Thrombophilia and cancer in the pathogenesis of arterial thrombosis

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Thrombophilia and Cancer in the Pathogenesis of Arterial Thrombosis

B. Brenner

Hereditary and acquired abnormalities in blood coagulation may predispose for arterial thrombosis. The rapidly growing list of heritable thrombophilic states involves mutations in coagulation factors and deficiencies of inhibitors of the coagulation system. Hyperhomocysteinaemia is an emerging risk factor for arterial thrombosis resulting from hereditary causes like thermolabile methylene tetrahydrofolate reductase and from nutritional abnormalities, notably folic acid deficiency. Cancer is a well known cause of arterial thrombosis by several pathogenic mechanisms which may activate blood coagulation. J Clin Basic Cardiol 2000; 3: 89–90

Key words: thrombophilia, homocysteine, cancer, arterial thrombosis

Inherited thrombophilia is a congenital tendency to thrombosis which may be manifested episodically usually in the presence of another predisposing factor [1]. Hereditary thrombophilic states involve either mutations in coagulation inhibitors like the natural anticoagulants protein C and protein S or the serine protease inhibitor antithrombin III (Table 1). In addition, mutations in coagulation factors may also predispose for thrombosis. Thus, a point mutation R506Q in coagulation factor V (factor V Leiden) is a major cause of venous thrombosis. Likewise, certain disfibrinogenaemias resulting from point mutations in fibrinogen have been associated with thrombosis. While these thrombophilic states have been clearly associated with venous thrombosis, their role in arterial thrombosis is less obvious [2–4]. This dichotomy may be partly explained by the large amount of fibrin which is excessively formed in the large venous thrombi in patients with hereditary thrombophilic states involving coagulation factors and inhibitors compared to the relatively small amount of fibrin in arterial clots.

However, arterial thrombosis has been reported occasionally in virtually all thrombophilic states particularly in the presence of another hereditary or acquired thrombophilic state. Thus coexistence of factor V Leiden with lupus anticoagulant may result in arterial as well as venous thrombosis [5].

Hyperhomocysteinaemia and arterial thrombosis

Homocysteine is derived from dietary methionine and present in plasma in low concentrations of 5–15 µmol/l. Intracellular homocysteine is transsulfurated to cystathionine by cystathionine β-synthase or remethylated to methionine by a pathway involving methylene tetrahydrofolate reductase (MTHFR) and methylene synthase. Folic acid, vitamin B6, and vitamin B12 are important cofactors participating in these metabolic pathways (Table 2). Inherited deficiencies of enzymes of these pathways lead to homozygous hyperhomocysteinaemia associated with homocysteine plasma levels > 50 µmol/l and characterized by thromboembolism and atheroma progression in childhood [6, 7].

Nutritional deficiencies of folic acid and vitamin B12 are the main causes of acquired mild to moderate (15–50 µmol/l) hyperhomocysteinaemia [8, 9].

A large body of clinical and experimental evidence suggests an association between hyperhomocysteinaemia and arterial thrombosis. The spectrum of arterial thrombosis includes coronary artery, cerebral and peripheral arterial occlusion [10, 11]. Of interest, in patients with peripheral arterial disease, homocysteine levels of the highest quartile are associated with coexistence of coronary and cerebral artery disease. Metanalysis of 18 studies which included 1583 cardiovascular patients and 1410 controls revealed that ratio of patient to control homocysteine plasma levels was 1.31 ± 0.17 [12]. Furthermore, abnormal homocysteine response to methionine loading could be demonstrated by pooled results from 14 studies in 121/495 (24 %) patients with arterial thrombosis compared to 7/289 (2 %) controls (p < 0.0001) [12]. The Thromso study revealed significantly higher homocysteine levels in 123 patients with myocardial infarction (MI) compared to 21,000 controls (12.7 µmol/l vs 11.3 µmol/l; p = 0.002) [13] and a recent study suggested that the carotid artery wall is thickened in hyperhomocysteinaemic patients [14]. In the US physicians study, subjects with homocysteine levels above the 95 percentile had 3 fold increased risk for MI compared to individuals with levels lower than 90 percent [15].

As homozygous hyperhomocysteinaemia due to inherited enzymatic defects is a rare disorder, obligate heterozygotes are hardly identified. Theoretically common mutations or polymorphisms in one of the methionine pathway enzymes may lead to hyperhomocysteinaemia.

Table 1. Hereditary thrombophilia

<table>
<thead>
<tr>
<th>Inherited defects</th>
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<tbody>
<tr>
<td>Antithrombin III deficiency</td>
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<tr>
<td>Protein C deficiency</td>
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<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Factor II G20210A</td>
</tr>
<tr>
<td>Dysfibrinogenaemia</td>
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<tr>
<td>Dysplasminogenaemia</td>
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<tr>
<td>Hereditary hyperhomocysteinaemia</td>
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Table 2. Causes of hyperhomocysteinaemia

<table>
<thead>
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<th>Inherited defects</th>
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<tbody>
<tr>
<td>Cystathionine β-synthase</td>
</tr>
<tr>
<td>Methylenetetrahydrofolate reductase</td>
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<tr>
<td>Methionine synthase</td>
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<tr>
<td>Cobalamin coenzyme synthesis</td>
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Acquired defects

| Nutritional |
| Cobalamin (B12) deficiency |
| Folic acid deficiency |
| Pyridoxine (B6) deficiency |
| Metabolic |
| Chronic renal disease, hypothyroidism |
| Drug-induced |
| Methotrexate and other folate antagonists |
| Nitrous oxide and other cobalamin antagonists |

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Such a mutation has recently been demonstrated in MTHFR. The C677T substitution leads to a thermolabile MTHFR variant which has 50% abnormal activity. Homozgyosity for this mutation can be found in 5–15% of normal individuals across different ethnic populations. Several studies have suggested a 3-fold increase in the risk of cardiovascular disease in subjects homozygous for thermolabile MTHFR [16–18]. However, other investigators failed to reveal significant differences in the prevalence of this mutation in cardiovascular disease patients and normal individuals. A recent paper by the US study group suggests that while the prevalence of the mutation was not different in MI and control groups, homocysteine levels were increased in MI patients with low folate status who were also homozygous for the C677T mutation [19].

This brings into focus the concept that multiple hereditary and acquired risk factors may act synergistically to increase expression of thrombosis. Indeed, the Hordaland study has recently demonstrated that most subjects with homocysteine levels above 40 μmol/l had the C677T mutation combined with low folate status [20]. Since a number of studies have clearly suggested that folic acid supplementation may decrease and often normalize homocysteine levels in hyperhomocysteinaemic patients [21], the US food and drug administration has recently approved fortification of food in the USA by 140 μmol/l folic acid for 100 gr of food thereby envisioning a potential substantial reduction of mortality from coronary artery disease [21].

This forecast may be extrapolated from older studies in patients with homozygous hyperhomocysteinaemia where vitamin B₆ therapy resulted in significantly improved survival [22].

Coexistence of the rare hereditary hyperhomocysteinaemia due to inherited enzymatic defects and factor V Leiden mutation may explain severity of thrombotic manifestations in populations where the factor V Leiden is highly prevalent [23]. Whether association of the highly prevalent thermolabile MTHFR mutation with factor V Leiden in man on expression of thrombosis is now under investigation.

Several observations suggest that hyperhomocysteinaemia may inhibit components of the protein C thrombomodulin system thereby limiting its anticoagulant effects [24–26]. Other suggested mechanisms relating hyperhomocysteinemia to atheroma progression and thrombosis include increase in oxidized low density lipoprotein [27] and plasma lipoprotein(a) levels [28].

Thrombosis and cancer

Thrombosis is the most frequent complication and a major cause of death in cancer patients. Thromboembolism may affect both venous and arterial vasculature. Arterial clinical manifestations may include localized arterial occlusion, non-bacterial thrombotic endocarditis (NBTE), disseminated intravascular coagulation and thrombotic thrombocytopenic purpura. These variety of clinical syndromes may appear prior to diagnosis of cancer, in the course of overt malignant disease or following initiation of chemotherapeutic agents. Although certain tumors like mucous carcinoma of the pancreas, lung and gastrointestinal tract have been traditionally associated with thromboembolism [29], other solid neoplasms as well as haematological malignancies are often associated with thrombosis. Notably, NBTE in patients with solid tumors [30] is particularly prevalent in patients with myeloproliferative disorders in whom it may be associated with systemic thrombosis [31].

The pathogenic mechanisms of thrombosis in cancer patients are multifactorial. A major mechanism involves activation of factor VII at the extrinsic coagulation system by tissue factor which is expressed by most tumor cells [32]. Another important mechanism is triggered by cancer procoagulant (CP), a cysteine protease which directly activates factor X and is expressed by certain tumor cells [33].

Recurrent thrombosis in cancer patients may be resistant to oral anticoagulant therapy and recent preliminary data suggest that low molecular weight heparin is a potential alternative therapeutic modality in this setting.

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