Hereditary Coagulopathies: Practical Diagnosis and Management for the Plastic Surgeon

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Background: Venous thromboembolism is a devastating complication representing one of the major causes of postoperative death in plastic surgery. Within the scope of plastic surgery, body-contouring procedures are often considered to carry a higher risk of venous thromboembolism. Hereditary thrombophilias comprise a group of conditions defined by a genetic predisposition to thrombosis development. Collectively, hereditary thrombophilias are present in at least 15 percent of Western populations and underlie approximately half of thromboembolic events. Although the topic of venous thromboembolism is discussed widely throughout the literature, there is little published on the diagnosis and management of hereditary thrombophilias in the plastic surgery literature. The goals of this study were to present a review of the major inherited thrombophilias, to delineate the risk of these disorders, and to recommend a practical algorithm for patient screening and management before major plastic surgery.
Methods: A MEDLINE search was performed from 1965 to the present to review the literature on inherited thrombophilia disorders.
Results: Based on the English language literature and clinical experience, the authors suggest practical guidelines for screening and management of hereditary thrombophilias. A thorough medical history and preoperative evaluation are key to reducing venous thromboembolism complications.
Conclusions: Hereditary thrombophilias are present in a significant number of thromboembolic events. Preoperative vigilance on the part of the plastic surgeon may help to identify patients with undiagnosed hereditary thrombophilias and thereby decrease the incidence of venous thromboembolism. (*Plast. Reconstr. Surg.* 125: 1544, 2010.)

There are over 200,000 hospital admissions for pulmonary embolism annually in the United States, with an estimated mortality of 50,000 to 100,000.[1–4] Most thromboembolic complications related to surgery and immobilization occur within 30 days of surgery.[5–7] Underlying hypercoagulable states, or thrombophilias, are a common risk factor for venous thromboembolism, and the plastic surgeon should have a working knowledge of the diagnosis and management of these patients. Because of the high prevalence of these disorders, the plastic surgeon can identify previously undiagnosed patients through careful routine screening in the office.

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Received for publication August 1, 2009; accepted October 5, 2009.

DOI: 10.1097/PRS.0b013e3181d51344

CLINICAL CASE EXAMPLE

Patient with Undiagnosed Coagulopathy Presenting for Plastic Surgery Consultation

A 55-year-old woman was referred for consultation by her bariatric surgeon for panniculectomy following a 150-pound weight loss. She had a history of deep vein thrombosis 30 years ago during her second pregnancy. She had since undergone uneventful abdominal operations and denied any personal history of pulmonary embolus, stroke, or heart attack. She received perioperative deep vein thrombosis prophylaxis with heparin for some of her abdominal operations and denied any complications after her opera-

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article.*

tions. She also denied any significant family history of clotting or bleeding disorders.

Analysis and Management

Because her prior deep vein thrombosis was thought to be provoked and the patient had uneventful surgery, she had not been previously evaluated for hypercoagulable disorders. A full blood panel screen was ordered by the plastic surgery service and revealed the patient to be heterozygous for the factor V Leiden mutation. Her first-degree family members were also screened and her daughter was positive as well. The patient was referred to a hematologist, who advised a 10- to 14-day regimen of enoxaparin 40 mg daily after surgery, compressive stockings for her symptoms of chronic venous insufficiency, and sequential compression devices in the operating room. The patient underwent a panniculectomy without adverse events.

The term "thrombophilia" includes any inherited and acquired disorder associated with an increased tendency to suffer venous thromboembolism. The risk level is related to the type of defect and the number of major chromosomes affected (homozygous versus heterozygous).[8] It has been recently reported that a hypercoagulable state is present in more than half of the patients who present with an "unprovoked venous thromboembolism."[9] There is also a significant incidence in patients with presumably provoked venous thromboembolism, and it is a reasonable approach to perform a thrombosis workup on all patients who suffer venous thromboembolisms. This approach represents a paradigm shift in the way patients are evaluated before surgery and helps to reduce the incidence of thrombosis in patients who are found to be at high risk.

The aims of this article are to present a review of the major inherited thrombophilia disorders, to delineate the risk of these disorders, and to recommend a practical algorithm for patient screening and management before major plastic surgery. A MEDLINE search was performed from 1965 to the present to review the literature on inherited thrombophilia disorders. Based on these results, we have developed a set of recommendations for the preoperative and postoperative management of venous thromboembolism in high-risk patients contemplating body-contouring surgery or other major plastic surgery procedures.

OVERVIEW OF INHERITED THROMBOPHILIAS

Since the first case of inherited thrombophilia was described in 1965, various forms of inherited thrombophilia have been identified, and the risks for venous thromboembolism associated with each have been studied.[10] Generally, thrombogenic risk factors can be divided into two groups: inherited and acquired.

Thrombophilias are generally associated with venous rather than arterial thrombosis and may be detected in a significant number of patients who present with their first episode of venous thromboembolism.[1] Thromboembolism is increasingly viewed as a chronic systemic disease, with recurrence rates of 17.5 percent at 2 years and 30.3 percent at 8 years of follow-up.[11,12] These patients are at higher risk compared with the normal population in the setting of an inciting factor such as surgery. The relative risk increases based on the type and number of thrombophilias present and the significance of the thrombogenic trigger.[1] Thrombophilias can be further divided based on the mechanisms involved. The two main subsets are (1) abnormal function of naturally occurring coagulation factors and (2) deficiencies of naturally occurring coagulation factors (Table 1).

Table 1. Major Hereditary Thrombophilia Disorders, Risk Level, and Commonly Recommended Venous Thromboembolism Prophylaxis

Condition	Risk for VTE	Generally Recommended Prophylaxis*
Genetic mutations of coagulation factors		
Activated protein C factor V Leiden	Mild	Mechanical device (e.g., SCDs) and perioperative chemoprophylaxis; consideration may be given to continuing pharmacologic agents for up to 28 days after discharge[13]
Prothrombin G20210A	Mild	
Elevated levels of factors VIII, IX, and XI	Mild	
Deficiency of anticoagulant protein		
Protein S deficiency	Moderate	
Protein C deficiency	Moderate to severe	
Antithrombin deficiency	Severe	

VTE, venous thromboembolism; SCDs, serial compression devices.
*Only applicable to patients who are not already on prolonged anticoagulation therapy before surgery. Exact regimens for specific cases may vary based on a detailed evaluation and risk assessment by a hematologist.

Hereditary Thrombophilia Subset I: Abnormal Function of Coagulation Factors

These thrombophilia disorders are approximately five times more common among the Caucasian population than the second subset (Table 2).[14]

Activated Protein C Resistance and Factor V Leiden

Activated protein C, together with its cofactor protein S, inhibits the coagulation cascade by inactivating factor Va and factor VIIIa. Activated protein C cleaves factor Va in three sites; a mutation in the first site is known as factor V Leiden. Mutations in the other sites are described as factor V Cambridge and factor V Hong Kong, respectively.[10] In carriers of factor V Leiden, factor Va is inactivated approximately 10 times more slowly than normal.

Factor V Leiden was first described in 1994 and is responsible for at least 90 percent of the activated protein C–resistant conditions. It is the most prevalent thrombophilic defect, occurring in 5 to 15 percent of the general population.[2] The HR2 haplotype of the Factor V gene has also been associated with activated protein C resistance, though an exact mutation has not been found. It is the most common genetic risk factor for venous thromboembolism, found in 20 percent of patients presenting with a first episode of venous thromboembolism.[12,18–22] The prevalence of the homozygous form is 1.5 percent of the general population.[21]

The relative risk for venous thromboembolism among heterozygotes is 3 to 10, but this risk significantly increases when an acquired hypercoagulability factor is added, such as oral contraceptives, which increases the relative risk to 30 to 40.[11,15,19] Homozygotes develop more significant thrombophilia, with a relative risk of 79 increasing to 100 with oral contraceptives.[11,23] Prospective cohort studies have found that 20.5 percent of the heterozygote carriers develop a recurrence after an initial unprovoked venous thromboembolism compared with 14.4 percent of patients without an identifiable thrombophilia.[23]

Table 2. Frequency of Hereditary Thrombophilia

Thrombophilia	General Population (heterozygous frequency)[11,15-17]	Individuals with a VTE Who Test Positive[11,15-17]
Factor V Leiden	1 in 20	1–2 in 10
Prothrombin gene variant	2–3 in 100	5–10 in 100
Antithrombin deficiency	1 in 500	1 in 25
Protein C deficiency	1 in 500	1 in 50
Protein S deficiency	3–13 in 1000	1 in 50

VTE, venous thromboembolism.

Prothrombin Mutation G20210a

The G20210A mutation in the prothrombin gene is the second most prevalent form of inherited thrombophilia, found in 1 to 5 percent of the population and up to 9 percent of patients presenting with their first episode of venous thromboembolism.[11,24] It is an autosomal dominant mutation causing elevated levels of the normal plasma prothrombin concentration.[24] The relative risk for venous thromboembolism is 2 to 5 in carriers and increases to 16 when combined with oral contraceptive use.[25] However, a prothrombin level higher than 115 percent results in a doubled risk of venous thromboembolism, even in the absence of the prothrombin mutation. Therefore, carriers, and noncarriers cannot be distinguished using the prothrombin level alone because there is a high degree of overlap between the groups.[11]

Elevated Levels of Coagulation Factors

Increased levels of factor VIII, factor IX, and factor XI and fibrinogen may also increase the risk of venous thromboembolism.[26–29] This is most strongly supported for factor VIII, with a 10 percent increase raising relative venous thromboembolism risk by 10 percent.[30] Similarly, elevated factor IX and factor XI may increase the risk of venous thromboembolism by 2.5-fold and 2-fold, respectively.[26–29] Finally, elevated fibrinogen levels (>500 mg/dl) are associated with a 4-fold increased risk of venous thromboembolism.[29] Some disturbances in factor levels may be revealed by abnormally short coagulation times. The value of specific testing for these conditions is still being explored.

Hereditary Thrombophilia Subset II: Deficiency of Coagulation Factors

Antithrombin III Deficiency

Antithrombin III inhibits the coagulation cascade through direct inhibition of thrombin and other coagulation factors. This process is accelerated 1000-fold by heparin.[12] Antithrombin III deficiency is an autosomal dominant trait found in 0.02 percent of the general population and in 0.5 to 7.5 percent of patients who present with their first venous thromboembolism.[31] Traditionally, these patients were considered to have a higher risk for thrombosis compared with those with other thrombophilias.[11] However, its rarity has prevented accurate assessment of the increase in relative risk after an initial thromboembolic episode. It has been shown that this defect in combination

with oral contraceptive use causes an increased risk of venous thromboembolism (relative risk, 10).[12,17] It has been estimated that 60 percent of heterozygotes will develop venous thromboembolism by the age of 60 years, whereas the homozygous state is generally incompatible with life.[11,31]

Protein C Deficiency

Protein C deficiency is a rare thrombophilia, with a general population prevalence of 0.2 percent found in approximately 2.5 to 6 percent of patients presenting with their first venous thromboembolism.[11,32,33] There are several known mutations in the gene encoding for protein C.[10] Most patients have the heterozygous form of protein C deficiency, with a protein C level approximately half of normal. Approximately 50 percent of heterozygotes develop venous thromboembolism by the age of 60 years.[33] These patients may present with venous thromboembolism in adulthood or they may develop skin necrosis if they are administered vitamin K antagonists (e.g., warfarin).[11,34] The homozygous genotype completely lacks protein C and may be fatal shortly after birth unless protein C is given in the form of protein C concentrate, fresh frozen plasma, or factor IX concentrate.[11,33] A variant of protein C deficiency with two different genetic mutations is called compound heterozygosity and leads to severely reduced but not absent levels of protein C.

Protein S Deficiency

Protein S deficiency is another rare thrombophilia with a prevalence of 0.026 to 0.13 percent and is found in 1 to 2 percent of patients presenting with their first venous thromboembolism episode.[11,35] Protein S is a cofactor of protein C and can independently inhibit the prothrombinase and tenase complexes.[36] Thirty percent of protein S–deficient heterozygotes will develop venous thromboembolism by the age 60 years.[11] The homozygous form is associated with severe thrombophilia and neonatal purpura fulminans.[11,37] Warfarin-related skin necrosis has also been reported in protein S–deficient patients.[11]

Miscellaneous Hypercoagulable States

Hyperhomocysteinemia

Hyperhomocysteinemia is another finding that may lead to a mild hypercoagulable state and can be either heritable or acquired. The heritable state is related to two genes associated with homocystinemia, *MTHFR* polymorphisms and the rare, classic, congenital homocystinuria, which causes deficiency of cystathionine-β-synthase.[16,38] *MTHFR* gene polymorphisms are common enough that 12 percent of Caucasians are homozygous, although the heterozygous polymorphism is not a risk factor for venous thromboembolism.[11,39] Significantly elevated homocysteine levels are also known risk factors for both venous and arterial embolisms in multiple clinical trials, with a relative risk for venous thromboembolism of 2 to 3.[11,38] Acquired conditions that can cause mild to moderate homocystinemia include deficiencies of vitamin B_{12}, vitamin B_6, and folate and other chronic medical conditions.[39–42] However, it has been shown in randomized trials that lowering the plasma homocysteine level has no effect on thrombotic risk.[42,43] Because the heterozygous carrier status is not associated with thrombosis and the homozygous phenotype is associated with only a slightly elevated risk of thrombosis, routine screening is not justified and genetic abnormalities should not be treated.[39–41]

Fibrinolytic System Abnormalities

Generally, impaired fibrinolysis appears to be associated with an increased risk of venous thromboembolism, although the role of the individual components has not yet been elucidated.[11,43]

Acquired Thrombophilia

Although they are not the main focus of this review, acquired disorders are mentioned for thoroughness. The most common acquired cause of thrombophilia is antiphospholipid syndrome: an autoimmune disorder defined as thrombosis or miscarriage with persistent antibodies against phospholipids, the most well known of which are anticardiolipin, lupus anticoagulant, and anti–β_2-glycoprotein I.[17] These antibodies are found in 1 to 5 percent of young healthy subjects and increase with age.[45] Lupus anticoagulant is the most strongly associated with thrombosis and is associated with 5- to 16-fold increased odds for venous thromboembolism in case-control studies.[11,44,45] The isolated presence of antiphospholipid antibodies in the absence of the syndrome is considered a weak risk factor for venous thromboembolism that does not require long-term anticoagulation.[45]

Idiopathic Thromboembolism

Approximately half of the patients who present with an "unprovoked venous thromboembolism" will be found to be negative in the current thrombophilia genetic screenings. These idiopathic cases still have an approximately 15 percent risk of unprovoked recurrence, a rate not much lower than

heterozygous factor V Leiden carriers.[23] This is one basis for the theory that most, if not all, cases of venous thromboembolism represent a convergence of genetic predisposition with precipitating events.[1] According to this view, the only reason that thrombophilia is not detected in all cases of venous thromboembolism is that not all genetic defects are identified yet. Idiopathic superficial venous thrombosis is a separate clinical entity but one that may not always be benign. Underlying conditions should be considered in cases of migrant and recurrent superficial venous thrombosis, especially in the absence of varicose veins.[46]

Despite some data suggesting higher rates of provoked venous thromboembolism in African Americans, most known hereditary thrombophilias are substantially more common in the Caucasian population.[47] The incidence of factor V Leiden in African and Southeast Asian populations is extremely low (<0.1 percent), and fewer than one in 1000 African Americans carry the prothrombin mutation G20210A.[47] In contrast, African American and Asian American populations do carry factor V Leiden, with carrier rates of approximately 1.2 percent and 0.5 percent, respectively, as compared with a 9 percent carrier rate for Caucasian Americans. Comparison of coagulation deficiency rates is made challenging by differing reference ranges across races, but Asian populations have been found to have higher rates of protein C, protein S, and antithrombin III deficiency, with one study suggesting that up to half of Chinese patients with an unprovoked deep vein thrombosis will have a deficiency in one of these proteins.[47,48]

Clinical Significance of Thrombophilia in Body-Contouring Procedures

Body-contouring procedures, especially abdominoplasty, have had the highest association with deep vein thrombosis among plastic surgery operations. This underscores the need for identifying patients who are already at increased risk for venous thromboembolism because of underlying coagulopathies. Grazer and Goldwyn published the first cohort studying venous thromboembolism complications in body contouring[49] and found a 1 percent incidence of pulmonary embolism in a survey of over 10,000 abdominoplasties. Since then, subsequent studies have shown that abdominoplasty has the highest rates of venous thromboembolism among plastic surgery procedures, ranging from 1 to 9.4 percent.[49–53]

Body-contouring procedures create a highly thrombogenic environment for several reasons. These procedures result in wide dissections, long operative time, disruption of superficial veins, elevated intraabdominal pressure, and at times difficult postoperative mobilization.[52] A subset of our patients also present with a body mass index over 30, which has been demonstrated to be an independent risk factor for deep vein thrombosis.[54] Oral contraceptive use and hormone replacement therapy are additional known thrombogenic factors, and all of our patients are advised to stop taking them 1 month before surgery.

Because of the thrombogenic state induced by major surgical procedures, patients with a diagnosis of hereditary thrombophilia who may be at low risk for venous thromboembolism under normal circumstances are at much higher risk when undergoing surgery. This synergy of risk factors is consistent with reports in the literature showing that close to half of patients diagnosed with provoked thrombosis have a mild thrombophilia syndrome.[14]

Recommended Screening for Inherited and Acquired Thrombophilia

We advise plastic surgeons to specifically inquire about a patient's personal and family history of any venous thromboembolism events and anticoagulation treatment. It should be routine to ask about the historical risk factors listed in Table 3. Although it may seem complex to incorporate

Table 3. Historical Risk Factors to Consider in Routine Patient Screening

- Personal history of VTE (including during pregnancy or while taking oral contraceptives). Unusual site of thrombosis (mesenteric, splenic, portal, hepatic, cerebral) also increases suspicion.
- Personal history of idiopathic, migratory, or recurrent SVT in the absence of varicose veins.
- Personal or family history of skin necrosis when receiving warfarin. Warfarin decreases the level of natural anticoagulants, rendering the patient temporarily hypercoagulable. Development of skin necrosis is suggestive of preexisting protein C or S deficiency.
- Personal history of adverse pregnancy outcomes, including consecutive spontaneous abortions later than 10 weeks of gestation, three nonconsecutive spontaneous abortions, severe unexplained intrauterine growth restriction, intrauterine fetal death, placental abruption, or severe preeclampsia.
- First-degree relative who had a VTE, especially at a young age.
- First-degree relative with known hereditary coagulopathy.
- First-degree relative of a neonate with purpura fulminans without sepsis. This suggests a homozygous state of protein C and S deficiencies.

VTE, venous thromboembolism; SVT, superficial venous thrombosis.

into a routine patient screen, these risk factors can be identified by starting with six simple questions that the patient can answer on a standard intake form (Table 4). A positive response to any of the questions would warrant further direct questioning by the surgeon. A yes answer to any question can be explored further to identify the presence of historical risk factors in Table 3.

There are no data regarding the cost effectiveness of thrombophilia screening in the plastic surgery population. The United Kingdom's National Institute for Health Research conducted a cost effectiveness study that considered thrombophilia testing before major orthopedic surgery.[55] It concluded that with an average U.K. screening cost of £50, history-based selective screening for thrombophilia was reasonably cost effective. Studies conducted in the United States have estimated a cost of approximately $150 for screening.[56,57] Despite the lack of cost effectiveness data in the United States plastic surgery patient population, we feel it is reasonable to test patients with historical risk factors. There is no question that the cost of treating a thrombotic complication is unquestionably high.

Management of Known or Suspected Hereditary Thrombophilia

Patients with a known diagnosis of a coagulopathy can be referred to a hematologist for specific recommendations on management. Patients with no preexisting diagnosis who are suspected to be at risk based on historical factors should be evaluated further. The plastic surgeon can initiate the workup by ordering the laboratory panel shown in Table 5.[16] There may be several available tests for each thrombophilia; prothrombin mutation can only be assessed by means of genetic testing, whereas functional (activity) assays are recommended for factor V Leiden, protein C, protein S, and antithrombin III.[57] Figure 1 shows a practical algorithm that plastic surgeons can incorporate into their practice.

Table 4. Six Simple Questions to Ask Every Patient

Sample Questionnaire for Patients		
Have you or anyone in your family ever had a blood clot?	Yes	No
Have you or anyone in your family ever been on blood thinners?	Yes	No
Have you or anyone in your family ever been diagnosed with a blood clotting disorder?	Yes	No
Has anyone in your family had a disease called "purpura fulminans?"	Yes	No
Have you ever been diagnosed with lupus or any other autoimmune disease?	Yes	No
For female patients: have you ever had a miscarriage?	Yes	No

Table 5. Blood Panel to Screen for Hypercoagulable State*

- Complete blood count
- PT, PTT
- Activated protein C resistance (factor V Leiden testing if abnormal)
- Prothrombin G20210A genotype (factor II mutation)
- Antithrombin III activity
- Protein C activity
- Protein S activity
- Antiphospholipid antibody testing (lupus anticoagulant, anticardiolipin, anti–β_2-glycoprotein I)

PT, prothrombin time; PTT, partial thromboplastin time.
*The plastic surgeon can initiate this work-up if historical factors suggest a risk.

Venous Thromboembolism Prophylaxis in the Setting of Hereditary Thrombophilia

Long-term prophylaxis for most previously asymptomatic individuals with hereditary thrombophilia is not recommended, as the lifetime risk of death from bleeding on anticoagulants is greater than the risk of death from thrombosis.[11,52] However, major surgery and postoperative immobilization are considered additional acquired risk factors that increase the risk of venous thromboembolism and therefore necessitate appropriate prophylaxis. The risk of venous thromboembolism is highest within the first 2 weeks after surgery and remains elevated for at least 1 month.[52,54]

Compared with most plastic surgery patients, those with a known diagnosis of a hypercoagulable state are at higher risk for perioperative venous thromboembolism when undergoing a major procedure. Because of the varied risk level associated with thrombophilias, we routinely seek guidance from a medical specialist for the exact prophylaxis regimen in each specific case. Although there are no specific recommendations for surgical patients with known thrombophilia, these patients are considered most analogous to high-risk general surgery patients and, according to the American College of Chest Physicians guidelines for prevention of venous thromboembolism, would be treated with both chemoprophylaxis and perioperative mechanical devices (i.e., sequential compression devices).[13] In addition, consideration may be given to continuing chemoprophylaxis for up to 28 days after discharge for selected patients.

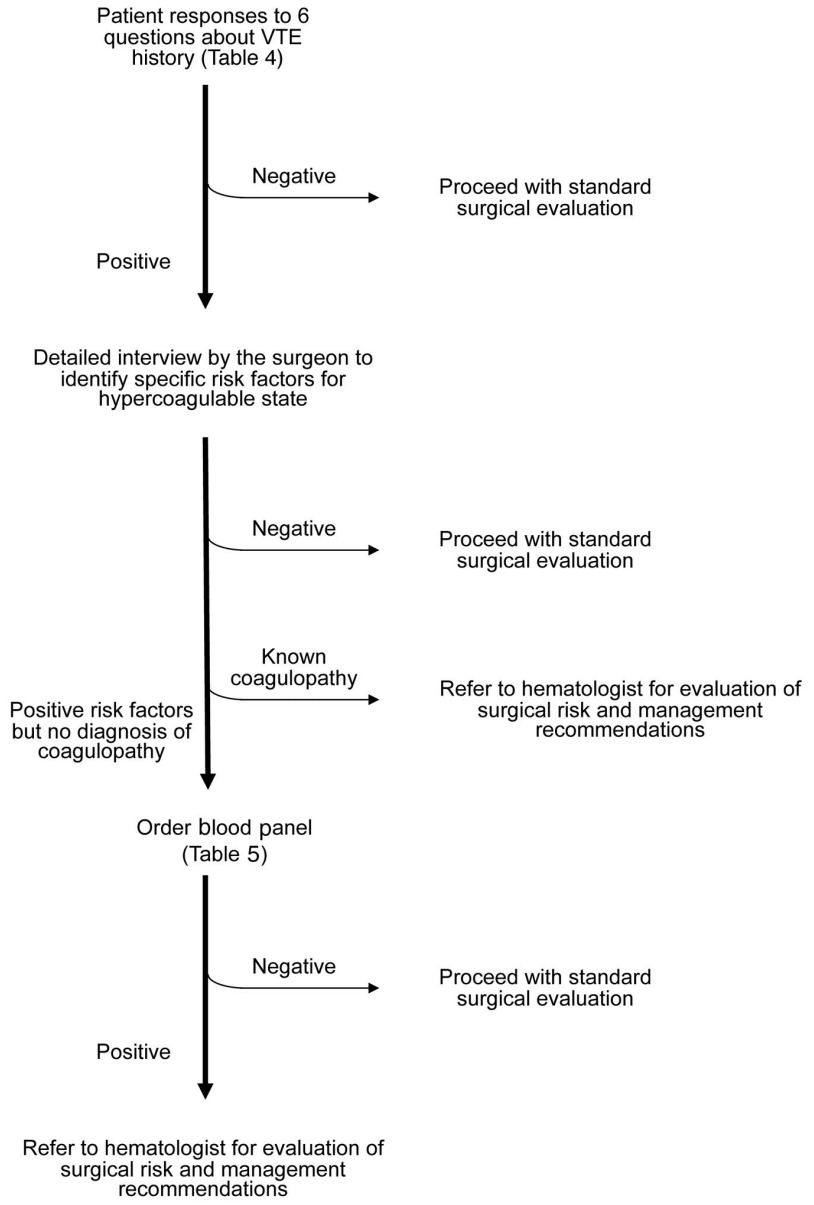

Fig. 1. Practical algorithm for screening and management of patients with hypercoagulable state. VTE, venous thromboembolism.

The placement and activation of sequential compression devices before induction of anesthesia is a noninvasive and easy measure to apply. The efficacy of sequential compression devices in reducing thromboembolism is well established.[58] Less clear is whether they operate purely by reducing venous stasis or whether they may enhance the fibrinolytic system; early studies suggested that decreases in plasminogen activator inhibitor could have an additive effect, whereas some later studies have challenged this.[59,60]

The authors recognize that the routine use of chemoprophylaxis without significant risk factors such as a known coagulopathy is still a controversial topic in plastic surgery. No clear evidence-based guidelines have been established for the plastic surgery population. Practice patterns are varied: a 2007 survey of American Society of Plastic Surgeons members suggested that in a combined abdominoplasty-liposuction case less than 20 percent of surgeons would use anticoagulation.[61] Multicenter pro-

spective trials are necessary to determine the ideal indications and regimens for chemoprophylaxis in plastic surgery. Until then, there is no true standard of care we can follow.

CONCLUSIONS

Venous thromboembolism remains the most common cause of death in plastic surgery patients. Inherited thrombophilic disorders are significant risk factors for venous thromboembolism that exist among patients having body-contouring operations. A heightened awareness of these disorders may enable previously undetected coagulopathies to be diagnosed by the plastic surgeon through careful screening. Appropriate adjustment of surgical management can then be applied to reduce the risk of venous thromboembolism.

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