J Lab Med 2008;32(4) © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/JLM.2008.036et

Controversies of laboratory medicine
Haemostaseology

Editor: C.M. Schambeck

Global test versus profile: Will endogenous thrombin potential replace established thrombophilia screening? Contra

Global coagulation assays versus differentiated testing: Will endogenous thrombin potential replace established thrombophilia screening? Contra.[1)]

E. Lindhoff-Last*

Department of Internal Medicine, Division of Vascular Medicine and Haemostaseology, D-60590 Frankfurt, Germany

Global coagulation tests, such as activated partial thromboplastin time (aPTT), D-dimer test or endogenous thrombin potential record coagulation activation, which may be induced by several causes. Increased D-dimers may, for example, be detectable several weeks after an operation [1]. Moreover, severe infections, tumors or pregnancy may cause coagulation activation and thus positive D-dimers or shortening of the aPTT, whereby these coagulation changes will not specifically indicate an increased tendency to thrombosis, but merely multifactorially induced coagulation activation. Therefore, the D-dimer test has a negative predictive value in patients with suspected deep venous thrombosis, whereas a positive test result may be caused by many other conditions, including advanced age [2]. This equally applies to the validity of global coagulation methods, when performed in order to assess the risk of recurrent thrombosis after discontinuation of oral anticoagulation therapy.

It is therefore desirable to detect not only global coagulation activation, but to define more accurately the causality behind the in-vivo, clot-formation tendency. Being able to determine specifically an existing tendency to thrombosis is useful, particularly when clinical consequences arise not only regarding secondary prevention, but also regarding primary prevention of thromboembolic events in case of a positive family history, intake of oral contraceptives or post-menopausal hormone replacement, during pregnancy or after recurrent abortion.

Thrombophilia is defined as a genetically conditioned or acquired tendency to thrombosis and/or embolisms. The most important hereditary pro-thrombotic risk factors are APC resistance, generally caused by the factor V-Leiden mutation or by a point mutation in the prothrombin gene at position 20210 (G>A), and inherited deficiency of antithrombin, proteins C or protein S, which however, in contrast to factor V-Leiden- and prothrombin mutation, occurs considerably more rarely and may be the result of more than 200 different mutations. In addition, increased coagulation factor VIII is associated with an increased risk of thrombosis, as are coagulation factors IX and XI [3], whereby the causes of these increased factor activities may be acquired or inherited.

The most important acquired cause of thrombophilia are the so-called antiphospholipid antibodies, which may be detected in form of lupus anticoagulants or increased anticardiolipin- or anti-beta2-glycoprotein I-antibodies [4]. This heterogeneous group of antibodies is directed against phospholipid-coagulation protein complexes and may trigger not only arterial or venous thromboses, but also recurrent miscarriages. Only repeated detection of these antibodies is of clinical relevance.

Venous thrombosis represents a multifactorial disease and pathological thrombophilia results are only partially responsible for the occurrence of venous thrombosis. A negative screening does not exclude an inherited risk for venous thrombosis. Moreover, identical thrombophilia predisposition in a family affected by thrombosis may exhibit different clinical penetrance in the different family members [5]. Therefore, thrombophilia screening is only useful, if future anticoagulation management depends on the result of these examinations. So far, prospective studies were unable to find any correlation with a significantly elevated risk of recurrent thrombosis regarding either the heterozygous form of the factor-V Leiden var-

[1)]Original German online version at: http://www.reference-global.com/doi/pdf/10.1515/JLM.2008.036.
The German article was translated by Compuscript Ltd. and authorized by the authors.
*Correspondence: Prof. Dr. med. Edelgard Lindhoff-Last, Department of Internal Medicine, Division of Vascular Medicine and Haemostaseology, Theodor-Stern-Kai 7, D-60590 Frankfurt, Germany
Tel.: +49-69-6301-5096
Fax: +49-69-6301-7219
E-mail: lindhoff-last@em.uni-frankfurt.de

iant or the prothrombin mutation G20210A [6, 7]. When detecting combined thrombophilia, the risk of recurrent thrombosis was borderline significantly elevated. Unfortunately, the available data related to the risk of recurrent thrombosis of rare thrombophilias, such as the homozygous forms of the factor-V Leiden mutation and the prothrombin mutation, as well as inherited forms of antithrombin-, protein-C and protein-S deficiency are unclear, although it can be assumed that these patients may benefit from prolonged oral anticoagulation due to their higher overall risk. For these patient groups, prospective multi-center studies are urgently needed in order to assess more precisely the risk of recurrence.

On the other hand, the available data concerning the risk of recurrent thrombosis for patients with proven antiphospholipid syndrome are convincing. It is known that these patients have a clearly increased risk of recurrence and therefore benefit from prolonged anticoagulation even after the first occurrence of thrombosis [8, 9]. Patients with antiphospholipid syndrome were therefore not included in studies investigating global coagulation tests, such as the D-dimer test or the endogenous thrombin potential as a marker for recurrent thrombosis [10]. Without differentiated thrombophilia screening, this high risk patient group would not have been identified. Therefore, a global test cannot replace differentiated thrombophilia screening related to the risk of recurrent thrombosis but may add additional information.

Differentiated thrombophilia screening may also be useful in numerous other situations, e.g., pregnancy, post-menopausal hormone replacement as well as repeated fetal loss, particularly since global tests may be non-specifically elevated in these situations, e.g., during pregnancy.

Venous thromboembolisms occur in one out of 1000 pregnancies, and pulmonary embolism continues to be one of the leading causes of death during pregnancy [11]. The risk of venous thrombosis during pregnancy is increased about 5-fold compared with non-pregnant women of childbearing age, and increases after childbirth to 60-fold during the first three months after delivery [12]. The risk of a pregnancy-associated venous thrombosis is about 50 times greater, when factor-V Leiden mutation is detected, and about 30 times greater in carriers of the prothrombin 20210 mutation compared with pregnant women lacking these mutations. Therefore, differentiated thrombophilia screening is indicated prior to pregnancy in women with a history of venous thrombosis, with a positive family history or when an antiphospholipid syndrome is suspected, and may not be replaced by a global screening test, whose sensitivity to these thrombophilic risks is yet unknown.

Fetal loss is a common and significant problem, since about 20% of all women of childbearing age experience at least one fetal loss, and at least five percent have two or more spontaneous abortions. Furthermore, about 30–40% of recurrent abortions remain unexplained after comprehensive gynecological, hormonal and genetic investigations [13]. In a recently published review, several studies examining the correlations between recurrent abortion and thrombophilic risks were evaluated [14]. It was possible to show significant associations for early and late abortions in carriers of the heterozygous factor V-Leiden mutation, the heterozygous prothrombin mutation 20210 and in patients with positive anticardiolipin antibodies, while protein-S deficiency was significantly associated with the occurrence of late abortions. Moreover it has been known for a long time that recurrent abortions are a typical symptom in patients with antiphospholipid antibodies [15]. Therefore, thrombophilia screening is useful in women with repeated miscarriages.

For patients with antiphospholipid syndrome and recurrent fetal loss, the benefit of anticoagulation in a subsequent pregnancy has been proven, whereas for inherited thrombophilia, placebo-controlled studies for this indication have not yet been completed [5], so that anticoagulation with low-molecular heparin is therefore currently not recommended. Whether global coagulation tests exhibit any benefit in these situations remains unknown.

Use of oral post-menopausal hormone replacement therapy increases the relative risk to develop venous thrombosis two- to fourfold, which is similar to the relative risk induced by oral contraceptive use. The risk is greatest during the first year of therapy, and is also increased in women with thrombophilia or a positive history of venous thromboembolisms [16].

When assessing the overall risk for an individual, it should be remembered that the relative risk of venous thromboses during post-menopausal hormone replacement is increased only about two to four times, but with the simultaneous presence of thrombophilia, the absolute risk of venous thrombosis is considerably increased due to the greater age of the women in comparison to younger women taking oral contraceptives [17, 18]. Therefore, with a positive own or family history, differentiated thrombophilia screening may be useful before starting post-menopausal hormone replacement therapy. When thrombophilia is detected, it may be beneficial to start transdermal application of hormones, which is associated with a significantly smaller risk of venous thrombosis [19]. Also for this indication no data are available for global coagulation tests.

In summary, it can be stated that thrombophilia screening makes sense in many clinical situations. Global coagulation tests are currently not able to replace this type of screening, although they have proven useful for assessing the risk of recurrent thrombosis, and may potentially serve as screening tests for differentiated thrombophilia screening in the near future [20]. However, due to the great number of different global testing methods, numerous studies are required to clinically validate

the significance of these test methods for different indications.

References

1. Lindhoff-Last E. Wann ist der D-Dimer-Test nach Operationen verwertbar? Dtsch Med Wochenschr. 2004;129:972. [When to use the D-Dimer test after operations.]
2. Harper PL, Theakston E, Ahmed J, Ockelford P. D-dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly. Intern Med J 2007; 37:607–13.
3. Luxembourg B, Lindhoff-Last E. Genomische Diagnostik thrombophiler Gerinnungsstörungen bei Frauen – Klinische Relevanz. Hamostaseologie 2007;27:22–31. [Genomic diagnostics of thrombophilic coagulation disorders in women – clinical relevance. Haemostaseology]
4. Walker ID. Thrombophilia in pregnancy. J Clin Pathol 2000;53:573–80.
5. Lindhoff-Last E, Luxembourg B. Evidence-based indications for thrombophilia-screening. Vasa 2008;1:19–30.
6. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003;362:523–6.
7. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors and recurrent venous thrombotic events. J Am Med Assoc 2005;293: 2352–61.
8. Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wislof F, Musial J, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost 2005; 3:848–53.
9. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of anticoagulation study group. Am J Med 1998;104:332–8.
10. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, et al. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006;355:1780–9.
11. Hach-Wunderle V. Die Venenthrombose in der Schwangerschaft. Vasa 2003;32:61–8.
12. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost 2008;6:632–7.
13. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an pudate of the Utah experience. Obstet Gynecol 1992;80:614–20.
14. Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe DGO, et al. Thrombophilia in pregnancy: a systematic review. Br J Haematol 2005;132:171–96.
15. Rai RS, Regan L, Clifford K, Pickering W, Dave M, Mackie I, et al. Antiphospholipid antibodies and beta 2 glycoprotein I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. Hum Reprod 1995;10: 2001–5.
16. Moores L, Bilello KL, Murin S. Sex and gender issues and venous thromboembolism. Clin Chest Med 2004;25:281–97.
17. Herrington DM, Vittinghoff E, Howard TD, Major DA, Owen J, Reboussin DM, et al. Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. Arterioscler Thromb Vasc Biol 2002;22:1012–7.
18. Vandenbroucke JP, Rosing J, Bloemenkamp KWM, Middeldorp S, Helmerhorst FM, Bouma BN, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001;344:1527–35.
19. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al. Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study Circulation 2007;115:840–5.
20. Couturaud F, Duchemin J, Leroyer C, Delahousse B, Abgrall JF, Mottier D, et al. Thrombin generation in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. A pilot study. Thromb Haemost 2008; 99:223–8.