A STROBE cohort study of 755 deep and superficial upper-extremity vein thrombosis

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Abstract
Upper extremity vein thrombosis (UE-VT) are more and more frequent pathologies and yet little studied. The aim is to describe the clinical and ultrasound features, UE-VT-related diseases, and the prevalence of pulmonary embolism (PE) and associated deaths.

All UE-VT patients diagnosed by Doppler-ultrasound in Nantes University Hospital, from January 2015 to December 2017, were included retrospectively. UE-VT suspicion patterns, clinical features, UE-VT topography, and prevalence of PE and death were analyzed.

Seven hundred and fifty-five UE-VT were analyzed, including 427 deep thrombosis (UE-DVT) and 328 superficial thrombosis (UE-SVT). In 86.2% (n=651) UE-VT were related to endovascular devices. Among these thrombosis, one third is in connection with a PICC LINE and one quarter with a peripheral venous line. Forty nine percent (n=370) of the patients had solid neoplasia or hematological malignancies. An inflammatory or systemic infectious context was found in 40.8% (n=308) of the cases. The most frequently observed clinical sign at the UE-VT diagnosis was edema (28.6%). Among the UE-SVT it was the presence of an indurated cord (33.2%) and among the UE-DVT the indication of the Doppler-ultrasound was mainly a suspicion of infection on endovascular device (35.1%). In 10.6% (n=80) of the cases the UE-VT were asymptomatic. The most frequently thrombosed veins were brachial basilic veins (16.7% of all thrombosed segments) followed by jugular (13%) and subclavian (12.3%) veins; 61.3% (n=463) of UE-VT were in the right upper extremity; 63.3% (n=478) UE-VT were occlusive. The occurrence of PE is 4% and the death rate is 10.2%, mainly related to the severe comorbidities of patients with UE-VT.

UE-VT occurs in particular clinical contexts (hematological malignancies, solid cancers, systemic infections) and in the majority of endovascular devices (86.2%). The occurrence of PE is low.

Abbreviations: APLS = antiphospholipid syndrome, AVF = arteriovenous fistula, CT Scan = computerized tomography scan, CVC = central venous catheter, ECMO = extracorporeal membrane oxygenation, GNEDS = Groupe Nantais d’Ethique dans le Domaine de la Santé, HIT = heparin-induced thrombocytopenia, ICD = implantable cardioverter defibrillator, LE-DVT = lower extremity deep vein thrombosis, LE-SVT = lower extremity superficial vein thrombosis, LE-VT = lower extremity vein thrombosis, PE = pulmonary embolism, PICC LINE = peripherally inserted central catheter – Line, PM = pace maker, PVC = peripheral venous catheter, TOS = thoracic outlet syndrome, UE-DVT = upper extremity deep vein thrombosis, UE-SVT = upper extremity superficial vein thrombosis, UE-VT = upper extremity vein thrombosis, VTE = venous thromboembolism.

Keywords: catheter, Doppler-ultrasound, peripherally inserted central catheter – line, pulmonary embolism, upper extremity venous thrombosis.
1. Introduction

Venous thromboembolism (VTE) is a major public health problem because of its prevalence and severity. It is one of the leading causes of morbidity and mortality in hospitalized patients.\(^1\)

Venous thrombosis of the upper extremity (UE-VT) is an increasingly common pathology; in the 2000s, it accounted for 1% to 4% of all cases of venous thrombosis,\(^3,4\) today it represents about 10%.\(^3\) This is mainly explained by the increasing use of central venous catheters (CVC) and in particular the use of PICC LINE (Peripherally Inserted Central Catheter – Line).

The major UE-VT-related diseases and conditions described in the literature are: venous catheterization\(^1\) and in particular a PICC LINE; a solid neoplasia\(^5\) or a hematological malignancy\(^6\); a thoracic outlet syndrome (TOS) or effort thrombosis (Paget-Schroetter syndrome);\(^7\) an estrogenic hormonal impregnation (pregnancy, contraceptive pill\(^9\)) with or without ovarian hyperstimulation\(^10\), hereditary or acquired hereditary thrombophilic antiphospholipid syndrome (APLS), de novo estrogenic hormonal impregnation of the thoracic outlet syndrome (TOS) or effort thrombosis (Paget-Schroetter syndrome)\(^8\); an estrogenic hormonal impregnation (pregnancy, contraceptive pill\(^9\)), a medically assisted procreation protocol\(^10\) with or without ovarian hyperstimulation\(^11\), hereditary or acquired hemostatic abnormalities\(^12\); severe kidney failure\(^13\), or other situations such as flares of inflammatory diseases (hemorrhagic rectocolitis, Crohn, Behcet, Buerger).\(^14\)

The pathophysiology, epidemiology and management of UE-VT, although much less studied than the lower extremities, have long been considered similar to lower extremity vein thrombosis (LE-VT), yet it is a particular form of VTE: diagnostic elements, clinical features, risk factors and evolutive risks seem different between these two types of thrombosis.\(^15\)\(^15\) UE-VT characteristics are poorly known, indeed few recent studies have been done on UE-VT and they only concerned deep thrombosis.\(^16\)\(^18\)

The purpose of this study was to describe the UE-VT presentations in a large cohort and to compare the deep and superficial UE-VT features.

2. Methods

We conducted a descriptive, retrospective, monocentric study. Patients were identified by performing at least one Doppler ultrasound of the upper extremity at Nantes University Hospital Center during the period from January 1, 2015 to December 31, 2017. The included patients had a UE-VT defined on the Doppler ultrasound by a hypo or isoechic image, without Doppler flow, associated with incompressibility of the vein. UE-VT linked to the central venous catheter was defined by a thrombus facing the catheter pathway with a wall adherent thrombus whose major axis was > 5 mm.

The topography of UE-VT is described according to the most proximal thrombosed venous segment. This description distinguishes upper extremity deep vein thrombosis (UE-DVT) from upper extremity superficial vein thrombosis (UE-SVT). The innominate vein, the internal jugular vein, the subclavian vein and the axillary vein belong to the deep proximal venous network. The humeral (or brachial) vein, ulnar veins and radial veins belong to the deep distal network. Brachial and antecubital cephalic veins, brachial and antecubital basilic veins, dorsal veins of the hand and their collaterals belong to the superficial network.

The included patients had an acute UE-VT episode diagnosed by Doppler ultrasound. If the patient had multiple episodes of UE-VT distinct in time, each episode was included.

Pulmonary embolism (PE) diagnosed by thoracic angiogram or ventilated perfusion scan in the 14 days prior to UE-VT diagnosis or within 90 days of diagnosis, and all deaths within 90 days of diagnosis were analyzed.

Based on the patient’s computerized care record, a standardized collection chart made it possible to evaluate the demographic characteristics of the patients, the presence or absence of factors favoring thrombosis, the indication of the Doppler ultrasound and the clinical signs at diagnosis, the characteristics of thrombosis, as well as the occurrence of PE and/or death. Patients for whom the medical record was incomplete were excluded. Isolated superior vena cava thrombosis were excluded. Episodes of recurrence or extension of thrombosis already diagnosed before January 1, 2015 were also excluded.

The study was approved by the “Groupe Nantais d’Éthique dans le Domaine de la Santé” (GNEDS), the ethics committee of the Nantes university hospital, and complied with the requirements of the “Commission Nationale de l’Informatique et des Libertés”, in accordance with current French legislation.

Continuous data are presented as the means ± standard deviation or, for non-normal distributions, as medians with minimum and maximum. Categorical data are given as count and percentage. Continuous data were compared with the use of the Student’s test or Mann-Whitney test; Chi-square test or Fischer’s exact test were used for comparison of categorical data. All P values are two-sided; P < .05 indicated a statistically significant difference, no correction for multiple comparisons. All statistical analyses were performed using Prism6 (San Diego).

3. Results

Seven hundred and fifty-five UE-VT were included (Fig. 1) among which 427 (56.6%) UE-DVT and 328 (43.4%) UE-SVT.

Patients were included in a university hospital, consisting of an emergency department (376,908 admissions during the period from January 1, 2015 to December 31, 2017), 1,021 hospitalization beds, 568 surgical beds (138,990 surgeries over the studied period) and 155 intensive care unit beds. Also during this period, 1824 PICC LINE were inserted, 45 MID LINE, 1172 PM and 1830 coronaryography were performed and 1830 patients were dialyzed. There were also 12501 births. During the analyzed period, 1988 venous Doppler of the upper limb were performed, 62 patients were excluded due to insufficient information in the medical file and 735 UE-VT were diagnosed (38% positive tests).

The median age of UE-VT patients was 59 years [12 days-95 years]; 472 were men (61.2%), respectively 61.8% (n = 611) had a single UE-VT; 8.3% (n = 56) had 2; 0.9% (n = 6) had 3; 0.1% (n = 1) had 4 and 0.3% (n = 2) had 5.

The clinical signs found at the time of diagnosis are as described in Table 1. Their presence was very different depending on whether it was a UE-DVT or a UE-SVT except for catheter dysfunction, purulent flow and edema, which were present in the same proportions for UE-DVT and UE-SVT. A superior vena cava syndrome was found in 3.5% (n = 15) cases of UE-DVT.

Eighty UE-VT (10.6%) were asymptomatic. In these cases, the reason for performing the Doppler ultrasound was: systemic identification before the placement of a venous device in patients with history of central catheter placement (42.5%, n = 34); accidental discovery of a suspicious image of
UE-VT on CT-scan (37.5%, n = 30); after failure of catheter placement (15.0%, n = 12); in the investigation of PE (3.8%, n = 3) and thrombosis testing for heparin-induced thrombocytopenia (HIT) (1.3%, n = 1).

At diagnosis of UE-VT, hematologic or progressive solid cancer was noted in 49% of cases (n = 370). Among patients with UE-VT, 33.1% (n = 250) had hematological malignancy and 15.9% (n = 120) had solid cancer. The different types of neoplasia and the differences between UE-DVT and UE-SVT are presented in Table 2: acute leukemia was present in 14.4% of UE-VT cases (n = 109), lymphoma in 10.5% of UE-VT cases (n = 79), colonic or gynecologic neoplasia in 3.4% of UE-VT cases (n = 26) and pulmonary neoplasia in 2.9% of UE-VT cases (n = 22).

UE-VT were associated with specific clinical settings which are presented in Table 2. A systemic inflammatory or infectious context was found in 40.8% of UE-VT cases (n = 308); kidney failure in 9.7% (n = 73); arteriovenous fistula thrombosis (AVF) in 2.1% (n = 16); thoracic outlet syndrome (TOS) in 1.7% (n = 13); obesity in 1.6% (n = 12); an APLS in 1.2% (n = 9) and a local infection not related to endovenous device in 1.1% (n = 8).

Shoulder surgery was found in one case of UE-DVT (0.1% of UE-VT) and two cases of arteriovenous malformation of the upper extremity resulted in 2 UE-SVT (0.3% UE-VT). Concerning inherited bleeding disorders, only one UE-DVT in a context of antithrombin deficiency as well as a UE-DVT and a UE-SVT linked to a heterozygous factor V Leiden mutation have been identified. No UE-VT occurring in the context of estrogen treatment (pill, medically-assisted procreation, menopausal hormone replacement therapy) has been identified; 2 UE-DVT and 16 UE-SVT were reported during periods of pregnancy or postpartum.

Six hundred and fifty-one thrombosis (86.2%) were associated with the presence of endovenous device including 29.1% (n = 220) of PICC LINE; 27.4% (n = 207) of peripheral venous catheters (PVC); 8.7% (n = 66) of implantable ports; 4.8% (n = 36) of dialysis catheters; 2.4% (n = 18) of MID LINE. The 75 thrombosis on CVC were exclusively UE-DVT and the same finding was made for Pace-Maker (PM) or implantable cardioverter defibrillator (ICD) thrombosis. New UE-VT (1.4%) were associated with other endovenous devices: extracorporeal membrane oxygenation.
One hundred and four thrombosis were not catheter-related (13.8%). The diseases and specificities associated with these thrombosis were: infectious or inflammatory context (n=26; 25%), solid neoplasia (n=25; 24%), haematological malignancy (n=17; 16.3%), renal failure (n=17, 16.3%), arterial catheter implanted in radial vein (n=1), and intravenous drug abuse context (n=4).

The topographic distribution of UE-VT is described in the Table 3. The median number of thrombosed venous segments was 1. The maximum number of thrombosed segments was 9. In more than one out of two cases (n=429) the thrombus length at diagnosis was not described; the median length of the UE-VT was 5 cm, the maximum length 49 cm and the minimum length 0.5 cm. UE-DVT were shorter than UE-SVT, with a median length of 2.7 cm versus 8 cm for UE-SVT (P<.0001).

The topographic distribution of UE-VT is described in the Table 3. The median number of thrombosed venous segments was 1. The maximum number of thrombosed segments was 9.

### Table 3

| Topography of UE-VT | n = 1315 | 100% |
|---------------------|----------|------|
| Deep                | 748      | 56.9%|
| Proximal            | 614      | 46.7%|
| Internal jugular vein| 171     | 13.0%|
| Innominate vein     | 135      | 10.7%|
| Subclavian vein     | 162      | 12.3%|
| Axillary vein       | 146      | 11.1%|
| Distal              | 134      | 10.2%|
| Humeral vein        | 127      | 9.7% |
| Ulnar vein          | 2        | 0.2% |
| Radial vein         | 5        | 0.4% |
| Superficial         | 567      | 43.1%|
| Brachial            | 337      | 25.6%|
| Cephalic brachial vein| 117   | 8.9% |
| Basilar brachial vein| 220     | 16.7%|
| Antebrachial and hands | 230  | 17.5%|
| Cephalic antebrachial vein| 160  | 12.2%|
| Basilar antebrachial vein| 54   | 4.1% |
| Dorsal veins of the hands | 16  | 1.2% |

UE-VT = upper extremity vein thrombosis.
4.1. Etiologies of UE-VT

UE-DVT or UE-SVT are associated with the presence of endovenous material in more than 85% of cases. The most commonly found devices are PICC LINE, followed by PVC, CVC and implantable ports. These proportions seem to be related to the number of patients carrying each of these devices in our hospital.

CVC and more specifically PICC LINE would be a major risk factor for UE-VT. Winters et al showed that the use of a central venous catheter increased the risk of UE-VT by 14-fold, but without increasing the risk of PE.$^{[4]}$ According to old data, PM appeared as the most thrombogenic devices (23% risk of developing thrombosis after exposure)$^{[19]}$ while the risk of developing UE-VT after laying a PICC LINE would be between 2.5 and 9%.$^{[20,21]}

Venous thrombosis occurs in specific clinical settings with the presence of solid cancer or hematologic disease in almost every other case, comparable to previous studies which found between 35 and 67% of UE-VT related to active neoplasia.$^{[16,18,22]}

The majority of UE-VT found in our study is of secondary origin. In addition to the presence of a catheter or active neoplasia, the most frequently found contributing factor was a systemic inflammatory or infectious context. This situation was found in more than 40% of UE-VT cases.

Little described in the literature, hepatogastro-intestinal diseases such as Crohn disease, hepatic cirrhosis, peptic ulcer, esophagitis and pancreatitis were in our study frequently found as associated with UE-VT. It is not possible to definitively determine whether this high rate was related to the pathologies themselves or to their treatments.

In rare cases, thrombosis were related to intravenous corticosteroid therapy or hypercorticism, 0.8% in this study: this can be explained by the plasma increase of coagulation and fibrinogen during exposure to high levels of endogenous or exogenous corticosteroids.$^{[23]}

More rarely, in the absence of a major thrombotic risk factor, UE-VT may reveal Paget-Schroetter syndrome (effort thrombosis) or TOS. These are axillary or subclavian venous thrombosis that occur during repetitive efforts of the upper extremities or during an effort in generally male subjects under age 30, with an incidence of 1/100 000 patient-year.$^{[2,24]}$ TOS with cervical rib, congenital fibrous band, scalene hypertrophy or abnormal insertion of the costoclavicular ligament associated with repetitive trauma of the subclavian vein endothelium are key factors in initiating thrombosis and its progression. Intense muscular arm activity is reported in approximately 25% of patients and is associated with twice the risk of primary UE-VT.$^{[25–28]}$ According to Lechner et al, 7% of UE-VT are related to TOS$^{[29]}$ compared to only 1.7% in our study.

4.2. Difference between UE-SVT and UE-DVT

Implantation of endovenous device in the superficial veins is progressing with the use of PICC LINE and MID LINE. There is very little research on UE-SVT. Yet, it occurs in particular contexts of hospitalization with peripheral or central venous route placement. They have specific clinical characteristics with more frequent presence of pains, indurated cords and local erythema; unlike UE-DVT which are more often asymptomatic or revealed by collateral circulation, superior vena cava syndrome or suspected catheter infection.$^{[30]}$ The presence of an upper vena cava syndrome, a collateral venous circulation, a central catheter placement failure have positive predictive values for a UE-DVT between 66.7 and 100%, whereas for the UE-SVT, the positive predictive value goes from 60.8 to 85.7% for the presence respectively of an erythema or an indurated cord.$^{[30]}$

UE-VT treatments are poorly codified, as are the evolution or predictors of post-thrombotic syndrome in the upper extremity. Unlike the UE-DVT where the objectives of the anticoagulant treatment are mainly the reduction of the incidence of pulmonary embolism and post thrombotic syndrome, the main challenge for the UE-SVT is the preservation of the venous capital. The use of peripheral venous catheters is trivialized, yet more than a quarter of UE-VT are related to PVC and the impact of these UE-SVT is underestimated in particular for patients with chronic diseases requiring intravenous treatment and for whom the residual occlusion of these veins alters the quality of life and delays the administration of treatments. To specify their evolution, prospective studies are necessary.

4.3. Difference between UE-VT and LE-VT

The diseases and contexts associated with the occurrence of UE-VT and LE-VT are different: the discovery of an occult cancer in the 12 months following the UE-VT diagnosis is 23% compared to only 11% after the diagnosis of LE-VT$^{[31]}$ and biological thrombophilia is found in 55.3% of LE-VT cases compared with only 34.2% of UE-VT cases.$^{[12]}$ For lower extremity superficial venous thrombosis (LE-SVT), the most common causes are obesity and varicose veins.$^{[32]}$ In the upper extremity the occurrence of venous thrombosis is mainly related to the presence of a catheter and a neoplasia.$^{[16,18,22]}

In our study, 4% of UE-VT were complicated by a PE. This rate is comparable to two American studies of 300 and 546 patients presenting only UE-DVT, respectively 2 and 5%.$^{[13,34]}$ In comparison with lower extremity deep venous thrombosis (LE-DVT), UE-DVT are less complicated with pulmonary embolism (5.4% versus 27.9%); however UE-VT mortality rate is higher than that of LE-DVT (7.6% versus 4.2%).$^{[33]}$ In our study, a minority of patients (6.4%) died of a cause directly related to the occurrence of UE-VT. The remaining deaths were overwhelmingly (93.6%) related to the progression of an underlying disease or multiple comorbidities. This result is consistent with studies showing that the occurrence of UE-VT is not associated with a major risk of death, but that it is the co-morbidities associated with the occurrence of UE-VT that explain the significant mortality rate in the aftermath of UE-VT diagnosis.$^{[16–38]}$

4.4. Limitations

The limits of this work come from its lack of completeness and its retrospective nature. The frequency of asymptomatic venous thrombosis is probably underestimated since the patients were identified from the realization of a doppler ultrasound which was in the vast majority of cases performed due to symptoms especially in the EU-VT. In addition, a search for PE was not performed systematically.

5. Conclusion

UE-VT occur most often in specific clinical settings: hematological malignancy, solid neoplasia or progressive infection. For UE-DVT as for UE-SVT, endovenous device is present most of the
time (in 85.5 and 87.2% of cases respectively). Edema is the most commonly found clinical sign but does not point to a deep or superficial localization. Other clinical manifestations such as fever, pain, erythema or an indurated cord are frequently found. However a significant proportion of UE-VT is asymptomatic, in particular the UE-DVT.

UE-DVT are rarely complicated by PE (4%) and even more rarely in UE-SVT (0.9%). UE-VT high mortality rate is related to the evolution of the underlying pathology and not to the evolution of VTE.

The UE-VT interest in about half of the cases the superficial network. The most frequently affected segments are the jugular veins, the innominate veins and the cephalic and brachial basilic veins.

The management of UE-VT is poorly codified and requires specific prospective studies to define the anticoagulation strategy and duration as well as to assess the post-thrombotic syndrome.

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