Central venous thrombosis and thrombophilia in cystic fibrosis: A prospective study

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Abbreviations: CF, cystic fibrosis; TIVAD, totally implantable vascular access device.
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Abstract

Background and Aims: Catheter venous thrombosis may result in life-threatening embolic complications. Recently, a thrombophilic tendency was described in cystic fibrosis (CF), the significance of which remains unclear. The aims of this study were to (1) document the frequency of catheter venous thrombosis detected by colour-Doppler-ultrasound (Doppler-US), (2) assess genetic and acquired thrombophilia risk factors for catheter venous thrombosis and hypercoagulability status and (3) provide recommendations on laboratory screening when considering insertion of a totally implantable vascular access device (TIVAD) in CF patients. 

Methods: We designed a multicentre prospective study in patients selected at the time of catheter insertion. Doppler-US was scheduled at 1 and 6 months after insertion and before insertion in case of a previous central line. Blood samplings were drawn at insertion and at 1 and 6 months later.

Results: One-hundred patients received a TIVAD and 90 completed the 6-month study. Prevalence of thrombophilia abnormalities and hypercoagulability was found in 50% of the cohorts. Conversely, catheter venous thrombosis frequency was low (6.6%).

Conclusion: Our data do not support biological screening at the time of a TIVAD insertion. We emphasise the contribution of a medical history of venous thromboembolism and prospective Doppler-US for identifying asymptomatic catheter venous thrombosis to select patients who may benefit from biological screening and possible anticoagulant therapy.

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Keywords: Cystic fibrosis; Thrombosis; Thrombophilia

1. Introduction

Respiratory degradation, closely related to recurrent pulmonary infections, remains the main cause of morbidity and mortality in patients with cystic fibrosis (CF). Thus, patients must undergo frequent antibiotic treatments that – depending on the pathogen involved – are often delivered intravenously. Increasing problems with peripheral venous access may indicate implantation of central venous access devices. Totally implantable vascular devices (TIVADs) were initially introduced in clinical oncology practice [1] and, more recently, in CF patients [2]. They are usually well tolerated for long periods. Nevertheless, they may be associated with numerous complications [3] and, in large retrospective studies, symptomatic catheter venous thrombosis rates ranged from 3.5% to 16.4% [4,5] with clinical reports of pulmonary embolism [6].

The thrombogenic role of the indwelling catheter has been studied mainly in cancer patients. In these patients, the incidence of clinically symptomatic deep venous thrombosis has been reported in up to 9.3% of adults [7] and 14% of paediatric cohorts [8]. In prospective studies, the incidence of catheter venous thrombosis detected through venography was 58% in adults [9] and 50% in children [10] in small cohorts. Verso et al. [11] reported the main pathogenic factors for TIVAD-catheter venous thrombosis: vessel injury caused by the procedure of insertion, venous stasis and catheter tip position, previous TIVAD, catheter infections, cancer-related hypercoagulability and thrombophilic molecular abnormalities. Concerning the delay in catheter venous thrombosis occurrence after TIVAD insertion and detection by Doppler-ultrasound (Doppler-US), two prospective studies in cancer patients found that catheter venous thrombosis was an early complication, occurring between 8 and 30 days [12] or after a mean delay of 42 days [13].

One-hundred patients received a TIVAD and 90 completed the 6-month study. Prevalence of thrombophilia abnormalities and hypercoagulability was found in 50% of the cohorts. Conversely, catheter venous thrombosis frequency was low (6.6%).

Conclusion: Our data do not support biological screening at the time of a TIVAD insertion. We emphasise the contribution of a medical history of venous thromboembolism and prospective Doppler-US for identifying asymptomatic catheter venous thrombosis to select patients who may benefit from biological screening and possible anticoagulant therapy.

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1.1. Patients and methods

We conducted a prospective study in 41 paediatric and adult CF centres that agreed to participate. Patients who were regularly followed up at one of these centres received comprehensive information on the study when TIVAD insertion was planned. The study was approved by the ethical committee IRB APHP, N° CCP0511153 and was registered on www.clinicaltrials.gov: NCT 00244270. Written informed consent form was obtained from all adults or from both parents of children at inclusion (initial visit). Blood sample (12 mL) was drawn and analysed locally within 4 h. C-reactive protein (>15 mg/L) and fibrinogen (>4.5 g/L) served as markers of inflammatory activity. Prothrombin time (reference value >80%) was chosen as a global test of coagulation to assess liver function and vitamin K status. Thrombophilia screening included: (i) genetic factors: protein C and protein S abnormal if ≤70% and ≤60%, respectively, in the absence of inflammatory markers and vitamin K deficiency [19,20], antithrombin abnormal if <79% in the absence of cirrhosis [19], identification of factor II G20210A gene mutation or factor V Leiden mutation; (ii) acquired factors: cardioliop antibodies tested by enzyme-linked immunosorbent assay (ELISA) (IgG
or IgM >40 IU/ml [21] in the absence of inflammatory markers). Hypercoagulability status was defined by increased D-dimers >530 ng/ml. We defined three groups of patients: subjects presenting thrombophilic abnormalities (group A), hypercoagulability status (group B) and no identified abnormality (group C). At initial visit, a Doppler-US was performed prior to TIVAD insertion in case of previous central lines. Vessel exploration performed on the body side of previous TIVAD insertion included jugular, axillary and subclavian, innominate and superior caval veins. The main criteria for establishing the diagnosis of catheter venous thrombosis on initial visit Doppler-US were visualisation of mural thrombi or incompressibility of veins, absence of spontaneous flow or presence of turbulent blood flow, absence of transmission of cardiac pulsatility and visualisation of increased venous collaterals [11]. In case of difficult diagnostic situations, according to the current practice in each centre, contrast venography or magnetic resonance was performed. The following data were collected at the time of TIVAD insertion: demographic data, cystic fibrosis transmembrane conductance regulator (CFTR) genotype, personal and first-degree relative thromboembolism history, co-morbidity factors (CF-related diabetes (CFRD), cirrhosis), patient’s weight and height to calculate body mass index (BMI), z score in children and absolute values in adults [22], most recent data on lung function (forced expiratory volume in 1 s (FEV₁)) using published reference ranges in children and adults [23,24] and sputum microbiology status. Concerning the TIVAD procedure, data were collected on the operator (anaesthetist or surgeon), location of the catheterised vessel, modality of catheter insertion (denudation or puncture), catheter material (polyurethane, silicone), blood sampling through the catheter and maintenance of TIVAD current practice in the CF centre (none, counterpressure, regular heparin). At insertion, a chest X-ray was performed to confirm the correct position of the distal extremity of the catheter. One month (follow-up visit 1: 30–45 days) and 6 months later (follow-up visit 2: 6 months ± 15 days), the patient had a complete re-evaluation, including data on TIVAD complications, Doppler-US, blood sampling for acquired thrombophilia factors and hypercoagulability profile. A second chest X-ray was performed at the end of the study to re-evaluate the catheter tip position.

In case of clinical symptoms of catheter venous thrombosis, the patient was asked to come immediately to the CF centre for a complete assessment.

1.2. Statistical analysis

Qualitative variables were described as numbers and/or percentages and quantitative variables as medians with their quartiles (Q1–Q3). Differences were tested by the chi-square test and Fischer’s exact test to compare proportions across categories and by non-parametric Kruskal–Wallis’s test for quantitative variables. Statistical analyses were performed with SAS 9.3 (Cary, NC, USA) software for PC computer. All tests were bilateral and statistical significance was set at \( p < 0.05 \).

2. Results

2.1. Study population

Initial visits involved 104 patients, who were regularly followed at 28 CF centres that recruited 1 to 20 patients per centre. Informed consent withdrawal signatures occurred in three cases before TIVAD insertion. At the time of TIVAD insertion, one patient with an uncontrolled catheter infection could not be recruited. Thus, 100 patients underwent TIVAD insertion between January 2006 and March 2009. They included 65 adults and 35 children, 60 females and 40 males, with a median age of 19.8 (15.5–27.2) years. The genotype was F508del/F508del in 44%, F508del/other in 42% and unknown for at least one allele in 15%. Ninety patients completed the 6-month study (two deaths related to pulmonary deterioration, one consent withdrawal, three TIVAD removals (lung transplantation, catheter occlusion and palpitations) and, lastly, four patients who did not undergo Doppler-US at the second follow-up visit).

2.2. Doppler-US and catheter venous thrombosis identification

Among the 44 patients who had had a previous central line, a Doppler-US was performed prior to TIVAD insertion at initial visit and a catheter venous thrombosis was identified in four (4/44, 9.1%). Radiographic images were consistent with sequelae of long-standing obstruction including vessel collateralisation, organised thrombus and parietal thickness. In one patient, diagnosis of catheter venous thrombosis had to be confirmed by magnetic resonance.

Then during the 6-month study, a catheter venous thrombosis was reported in two additional patients. One was symptomatic with neck pain at the first follow-up visit, while the other, asymptomatic, was diagnosed at the second follow-up visit. In the first patient, Doppler-US showed a localised occluded right jugular vein with dilatation of the external and anterior jugular veins without collateralisation; in the second patient, it showed extensive thrombus partially occluding the innominate vein with stasis but no collateralisation. Hence, the frequency of catheter venous thrombosis diagnosed based on symptoms or detected by Doppler-US was 6/90 (6.6%).

2.3. Thrombophilia and hypercoagulability abnormalities

Thrombophilia screening for inherited and acquired risk factors for catheter venous thrombosis identified abnormalities in up to 17/100 (17%) patients (Table 1). These abnormalities included protein C deficiency (1/100, 1%), protein S deficiency (3/100, 3%), antithrombin deficiency (2/100, 2%), factor V Leiden heterozygosity (4/100, 4%), prothrombin G20210A heterozygosity (2/100, 2%) and combined abnormalities in three patients (3%). None of the patients carrying low values of antithrombin, protein C or protein S presented liver disease, vitamin K deficiency or increased inflammatory markers. Increased IgG anticardiolipin was found for two patients (2%).
Double heterozygosity prothrombin
Protein S deficiency + antithrombin
Thrombophilia abnormalities

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>22.9 [15.7; 28.1]</th>
<th>22.2 [17.1; 28.2]</th>
<th>19.1 [14.3; 26.2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 % &lt;18y</td>
<td>46.2 [27.7; 88.7]</td>
<td>68.2 [41.1; 95.0]</td>
<td>57.2 [51.4; 75.1]</td>
</tr>
<tr>
<td>≥18y</td>
<td>35.4 [26.3; 52.8]</td>
<td>35.8 [27.4; 50.4]</td>
<td>37.0 [23.0; 52.2]</td>
</tr>
<tr>
<td>Median BMI &lt;18y (z-score)</td>
<td>-1.0 [-1.5; -0.9]</td>
<td>-1.2 [-2.1; 0.7]</td>
<td>-1.1 [-1.6; 0.1]</td>
</tr>
<tr>
<td>≥18y</td>
<td>19.2 [17.6; 20.6]</td>
<td>18.8 [17.6; 19.9]</td>
<td>18.9 [17.9; 20.7]</td>
</tr>
<tr>
<td>Thromboembolism history, personal or first-degree, N (%)</td>
<td>4 (24)</td>
<td>5 (16)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Median C-reactive protein (mg/L)</td>
<td>10 [6;16]</td>
<td>23 [10; 52]</td>
<td>13 [5;31]</td>
</tr>
<tr>
<td>Median fibrinogen (g/L)</td>
<td>4.2 [3.5; 5.6]</td>
<td>5.0 [4.4; 5.9]</td>
<td>4.2 [3.5; 5.6]</td>
</tr>
<tr>
<td>Cirrhosis, N (%)</td>
<td>2 (12)</td>
<td>4 (12)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>6 (35)</td>
<td>8 (24)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa, N (%)</td>
<td>15 (88)</td>
<td>27 (82)</td>
<td>37 (94)</td>
</tr>
<tr>
<td>Burkholderia cepacia, N (%)</td>
<td>0</td>
<td>1 (3)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Oral contraceptives, N (%)</td>
<td>3 (0/30)</td>
<td>8 (19/42)</td>
<td>8 (30/27)</td>
</tr>
<tr>
<td>Previous catheter, N (%)</td>
<td>10 (59)</td>
<td>11 (34)</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Vessel: jugular/subclavian (%)</td>
<td>63 (13)</td>
<td>58 (26)</td>
<td>50 (37)</td>
</tr>
<tr>
<td>Catheter material (%): polyurethane/silicone</td>
<td>19 (81)</td>
<td>25 (75)</td>
<td>35 (65)</td>
</tr>
<tr>
<td>Blood sampling, N (%)</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>TIVAD maintenance, N (%)</td>
<td>6 (35)</td>
<td>9 (26)</td>
<td>24 (44)</td>
</tr>
</tbody>
</table>

Table 2
Demographic data, acquired risk factors for CVT in CF patients carrying a TIVAD: group A (TB abnormalities), group B (HC abnormalities) and group C (without TB or HC abnormalities).

Table 1
Thrombophilia and HC rates (%) in 100 CF patients carrying a TIVAD and expected abnormality rates in a healthy population [26,27].

Table 1
Thrombophilia and HC rates (%) in 100 CF patients carrying a TIVAD and expected abnormality rates in a healthy population [26,27].

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Expected abnormality rate in healthy population (%) [26,27]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C deficiency, N(%)</td>
<td>(0.2–0.4)</td>
</tr>
<tr>
<td>Protein S deficiency, N(%)</td>
<td>(0.13–0.3)</td>
</tr>
<tr>
<td>Antithrombin deficiency, N(%)</td>
<td>(0.02–0.16)</td>
</tr>
<tr>
<td>Factor V Leiden mutation, N(%)</td>
<td>(4.8)</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation, N(%)</td>
<td>(2)</td>
</tr>
</tbody>
</table>

Considering hypercoagulability status, increased D-dimers were found in 38 (38%) patients. Five patients had both thrombophilic and hypercoagulability risk factors for catheter venous thrombosis.

Data on age, lung function, nutritional status, medical history of thromboembolism, modalities of TIVAD insertion and maintenance were not different in the three groups. Likewise, the prevalence of inflammatory markers (e.g., C-reactive protein, fibrinogen), CF co-morbidity factors, respiratory colonisation with Pseudomonas aeruginosa, Burkholderia cepacia, oral contraceptives and previous central catheter (Table 2) was also not different.

2.4. Description of patients with central venous thrombosis

Six patients presented catheter venous thrombosis (Table 3). In asymptomatic patients, five cases of catheter venous thrombosis was detected by Doppler-US. In four cases (two adults and two adolescents), catheter venous thrombosis was found at initial Doppler-US performed because of a previous central line (n = 44). A previous history of catheter venous thrombosis was identified in two patients. Inherited thrombophilia abnormalities were present in both adults (antithrombin deficiency, double heterozygosity factor V Leiden + prothrombin G20210A); the female patient had combined hypercoagulability status with other risk factors (diabetes, oral contraceptive use). Conversely, both children had normal thrombophilia profiles; the male adolescent had very severe cirrhosis with hypercoagulability status. For all four patients, subsequent TIVAD had to be inserted in the contralateral catheter venous thrombosis body side. Long-term anticoagulant therapy was prescribed in both adults, in agreement with the local haematology team. Neither of the two adolescents was started on anticoagulant therapy, because of an increased bleeding risk related to severe liver disease in the male and because of normal thrombophilic and hypercoagulability profiles in the female. All four patients had an uneventful clinical course, with normal Doppler-US exploration during the entire prospective study period. Three cases remained clinically asymptomatic for 29–40 months but the fourth patient died several weeks after the second follow-up visit from end-stage cirrhosis.

During the study period, catheter venous thrombosis was identified in two other adults, one at the first follow-up visit...
with hypercoagulability status and one at the second follow-up visit with cirrhosis as a risk factor for catheter venous thrombosis. None of these two adults presented abnormal thrombophilia profiles and their C-reactive protein concentrations were 27 and 12 mg/L. TIVADs were not removed and both patients received long-term anticoagulant therapy with clinical uneventful follow-up, thereby preventing catheter venous thrombosis recurrence.

3. Discussion

To our knowledge, this is the first prospective multicentre analysis to evaluate the frequency of catheter venous thrombosis and to study markers of thrombophilic and hypercoagulability status in CF patients carrying a TIVAD. We studied a large cohort of 100 patients who had been screened via a standardised panel of thrombophilia risk factors. Catheter venous thrombosis detection by Doppler-US was performed prospectively and longitudinally. We found a very high rate of thrombophilia and hypercoagulability status, attaining 50%, but a very low frequency of catheter venous thrombosis (6/90, 6.6%). Rates of catheter venous thrombosis were close to this value in adult (4/65, 6.1%) and paediatric patients (2/35, 5.7%). We may have underestimated the prevalence of asymptomatic catheter venous thrombosis by Doppler-US detection, compared with contrast venography, which is considered the gold standard in detecting catheter venous thrombosis. However, repeated procedures of this technique are not applicable for surveillance because of invasiveness and cost [11]. Reported data regarding the diagnostic value of colour-Doppler-US compared with venography demonstrated excellent sensitivity and specificity for diagnosis of catheter venous thrombosis in axillary-subclavian veins (95%) and jugular veins (100%) [24] but were less reliable for innominate and superior caval veins [25]. To minimise variability in Doppler-US analysis, a referring radiologist was designated at each CF centre. As regards the low incidence of catheter venous thrombosis, our study enabled only a descriptive analysis of data, hampering statistical analysis of catheter venous thrombosis risk factors.

Inherited thrombophilia factors for venous thrombosis in adults [26] and children [27] fall mainly into two categories: hereditary antithrombin, protein C or S deficiencies, and factor V Leiden or prothrombin G20210A mutations. We found an unusually high prevalence of these abnormalities compared to healthy populations [26,27], but this was in agreement with previous publications on thrombophilia in CF [14–17]. In our study, the laboratory thrombophilic panel did not assess factors identified as hypothetic risk factors for thrombosis in the general population and possibly in CF patients such as a rise in factor VIII [16] or hyperhomocysteinaemia. Given the current state of our knowledge, the significance of these abnormalities remains questionable [28].

Previous retrospective studies in CF reported clinically symptomatic catheter venous thrombosis rates varying from 3.5% [4] to 16.4% [5]. In asymptomatic oncology patients, venographic catheter venous thrombosis incidence reached 50% of adult and paediatric cohorts [9,10]. None of those studies evaluated thrombophilic risk factors for catheter venous thrombosis.

If we consider the 41 CF patients reported in the literature (Table 4) carrying a TIVAD and who were evaluated for a variety of heterogeneous thrombophilic risk factors, asymptomatic catheter venous thrombosis was identified in four cases (9.7%) and thrombophilic abnormality was identified in two of these (50%); by contrast, the prevalence of thrombophilia was 16% (6/37) in patients who did not present symptomatic catheter venous thrombosis. However, considering the small number of patients included, the diversity of thrombophilic factors evaluated in those three cohorts and detection of asymptomatic catheter venous thrombosis only, these data do not enable definitive conclusions or a comparison with our study.

The incidence of inherited thrombophilic abnormalities in the healthy population is low, ranging from 0.2% for antithrombin deficiency to 4.8% for factor V Leiden. The significance of inherited thrombophilia, acquired thrombophilia abnormalities and hypercoagulability status is not clear, as it is widely recognised that many individuals who carry these defects remain asymptomatic. Furthermore, at least 50% of

Table 3

<table>
<thead>
<tr>
<th>Description of patients with CVT.</th>
<th>25,2, M</th>
<th>23, F</th>
<th>17, M</th>
<th>14.4, F</th>
<th>24.6, M</th>
<th>27.2, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time at CVT diagnosis (initial, follow-up 1, follow-up 2)</td>
<td>initial</td>
<td>initial</td>
<td>initial</td>
<td>initial</td>
<td>follow-up 1</td>
<td>follow-up 2</td>
</tr>
<tr>
<td>Asymptomatic (A) or symptomatic (S)</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>S</td>
<td>A</td>
</tr>
<tr>
<td>Number of previous central catheters</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Personal or first-degree relative history of venous thrombosis</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Inherited TB abnormalities</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Increased D-dimers</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Diabetes</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>NA *</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Catheter material: polyurethane/silicone</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>TIVAD removal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Clinical follow-up (months)</td>
<td>30</td>
<td>29</td>
<td>28</td>
<td>40</td>
<td>31</td>
<td>17</td>
</tr>
</tbody>
</table>

* NA: not applicable.
person with a history of thrombosis have no identified defect [30]. Venous thromboembolism is a multifactor disease and may result from the simultaneous conjunction of several genetic or acquired risk factors. It has been reported that, in the absence of other acquired risk factors, the relative risk of thromboembolism for factor V Leiden varies from 3.7 to 7.9 and for prothrombin G20210 from 1.9 to 2.8 [31]. However, the importance of detecting thrombophilic abnormalities is supported by the increased risk of venous thromboembolism, especially in the presence of additional risk factors such as factor VIII [16] or activated platelets [17] (though many affected individuals remain asymptomatic). It is generally accepted, at least in adults [27], that antithrombin deficiency, associated inherited thrombophilia factors and homozygosity for factor V Leiden represent the most severe relative risk factors for recurrent venous thrombosis, well ahead of protein S or C deficiencies [29]. The role of these abnormalities in childhood thrombosis has not yet been established [32].

A potential weakness of this study is that inherited thrombophilic abnormalities were not retested, because this was not scheduled in the protocol. This control, which separates congenital from acquired or possibly temporary risk factors for thrombophilia, enables avoiding mislabelling of patients as thrombophilic. In the literature involving CF patients, Barker et al. [14] identified a thrombophilic state in 53% of 66 patients, which persisted after resampling in 37/38. Barker et al. [14] identified a thrombophilic state in 53% of 66 patients; when retesting after a mean period of 3 years, they confirmed protein S deficiency in 86%, but protein C and anticardiolipin antibodies demonstrated poor reproducibility. Williams et al. [18], in a CF paediatric cohort, demonstrated 10–20% consistency for protein S and C deficiencies.

Because many other acquired factors [11], in addition to the presence of the indwelling catheter [33], may promote thrombophilia and possibly catheter venous thrombosis, we collected data on personal and first-degree relative history of thromboembolism, oral contraceptives use and those most relevant to CF: cirrhosis, diabetes, Pseudomonas aeruginosa and Burkholderia cepacia infections. We found an equal prevalence of these factors in the three studied groups.

More specifically, among the 12 subjects having a personal or first-degree relative history of venous thrombosis and who have been screened for thrombophilia and hypercoagulability status, a thrombophilia profile was identified in 75% (9/12). Among them, two patients had asymptomatic catheter venous thrombosis diagnosed during our study (22%). It is crucial to collect a comprehensive medical history on previous venous thrombosis, thus enabling selection of patients who will benefit from biological screening.

Recently, Raffini et al. [34] reported increased risk of catheter venous thrombosis in CF patients carrying Burkholderia cepacia (27% vs. 3.7%). This organism, identified in 7% of our entire cohort, was not carried among those presenting a catheter venous thrombosis.

We confirmed an increased incidence of thrombophilia abnormalities in our cohort, in agreement with previous reports in CF subjects. The consistency between these recent reports suggests that, rather than inherited thrombophilia, there may be a common underlying predisposing factor such as systemic inflammation that in combination with other factors may be responsible. Although thrombophilia abnormalities appear to be a true risk factor for thrombosis in CF patients, the clinical benefit of screening patients as a prelude to catheter or TIVAD insertion remains a subject of debate.

Despite a high incidence of prothrombotic and hypercoagulability risk factors, our prospective study involving a large cohort demonstrated a low prevalence of catheter venous thrombosis. Laboratory thrombophilia screening had contributed little and was poorly predictive for those presenting a catheter venous thrombosis. Thus, in contrast to some authors and based on our data, we cannot recommend including thrombophilic screening prior to catheter insertion for all CF patients. We emphasise the contribution of a medical history of venous thromboembolism and of prospective Doppler-US for all patients carrying a catheter for identifying asymptomatic catheter venous thrombosis, in order to select those who will undergo biological screening. Subsequently, for those presenting positive thromboembolism or biological abnormalities, and for catheter venous thrombosis, the modalities of therapeutic anticoagulation and contraceptive counselling will be defined in cooperation with the haematology department. A better understanding of the role of thrombophilia risk factors for catheter venous thrombosis can be clarified only by comparing the prospective incidence of thrombosis between patients with and without indexes of thrombophilia in larger studies. This will hopefully enable caregivers to make a more accurate
evidence-based assessment for the benefit of individual patients.

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References


