Research Article

Sonographic and Clinical Features of Upper Extremity Deep Venous Thrombosis in Critical Care Patients

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Received 23 February 2012; Accepted 5 March 2012

Academic Editor: Apostolos Papalois

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Background-Aim. Upper extremity deep vein thrombosis (UEDVT) is an increasingly recognized problem in the critically ill. We sought to identify the prevalence of and risk factors for UEDVT, and to characterize sonographically detected thrombi in the critical care setting. Patients and Methods. Three hundred and twenty patients receiving a subclavian or internal jugular central venous catheter (CVC) were included. When an UEDVT was detected, therapeutic anticoagulation was started. Additionally, a standardized ultrasound scan was performed to detect the extent of the thrombus. Images were interpreted offline by two independent readers. Results. Thirty-six (11.25%) patients had UEDVT and a complete scan was performed. One (2.7%) of these patients died, and 2 had pulmonary embolism (5.5%). Risk factors associated with UEDVT were presence of CVC [(odds ratio (OR) 2.716, \(P = 0.007\)], malignancy (OR 1.483, \(P = 0.036\)), total parenteral nutrition (OR 1.399, \(P = 0.035\)), hypercoagulable state (OR 1.284, \(P = 0.045\)), and obesity (OR 1.191, \(P = 0.049\)). Eight thrombi were chronic, and 28 were acute. We describe a new sonographic sign which characterized acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall; but its clinical significance remains to be defined. Conclusion. Presence of CVC was a strong predictor for the development of UEDVT in a cohort of critical care patients; however, the rate of subsequent PE and related mortality was low.

1. Introduction

Upper extremity deep venous thrombosis (UEDVT) may be underdiagnosed as imaging of these vessels is not a routine part of pulmonary embolism (PE) investigation [1]. Moreover, PE is thought to occur at low rates (7 to 9%) in patients with UEDVT [1–3]. The clinical significance of UEDVT remains uncertain and much variability in reported treatment [4]. Nevertheless, current guidelines recommend that UEDVT should be treated similarly to lower extremity deep venous thrombosis [5]. In various series, 35 to 75% of patients who have upper extremity, neck, or torso central venous catheters (CVCs) develops thrombosis, with 75% being asymptomatic [6–10]. CVCs have been increasingly used in the intensive care unit (ICU) hence there is rationale to further investigated UEDVT [11–15]. CVC-associated UEDVT may be related to the material the catheter is made of and its diameter [11–17]. Other commonly reported risk factors for development of UEDVT are malignancy and thrombophilia. Less frequently reported risk factors include an obstructing tumor, pregnancy, and estrogen use [1, 18–21]. However, it is difficult to find extensive data on the incidence and clinical characteristics of UEDVT in the ICU [9, 10, 12].

The situation is further complicated by the use of different imaging techniques to diagnose UEDVT such as radionuclide scanning, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), and contrast
venography. Venography remains the reference standard but cannot be used readily in the critically ill and has a small incidence of complications [10, 22]. Ultrasonography is considered the initial imaging test of choice as it can exclude deep venous thrombosis and identify proximal venous obstruction [1, 3, 8–11, 21, 23]. The advantages of this test include its noninvasiveness, portability, lack of ionizing radiation, and high sensitivity and specificity [23].

In this study, we aimed to clarify the clinical uncertainties and risk factors associated with the diagnosis and significance of UEDVT by retrospectively analyzing ultrasound data derived from a cohort of critical care patients. Moreover, we analyzed the sonographic features of detected thromboses in order to assess thrombus age.

2. Materials and Methods

We extracted data from the archives of previously registered trials, which were conducted by our team and concerned subclavian (SCV) and internal jugular vein (IJV) ultrasound-guided cannulation (ISRCTN-61258470) [24, 25]. The present study was approved by the General State Hospital of Athens ethical committee. Three hundred and twenty critical care patients, who were hospitalized in a multipurpose intensive care unit (ICU) from 2006 to 2012, and in whom complete sonographic records were available for retrieval, were enrolled. All patients were sedated and mechanically ventilated (Servo-I ventilator, Maquet Inc., Bridgewater, NJ, USA). All patients were routinely scanned before, during and after ultrasound-guided IJV and SCV cannulation by means of a portable HD11 XE ultrasound machine (Philips, Andover, MA, USA) equipped with a high-resolution 7.5–12 MHz transducer, as described in detail elsewhere [1, 2]. When an UEDVT was identified, a complete scanning protocol was initiated [23, 26]. In brief, the IJV was examined from the level of the mandible to the point at which it traveled under the clavicle. The junction of the SCV and IJV originating at the innominate vein is difficult to visualize, therefore Doppler was utilized to provide indirect information regarding the patency of the veins in this area. Next, the SCV was followed in the direction of the clavicle distally until it anatomically changed to the axillary vein, which in turn was followed in the direction of the upper arm where the brachial vein was identified. The latter was followed distally until the junction of the radial and ulnar veins, which in turn were followed until the region of the wrist. Thus, a complete assessment of the deep veins of the upper extremity and torso was completed. Ultrasound scanning included utilization of two-dimensional (2D) scanning with compression testing and Color-Doppler modes. Venous thromboses were identified according to American College of Radiology criteria [23].

All ultrasound data were stored in a computerized off-line system. Sonographic images were reviewed retrospectively by one independent radiologist and one intensivist trained in vascular ultrasound, both of whom were blinded to the subjects’ clinical characteristics. When a visible intraluminal thrombus was identified, several of its characteristics were evaluated to determine its relative age. Sonographic features suggesting chronic thrombosis were a contracted venous segment, thrombus adherence to the venous wall, hyperechoic and heterogeneous appearance of the clot, partial recanalization of the vessel, and presence of venous collaterals. Features suggestive of acute thrombosis were venous distention, a partially compressible or noncompressible lumen, hypechoic, homogeneous appearance of clots, and presence of free floating thrombi [26–35]. UEDVT was characterized either as spontaneous if no intravascular catheters were related to the thrombus or as CVC associated [1, 8, 9, 21, 24]. The segmental location of thrombosis was analyzed according to the affected veins (IJV, SCV, innominate, axillary and brachial veins). All ultrasound images were analytically reviewed to investigate whether any other sonographic findings related to thrombosis age existed.

Clinical parameters included: patient age, diagnosis upon admission, days of hospitalization, CVC insertion location, type of CVC (triple lumen, double-lumen catheter used for hemodialysis), other indwelling vascular devices (i.e., pacemakers), administration of total parenteral nutrition (TPN), known anatomic vascular anomaly and hypercoagulable disorder, untreated coagulopathy, increased (≥35 kg/m²) body mass index (BMI), and known malignancy [1, 2, 8, 12, 14–21]. Use of prophylactic treatment with low molecular weight heparin (LMWH) and subsequent incidence of PE and ICU death was investigated [1–3]. Moreover, we analyzed the sonographic features of recorded thrombosis in an effort to assess the relative age of the thrombus.

3. Statistical Analysis

Continuous data were expressed as mean ± standard deviation (SD). The student’s t-test or Fisher’s exact test was used as appropriate to compare group means for patient data. A two-sided P value of <0.05 was considered significant. Agreement between the two observers in the evaluation of sonographic data was evaluated by Cohen's weighted κ, with 2.5th and 97.5th percentiles of 5,000 bootstrap replicates estimated, using 95% confidence intervals [13]. Multivariate logistical regression in determining potential risk factors facilitating the development of UEDVT, as well as all other statistical analyses, was performed using the R2.10.1 statistical package (R Development Core Team, 2009. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

4. Results

Demographic and clinical characteristics of the total study population are presented in Table 1. Thirty-six cases of UEDVT were recorded out of 320 patients reviewed (11.25%). The vast majority of patients in this cohort were trauma victims. All patients had CVC inserted and received prophylactic treatment with LMWH (Table 1).

Clinical and sonographic characteristics of the 36 cases identified with UEDVT are shown in Table 2. UEDVT was most commonly observed in the SCV and IJV sites, while the number of veins involved was usually 1 to 3. The vast majority of UEDVTs recorded were CVC-associated...
Table 1: Baseline characteristics of the study population.

| Characteristic                        | Patients n = 320 |
|---------------------------------------|------------------|
| Age (years)                           | 51 ± 15.5        |
| Gender (male/female ratio)            | 0.52 ± 0.4       |
| APACHE II score                       | 20.2 ± 3.1       |
| Diagnosis upon admission              |                  |
| Trauma                                | 205 (64%)        |
| Burn                                  | 12 (3.75%)       |
| ARDS                                  | 26 (8.12%)       |
| Sepsis                                | 48 (15%)         |
| Postsurgical complications            | 29 (9.13%)       |
| Body mass index (kg/m²)               | 27.2 ± 10.3      |
| Anatomic vascular abnormality (%)     | 6 (1.87%)        |
| Untreated coagulopathy (%)            | 0 (0%)           |
| Prophylactic treatment with LMWH (%)  | 320 (100%)       |
| Hypercoagulable state (%)             | 16 (5%)          |
| Malignancy (%)                        | 23 (7.18%)       |
| Total number of UEDVT (%)             | 36 (11.25%)      |
| Central venous catheters              | 177 (55.3%)      |
| Other intravascular devices           | 16 (5%)          |
| Days of hospitalization               | 59 ± 26          |

Table 2: Characteristics of the 36 cases with upper extremity deep venous thrombosis (UEDVT).

| Characteristics                        | Number (percent) |
|----------------------------------------|------------------|
| **Location of UEDVT**                  |                  |
| Internal jugular vein                  | 25               |
| Subclavian vein                        | 27               |
| Innominate vein                        | 9                |
| Axillary vein                          | 11               |
| Brachial                               | 6                |
| **Number of venous segments involved** |                  |
| Single segment                         | 14               |
| Two segments                           | 12               |
| Three segments                         | 10               |
| Four segments                          | 4                |
| Five segments                          | 2                |
| **Clinical characteristics**           |                  |
| Spontaneous thrombosis                 | 3 (8.3%)         |
| Catheter-associated thrombosis         | 33 (91.7%) *     |
| Triple-lumen catheter                  | 14 (38.8%)       |
| Hemodialysis (double-lumen catheter)   | 19 (52.7%)       |
| Malignancy                             | 14 (38.8%)       |
| Hypercoagulable state                  | 8 (22.2%)        |
| Total parenteral nutrition             | 9 (25%)          |
| Body mass index ≥35 kg/m²              | 8 (22.2%)        |
| Asymptomatic thrombosis                | 16 (44.4%)       |
| Symptomatic thrombosis                 | 20 (55.6%)       |
| Subsequent pulmonary embolism          | 2 (5.5%)         |
| ICU deaths                             | 1 (2.7%)         |
| Therapeutic anticoagulation            | 36 (100%)        |

* Catheter-associated versus spontaneous thrombosis and ** acute versus chronic thrombosis (both P < 0.01; Fisher’s test).

The sonographic findings was significant ($\kappa = 0.88$, 95% confidence intervals by bootstrap analysis = 0.85–0.93, $P < 0.02$).

Multivariate logistic regression analysis (Table 4) identified that insertion of CVC (both triple lumen and double-lumen catheters for hemodialysis), administration of TPN, presence of malignancy, presence of thrombophilia as well as body mass index ≥35 kg/m² were all significantly correlated with the occurrence of UEDVT (all $P < 0.05$). Notably, insertion of CVC was the factor with the strongest effect upon the incidence of UEDVT (odds ratio = 2.716, 95% confidence intervals = 2.312–2.911; $P = 0.007$).

5. Discussion

A rate of 11.25% of UEDVT in patients being examined for CVC placement was detected in this study, consistent with previously published series [1, 2, 9, 20, 21, 36]. Ultrasound...
Figure 1: Left subclavian vein catheter-associated chronic thrombosis with partial recanalization (a); proximal right internal jugular vein (b) and ipsilateral subclavian vein (c) with associated collateral flow (arrow) in a patient with chronic spontaneous thrombosis. SCV: Subclavian Vein.

Figure 2: Incompressible proximal right and medial left axillary veins (arrows) in two cases of spontaneous acute thrombosis, respectively ((a), (b)); two cases of catheter-associated thrombosis of the right internal jugular vein with fresh clots obstructing almost totally the venous lumen (c); one of the three lumens of the catheter (in this case delivering total parenteral nutrition, (d)).
Figure 3: Double hyperechoic line along fresh thrombus/wall interface (arrows) in limited segments of the subclavian vein ((a), (b)) and in extended segments of the left brachial vein (panoramic view with zoom, (c)).

Table 3: Estimating the relative age of venous thrombus by ultrasound.

| Characteristics                        | Number/total cases |
|----------------------------------------|--------------------|
| **Chronic thrombosis (n = 8)**         |                    |
| Contracted venous segment              | 6/8                |
| Clot adherence                         | 8/8                |
| Free-floating thrombi                  | 1/8                |
| Hyperechoic thrombi                    | 4/8                |
| Homogeneous thrombi                    | 1/8                |
| Partial recanalization                 | 7/8                |
| Venous collaterals                     | 7/8                |
| **Acute thrombosis (n = 28)**          |                    |
| Venous distention                      | 22/28              |
| Lumen partially and/or noncompressible | 26/28              |
| Hyperechoic thrombi                    | 22/28              |
| Homogeneous thrombi                    | 22/28              |
| Free-floating thrombi                  | 20/28              |
| Double hyperechoic line                | 20/28              |
| along the thrombus/wall interface      |                    |

was able to diagnose UEDVT and a high agreement was registered between the two independent observers as previously suggested [8, 11, 22, 23, 26, 28–30, 32, 36]. The sensitivity of Doppler sonography in the diagnosis for UEDVT has been reported to range from 78% to 100% and its specificity from 82% to 100% in various series [8–11, 22, 23, 32, 36]. Our results add to the prior literature on detection of UEDVT in ICU patients.

The subsequent rate of PE was on the low end of previously published data [1–4, 12, 20, 21, 36, 37]. The reasons for this are not entirely clear; however, we note that in this study, all patients with UEDVT were fully anticoagulated as per recommended guidelines [5]. Notably, in the study of Mustafa et al., all patients with symptomatic UEDVT received anticoagulant therapy and none developed PE [9]. However, despite guideline recommendations, prescribing full anticoagulation for UEDVT remains controversial [1–3].

The highest risk for UEDVT was having a CVC. Of note, these were all critically ill patients who were being examined for CVC insertion. Risk factors have been established for catheter-related DVT which include catheter material, diameter, and position of the catheter. Clinical and in vitro studies have demonstrated that both polyurethane and silicone catheters are associated with a lower rate of catheter-related DVT as compared with polyethylene or Teflon-coated catheters [16, 17]. In our study all CVCs were polyurethane.

The pathogenesis of thrombosis is multifactorial and ICU patients may have a higher incidence of risk factors than the general population. We confirmed previously published data which suggested that obesity, malignancy, a hypercoagulable state, and administration of TPN are potential risk factors for UEDVT [9, 12, 14, 15, 37, 38]. Obesity may
We also described a new sonographic sign in 2D images that was present in 20 out of 28 cases of acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall. Histology studies show that a smooth coat of fibrin lines the external surface of an acute thrombus [48]. The latter are three-dimensional networks of fibrin fibers stabilized by factor XIIIa. Fibrin fibers are long, thin fibers that easily bend rather than stretch; however, fibrin itself is very dense and stiff thus exhibiting high acoustic impedance [26–30]. We speculate that this double hyperechoic line might represent fibrin fibers coating acute clots. If confirmed in other studies, this finding may assist in determining thrombus age. Recently, Rubin et al. suggested that sonographic elasticity imaging, a technique measuring tissue hardness, can discriminate between acute and chronic thrombi [49, 50].

There were several limitations in this study. First, the study was performed retrospectively solely in patients receiving a CVC and may not be extrapolated to all critically ill patients. Second, ultrasound is an operator-dependent technique, and the amount of training required to become facile at upper extremity DVT examination is unknown. Third, there were a small number of cases of UEDVT, confirming previously reported studies. The small numbers precluded subgroup analyses. However, despite the small numbers we were able to find various parameters that were significantly related to thrombosis. Fourth, our cohort consisted of a high percentage of trauma patients which may affect the generalizability of our findings. Further prospective studies would be required to confirm that a strategy of universal anticoagulation is correct for all ICU patients with this problem.

6. Conclusions

The present study characterized the incidence of UEDVT in a mixed ICU population. We confirmed risk factors associated with UEDVT including presence of a CVC, BMI > 35, a hypercoagulable state, malignancy, and use of TPN. We have fully characterized the locations, extent, and ultrasound findings of UEDVTs in an ICU population. In this study, a clinical strategy of universal anticoagulation led to favorable outcomes. We also describe a new ultrasound finding of acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall. Further studies
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