



Advances in Basic, Laboratory and Clinical Aspects of Thromboembolic Diseases*

VENOUS AND ARTERIAL THROMBOPHILIA

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ABSTRACT

Background and Objective. The thrombophilic state may be defined as a condition which predisposes to thrombosis. It is well known that the pathogenesis of venous and arterial thrombosis may be different. However, such differences may be more apparent than real. In fact, both venous and arterial thrombosis may occur in any given patient with a thrombophilic state. The aim of this review is to critically analyze the thrombophilic state and define a rational approach to the patient with overt or suspected venous and/or arterial thrombosis.

Evidence and Information Sources. The material examined in the present review includes personal papers in this field, and articles and abstracts published in journals covered by the Science Citation Index®.

State of Art and Perspectives. Both venous and arterial thrombosis may occur in thrombophilic states such as APC resistance, protein C or S defects, and antiphospholipid antibody syndrome. Venous thrombosis is surely more frequent than arterial thrombosis in such conditions but, fortunately, it is usually less severe. Antithrombin deficiency is almost exclusively associated with venous thrombosis. In foreseeing the occurrence of venous or arterial thrombosis in a given thrombophilic

patient, one must explore the state of the vessels carefully. Often venous or arterial thrombosis occurs only because a vessel injury is present. Severely decreased blood flow, such as that seen in polycythemia vera, may be responsible for arterial or venous thrombosis without any other predisposing cause. From a laboratory standpoint there is no sure demonstration that some changes may indicate a more likely occurrence of arterial or venous thrombosis. The same alteration of one or more than one test may be accompanied by either arterial or venous thrombosis or both. One exception to this rule is represented by increased blood viscosity, which is usually associated with arterial thrombosis. The hypercoagulable or thrombophilic state is a single clinical entity that cannot be divided into arterial and venous thrombophilia, although the unfortunate outcome, namely thrombosis, tends to manifest itself in just one district. The preexisting condition of the vessels, together with sudden triggering factors, plays an important role in the transformation of the "sol" into the "gel" that is a thrombosis in any given district.

Key words: venous thrombosis, arterial thrombosis, thrombophilia, hypercoagulable state

The thrombophilic state may be defined as a condition which predisposes to thrombosis. It is synonymous with prothrombotic or hypercoagulable state.¹⁻⁶

The term *prethrombotic state* should be avoided since it is not synonymous with the others. The preposition "pre", in fact, unlike the preposition "pro", does not indicate a predisposition to thrombosis, but a condition temporally related to thrombosis, something which comes "before" thrombosis. Fortunately, a great number of patients with a thrombophilic state do not show actual thrombosis. For example, even the protracted administration of ellagic acid in dogs and humans failed to cause thrombosis, in spite of the appearance of a

hypercoagulable state.⁷ For this reason it is also advisable to avoid the term "hypercoagulable state". The best definitions remain those of thrombophilic or prothrombotic state.

Furthermore, on a strictly semantic basis, a hypercoagulable state refers only to changes in blood coagulation and does not reflect changes in vessel walls or blood flow.

It is well known that the pathogenesis of venous and arterial thrombosis may be different; however, such differences may be more apparent than real. In fact, both venous and arterial thrombosis may occur in any given patient with a thrombophilic state. Vessel wall changes seem to play an important role in arterial thrombosis and, to a lesser

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*This paper was presented at the Second International Winter Meeting on Basic, Laboratory and Clinical Aspects of Thromboembolic Diseases, held in La Thuile, Italy, on March 17-23, 1996. The Meeting organizers (A. D'Angelo, A. Girolami & F. Piovella) have acted as Guest Editors and assumed the responsibility for peer review of this manuscript.

Received October 23, 1996; accepted December 31, 1996.

extent, in venous thrombosis (varicosities). However, even venous changes, such as those created by valve destruction and varicosities, often play a role in the pathogenesis of thrombosis.

Thrombophilia associated mainly with venous thrombosis

The congenital conditions associated mainly with venous thrombosis include: antithrombin, protein C protein S deficiency and APC resistance. Plasminogen defects are also associated mainly with venous thrombosis.^{8,9} APC resistance was discovered only a few years ago¹⁰ and is due to an abnormality of factor V.¹¹ Factor V has therefore become the focus of interest since it is both a *coagulant* and an *anticoagulant* protein.¹²

Protein S defect and APC resistance seem to predispose to both venous and arterial thrombosis, even though the former are more frequent.

Among acquired conditions, oral contraceptives, bed immobilization, stasis due to heart failure or any other cause, trauma, surgery, i.v. catheters and i.v. antiproliferative medications are known to predispose to venous thrombosis. Oral contraceptives have been shown to be particularly dangerous in women with congenital defects of clotting inhibitors.¹³ Cancers of almost any type are frequently associated with the presence of thrombophilia and/or actual thrombosis.⁵ In many instances, the thrombotic manifestation, usually venous, may precede by weeks or months the detection of the tumor¹⁴ (Table 1).

The antiphospholipid antibody syndrome (APA syndrome) seems to be associated with both venous and arterial thrombosis.

Thrombophilia associated mainly with arterial thrombosis

The most important congenital conditions associated with an elevated incidence of arterial thrombosis are homocystinuria and Lpa increase.^{7,15} However, occasional arterial thromboses have been seen in patients with protein C protein S defects (especially in homozygous patients) and in APC resistance.¹⁶⁻¹⁸ Protein S and APC resistance patients seem somewhat more prone to arterial thrombosis than those with antithrombin deficiency.^{12,16,19,20,21}

Among acquired conditions, athero-arteriosclerosis, diabetes, increased blood viscosity, paroxysmal nocturnal hemoglobinuria, sickle cell anemia and thrombocytosis are surely associated with arterial thrombosis.²² In the case of thrombocytosis, it has to be remembered that primary thrombocytosis (*essential thrombocythemia*) is more frequently associated with arterial thrombosis than secondary thrombocytosis²³ (Table 2).

Of particular interest is the hyperviscosity syndrome, which may be due to increased hematocrit

Table 1. Main conditions associated with venous thrombophilia and/or thrombosis.

<i>Congenital:</i>	Antithrombin, protein C (protein S) deficiency APC resistance Plasminogen deficiency t-PA decrease or PAI increase
<i>Acquired:</i>	Bed immobilization Trauma Surgery Pregnancy and/or puerperium Oral contraceptives Stasis Cancers Antiproliferative i.v. drugs Indwelling catheters APA syndrome

Table 2. Prevalence of arterial and venous thrombosis in thrombocytosis.

	<i>N. of pts.</i>	<i>Arterial</i>	<i>Venous</i>
Primary	197	68 (34.5%)	30 (15.2%)
less than 40 years	56	12 (21.4%)	4 (7.1%)
more than 40 years	141	60 (42.5%)	26 (18.4%)
Secondary	63	13 (20.6%)	5 (7.9%)
less than 40 years	23	2 (8.7%)	2 (8.7%)
more than 40 years	40	11 (27.5%)	3 (7.5%)

and to plasma protein changes (macroglobulinemia). It is also worth remembering that type II heparin-induced thrombocytopenia is mainly accompanied by arterial thrombosis (Table 3).

The overall picture seems to suggest that arterial thrombosis occurs mainly when vessel walls and platelets are involved. In this regard, the large vessel massive thrombosis seen in severe heparin-induced thrombocytopenia is particularly significant.

Special problems in thrombophilia

There are at least three special problems in thrombophilia, namely venous or arterial thrombosis in unusual sites, thrombosis in childhood, thrombosis of the heart.

- A. Under the heading of thrombosis in unusual sites it is commonly accepted today to list all venous thromboses which occur in sites other than the veins of the limbs.³ The main examples are: 1) thrombosis of the cerebral sinuses; 2) thrombosis of the portal system; 3) thrombosis of the renal veins; 4) thrombosis of the suprahepatic veins; 5) thrombosis of the venae cavae. Each of these conditions may represent a diagnostic challenge. Focal factors, in addition to systemic thrombophilia, may play a role in the occurrence of these thromboses. They are mainly venous thromboses but a few examples of arteri-

Table 3. Main conditions associated with arterial thrombophilia and/or thrombosis.

<i>Congenital:</i>	Homocystinuria Lpa increase (Protein S deficiency) (APC resistance)
<i>Acquired:</i>	Athero-arteriosclerosis Diabetes Oral contraceptives and smoking Polycythemia and other hyperviscosity conditions Thrombocytosis Hypertension Paroxysmal nocturnal hemoglobinuria Sickle cell anemia APA syndrome Heparin-induced thrombocytopenia

al thrombosis in unusual sites are also seen, e.g. mesenteric artery thrombosis.

- B. Thromboses in the neonatal period and in childhood are mainly arterial. This is puzzling since infancy is often accompanied by a hypocoagulable state. Normal levels of clotting factors are usually achieved within 6-12 months. However, it has to be remembered that vascular lesions play an important role in neonatal thrombosis.
- C. Thrombosis of the right or left heart is often underdiagnosed and underestimated in the pathogenesis of both venous and arterial thromboembolism. Atrial thrombosis has been described in a variety of conditions with or without atrial fibrillation; it has also been documented in defects of clotting inhibitors.²⁴ It is commonly thought that thrombosis of the heart occurs in patients with dilatative cardiomyopathy, in post myocardial infarction and in drug addicts (right side heart). This is not the case. Cardiac thrombosis has to be taken in due consideration in every instance of peripheral or pulmonary embolic disease. Furthermore, it should be remembered that interatrial septal defects are frequent, so that peripheral arterial emboli may result even from right side heart thrombosis.

Laboratory evaluation of thrombophilia

An accurate laboratory evaluation is needed.^{2, 25} Unfortunately, there is no agreement as to the significance of changes. In other words, there is no single thrombophilic state but several different changes which lead to thrombophilia. Any of the thrombophilic states determined by laboratory tests listed in the table indicate, at least theoretically, the existence of a prothrombotic state. It has to be kept in mind that sometimes marked alterations of only one of the tests listed in the table may cause thrombosis (Table 4).

More often the presence of such conditions is brought to the surface when, because of a triggering factor, a given patient becomes symptomatic. There is no way to quantitate or foresee a triggering factor; therefore the main objective for a clinician is to identify the type of thrombophilic state presented by a given patient and to take adequate measures. Usually only one congenital abnormality is present in a given person or family. Rarely are congenital abnormalities multiple, for example associated antithrombin and protein C deficiencies. Acquired conditions often show multiple alterations involving two or more laboratory tests.

Strictly speaking, the tests for thrombin formation indicate mainly subclinical thrombosis since they reflect thrombin formation and activity *in vivo*. One or more of the changes may be present in a given patient and may vary in degree from day to day in acquired conditions. By contrast, a laboratory abnormality is always fixed in congenital forms. It has to be remembered that congenital forms must always be investigated with clotting, chromogenic and immunological methods to rule out abnormalities. Furthermore, it should be kept in mind that more than one clotting defect may be present in the same person or in the same family. Associations are often difficult to find if the propositi are not fully investigated.

Adequate laboratory investigation has become time-consuming and expensive. For example, the tests indicated for a complete investigation of the fibrinolytic system are reported in Table 5.

Laboratory investigation of the fibrinolytic system has received considerable attention in recent years because of the new methods which have become available. In Table 6 we have gathered a list of abnormalities seen in a group of patients with idiopathic venous thrombosis. These procedures may be time-consuming and difficult. Particularly time-consuming may be a complete evaluation of the fibrinolytic system, since *in vivo* stimulation tests may be needed (venous stasis - DDAVP administration)(Table 5).

It is also important to remember that careful evaluation of an arterial thrombophilic state has to

Table 4. Main laboratory findings in the diagnosis of hypercoagulable states.

<ul style="list-style-type: none"> • Short global tests (PTT, TEG, etc., except for lupus anticoagulant) • Decreased levels of inhibitors (AT III, etc.) • Increased resistance to activated protein C • Defective fibrinolysis (basal and after stimuli) • Increased levels of clotting factors (fibrinogen, factor VII, factor VIII, etc.) • Increased and/or hyperactive platelets • Increased whole blood and/or plasma viscosity • Antiphospholipid antibodies • Positive tests for thrombin formation (F1+2 fragment, TAT complexes, FPA)
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Table 5. Laboratory evaluation of the fibrinolytic system.

1. Global tests: Whole blood clot lysis time Euglobulin lysis time Fibrinolytic activity on fibrin plates Thromboelastogram (TEG)
2. Tissue-type plasminogen activator (t-PA) and urokinase a) Functional assay: chromogenic methods b) Antigen assay: ELISA methods
3. Plasminogen activator inhibitor (PAI) a) Functional assay: chromogenic method b) Antigen assay: ELISA method
4. Plasminogen and α 2-antiplasmin a) Functional assay: chromogenic method b) Antigen assay: electroimmunoassay, radial diffusion, crossed immunoelectrophoretic assay, laser nephelometer
5. Tests for fibrinolytic capacity evaluation a) Venous occlusion test (10 - 20 min.) b) DDAVP infusion (0.3 - 0.4 μ g/kg b.w.) c) Standardized physical exercise
6. Fibrinogen/fibrin degradation products and D-Dimer a) Latex agglutination b) ELISA
7. Molecular biology analysis

Table 6. Prevalence of fibrinolytic potential defects found in 64 patients suffering from idiopathic deep vein thrombosis.

Fibrinolytic defect	N° of cases	Prevalence (%)
Compensated basal PAI-1 excess	10	15.6
Isolated basal ELT prolongation	2	3.1
Compensated basal PAI-1 excess and isolated basal ELT prolongation	8	12.5
Impaired fibrinolytic potential after venous occlusion test (total)	18	28.1
a) Uncompensated basal PAI-1 excess	12	18.7
b) Reduced t-PA release	6	9.4

be completed by a study of the state of the arteries and of basic metabolic parameters (Table 7).

As far as the vein walls are concerned, laboratory investigation is less complicated but equally important. Careful echodoppler and/or compression ultrasonography of the veins of the extremities, CT and/or MRI of the thorax and/or abdomen for the venae cavae, and phlebography may be needed.

Management

The management of a thrombophilic state has to be based on the following findings:

1. recognition of the type of defect (congenital or acquired, single or multiple);
2. therapeutic decision when the patient becomes symptomatic;
3. decision about secondary prophylaxis;
4. decision about the need for primary prophylaxis.

Table 7. Evaluation of the state of the arterial tree.

· Chest X-rays for aorta
· Flat X-rays of abdomen for aorta
· Evaluation of arterial flow in limbs (echodoppler, etc.)
· Lipid metabolism evaluation
· Carbohydrate metabolism evaluation
· Fundus oculi examination
· CT and/or MRI
· Arterial biopsy
· Arteriography

It has to be kept in mind that hypercoagulability does not necessarily mean thrombosis and that the relationship between thrombophilia and thrombosis may be extremely variable and unpredictable.

A severe hyperviscosity syndrome may be followed by the appearance of an ischemic stroke within a short period of time without any added risk as triggering factor. In contrast, an antithrombin deficiency may remain asymptomatic for many years and become symptomatic, usually with venous thromboembolism, after an added risk has appeared (for example, oral contraception).

Conclusions

It is our impression that no clear distinction can be made between venous and arterial thrombophilia. Laboratory evaluation is common to the two conditions since all aspects of blood coagulation, platelet function, the fibrinolytic system and rheological parameters should be carefully evaluated in every patient with a family history of thrombosis or with a past history of thrombosis. Arterial wall changes should also be taken into due account.

A thrombophilic state is a prothrombotic state, namely a condition predisposing to thrombosis, and therefore should be carefully considered as such. The thrombotic event, venous or arterial, may merely be the result of additional acquired conditions which act as a trigger. The role of these triggering factors is widely recognized but few, if any, systematic studies have been carried out. For example, given a thrombophilic state, regardless of the type and nature, arterial thrombosis may manifest itself only if vascular lesions are present.

It is possible that arterial thrombosis is a more severe manifestation of a thrombophilic state than venous thrombosis.

This appears to be sustained, for example, by the observation that the homozygous protein C and protein S deficiency is associated with severe arterial thrombosis, whereas heterozygous patients present mainly venous thrombosis. Furthermore, arterial thrombosis may be less frequent than venous thrombosis but it is still present, at least once, in

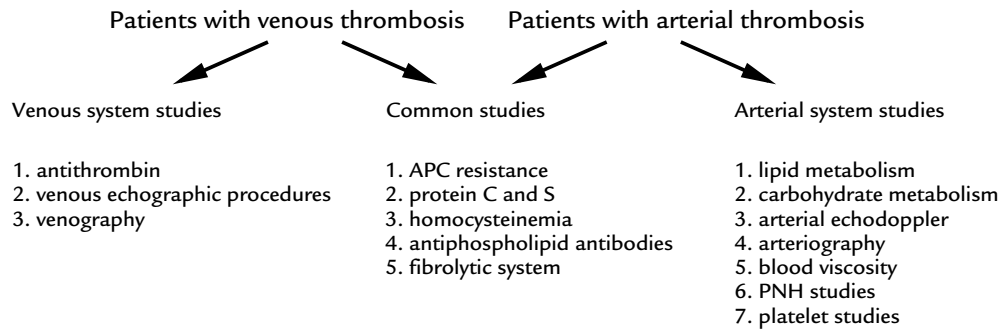


Figure 1. A practical approach to patients with overt or suspected thrombosis.

about 20% of patients with hereditary defects of clotting inhibitors. Since advancing age is also associated with an increased prevalence of arterial thrombosis, one could speculate that the state of the arterial walls plays a role in the pathogenesis of arterial thrombosis even in patients with coagulation defects. This assumption, however, is in contrast with the observation that arterial thrombosis in childhood is mainly arterial.

Once discovered, a thrombophilic state should be carefully monitored and any potential triggering factor eliminated. For example, OCT should never be given to a patient with a congenital deficiency of clotting inhibitors or with APC resistance. Furthermore, high-risk patients should receive careful pro-

phylaxis in the event of conditions known to be associated with a high risk of thrombosis (e.g. hip surgery, pregnancy, etc.). A practical approach to patients with overt or suspected thrombosis may be summarized in the flow chart presented in Figure 1.

The hypercoagulable or thrombophilic state is a single clinical entity. It cannot be divided into arterial and venous thrombophilia. The unfortunate outcome, namely thrombosis, may manifest itself more frequently in the venous system but often occurs also in the arterial tree. The preexisting condition of the vessels, together with sudden triggering factors, plays an important role in the transformation of the "sol" into the "gel" that is a thrombosis in any given district.

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