongoing PIOPED II study is being performed with the goal of analyzing state-of-the-art spiral CT (including pelvic/leg views) for the diagnosis of PE versus pulmonary angiography and the integration of ventilation–perfusion scans, lower-extremity ultrasonography, standard clinical assessment, and 3-month follow-up. This large multicenter study should resolve some of the issues involving the role of spiral CT for the diagnosis of PE. Unfortunately, the trial excludes critically ill and mechanically ventilated patients; therefore, future studies focusing on this patient population will be needed.

Frequently, it is desirable to image the deep venous system of the lower extremities as part of the evaluation of PE. Spiral CT venography has the potential of evaluating the pelvis and upper thighs for DVT without any additional intravenous contrast, minimal added study time, and radiation. Spiral CT venography was as effective as ultrasonography for femoropopliteal DVT in one study, showing a sensitivity of 100% and specificity of 100% [119]. In an investigation of 116 patients undergoing spiral CT venography and venous ultrasonography, 15 patients with DVT were diagnosed by both tests, but spiral CT venography also detected four pelvic DVTs not depicted by ultrasonography [105]. Spiral CT venography increased the detection of VTE by 18% because of the detection of DVT in patients with negative spiral CT angiography for PE.

Spiral CT may be considered as part of the diagnostic evaluation of PE; however, the utility of spiral CT for the diagnosis of VTE needs to be clarified in the ICU population. Spiral CT should probably not be used alone for suspected PE but could replace pulmonary angiography in combined strategies that include preclinical assessment, spiral CT venography, and ultrasound of the extremities.

### *Magnetic resonance imaging*

Recent advances in MRI permit the evaluation of both lungs, simultaneous bilateral lower-extremity imaging, and excellent resolution of the inferior vena cava and pelvic veins. In a study of 101 patients with suspected DVT, the sensitivity and specificity of MRI were maintained below the knee when MRI was compared with venography [120]. MRI seems to be sensitive in detecting acute DVT, offering an accurate noninvasive alternative to venography, and may accurately distinguish acute DVT from chronic DVT [121].

Small studies have supported the potential use of MRI, particularly with gadolinium, in diagnosing PE [122,123]. The technique seems to be rapid and accurate, avoids nephrotoxic contrast, and is frequently more acceptable to patients than pulmonary angiography. Potential disadvantages for critically ill patients include contraindications to MRI, the need for transportation to the radiology suite (a problem for mechanically ventilated patients), and the lack of sensitivity for subsegmental emboli. MRI has been compared with spiral CT in patients with proven PE by angiography or by high-probability, ventilation–perfusion scans plus a high clinical suspicion [124]. The average sensitivity and specificity of MRI for two expert readers were 71% and 97%, respectively, versus 73% and 97%, respectively, for spiral CT scanning. This pilot study was somewhat limited by the small number of patients and the small number of angiographic correlations. Larger studies employing more readily available equipment used by skilled readers are needed for confirmation of these encouraging results.

### *Pulmonary angiography*

Currently, pulmonary angiography remains the most reliable technique to confirm or exclude PE in patients with respiratory failure. Angiography is not without risk, but serious morbidity and mortality are limited to 1% and 0.5% of cases, respectively [114]. Serious complications associated with pulmonary angiography include respiratory failure (0.4%), renal failure (0.3%), and bleeding requiring transfusion (0.2%) [125]. Although pulmonary angiography is considered the gold standard for the diagnosis of PE, interobserver agreement on the presence of PE in the PIOPED study was 92%, which suggests that even angiography can be difficult to interpret in some cases. Since the advent of less invasive diagnostic techniques, pulmonary angiography has been used with less frequency and is now generally reserved for patients with nondiagnostic ventilation–perfusion scans or technically inadequate spiral CT and a high clinical suspicion of PE.

## Treatment

Standard unfractionated heparin is being increasingly replaced by LMWH for therapy and prophylaxis of VTE. Heparins and derivatives do not directly cause lysis of the thrombus but inhibit further clot formation while allowing the endogenous fibrinolytic system to dissolve the thrombi. For the treatment of acute VTE in ICU patients, unfractionated heparin is administered intravenously to achieve an activated partial thromboplastin time that is 1.5 to 2.0 times the control value. The short half-life and the easy reversibility of

unfractionated heparin are ideal in treating patients who frequently need invasive procedures. Weight-based normograms for initial unfractionated heparin dosing should be applied, because they lead to more reliable therapeutic levels within 24 hours [126]. Failure to achieve full anticoagulation within 24 hours of the thrombotic event has been shown to increase the risk for recurrent thrombosis [127]. The platelet count should be monitored between days 3 and 5. Once the physician decides that is appropriate to convert anticoagulation to an oral regimen, warfarin should be initiated and overlapped until the international normalized ratio (INR) is therapeutic for two consecutive days before UFA (or LMWH) is discontinued. For most patients, anticoagulation should be continued for greater than 3 months with the goal of reaching an international normalized ratio (INR) of 2.5 (range, 2.0–3.0) [128]. Recently published guidelines specify the INR goal and the duration of anticoagulation in special circumstances [128].

Subcutaneous administration of LMWH once or twice daily for VTE prophylaxis and treatment has been evaluated in many randomized trials among different patient populations [129–132]. Currently, dalteparin, enoxaparin and ardeparin have been approved for DVT prophylaxis, whereas enoxaparin and tinzaparin have been approved for the treatment of acute VTE in the United States, only enoxaparin is FDA-approved for use in medically ill patients as prophylaxis. It is convenient to use LMWH from the patient and nursing viewpoint, particularly for the prophylaxis of VTE. No monitoring is required with LMWH, except in special therapeutic circumstances, but its much longer half-life may be disadvantageous for ICU patients.

Central venous catheter–related thrombosis should generally be treated in a similar fashion as other uncomplicated DVTs with a caveat of prompt CVC removal after the diagnosis. The risk for chronic thrombotic complications and potential infection outweighs the risk of inducing embolization of the thrombus with catheter removal.

In the setting of massive PE, initial efforts should focus on stabilizing blood pressure, enhancing coronary artery blood flow, and minimizing right ventricular ischemia. Supplemental oxygen must be administered, and, when necessary, intubation and mechanical ventilation should not be delayed. Intravenous fluids should be administered cautiously. If hypotension persists after the administration of 500 to 1000 mL of isotonic saline, vasoactive medications are appropriate. Norepinephrine is preferred when there is a marked decrease of cardiac output. Dobutamine may be used to increase flow when a moderate decrease in cardiac output complicates an increase in right ventricular afterload [133]. Therapeutic options aimed directly at reducing the embolic burden include systemic thrombolytic therapy, surgical embolectomy, and the use of intrapulmonary arterial catheter techniques. Thrombolytic therapy continues to be reserved for severe, life-threatening, acute PE. In the absence of contraindications, thrombolytic therapy is indicated in hypotensive patients. Surgical embolectomy for acute PE is controversial, but this modality seems to have a role in select patients. Various intrapulmonary arterial catheter techniques, with or without low-dose thrombolytic therapy, have been used successfully to reduce the embolic burden, although no particular technique has clear advantages over others. Placement of an inferior vena cava filter may prevent additional potentially fatal emboli and seems appropriate in select patients with massive emboli [81]. Special aspects of therapy for VTE, including thrombolytic therapy, and embolectomy are discussed elsewhere in this issue.

## Summary

Venous thromboembolism frequently complicates the management of patients with severe medical and surgical illnesses. Because the diagnosis of VTE is especially challenging in critically ill patients, the focus of intensivists should be on characterization of risk factors and the appropriate choice of VTE prophylaxis. LDUH or LMHW is the preferred choice for VTE prophylaxis in ICU patients. Mechanical methods of prophylaxis should be reserved for patients with a high risk for bleeding. The effectiveness of mechanical methods and of combined strategies of prevention and the clinically important outcomes of therapy need to be explored further in critically ill patients.

Few diagnostic strategies have been assessed in ICU patients with suspected PE. Ventilation–perfusion lung scans remain a pivotal diagnostic test but retain the same limitations in critically ill patients as seen in other patient populations. Newer noninvasive techniques, such as spiral CT associated with imaging of the extremities, are gaining more wide-spread use, but, thus far, pulmonary angiography remains the most reliable technique to confirm or exclude PE in patients with respiratory failure. A consensus must be reached regarding the most appropriate combination of tests for adequate and cost-effective diagnosis of VTE. Further investigation of diagnostic strategies that include adequate consideration of clinical diagnosis using standardized models and noninvasive imaging are warranted.

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