Role and Management of Coagulopathies in Vascular Erectile Dysfunction

B Chughtai, S Khan, J Rehman, D Sciullo, E Mohan, H Rehman

Citation

B Chughtai, S Khan, J Rehman, D Sciullo, E Mohan, H Rehman. *Role and Management of Coagulopathies in Vascular Erectile Dysfunction*. The Internet Journal of Urology. 2009 Volume 6 Number 2.

Abstract

Erectile dysfunction (ED) is frequently a symptom of underlying vascular disease. Vascular risk factors are the most common cause of erectile dysfunction. Endothelium of the penile vasculature plays an important role in the physiology of penile erection. Most patients presenting with vascular erectile dysfunction have a combination of trivascular disease, that being diabetes, hypertension and dyslipidemia, which may result in endothelial dysfunction. Other co-morbidities for vascular erectile dysfunction include smoking, sedentary life style, obstructive sleep apnea syndrome and obesity. When common vascular risk factors are absent, the critical role of a hypercoagulable state as contributing risk factor should be suspected. The inherited hypercoagulable syndromes primarily have an effect on veins, and only occasionally result in arterial thrombosis. The acquired hypercoagulable states which may cause endothelial dependent erectile dysfunction include antiphospholipid antibody syndrome, protein s, protein c and antithrombin III deficiencies, factor V Leiden and prothrombin gene mutation, hyperhomocysteinemia, dysfibrogenenmia and plasminogen deficiency. This paper reviews common hypercoagulable states that may result in endothelial dysfunction, and be an unsuspected cause of ED.

INTRODUCTION

ED may be the result of undetected life threatening diseases, as it is the natural consequence of a wide variety of systemic and local factors. Multiple studies have shown the risk factors for ED to be diabetes mellitus, hypercholesterolemia, smoking and cardiovascular disease.(1) In the absence of these risk factors, a significant number of persons with ED may have a previously undiagnosed clotting disorders or "hypercoagulable state." These coagulopathies appear to provide a logical pathophysiologic mechanism for infarctions, clots, and endothelial dysfunction leading to either difficulty maintaining or loss of an erection.

COAGULOPATHIES

Hypercoagulability is the increased risk of thrombosis or blood clot formation in blood vessels. The disorder comes in two forms, thrombophilia (increased tendency to form thrombi) and hypofibrinolysis (reduced ability to lyse thrombi once they form), both of which imply poor control of one or more aspects of the coagulation homeostasis system. Hypercoagulable states lead to endothelial dysfunction, local inflammation, and scarring in the intima of blood vessel walls. This causes decreased compliance and vasomotion in the blood vessels of major organ systems. At least 6% of Western populations have a hypercoagulability state, usually as an autosomal dominant inherited defect or mutation.(2) Hypercoagulability can also be caused by an ongoing environmental stimulus to thrombosis, such as a focal infection, medications (corticosteroids), autoimmune diseases (lupus erythematosus), or malignancies (hepatoma). Moreover, the inherited disorders can be amplified by environmental factors.

THROMBOPHILIA

PROTEIN C, PROTEIN S, AND ANTITHROMBIN III (AT3) DEFICIENCY

Protein S is a vitamin K-dependent protein that is synthesized in the liver and is a co-factor for protein C, helps to suppress factor Va activity. When deficient, there is excessive factor Va leading to thrombophilia. This autosomal dominant hereditary deficiency is found in 0.5% of the general population.(3) Both heterozygotic and homozygotic mutations may produce hypercoagulability.

Protein C deficiency is another vitamin K-dependent protein synthesized in the liver. It is activated by endothelial cell surface thrombin-thrombomodulin complex and, along with its co-factor protein S, inhibits the prothrombotic factors V and VIII. Protein C especially suppresses activity of factor Va and when it is diminished there is increased procoagulant

activity. This autosomal dominant hereditary deficiency is found in 0.3% of the general population.(4) Both heterozygotic and homozygotic mutations may produce hypercoagulability but the latter defect usually produces more severe disease.

Antithrombin (antithrombin III, AT-III) is a potent inhibitor of the coagulation cascade. It is a non-vitamin K-dependent protease that inhibits the action of thrombin as well as other procoagulant factors (eg, factor Xa). Congenital AT-III deficiency is an autosomal dominant disorder that leads to increased risk of venous and arterial thrombosis, with onset of clinical manifestations typically presenting in young adulthood.(5)

FACTOR V LEIDEN MUTATION (FVLM)

Mutant Factor V gene (Leiden mutation) produces activated protein C resistance (APCR). A defect in the procoagulant protein, Factor V, does not allow binding by activated protein C, leading to unopposed procoagulant activity and increased risk of clot formation. It is caused by an autosomal dominant mutation, which blocks binding of activated protein C to the prothrombotic Factor V. APCR is the most common heritable thrombophilic factor, found in 3-7% of the population.(4) APCR is found in 11-64% of persons with hypercoagulability.(4)

PROTHROMBIN GENE MUTATION

Prothrombin is the precursor of the serine protease thrombin. A mutation in the prothrombin gene results in high levels of prothrombin and subsequently a thrombotic predisposition. A review of 13 studies found a cumulative prothrombin mutation prevalence of 4.5% at all ages and 5.7% among those less than 50 years of age.(6)

CYSTATHIONINE ß-SYNTHASE (CBS) GENE MUTATION/ HYPERHOMOCYSTEINEMIA

The CBS enzyme converts homocysteine to cystathionine. Mutation allows a build-up of homocysteine in the blood, i.e. hyperhomocysteinemia. Methylene tetrahydrofolate reductase MTHFR mutation/polymorphism controls serum levels of homocysteine, a major thrombophilic risk factor. Homozygous persons have a 70% reduction in MTHFR activity and twice the normal level of homocysteine in their blood (i.e. hyperhomocysteinemia), resulting in thrombophilia.(7) Usually, it is inherited as an autosomal dominant mutation but it can be acquired by a deficiency of vitamin B12 or folate, or renal insufficiency.

Numerous mechanisms for homocysteinemia-induced ischemia have been proposed. These include an increase in adhesiveness of platelets, activation of the coagulation cascade, conversion of LDL cholesterol into proatherogenic forms, and endothelial damage with increased tissue factor expression.(8)

Evidence from studies has validated the relationship between elevated homocysteine and accelerated atherosclerosis.(9) Patients with increased homocysteine have more severe endothelial disease than those with normal levels.(8) Elevated homocysteine increases the odds of intimal thickening of blood vessels more than three-fold.(8) It is this intimal thickening and inhibition of nitric oxide mediated cavernosal smooth muscle relaxation that can lead to resistant endothelium in the penis and resultant ED.(10)

DYSFIBRINOGENEMIA

The majority of patients with dysfibrinogenemia are asymptomatic, about one-third have a bleeding tendency, and a much smaller proportion are predisposed to thrombosis. (11) Acquired dysfibrinogenemia occurs in patients with severe liver disease or malignancy. The resulting coagulopathy is due to a structural defect caused by an increased carbohydrate content impairing the polymerization of the fibrin. This leads to local reactions and inflammation leading to scarring and thickening of blood vessel walls.

PLASMINOGEN DEFICIENCY

Plasminogen deficiency is a rare autosomal recessive disorder that may lead to decreased activity of the fibrinolytic pathway and present in 1-3% of families with inherited thrombosis versus 0.4% in general population.(12) The deficiency can be determined via immunologic and functional assays for plasminogen. The loss of plasminogen greatly accelerates the formation of intimal lesions that lead to atherosclerosis in mice.(13)

ANTIBODY MEDIATED COAGULOPATHY

Autoimmune or chronic “connective tissue” diseases, especially lupus erythematosus, chronic fatigue syndrome and myofascial pain syndrome, can develop antibodies directed against protective proteins in the walls of endothelial cells. These patients have increased markers of coagulation activation and increased blood viscosity due to the generation of Soluble Fibrin Monomer (SFM). SFM dimerizes easily, increasing blood viscosity and precipitating out on the surface of endothelial cells as fibrin deposits, creating local ischemia by blocking nutrient and oxygen

delivery in the capillary beds.(14) Initially, endothelial coating is all that is seen, but long-standing cases typically show complete blockage of vessels.

Anticardiolipin antibodies and lupus anticoagulant (ACLA) are antiphospholipid autoantibodies which are directed against negatively charged phospholipid antigens. They are prothrombotic via several mechanisms, including inhibition of prostacyclin synthesis, impairment of the thrombomodulin-protein C-protein S anticoagulant system, action as anti-endothelial cell antibodies, or interaction with platelet membrane phospholipids.

ADDITIONAL THROMBOPHILIA OR COAGULATION PROTEIN REGULATING DEFECTIONS

Decreased antithrombin, antithrombin III deficiency (found in 0.1% of the general population and in 0.5-4.9% of persons with hypercoagulability), Factor II gene mutation, decreased thrombomodulin, decreased heparin co-factor II, increased Factors II, VIII, IX, X, XI, XII are all inheritable cofactors for hypercoagulability. One significant abnormality may contribute to a hypercoagulable state. Thrombophilia may be caused by more than one genetic abnormality in any of the proteins mentioned here.

HYPOFIBRINOLYSIS

DECREASED TISSUE PLASMINOGEN ACTIVATOR ACTIVITY (TPA-FX)

Tissue plasminogen activator is the major stimulator of fibrinolysis. When it is not stimulated or is diminished the homeostatic process of thrombus lysis cannot begin or is considerably slowed, resulting in a hypercoagulable state. Poorly stimulated tissue plasminogen activator is often accompanied by high plasminogen activator inhibitor activity, the major inhibitor of fibrinolysis. High plasma triglycerides and/or hyperinsulinemia can increase inhibitor activity and thereby reduce fibrinolysis.

INCREASED LIPOPROTEIN (A) [LP(A)]

Lp-a is a lipoprotein particle with a structure very similar to an LDL particle linked to a plasminogen molecule. The function of Lp(a) is unknown. Lp-a is a marker for the development of atherosclerotic vascular disease. Individuals with elevated Lp-a are at an increased risk of developing endothelial dysfunction. It is not clear in the literature, whether Lp-a is directly involved in the atherogenic process. High levels of Lp(a) appear to reduce fibrinolysis, especially in the presence of corticosteroid therapy. In one study, it was demonstrated that Lp-a was not an independent risk factor for ED.(15)

ADDITIONAL HYPOFIBRINOLYSIS FACTORS AND ACQUIRED INHIBITORS IN COAGULATION HOMEOSTASIS

Two or more hypofibrinolysis factors can interrelate and contribute to a hypercoagulable state. These include decreased levels of plasminogen, decreased urokinase, increased homocysteine, and increased Factor XI. Antibody inhibitors may be seen as IgA or IgM, or both. These acquired factors may also lead to hypercoagulability; which include increased anticardiolipin antibody, lupus anticoagulant, antiphosphatidyl serine, B-2 glycoprotein I antibodies, and annexin V antibodies.

VASCULAR EVALUATION OF PATIENTS WITH ERECTILE DYSFUNCTION

Hypercoagulability should be suspected in persons with one or more of the following clinical features: thrombosis at a young age, family history of thrombosis, recurrent thrombosis, thrombosis in an unusual site, thrombosis for which no underlying mechanism can be identified, hip pain or replacement at an early age, stroke or myocardial infarction at an early age, osteonecrosis, Behçet's disease, and idiopathic death of tooth pulps.

The decision to evaluate ED patients for hypercoagulable states should depend on the expectation of a positive yield of the tests and on whether positive results would change the intended therapy. A study investigating the appropriateness of coagulation tests on patients with hypercoagulation found that 29% of those tested were not likely to have their management affected by the result.(16)

However, there are certain features that should guide testing toward specific entities. For example, clinical features that suggest a workup for hypercoagulability are idiopathic thrombocytopenia, thrombosis on both arterial and venous side, livedo reticularis, early age of thrombosis, noninfectious endocarditis, or a history consistent with a collagen vascular disease. When testing for a hypercoagulable state, it is useful to wait until after there is no evidence of active infection or inflammation. Testing for activated Protein C resistance from FVLM or prothrombin gene mutation should be considered in patients without any precipitating factors of a thrombophilic state or a positive family history. Features that should prompt testing for protein S, protein C, and antithrombin III deficiencies include venous or arterial thrombosis occurring in patients

aged below 45 years, recurrent thrombosis without precipitating factors, thrombosis in unusual locations, a positive family history of thrombosis, warfarin-induced skin necrosis (protein S, protein C) or resistance to heparin (AT3 deficiency). Anti-phospholipid syndrome should be suspected when an unexplained prolongation of the partial thromboplastin time (PTT) occurs. Testing is best performed in the absence of heparin or warfarin.

Hyperhomocysteinemia may respond to nutritional supplementation, it is reasonable to check for this congenital or acquired condition in all patients. Although there is not yet strong evidence that treatment prevents further recurrences, vitamin supplementation is quite safe and should be considered. Testing for the rare conditions of plasminogen and dysfibrinogenemia might be considered in patients when there is a high suspicion of a hypercoagulable state in the face of negative tests for the more common hypercoagulable disorders.

TREATMENT OF VASCULAR ERECTILE DYSFUNCTION

Treatment with the anticoagulants heparin and warfarin (targeted INR of 2.0-2.5) can help to normalized thrombophilia and hypofibrinolysis in patients with underlying hypercoagulable states. Patients with antibody mediated coagulopathies can be treated with plasmapheresis to reduce circulating antibodies that cause endothelial dysfunction. In addition to these treatments, lifestyle modifications of controlling obesity by diet, encouraging exercise, and cessation of smoking would decrease the progression of endothelial damage.

Patients with a hypercoagulable state who suffer from erectile dysfunction likely have an arteriogenic and/or venogenic component. Recurrent thrombosis associated with thrombophilia and hypofibrinolysis can result in endothelial dysfunction and abnormal vasomotor function such as that seen in diabetes and hypercholesterolemia.(17) L-Arginine, a nitric oxide donor, has been shown in a rabbit model of cavernosal ischemia to restore endothelium-dependent smooth muscle relaxation. (18) Clinical trials are few, with mixed results. However, in a randomized, double-blind placebo-controlled trial where large doses of L-arginine were used, a significant improvement in sexual function was seen in the subjects taking L-arginine.(19)

Oral phosphodiesterase-5 (PDE5) inhibitors are now first line therapy for ED. By inhibiting PDE5, cGMP is propagated which results in increased relaxation of vascular smooth muscle. This results in both enhanced arterial inflow and reduced venous outflow. With other systemic vascular diseases resulting in endothelial dysfunction, such as diabetes and hypercholesterolemia, PDE5 inhibitors have been successful in the treatment of ED.(20, 21)

In patients who are refractory to oral therapy or who have a contraindication to their use, intraurethral or intracavernosal therapy will likely be needed. However, caution must be taken. One of the few contraindications of intracavernosal injections of vasoactive drugs is a severe hypercoagulable state, such as sickle cell disease, which could lead to a priapism episode.

CONCLUSION

There has been ample research in the development of ED secondary to cardiovascular disease. Little research has looked into hypercoagulability as a primary risk factor for endothelial dysfunction compromising erectile function. With a wide variety of screening tests and treatments for the hypercoagulable states, these should be tested for in the appropriate clinical scenarios. Early detection of hypercoagulable states resulting in endothelial dysfunction may be a useful measure to guide systemic therapy prior to the development of symptomatic atherosclerosis or thromboses. Clearly, more studies are required to determine the prevalence of ED in this population, as well as the effectiveness of available treatments.

Figure 1

Table 1: Hypercoagulable States

Thrombophilia	Hypofibrinolysis
• *Protein C, Protein S, And Antithrombin III Deficiency* • *Factor V Leiden Mutation* • *Prothrombin Gene Mutation* • *Cystathionine ß-synthase gene mutation* • *Hyperhomocysteinemia* • *Dysfibrinogenemia* • *Plasminogen Deficiency* • *Antiphospholipid Antibodies* • *Anticardiolipin antibodies and lupus anticoagulant* • *Apolipoprotein mutation* • *Additional thrombophilia or coagulation protein regulating defections*	• *Decreased tissue plasminogen activator activity* • *Increased plasminogen activator inhibitor gene polymorphism* • *Increased lipoprotein (a)* • *Additional hypofibrinolysis factors* • *Acquired inhibitors in coagulation homeostasis*

References

1. Sullivan ME, Keoghane SR, Miller MA: Vascular risk factors and erectile dysfunction. BJU Int 2001; 87(9):838-45
2. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, et al.: Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med 1995; 332(14):912-7
3. Bombeli T, Basic A, Fehr J: Prevalence of hereditary thrombophilia in patients with thrombosis in different

venous systems. Am J Hematol 2002; 70(2):126-32
4. Middendorf K, Gohring P, Huehns TY, Seidel D, Steinbeck G, et al.: Prevalence of resistance against activated protein C resulting from factor V Leiden is significantly increased in myocardial infarction: investigation of 507 patients with myocardial infarction. Am Heart J 2004; 147(5):897-904
5. Demers C, Ginsberg JS, Hirsh J, Henderson P, Blajchman MA: Thrombosis in antithrombin-III-deficient persons. Report of a large kindred and literature review. Ann Intern Med 1992; 116(9):754-61
6. Tamim H, Finan RR, Almawi WY: Prevalence and distribution of the prothrombin G20210A mutation. Am J Hematol 2002; 71(3):235-6
7. Janson JJ, Galarza CR, Murua A, Quintana I, Przygoda PA, et al.: Prevalence of hyperhomocysteinemia in an elderly population. Am J Hypertens 2002; 15(5):394-7
8. Papa A, De Stefano V, Danese S, Chiusolo P, Persichilli S, et al.: Hyperhomocysteinemia and prevalence of polymorphisms of homocysteine metabolism-related enzymes in patients with inflammatory bowel disease. Am J Gastroenterol 2001; 96(9):2677-82
9. Selhub J, D'Angelo A: Relationship between homocysteine and thrombotic disease. Am J Med Sci 1998; 316(2):129-41
10. Khan MA, Thompson CS, Emsley AM, Mumtaz FH, Mikhailidis DP, et al.: The interaction of homocysteine and copper markedly inhibits the relaxation of rabbit corpus cavernosum: new risk factors for angiopathic erectile dysfunction? BJU Int 1999; 84(6):720-4
11. Lijnen HR, Soria J, Soria C, Collen D, Caen JP: Dysfibrinogenemia (fibrinogen Dusard) associated with impaired fibrin-enhanced plasminogen activation. Thromb Haemost 1984; 51(1):108-9
12. Okamoto A, Sakata T, Mannami T, Baba S, Katayama Y, et al.: Population-based distribution of plasminogen activity and estimated prevalence and relevance to thrombotic diseases of plasminogen deficiency in the Japanese: the Suita Study. J Thromb Haemost 2003; 1(11):2397-403
13. Xiao Q, Danton MJ, Witte DP, Kowala MC, Valentine MT, et al.: Plasminogen deficiency accelerates vessel wall disease in mice predisposed to atherosclerosis. Proc Natl Acad Sci U S A 1997; 94(19):10335-40
14. Watanabe R, Wada H, Sakakura M, Mori Y, Nakasaki T, et al.: Plasma levels of activated protein C-protein C inhibitor complex in patients with hypercoagulable states. Am J Hematol 2000; 65(1):35-40
15. Sullivan ME, Miller MA, Bell CR, Jagroop IA, Thompson CS, et al.: Fibrinogen, lipoprotein (a) and lipids in patients with erectile dysfunction. A preliminary study. Int Angiol 2001; 20(3):195-9
16. Fritsma GA, Southern DK: Hematologic effects of thrombophilia. Clin Lab Sci 1998; 11(4):233-8
17. Azadzoi KM, Saenz de Tejada I: Hypercholesterolemia impairs endothelium-dependent relaxation of rabbit corpus cavernosum smooth muscle. J Urol 1991; 146(1):238-40
18. Masuda H, Tsujii T, Okuno T, Kihara K, Goto M, et al.: Accumulated endogenous NOS inhibitors, decreased NOS activity, and impaired cavernosal relaxation with ischemia. Am J Physiol Regul Integr Comp Physiol 2002; 282(6):R1730-8
19. Chen J, Wollman Y, Chernichovsky T, Iaina A, Sofer M, et al.: Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. BJU Int 1999; 83(3):269-73
20. Rendell MS, Rajfer J, Wicker PA, Smith MD: Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. Jama 1999; 281(5):421-6
21. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, et al.: Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998; 338(20):1397-404

Author Information

Bilal Chughtai
Department of Urology, School of Medicine, SUNY-Stony Brook University Medical Center

Sardar Ali. Khan
Department of Urology, School of Medicine, SUNY-Stony Brook University Medical Center

Jamil Rehman
Department of Urology, School of Medicine, SUNY-Stony Brook University Medical Center

Daniela Sciullo
Surgery Service, VA Medical center

Eugene Mohan
Surgery Service, VA Medical center

Herra Rehman