Management of venous thromboembolism. Etiology, diagnosis, prognosis and treatment

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Screening of high factor VIII levels is not recommended in patients with recently diagnosed pulmonary embolism

Pieter W. Kamphuisen, Marije ten Wolde, Esther M.G. Jacobs, Erik F. Ullmann, Maria M.W. Koopman, Harry R. Büller

Factor VIII (FVIII) levels ≥150 IU/dl increase the risk of venous thromboembolism (VTE), are highly prevalent and may be associated with an increased risk of recurrent VTE. Since thrombophilia screening is generally performed in patients with recently diagnosed VTE, FVIII levels measured at that time may be elevated due to an acute phase reaction and do not reflect a reliable value. We investigated whether FVIII levels ≥150 IU/dl measured in patients suspected for pulmonary embolism (PE) were persistent over time and, by measuring C-reactive protein (CRP) levels, to what extent an acute phase reaction was associated with high FVIII levels. Thirty-one patients with objectively confirmed PE and 41 controls who both had FVIII levels ≥150 IU/dl were included for further analysis. FVIII and CRP measurements were repeated after three months. Initially, FVIII levels were not different between patients (means ± SE: 197±1.1 IU/dl) and controls (194±0.8 IU/dl). After three months, FVIII levels clearly decreased, in patients (46 IU/dl (33-60)) and controls (45 IU/dl (95% CI 29-61)) alike. Only 12 (39%) patients with PE had persistently elevated FVIII levels. Most (67%) of these patients had no concurrent disease. The association between CRP and FVIII levels was weak. This study shows that screening of patients with PE for high FVIII levels during admission is not recommended, since most of these patients have transient high FVIII levels due to the thrombotic event. Furthermore, CRP is not a reliable parameter to estimate elevation of the FVIII level due to an acute phase reaction.
Factor VIII activity (FVIII) levels ≥150 IU/dl are associated with an increased risk of venous thromboembolism (VTE) \(^1\). Twenty-five percent of patients with a first episode of venous thrombosis and 11% of the healthy population have these high FVIII levels \(^1\). Furthermore, high FVIII levels may increase the risk of recurrences of thrombosis \(^2\). Routine screening of patients with VTE for high FVIII levels thus seems warranted.

FVIII is an acute phase reactant and may be elevated due to the thrombotic event. High FVIII levels measured in thrombosis patients at least six months after the event, persist over time and are in general not influenced by acute phase reactions \(^3\). Since routine thrombophilia screening is generally performed shortly after the diagnosis of VTE, it is unclear whether measurement of FVIII at that time is reliable. In the acute phase of the thrombosis, inflammatory reactions can influence the FVIII level, and elevated FVIII levels may merely reflect the consequence rather than the cause of the thrombosis.

In the present study we investigated whether FVIII levels ≥150 IU/dl measured in patients suspected for pulmonary embolism (PE) were persistent over time and, by measuring C-reactive protein (CRP) levels, to what extent an acute phase reaction was associated with high FVIII levels.

**Patients and Methods**

The patients and controls included in this study came from two studies, Antelope and Leventas, which were performed between May 1999 and July 2001 in two teaching hospitals in The Netherlands (Amsterdam and Arnhem). Both studies involved consecutive in- and outpatients with a clinical suspicion of acute pulmonary embolism. In all patients FVIII levels were measured during the diagnostic work-up. Patients with FVIII levels ≥150 IU/dl were included in the present study. Patients were excluded if they had received vitamin K antagonists or heparin in a therapeutic dose for more than 24 hours, had already undergone objective testing for venous thromboembolism, were pregnant, younger than 18 years, had an indication for thrombolysis, or if written informed consent was not obtained. The Institutional Review Boards approved the protocol.

The presence of PE was objectively confirmed or excluded by lung scintigraphy, compression ultrasonography of the legs or pulmonary angiography. All patients were followed for three months to record possible thromboembolic events and blood samples were drawn at that time. Patients with a clinical suspicion for pulmonary embolism, excluded by objective testing and by an uneventful 3 month clinical follow-up, served as controls.

Factor VIII:C levels were measured by a one-stage clotting assay. C-reactive protein levels were measured by a sandwich enzyme immunoassay, based on two polyclonal rabbit antibodies against CRP.

For calculations of the mean CRP level, C-reactive protein values were logarithmically transformed.
because the distribution of the values was skewed. Geometric mean concentrations were calculated for both patients and controls. The influence of CRP levels on FVIII levels was calculated by linear regression. Exact 95% confidence intervals were calculated from the binomial distribution (SPSS Inc., Cary, NC, version 10.0).

**Results**

31 patients with PE and 41 controls in whom PE was objectively excluded had FVIII levels ≥150 IU/dl during admission. 29 were men, 43 women. The mean age was 55 years (range 31-84) for patients and 52 years (22-88) for controls. Twenty-five (61%) controls had alternative diagnoses like pneumonia, heart failure or malignancy.

Initially, mean plasma FVIII levels (±SE) were not different between patients with PE (197±1.1 IU/dl) and controls (194±0.8 IU/dl) (Table 1). Three months later, FVIII levels clearly decreased in both groups when compared to the first measurement, with a mean difference of 46 IU/dl (33-60) for patients with PE and (45 IU/dl (95% CI 29-61)) for controls, whereas FVIII levels were the same in patients (150±1.1 IU/dl) and controls (149±1.0 IU/dl). Also the CRP levels clearly decreased after three months in both patients (10.7±1.0 mg/l to 5.0±1.0 mg/l) and controls (12.4±2.2 mg/l to 6.5±1.3 mg/l), without a difference between these two groups.

In order to investigate whether FVIII levels measured at the diagnosis of PE were elevated due to the thrombotic event itself, we looked at the persistence of high FVIII levels in these patients. If FVIII levels were elevated due to an inflammatory response due to PE, FVIII levels should decrease in time. Table 2 shows that in our population 19 (61%) patients with PE and 22 (59%) controls with initially high FVIII levels had lower levels after three months. Consequently, a minority (39%) of patients

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Difference</th>
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<tbody>
<tr>
<td>FVIII t-0 months</td>
<td>197 ± 1.1</td>
<td>194 ± 0.8</td>
<td>ns</td>
</tr>
<tr>
<td>FVIII t-3 months</td>
<td>150 ± 1.1</td>
<td>149 ± 1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>46 (33-60)*</td>
<td>45 (29-61)*</td>
<td></td>
</tr>
<tr>
<td>CRP t-0 months</td>
<td>10.7 ± 1.0</td>
<td>12.4 ± 2.2</td>
<td>ns</td>
</tr>
<tr>
<td>CRP t-3 months</td>
<td>5.0 ± 1.0</td>
<td>6.5 ± 1.3</td>
<td>ns</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>5.8 (3.4-8.1)*</td>
<td>5.8 (0.3-12)*</td>
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*p<0.0001
Table 2. Factor VIII levels as measured three months after the diagnosis or exclusion of pulmonary embolism in patients with initially elevated FVIII levels

<table>
<thead>
<tr>
<th>FVIII (IU/dl)</th>
<th>Cases (n=31)</th>
<th>Controls (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>1 (3%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>100-125</td>
<td>8 (26%)</td>
<td>11 (27%)</td>
</tr>
<tr>
<td>125-150</td>
<td>10 (32%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>≥150</td>
<td>12 (39%)</td>
<td>17 (41%)</td>
</tr>
</tbody>
</table>

with PE had persistently FVIII levels ≥150 IU/dl. Most (67%) of these patients had idiopathic PE without a concurrent disease. Three patients suffered from a malignancy, one was infected with the human immunodeficiency virus (HIV). Of the 17 patients with persistently elevated FVIII without PE, two patients had chronic obstructive pulmonary disease, three patients had heart failure, and two had pneumonia, whereas in 10 patients we found no alternative diagnosis that could explain the clinical picture of these patients.

We analysed the influence of CRP on FVIII levels by linear regression, in order to see whether the acute phase reaction, which increased FVIII levels in the majority of PE patients, was (partially) mediated through CRP levels. Overall the influence of CRP on factor VIII:C levels (IU/dl) was weak in both patients and controls (regression coefficient patients 1.01, 95% CI: 1.00-1.02; regression coefficient controls 1.02, 95% CI: 1.00 to 1.03). After three months, this association remained the same (regression coefficient patients 0.99, 95% CI: 0.98-1.01; regression coefficient controls 1.02, 95% CI: 1.00 to 1.03). About half (54%) of the patients who initially had FVIII levels ≥150 IU/dl in combination with relatively low CRP levels (below the 20th percentile) still had high FVIII levels three months later.

**Discussion**

This study shows that screening patients for high FVIII levels at the diagnosis of PE is not recommended, since most of these patients have transient high FVIII levels due to the thrombotic event. Furthermore, it is difficult to determine which patients will have persistent high FVIII levels. Several studies have shown that elevated factor VIII levels increase the risk of venous thromboembolism, although the precise role of high factor VIII levels in the development of venous thrombosis is still unknown. High levels of factor VIII not only are a risk factor for a first thrombotic event, but also seem to increase the risk of recurrences, which may indicate that sustained anticoagulant treatment is needed in these patients. Considering the high prevalence of high FVIII levels in both patients and controls it may be advisable to include the screening of high factor VIII.
levels in a thrombophilia work-up. Since screening of these patients is mostly performed right after the diagnosis of VTE (and before the start of anticoagulant treatment) a substantial number of elevated FVIII levels measured at that time may be the result of acute phase reactions. In general, there are several factors that can induce a transient or sustained increase in the factor VIII level, like exercise\(^7\), pregnancy, surgery, chronic inflammation, malignancy, liver disease, intravascular hemolysis and renal disease\(^8\). In most conditions, this rise in the FVIII level is caused by inflammatory reactions. Recently it was shown that high FVIII levels decrease after treatment with beta-blockade, suggesting that elevation of the FVIII level could be mediated by the adrenergic system\(^9\).

FVIII levels of patients with VTE are generally not influenced by acute phase reactions when measured at least six months after the event\(^{10}\). It is unknown how long the thrombotic event itself elevates the FVIII level, i.e. through an inflammatory response. We found that only 39% of the patients with an objectively confirmed episode of pulmonary embolism and FVIII levels \(\geq 150\) IU/dl still had elevated FVIII levels three months after the event. This implies that when screening of these patients was performed right after the initial diagnosis, 61% of the patients with PE would have been misdiagnosed for having sustained high FVIII levels as a (potential) cause for the thrombotic event. Consequently, most patients with a recent diagnosis of PE show a transient rise in the FVIII level caused by the thrombotic event itself. Most of the patients with persistent high FVIII levels had idiopathic PE.

The finding that FVIII levels were mainly elevated due to acute phase reactions is further supported by the transient rise of the CRP level, an established acute phase marker. CRP levels clearly decreased after three months when compared to the measurement at the time of the diagnosis in both patients with PE and controls. The association between FVIII and CRP levels however was weak, in the acute phase and three months later. This suggests that systemic inflammation does not increase the levels of CRP and FVIII through shared common pathways. In addition, only half of the patients with initially low CRP levels in combination with high FVIII levels, had persistently high levels three months later. Consequently, it is difficult to determine on the basis of the CRP level which patient will have sustained elevated FVIII levels and to what extent FVIII levels are elevated due to inflammatory responses.

The question remains at what time after the diagnosis of VTE a reliable FVIII level is obtained. Although we only analysed patients with PE, it is logical to assume that acute phase reactions due to venous thrombosis will show the same pattern. From our study we cannot deduce how long acute phase reactions will influence FVIII levels. Reliable FVIII levels may be obtained at least six months after the thrombotic event\(^{11}\), although transient rises due to infections or other inflammatory responses can still occur. To our opinion, at present there are several other drawbacks to recommend
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FVIII measurement for thrombophilia screening, like the intra-individual variation in FVIII levels, the FVIII assay itself, and the uncertainty about the proper cut-off value to be used.

In conclusion, screening of patients with PE for high FVIII levels at the time of the diagnosis is not recommended, since most of these patients have transient high FVIII levels due to the thrombotic event. Furthermore, CRP level is not a reliable parameter to estimate elevation of the FVIII level due to an acute phase reaction.

Acknowledgements
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References