Associations between cardiovascular risk factors, hyper- and hypocoagulability

Rafi, S.

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Chapter 1

Venous thrombo-embolism and aortic calcifications; more evidence on the link between venous and arterial thrombosis

Sara Rafi, Frederiek F van Doormaal, Krijn P van Lienden, Pieter W Kamphuisen, Victor EA Gerdes

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INTRODUCTION

Recently, studies have shown a possible link between venous thromboembolism (VTE) and atherosclerotic disease [1–3]. Although not all studies found an association [4,5], several showed a higher risk of subsequent (fatal and nonfatal) arterial thrombotic events in patients with VTE compared to healthy controls [2,3,6]. This association seemed more pronounced in patients with unprovoked VTE [1,7]. It is unknown whether patients with VTE also have an increased prevalence of calcifications of the aorta compared to controls. Calcifications of the aorta represent an advanced stage of atherosclerosis and are associated with an increased risk of future atherosclerotic events [8–11].

METHODS

We performed a retrospective case-control study and assessed the presence of calcium deposits on the chest X-ray of patients with either provoked or unprovoked VTE. Cases consisted of patients with documented VTE, who participated in studies on the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism conducted at the Academic Medical Centre, Amsterdam, The Netherlands [13–15]. Controls were randomly selected from patients admitted to the emergency department of the AMC with complaints of chest pain for which a chest X-ray was performed. None of these patients had pulmonary embolism. Patients without a chest X-ray were excluded from analysis. When multiple chest X-rays were available, the one closest to the date of the event was used. VTE was classified as unprovoked or provoked. Provoked VTE was defined as related to pregnancy or post-partum state, surgery or leg trauma within the previous 3 months, known cancer, prolonged immobilization or use of oral contraceptives. All other events were classified as unprovoked. The diagnosis of DVT was objectively confirmed by ultrasound, which was repeated after one week when negative on the first occasion. Pulmonary embolism was confirmed by either a multidetector CT scan or ventilation-perfusion scan. Patients with DVT were not routinely screened for the presence of pulmonary embolism and vice versa.

Chest X-rays were screened for calcifications located specifically on the aortic arch. One experienced radiologist reviewed all chest radiographs for the presence or absence of calcium deposits which were recognized as typically shaped densities [11] in both the cases and controls. No quantification was made of the calcium deposits. The radiologist was blinded to the diagnosis of each patient.
RESULTS

In 456 patients with documented VTE a chest X-ray was performed. 137 (30%) patients had pulmonary embolism, 306 (67%) DVT, and 13 patients (3%) had both DVT and pulmonary embolism. Patients with VTE were compared with 197 control patients. In the patients with VTE, 50% was male, and the mean age was 60 years, whereas in the control patients, the mean age was 51 years and 57% was male. The thrombotic episode was unprovoked in 205 subjects and provoked in 251 subjects. Aortic calcifications were present in 33.3% of the subjects with a VTE, compared to 18.3% in the patients without VTE (odds ratio (OR) 2.24 (95% confidence interval (CI) 1.48-3.37). When adjusted for age, sex, and smoking, this association remained (OR 1.86 (95% CI 1.18-2.95). Calcifications were present in 37.9% of the unprovoked and in 29.5% of the provoked events (p=0.054) (Table 1). Compared to controls, the odds ratio for provoked VTE was 1.87 (95% CI 1.19-2.94) and of unprovoked 2.75 (95% CI 1.74-4.34). After adjustment for age, sex, and smoking, the OR was 1.73 for provoked VTE and 2.12 for unprovoked VTE (Table).

Table. Association between aortic calcifications and VTE in patients with unprovoked and provoked episodes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unprovoked VTE</th>
<th>Provoked VTE</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>205</td>
<td>251</td>
<td>197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>61 ± 17</td>
<td>59 ± 17</td>
<td>51 ± 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>96 (47)</td>
<td>133 (50)</td>
<td>112 (57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>54 (26)</td>
<td>62 (25)</td>
<td>62 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcifications (%)</td>
<td>78 (38)</td>
<td>74 (29.5)</td>
<td>36 (18.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Unprovoked VTE | 2.75 (1.74-4.34) | 2.12 (1.26-3.58) |
| Provoked VTE   | 1.87 (1.19-2.94) | 1.73 (1.04-2.87) |

*Adjusted for age, sex, and smoking

DISCUSSION

Our results show an association between VTE and aortic arch calcifications on chest X-rays. These calcifications were highly prevalent, especially in patients with unprovoked VTE. After adjustment for age, sex, and smoking, this association remained and tended to be somewhat more pronounced for unprovoked VTE. Since aortic calcifications are a marker of atherosclerosis and predispose patients to future cardiovascular events, this finding further supports an association between VTE and arterial thrombosis.

Some aspects of this retrospective study require comment. Because cardiovascular history and most risk factors were unknown in the majority of VTE patients and controls, we were unable to adjust our results for other cardiovascular risk factors than smoking. In addition, control patients all suffered from chest pain, and were at a potentially higher risk of coronary artery disease and
Aortic calcifications in venous thromboembolism

Aortic arch calcifications than the general population. However, this would only lead to an underestimation of the association between calcifications and patients with VTE, and therefore further strengthens the association between VTE and atherosclerosis. Although vascular calcifications on plain chest radiographs are associated with the presence of coronary artery disease, it is an indirect method to visualize atherosclerotic disease. Interestingly, coronary calcifications on multidetector CT scan, a more sensitive method to assess vascular calcifications, were shown in 51.7% of patients with VTE, compared to 28.1% in the controls (multivariate adjusted OR 4.3, 95% CI 1.9-10.1) [12].

In conclusion, aortic calcifications are more prevalent in patients with VTE, compared to patients with chest pain without VTE. This association seems slightly more pronounced in patients with unprovoked disease. These results further support an association between VTE and arterial thrombosis.
REFERENCES