Oral Anticoagulant Treatment: Friend or Foe in Cardiovascular Disease?

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Abstract

Calcification is a common complication in cardiovascular disease and may affect both arteries and heart valves. Matrix Gla-protein (MGP) is a potent inhibitor of vascular calcification the activity of which is regulated by vitamin K. In animal models, vitamin K-antagonists (oral anticoagulants, OAC) were shown to induce arterial calcification. To investigate whether also in man long term OAC treatment may induce calcification, we have measured the grade of aortic valve calcification in patients with and without pre-operative OAC treatment. OAC-treated subjects were matched with non-treated ones for age, gender and disease. Calcifications in patients receiving pre-operative OAC treatment were significantly (2-fold) larger than in non-treated patients. These observations suggest that OAC, which are widely used for anti-thrombotic therapy, may induce cardiovascular calcifications as an adverse side effect.
Introduction

Vitamin K-antagonists, also known as oral anticoagulants (OAC), are widely used for the treatment and prophylaxis of thromboembolic diseases. Short-term OAC-treatment is often applied after deep venous thrombosis whereas long-term treatment may be required for atrial fibrillation or after prosthetic heart valve implantation. In the Netherlands alone, some 270,000 people (1.7% of the total population) receive long-term OAC-treatment. Vitamin K is an essential micronutrient that serves as a cofactor for the transformation of selective glutamic acid (Glu) residues into $\gamma$-carboxyglutamic acid (Gla) during the biosynthesis of the so-called Gla-proteins including the vitamin K-dependent coagulation factors. In all known Gla-proteins the Gla residues are essential for the function of these proteins. OAC are used to block the $\gamma$-carboxylation of the vitamin K-dependent coagulation factors (II, VII, IX and X), and three anticoagulant proteins (C, S, and Z); OAC treatment leads to dysfunctional, undercarboxylated species also known as PIVKAs. OAC treatment also affects the synthesis and function of a number of other Gla proteins including the non-coagulation protein matrix Gla-protein (MGP) in cartilage and the vasculature. The first reports suggesting extra-hepatic effects of vitamin K antagonists were published in the nineteen seventies, when it was found that women receiving OAC treatment between the 6th and 12th week of pregnancy gave birth to children with severe bone abnormalities (chondrodysplasia punctata). Presently, it is commonly agreed that the most plausible mechanism underlying this phenomenon is incomplete $\gamma$-carboxylation of MGP, resulting in excessive cartilage calcification and subsequent nasal and distal digital hypoplasia, and epiphyseal stippling.
Recent publications have demonstrated that cardiovascular calcifications are the result of an actively regulated process. One of these regulatory proteins is MGP, a potent inhibitor of soft tissue calcification. Transgenic MGP-deficient mice were born to term, but died within 6-8 weeks after birth due to massive calcification and rupture of the arteries. Price et al. showed that the oral anticoagulant warfarin was capable of inducing a mild form of aortic calcification in rats within two weeks of treatment, thus confirming the importance of properly carboxylated Gla-proteins for adequate calcification inhibition. Since calcification only occurred in young animals, the model may not be representative for OAC treatment in adults and elderly subjects. Recently, however, Sweatt et al. directly demonstrated that under-carboxylation of MGP was also associated with aortic calcification in aging rats.

Whereas OAC treatment is effective for preventing thromboembolic disease, nothing is known of a potential adverse effect of OAC in the vasculature. Here we have addressed the question of whether coumarin anticoagulation is a risk factor for cardiovascular calcification. Since the etiology of arterial and aortic valve calcification has common pathomechanisms, we assembled in this study aortic valves obtained from patient after aortic valve replacement. Since the use of coumarin has not yet been demonstrated with the extent of aortic heart valve calcification, we have compared aortic valve calcification in anticoagulated and non-anticoagulated subjects.
Materials and methods:

Forty five aortic valves were obtained after routine cardiac replacement surgery. The specimens came from 26 women and 19 men (mean age: 71 years; Table 1) with clinically manifest aortic valve stenosis and/or insufficiency (Grade II-III). Ten patients had received a pre-operative marcoumar treatment with target INR values between 2 and 3. The duration of treatment varied between 16 and 35 months (mean: 25 months). Histopathologic inspection of the samples showed typical aspects with partial or total valve destrucions induced by basophilic-amorphous calcified deposits. Calcification was visualized by von Kossa staining. The calcified area was measured using a microscope coupled to a computized morphometry system (quantimed 570, Leica, the Netherlands). Five sections (20 µm apart) were used for morphometric analysis, and the calcification area was expressed as a percentage of the total section area. All morphometric measurements were conducted by two independent persons. The Medical Ethics Committee of the University of Tuebingen approved the study protocol and all subjects gave their written informed consent.
Results and discussion

A more than two-fold difference was observed between the marcoumar-treated and non-treated groups, with a mean calcified area of 16% in the non-treated group and 37% in the OAC-treated group (Figure 1). The difference was statistically significant at p<0.02 using the Wilcoxon signed-ranks test. A possible explanation for these observations is that marcoumar treatment results in a decreased protection against tissue calcification due to the impairment of MGP, thus leading to more pronounced valvular calcification. Even low dose OAC treatment combined with a relative short period of treatment (like in this study) resulted in significantly more calcification. Many patients, however, receive OAC life-long with INR values well above the range indicated in our study cohort. Since coumarin derivatives are widely used, physicians should be aware of this potential adverse effect on the vasculature.

Acknowledgements

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References


Table 1: Characteristics of the subjects

<table>
<thead>
<tr>
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<th>no preoperative OAC</th>
<th>pre-operative OAC</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Subjects (n)</td>
<td>35</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>70.1 ± 8.5</td>
<td>73.4 ± 5.3</td>
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</tr>
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<td>Gender (M / F)</td>
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<td>4 / 6</td>
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<td>Diabetes mellitus</td>
<td>3</td>
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<tr>
<td>Aortic valve stenosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>7</td>
<td>3</td>
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</tr>
<tr>
<td>Grade III</td>
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<td>7</td>
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<tr>
<td>Insufficiency</td>
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<td>6</td>
<td>ns</td>
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<tr>
<td>INR</td>
<td>&lt; 1.2</td>
<td>2.4 ± 0.4</td>
<td>p&lt;0.01</td>
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<tr>
<td>Calcification score (%)</td>
<td>16%</td>
<td>37%</td>
<td>p&lt;0.02</td>
</tr>
</tbody>
</table>

ns = not significant
Figure 1: Patients with (■) and without (○) pre-operative marcoumar treatment. Values are expressed as calcification area compared to total section area in percentage. Each value is the mean of five measurements per heart valve. Horizontal bar is the median of each group.
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