Microsurgery and the Hypercoagulable State: A Hematologist's Perspective

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Summary: Hypercoagulability can pose a significant problem in microsurgical reconstruction. Here, the authors provide a comprehensive review of macrovascular and microvascular clotting phenomena from the unique viewpoint of two microsurgeons and a hematologist. The authors review the literature surrounding prevention of microvascular clots and provide an extensive discussion of hereditary thrombophilia. The authors also make explicit recommendations regarding the utility of thrombophilia testing and preoperative and perioperative management strategies for patients with hypercoagulability. (*Plast. Reconstr. Surg.* 136: 545e, 2015.)

Hypercoagulability poses a significant problem in microsurgical reconstruction. As the consequences of thrombosis can be devastating, microsurgeons routinely interrogate patients regarding their propensity for hypercoagulability. The literature regarding hypercoagulability and the microsurgical patient is scant, but published data can help reconstructive microsurgeons counsel the patient preoperatively. Most microsurgical reconstructions are undertaken in patients without clinical evidence of hypercoagulability. Unfortunately, the initial manifestation of a hypercoagulable state is often in the operating room. The microsurgeon's technical proficiency is not enough to overcome the biology of the hypercoagulable state, and interventions to pharmacologically alter the clotting cascade may be too late.

Regardless of when a hypercoagulable state is discovered, most microsurgeons will enlist the help of a hematologist. Ultimately, the questions become (1) how to deal with an underlying hypercoagulable state in the microsurgical patient and (2) whether microsurgical reconstruction can be performed safely. Often, the standard hypercoagulability laboratory panel is uninterpretable secondary to recent surgery or medications affecting the clotting cascade. For patients that need a second free flap for coverage of vital exposed structures, this represents a real problem.

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This article aims to examine hypercoagulability among microsurgical patients through the viewpoints of two microsurgeons and a hematologist. Many of the data regarding hypercoagulability in surgical patients are derived from macrovascular thrombotic events; we extrapolate how these data may relate to microsurgical concerns.

Virchow's triad of factors that promote thrombosis includes stasis of the circulation, vascular intimal damage, and intrinsic hypercoagulability.[1] Vascular and microvascular operations involve manipulation and cutting of blood vessels and thus foster an inherently prothrombotic state. Macrovascular thromboses such as deep venous thrombosis and pulmonary embolism are well-recognized complications among surgical patients.[2,3] Venous thromboembolism can be fatal,[4] and surviving patients may experience long-term morbidity.[5] For most operations, macrovascular thromboses are managed medically without increased risk of failure of the operative procedure. In contrast, thrombotic events in the surgical bed among vascular and microvascular surgery patients place the operation itself at risk. In these patients, resultant critical limb ischemia or total flap loss can be devastating.

MACROVASCULAR VENOUS THROMBOEMBOLISM IN PLASTIC SURGERY PATIENTS

Pulmonary embolism is the leading cause of death after abdominoplasty and other cosmetic

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procedures.[6–8] Research has demonstrated venous thromboembolism rates among plastic surgery inpatients to range from 1.2 to 7.5 percent.[9–12] The 2005 Caprini Risk Assessment Model[3] identifies an 18-fold variation in 60-day venous thromboembolism risk among the overall plastic surgery population, and is an effective and efficient method to risk-stratify patients.[9] The 2005 Caprini score has been validated in other surgical populations, including general, vascular, and urology patients[13]; patients in the surgical intensive care unit[14]; and otolaryngology–head and neck surgery patients.[15] The Plastic Surgery Foundation–funded Venous Thromboembolism Prevention Study demonstrated that inpatient enoxaparin prophylaxis reduces 60-day venous thromboembolism incidence among high-risk (2005 Caprini score ≥7) patients by 50 percent. Absolute 60-day venous thromboembolism risk reductions of 1.4 percent and 4.5 percent were seen for patients with Caprini scores of 7 to 8 and greater than 8, respectively.[16] Inpatient enoxaparin prophylaxis did not significantly increase risk for reoperative hematoma.[17]

The American Society of Plastic Surgeons recently released evidence-based practices for thromboembolism risk stratification and prevention.[18] This summary document advocates for universal consideration of preoperative risk stratification and risk factor modification when possible. In addition, it recommends that surgeons consider use of chemoprophylaxis for known high-risk operations, including major body contouring, abdominoplasty, major breast reconstruction, major lower extremity procedures, and major head/neck cancer procedures. The American Society of Plastic Surgeons has an ongoing venous thromboembolism awareness campaign. Free, downloadable information for providers and patients is available on their Web site.[19]

MICROVASCULAR THROMBOSIS IN PLASTIC SURGERY PATIENTS

We agree with Askari and colleagues, who write in their excellent review of anticoagulation therapy specific to microsurgery[20]:

> The currently available data are not adequate to develop a rational evidence-based approach to anticoagulation for microsurgery. Animal studies exist to defend or refute the use of almost any pharmacologic means of anticoagulation for microsurgery. Insufficient human outcomes data exist to corroborate these animal studies.

Interestingly, as data on effectiveness of chemoprophylaxis are limited, many authors conclude that solid microsurgical training and excellent surgical technique[20–22] may be the best preventative measure for microvascular thrombosis events.

Rates of Free Flap Thrombosis

Success after free flap surgery has become the norm. Although advances in surgical technique have improved free flap outcomes, the surgeon's experience cannot be understated. Godina's series of free-flap salvage for mutilated extremities from 1976 to 1983 showed a 26 percent flap loss rate over the first 100 flaps that decreased to 4 percent for his final 100 flaps.[23] The M. D. Anderson group published a 4.4 percent total flap loss rate between 1988 and 1994 that decreased to 2.1 percent for 1995 to 2006.[24] High-volume centers have published contemporary total flap loss rates of 1.1 to 3.0 percent.[24–29] A "threshold" of 70 free flaps has been suggested as the cutoff for the learning curve.[24]

Intraoperative and Postoperative Thrombosis Prevention

Several randomized controlled trials have examined microvascular thrombosis rates based on provision of antithrombotic therapy. In a trial published by Disa and colleagues, there was no significant difference in flap loss in patients randomized to treatment with low-molecular-weight dextran for 48 hours, low-molecular-weight dextran for 120 hours, or aspirin for 5 days.[30] Khouri and colleagues examined free flap loss rates in patients randomized to different intraluminal irrigation solutions. There were no significant differences between low-concentration tissue factor pathway inhibitor, high-concentration tissue factor pathway inhibitor, or heparin for intraoperative revision of anastomosis (11, 12, and 13 percent, respectively), postoperative thrombosis (8, 8, and 7 percent, respectively), or flap failure (2, 6, and 5 percent, respectively).[31]

Various components of hemostasis have been targeted to reduce microvascular thrombosis. Platelets accumulate rapidly at the microvascular suture line after reflow is established but decrease after 20 minutes. In contrast, fibrin deposition begins slowly but increases steadily over time.[32] Pharmacologic inhibition of coagulation or platelet activation in mice decreases fibrin accumulation.[32] Eptifibatide inhibits platelet aggregation by means of blockade of the glycoprotein IIb/IIIa receptor. Eptifibatide

infusion can be an adjunctive therapy for flap salvage in cases of arterial thrombosis refractory to flap tissue plasminogen activator infusion or systemic heparin.[33] Surgeons' practice patterns for prevention of microvascular clotting target coagulation, platelet activation, or both.[33–35] Askari et al. provide an extensive review of pharmacologic manipulation of the clotting cascade as it relates to microvascular thrombosis, and we direct readers to their well-written article for additional information.[20]

Timing of Flap Thrombosis and Salvage Rates

Several large studies of flaps with arterial or venous obstruction have been published.[21,24,36] The vast majority of intraoperative thrombosis is arterial. Eighty percent of postoperative thrombosis occurs by postoperative day 4.[36] Yu and colleagues showed that 75 percent of arterial and 45 percent of venous thromboses present within 24 hours of surgery.[24] Venous thrombosis is more common as time from surgery increases (Fig. 1).[36–39] Flap salvage rates range between 45 and 73 percent.[21,24,27,36] Once thrombosis is recognized, faster return to the operating room predicts salvage.[28] Mirzabeigi and colleagues showed a decline in flap salvage rates over time, including 64 percent at 0 to 48 hours, 46 percent at 49 to 96 hours, and 0 percent at greater than 96 hours. Similar trends have been shown by others.[24,25]

HEREDITARY THROMBOPHILIA IN PATIENTS WITH POSTOPERATIVE VENOUS THROMBOEMBOLISM

Hereditary thrombophilias are germline genetic mutations associated with an increased risk of thrombosis, particularly venous thromboembolism. A number of hereditary thrombophilias have been identified. The most important hereditary thrombophilias are listed in Table 1 along with their prevalence in the general population and the relative risk of venous thromboembolism they confer.[40–42]

The presence of hereditary thrombophilia is predictive of venous thromboembolism including postoperative venous thromboembolism.[43,44] Nevertheless, authorities recommend against routine hereditary thrombophilia testing in patients with venous thromboembolism provoked by a major transient risk factor such as surgery for at least three reasons, as follows.[40,45]

Common Hereditary Thrombophilias Are of Uncertain Clinical Relevance in Postoperative Venous Thromboembolism

Approximately 10 percent of normal controls with no history of venous thromboembolism and 24 to 37 percent of patients with venous thromboembolism harbor a hereditary thrombophilia.[41–44] The most common hereditary thrombophilias, factor V Leiden and prothrombin G20210A

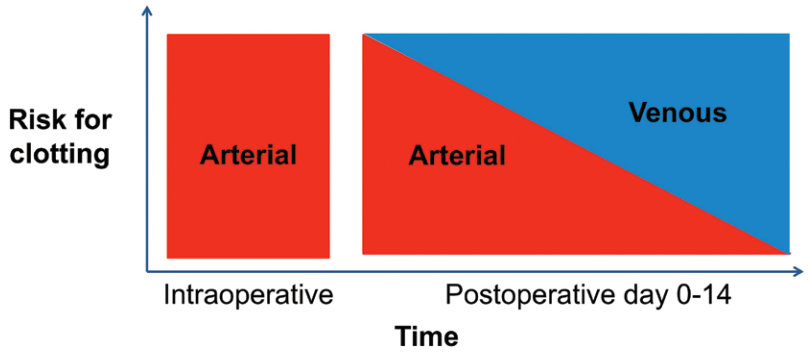

Fig. 1. Schematic depiction of flap microvascular thrombosis over time. Case series support the concept that thrombosis can occur out to postoperative day 14 (Mirzabeigi MN, Wang T, Kovach SJ, Taylor JA, Serletti JM, Wu LC. Free flap takeback following postoperative microvascular compromise: Predicting salvage versus failure. *Plast Reconstr Surg*. 2012;130:579–589; Chan RK, Mathy JA, Przylecki W, Guo L, Caterson SA. Case report: Superior gluteal artery perforator flap breast reconstruction salvage following late venous congestion after discharge. *Eplasty* 2010;10:e63; Trussler AP, Watson JP, Crisera CA. Late free-flap salvage with catheter-directed thrombolysis. *Microsurgery* 2008;28:217–222; and Nelson JA, Kim EM, Eftekhari K, et al. Late venous thrombosis in free flap breast reconstruction: Strategies for salvage after this real entity. *Plast Reconstr Surg*. 2012;129:8e–15e), and thromboses after this point are also possible.

Table 1. Relative Risk and Prevalence of Selected Hereditary Thrombophilias

Thrombophilia	Prevalence (%)	Relative Risk for VTE
Prothrombin G20210A carrier	1–5 in Caucasians	2.8
Factor V Leiden carrier	5–8 in Caucasians	4.9
Protein C deficiency	0.2–0.5	7.3
Antithrombin III deficiency	0.2–0.5	8.1
Protein S deficiency	0.03–0.13	8.5
Prothrombin G20210A/factor V Leiden heterozygosity	0.1	20.0
Factor V Leiden homozygosity	0.06–0.25	80

VTE, venous thromboembolism.

heterozygosity, are found in 5 to 8 percent and 1 to 5 percent of healthy individuals of European origin, respectively[46–49] (Table 1). Both mutations are relatively weak risk factors in the heterozygous state; the relative risk of venous thromboembolism they confer is similar to that reported for combination oral contraceptive use[50] and is dwarfed by the risk of venous thromboembolism associated with major surgery.[51,52] Thus, the contribution of these genotypes to postoperative venous thromboembolism is likely to be small. Deficiencies of protein C, protein S, and antithrombin and factor V Leiden homozygosity and factor V Leiden/prothrombin G20210A compound heterozygosity are associated with a greater risk of venous thromboembolism, but are considerably rarer (Table 1).

Negative Hereditary Thrombophilia Testing Does Not Equate with an Absence of Hereditary or Biological Risk

A standard hereditary thrombophilia panel screens for only a subset of the genetic factors contributing to thrombotic risk. Many others are not included or remain to be elucidated.[53] In addition, hereditary thrombophilia panels do not assess for the presence of acquired biological predispositions to thrombosis, which remain poorly understood. Therefore, the absence of an identifiable hereditary thrombophilia is not tantamount to absence of biological or hereditary risk. Indeed, only 24 to 37 percent of patients with venous thromboembolism have an identifiable hereditary thrombophilia.[41–44] It is likely that many remaining patients harbor one or more hereditary or biological risk factors that are not detected with current methods.

Hereditary Thrombophilia Testing Rarely Affects Management and May Cause Harm

One of the American Society of Hematology Choosing Wisely items is: "Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of a major transient risk factor (e.g., surgery, trauma, prolonged immobility)." In this scenario, hereditary thrombophilia test results do not influence the recommended duration or intensity of anticoagulation in patients with postoperative venous thromboembolism.[54] Hereditary thrombophilia testing has the potential to cause harm in this context if the duration of anticoagulation is inappropriately prolonged or if patients are labeled as having a thrombophilic disorder. Inappropriately labeling patients as having a thrombophilic disorder could affect their overall insurability or insurance premiums, and alter the way in which they are treated by providers caring for them in the future. Misdiagnosis of hereditary thrombophilia is also a concern if testing is not timed appropriately. Protein C, protein S, and antithrombin levels are reduced in the setting of acute thrombosis because of accelerated consumption. Protein C and protein S are vitamin K–dependent proteins and are decreased by warfarin. Unfractionated heparin and low-molecular-weight heparin decrease antithrombin levels. Hereditary thrombophilia testing must be timed carefully to differentiate true hereditary deficiency of these proteins from acquired deficiency caused by thrombosis and/or anticoagulation. Diagnosis of hereditary deficiency of protein C, protein S, or antithrombin deficiency is thus unfeasible in patients who have recently lost a flap and require a second free flap.

HEREDITARY THROMBOPHILIA IN FREE FLAP PATIENTS

Although their impact on venous thromboembolism risk is well studied (Table 1), it is unknown whether and to what extent hereditary thrombophilias influence the risk of microvascular thrombosis. The plastic surgery literature is riddled with case reports (which are subject to publication bias) of free flap losses among patients with hereditary thrombophilia.[55–59] A more rigorous study design is needed to determine the safety of microsurgery in patients with hereditary thrombophilia.

The only controlled study to address this issue was a retrospective cohort of 2032 consecutive free flaps (1355 patients) performed at a single institution between 2005 and 2010. Fifty-eight flaps (2.9 percent) were performed in 41 patients with a documented hypercoagulable state (defined as prior thrombosis and/or known thrombophilia). The authors identified a significantly greater rate of flap thrombosis (20.7 percent versus 4.2 percent; $p = 0.0001$) and flap failure (15.5 percent versus 1.8 percent; $p = 0.0001$) in this group compared

with the 1974 flaps performed in patients without known hypercoagulability.[34]

The authors concluded that the presence of a hypercoagulable state adversely impacts microsurgery outcomes. However, a closer analysis of the data suggests that the nature of the hypercoagulable state was a critical determinant of outcome. Among 58 flaps in the hypercoagulable group, 51 were performed in patients with a history of macrovascular venous or arterial thrombosis or another acquired hypercoagulable disorder and seven were performed in patients with a known hereditary thrombophilia without a personal history of thrombosis. Twelve flap thromboses and eight failures occurred in the former subgroup; there were no flap thromboses or failures in the latter subgroup.[34] Although the numbers are small, this analysis suggests that acquired risk factors including prior thrombosis appear to be more predictive of outcomes than hereditary risk factors. More data are needed to determine whether hereditary thrombophilia in the absence of a clinical history of thrombosis confers an increased risk of flap thrombosis or failure.

PREOPERATIVE VENOUS THROMBOEMBOLISM RISK ASSESSMENT IN THE MICROSURGERY PATIENT

We recommend that all microsurgery patients should undergo preoperative venous thromboembolism risk assessment using the 2005 Caprini score.[3] Most patients are classified as high risk or super high risk (Caprini scores of 7 to 8 or >8, respectively) for perioperative venous thromboembolism events[9,15] because the predominant indications for microsurgery are cancer or trauma reconstruction; each is an important risk factor in the Caprini score. Additional common risk factors include advanced age, long operative times, recent operative procedure, and central venous access, among others. The Caprini score can predict risk for macrovascular venous thromboembolism. The score's ability to predict microvascular thrombosis of the arterial or venous pedicle has not been evaluated. This is an important direction for future research.

PREOPERATIVE RISK STRATIFICATION FOR MICROVASCULAR THROMBOTIC RISK

Friedman and colleagues proposed an algorithmic approach to preoperative risk assessment in plastic surgery (Fig. 2), in which all patients are screened for personal or family history of thrombosis. Patients providing a positive response are referred to the surgeon for a more detailed history. If concern for an elevated risk of thrombosis remains and the patient does not have a known thrombophilia, the surgeon orders thrombophilia testing. If positive, the patient is referred

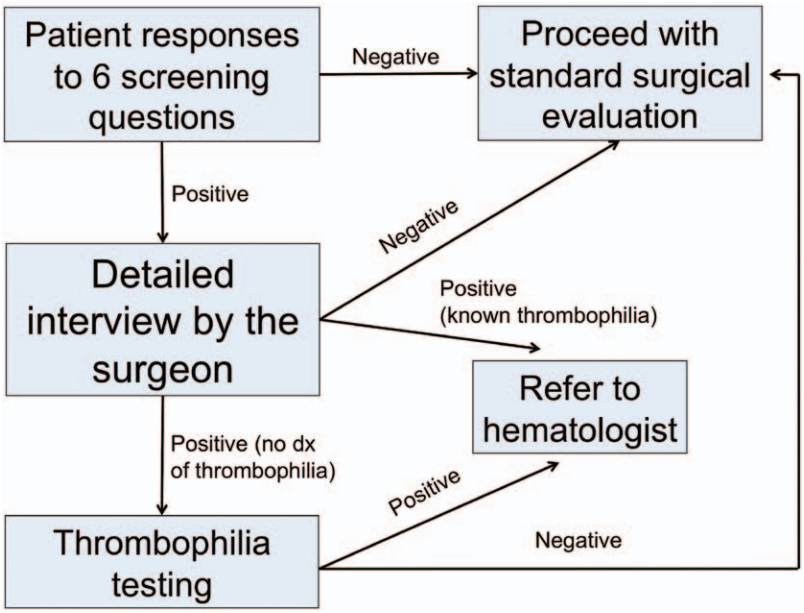

Fig. 2. Algorithm proposed by Friedman et al. for preoperative risk assessment for perioperative thrombosis. *dx*, diagnosis. (Adapted from Friedman T, O'Brien Coon D, Michaels V J, et al. Hereditary coagulopathies: Practical diagnosis and management for the plastic surgeon. *Plast Reconstr Surg*. 2010;125:1544–1552.)

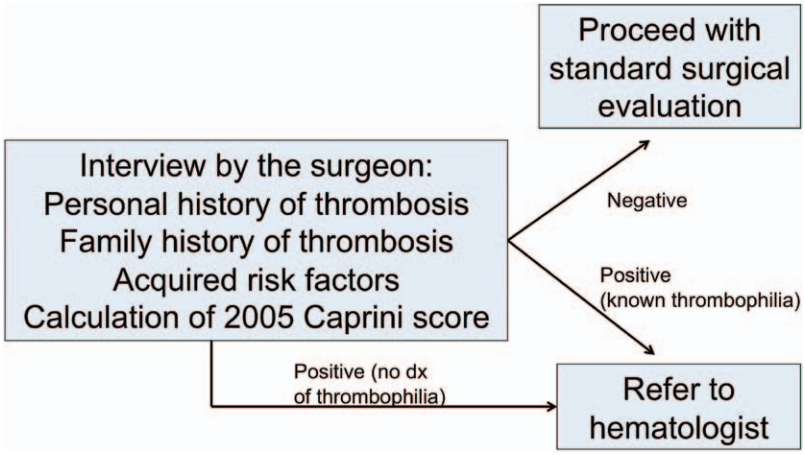

Fig. 3. The authors' algorithm for preoperative risk assessment for perioperative thrombosis. *dx*, diagnosis.

for preoperative evaluation by a hematologist. If negative, the patient proceeds with standard surgical evaluation.[60]

We disagree with the approach proposed by Friedman and colleagues, particularly as it relates to the microsurgical population, because of the primacy it places on thrombophilia testing. As discussed above, a pathophysiologic link between hereditary thrombophilia and flap thrombosis has not been established, and the presence of hereditary thrombophilia without a personal history of thrombosis was not associated with adverse flap outcomes in a retrospective cohort study.[34] Moreover, a negative hereditary thrombophilia panel does not exclude the presence of important hereditary or acquired biological predispositions and should not provide reassurance to the surgeon in the face of a concerning history.

We agree with Friedman and colleagues that the first and most important step in preoperative risk assessment is a focused history, as history of thrombosis or other acquired risk factors has been associated with flap thrombosis and failure.[34] Patients should be queried about a personal or family history of thrombosis and the presence of acquired risk factors (e.g., cancer, trauma, pregnancy). If the patient is classified as high risk using the Caprini score or the history suggests a level of risk that the surgeon feels is not adequately captured by the Caprini score (e.g., a patient with a history of venous thromboembolism in multiple first-degree relatives), referral to a hematologist should be considered. In the series published by Wang and colleagues, preoperative hematology consultation was associated with a trend toward superior flap outcomes in the hypercoagulable group ($p = 0.06$).[34] Thrombophilia testing is seldom appropriate. In our opinion, the decision to request thrombophilia testing should be deferred to the hematologist, who may be more familiar with the indications, limitations, interpretation, and appropriate timing of testing. An algorithm depicting our recommended approach to preoperative risk assessment is shown in Figure 3.

There is no high-quality evidence regarding management of patients at high risk for microvascular thrombosis in the preoperative, intraoperative, or postoperative setting. In the absence of evidence-based recommendations, our suggestions are based on the aggregate clinical experience of two microsurgeons and a hematologist. High-risk patients may benefit from intraoperative and/or postoperative antithrombotic therapy. Our practice is to use intravenous unfractionated heparin run at 800 U/hour during the operation and for 24 hours after surgery. Subsequently, the patient is started on prophylactic dose enoxaparin. At a minimum, we continue enoxaparin until discharge. In patients we judge to be particularly high risk, we consider extending prophylactic anticoagulation for 4 weeks, at which time the flap should no longer be solely dependent on its primary blood supply. Trials are urgently needed to define optimal antithrombotic regimens in high-risk patients.

Patients whose hypercoagulability is discovered in the operating room and who have actually lost a free flap require more aggressive management. These patients typically have multiple anastomotic revisions that clot on the operating table, and most receive pharmacologic interventions to decrease thrombosis, including intravenous heparin and intravascular irrigation with heparin or tissue plasminogen activator. Although these patients are

clearly hypercoagulable based on clinical examination, there is no role for hereditary thrombophilia testing in the acute setting. Results of hereditary thrombophilia testing will not alter management and may be uninterpretable because of acute thrombosis or anticoagulant use. For clinically hypercoagulable patients who require a second free flap, our approach is to start the second case on a low-dose heparin infusion, typically 800 U/hour. Before vessels are clamped, the patient receives a bolus dose of 3000 U of intravenous heparin and is started on a therapeutic dose of intravenous heparin (goal partial thromboplastin time of 50 to 70 seconds) during the anastomoses. Patients remain therapeutically anticoagulated during their hospitalization and are transitioned to a course of postdischarge therapeutic anticoagulation. Therapeutic dose enoxaparin (1.5 mg/kg/day or 1.0 mg/kg twice daily) obviates the need for monitoring and is our anticoagulant of choice. The total course of therapeutic anticoagulation is 4 weeks, at which point peripheral revascularization should be sufficient to support the flap if primary anastomotic failure occurs. Therapeutic anticoagulation can be withdrawn at this time.

CONCLUSIONS

We have reviewed thrombotic phenomena in the microsurgery population with an emphasis on both macrovascular venous thromboembolism and microvascular thrombosis. We recommend that all microsurgery patients be risk-stratified for perioperative venous thromboembolism risk using the 2005 Caprini Risk Assessment Model. Although the score's ability to predict microvascular thrombosis has not been evaluated, evidence suggests that conventional acquired risk factors for venous thromboembolism also predict flap thrombosis.[35] A pathophysiologic relationship between hereditary thrombophilia and microvascular thrombosis has not been established. We suggest preoperative consultation with hematology when formal risk assessment and/or the medical history indicates high perioperative thrombotic risk. We recommend against routine hereditary thrombophilia testing because the results are unlikely to affect management and may lead to harm. Trials are needed to define optimal antithrombotic therapy in the high-risk microsurgery population.

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